



A joint-stock company with capital of €915,163.15  
Registered office: 265, rue de la Découverte, 31670 Labège  
Toulouse Trade and Companies Register No. 481 637 718

## REGISTRATION DOCUMENT

### INCLUDING THE ANNUAL FINANCIAL REPORT



Pursuant to Article 212-13 of its General Regulations, the French Financial Markets Authority (“**AMF**”) filed this Registration Document on April 28, 2017, under number R.17-033. This document may be used to support a financial transaction only if it is supplemented by a prospectus approved by the AMF. It has been prepared by the issuer on the responsibility of the signatories.

Registration in accordance with Article L. 621-8-1-I of the French Monetary and Finance Code was made after the AMF had verified that the document is complete and comprehensible, and that the information it contains is accurate. This does not entail validation of the accounting and financial information presented by the AMF.

This document is available at no cost from the Company’s registered office, and can also be found in electronic format on the websites of the AMF ([www.amf-france.org](http://www.amf-france.org)) and of the Company (<http://www.cerenis.com>).

#### **Incorporation by reference:**

Pursuant to Article 28 of EC Regulation 809/2004, the following documents are included as a reference in this document:

- The consolidated financial statements prepared according to IFRS as adopted by the European Union for the year ended December 31, 2014, and the relevant audit report, presented on pages 179 to 214 and 215 respectively of the Registration Document, which was recorded by the AMF on March 3, 2015, under number I.15-009.
- The consolidated financial statements prepared according to IFRS as adopted by the European Union for the year ended December 31, 2015, and the relevant audit report, presented on pages 219 to 273 and 274 to 297 respectively of the Registration Document, which was recorded by the AMF on April 29, 2016, under number R.16-040.

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## GENERAL COMMENTS

### *Definitions*

In this Registration Document, and unless otherwise specified:

- The terms “**Company**” or “**Cerenis**” mean Cerenis Therapeutics Holding, a limited liability company with share capital of €915,163.15, registered office at 265, rue de la Découverte, 31670 Labège, France, and registered with the Toulouse Trade and Companies Register under number 481 637 718.

### *Disclaimer*

This Registration Document contains information on the Company’s business activities and the market in which it operates. This information originates from studies conducted by either internal or external sources (e.g. certain market sector publications, specialized studies, information published by market research companies, and analysts’ reports). The Company believes that this information provides a true and fair view of its reference market and its competitive position in this market. However, the information has not been checked by an independent expert, and the Company cannot guarantee that a third party using different methods to collect, analyze or process market data will obtain the same findings.

On March 1, 2017, the Company announced that it had not achieved the main objective of the CARAT study. It learned of this after the financial statements and consolidated financial statements were approved on February 17, 2017, and after the Statutory Auditors’ reports dated February 20, 2017, were issued. As a result, Note I.C to paragraph 20.1 and Note II to paragraph 20.3 do not refer to this event.

### *Forward-looking information*

This Registration Document also contains information on the Company’s goals and areas of development. This information is sometimes identified by the use of future or conditional tenses or by forward-looking terms such as “believes,” “considers,” “with the aim of,” “expects to,” “intends,” “should,” “wishes” and “could” or by other variants or similar terminology. The reader’s attention is drawn to the fact that these aims and areas of development are not based on historical data and should not be interpreted as a guarantee that the facts and data statements will occur, that the assumptions will prove true or that the objectives will be achieved. These goals may, given their very nature, not be attained, and the information provided in this Registration Document could prove to be erroneous without the Company being obliged in any way to update the information, while still complying with current regulations, in particular with the General Regulation of the Autorité des marchés financiers (the French Financial Markets Authority - “**AMF**”).

### *Risk factors*

Investors are also invited to consider the risk factors described in Section 4 “Risk factors” of this Registration Document before making any investment decisions. The occurrence of any or all of these risks may negatively impact the activities, position, financial results or goals of the Company. Moreover, other risks not yet currently identified or regarded as immaterial by the Company could have the same negative impact, causing investors to lose all or part of their investment.

### *Other points*

To facilitate readers’ understanding of this document, a glossary containing the main scientific and technical terms used is included in Section 27 of this Registration Document.

## 1. PERSON RESPONSIBLE

### 1.1. Person responsible for this Registration Document

Mr. Jean-Louis Dasseux, CEO

### 1.2. Statement of the person responsible

Having taken all reasonable measures, I hereby declare that the information contained in this present document is, to the best of my knowledge, factually accurate and does not contain any omission likely to affect its scope.

I furthermore declare that, to the best of my knowledge, the financial statements were prepared in accordance with the appropriate accounting standards and provide a true and fair view of the assets and liabilities, financial position and results of the Company and of all of the companies included in the consolidation scope, and that the management report whose cross-reference table is shown in Section 28 presents a true and fair view of changes in the business, results and financial position of the Company and of all of the companies included in the consolidation scope, as well as a description of the primary risks and uncertainties they face.

The Statutory Auditors have furnished me with a completion letter stating that they have verified the information related to the financial position and financial statements provided in this report and have read this report in its entirety.

Jean-Louis Dasseux,  
Chief Executive Officer

Labège, April 28, 2017

### 1.3. Person responsible for financial reporting

Cyrille Tupin,  
Chief Administrative and Financial Officer  
Address: 265, rue de la Découverte, 31670 Labège  
Telephone: +33 (0)5 62 24 09 45  
Email: investor@cerenis.com

## 2. STATUTORY AUDITORS

### 2.1. Primary Statutory Auditors

**Deloitte & Associés**, a member of the Regional Association of Statutory Auditors of Versailles, 185 C avenue Charles de Gaulle, 92200 Neuilly sur Seine represented by Etienne Alibert.

Deloitte & Associés was appointed by the General Shareholders' Meeting held on June 28, 2011 for a six-year term, i.e. until the end of the General Shareholders' Meeting to be convened in 2017 to approve the financial statements for the year ending December 31, 2016.

**HLP Audit S.A.S.**, a member of the Regional Association of Statutory Auditors of Rennes, 3 chemin du Pressoir Chênaie, 44100 Nantes represented by Freddy Garcin.

HLP Audit was appointed by the General Shareholders' Meeting held on December 23, 2014 for a six-year term, i.e. until the end of the General Shareholders' Meeting to be convened in 2020 to approve the financial statements for the year ending December 31, 2019.

### 2.2. Alternate Statutory Auditors

**BEAS S.A.R.L.**, a member of the Regional Association of Statutory Auditors of Versailles, 7-9 Villa Houssay, 92200 Neuilly sur Seine Cedex  
Alternate to Deloitte & Associés.

BEAS was appointed by the General Shareholders' Meeting on June 28, 2011 for a six-year term, i.e. until the end of the General Shareholders' Meeting to be convened in 2017 to approve the financial statements for the year ending December 31, 2016.

**OSIS S.A.R.L.**, a member of the Regional Association of Statutory Auditors of Rennes, 3 chemin du Pressoir Chênaie, 44100 Nantes  
Alternate to HLP Audit SAS.

OSIS S.A.R.L. was appointed by the General Shareholders' Meeting held on December 23, 2014 for a six-year term, i.e. until the end of the General Shareholders' Meeting to be convened in 2020 to approve the financial statements for the year ending December 31, 2019.

### 3. SELECTED FINANCIAL INFORMATION

The Company, which only owns one subsidiary in the United States and has no other shareholdings as of December 31, 2016, has prepared its financial statements in accordance with French GAAP and its consolidated financial statements in accordance with IFRS applicable in 2016.

The selected financial information presented below was taken from the financial statements as they appear in Section 20.1 “Financial Statements prepared according to IFRS for the year ended December 31, 2016” of this Registration Document. Items related to the year ended December 31, 2014 were taken from the 2015 Registration Document.

The accounting and operating data selected below must be read in conjunction with the information contained in Sections 9 “Analysis of the financial position and results” and 10 “Liquidity and capital resources” of this Registration Document.

#### Simplified balance sheet

Assets (EUR thousand)	12/31/16	12/31/15	21/31/14
Total non-currents assets	343	446	73
Total current assets	28.722	45.661	10.764
<b>TOTAL ASSETS</b>	<b>29,065</b>	<b>46,107</b>	<b>10,764</b>
Liabilities (EUR thousand)	12/31/16	12/31/15	21/31/14
Total shareholders' equity	14,610	33,198	12
Total non-currents liabilities	7,761	7,120	6,124
Total current liabilities	6,694	5,790	4,701
<b>TOTAL LIABILITIES</b>	<b>29,065</b>	<b>46,107</b>	<b>10,837</b>

#### Simplified income statement

Income statement (EUR thousand)	12/31/16	12/31/15	21/31/14
Revenue	0	0	0
Administrative and business expenses	(7,031)	(2,913)	(2,971)
R&D expenses	(17,004)	(12,561)	(3,098)
<b>Operating income</b>	<b>(24,035)</b>	<b>(15,474)</b>	<b>(6,069)</b>
Financial result	(841)	(1,164)	(531)
Tax on profit	5	0	37
<b>Net income</b>	<b>(24,871)</b>	<b>(16,638)</b>	<b>(6,563)</b>

#### Cash flow statement

Cash flow statement (EUR thousand)	12/31/16	12/31/15	21/31/14
Cash flow of operations	(19,197)	(13,711)	(3,303)
Cash flow from investments	(5-)	-(171)	1
Cash flow from financing activities	925	48,993	0
Changes in net cash flow	(18,277)	35,111	(3,302)
<b>Initial cash flow</b>	<b>42,951</b>	<b>7,843</b>	<b>11,141</b>
<b>Closing cash flow</b>	<b>24,675</b>	<b>42,951</b>	<b>7,843</b>

## 4. RISK FACTORS

*Investors are invited to consider all the information contained in this Registration Document, including the risk factors described in the present section, before deciding to purchase or subscribe to the Company's shares. In preparing this Registration Document, the Company has reviewed the risks that it believes, as of the date of this Registration Document, may have a material adverse effect on the Company, its business, finances, prospects, income or growth and considers that there are no other risks than the ones described.*

*However, investors are advised that the list of risks included in the present Section 4 is not exhaustive and that other risks either unknown or not considered at the date of this Registration Document may or could potentially and significantly undermine the Company, its business, prospects, finances, income and growth.*

*Cerenis has built up a portfolio of innovative products that are in different stages of development. These products are based on the reverse lipid transport (RLT) pathway that facilitates the elimination of cholesterol. These products in development are designed to treat cardiovascular disease and related metabolic diseases such as Non-Alcoholic SteatoHepatitis (NASH).*

*Since it was founded, Cerenis has concentrated most of its investments on developing CER-001 and its manufacturing process. On June 10, 2010, the Company signed a partnership agreement with Novasep Process SAS (Novasep), which manufactures the batches of CER-001.*

*CER-001 is a drug candidate intended to reduce atherosclerotic plaque in the vessel walls, intended for the treatment of cardiovascular diseases and the orphan disease FPHA (HDL deficiency). The Company holds property and licensing rights over seven families of patents related to CER-001.*

*Other products in Cerenis' portfolio are:*

- CER-522, an HDL mimetic based on a peptide analog of apoA-I, now ready to be entered into Phase I clinical development to treat Aortic Valve Stenosis (AVS). HDL mimetics are covered by family 6 of patents, which is fully owned by the Company.*
- CER-209 is the first drug candidate in the category of P2Y<sub>13</sub> receptor agonists delivered per os. Owing to the positive metabolic effects observed on the liver during pre-clinical trials, CER-209 may also offer a new mechanism to treat Non-Alcoholic SteatoHepatitis (NASH). These P2Y<sub>13</sub> receptor agonists are covered by family 7 of patents which is fully owned by the Company. The US Food and Drug Administration (FDA) informed Cerenis Therapeutics that CER-209 could enter into clinical development. This FDA authorization (IND – Investigational New Drug application) is for a Phase I clinical trial.*
- CER-002 is a selective PPAR $\delta$  agonist. One of the potential diseases targeted by CER-002 is metabolic syndrome. CER-002 is protected by family 8 of patents. The Company has filed for an exclusive license for this technology, which has been granted by its owner, Nippon Chemiphar Co., Ltd.*

*Cerenis' short and mid-term strategy centers on the development of CER-001 for the indication of the orphan disease FPHA through a Phase III clinical trial (TANGO). The principal criterion of the study should be achieved by the end of 2017. The results should lead to filing of the market authorization application for the drug by 2018 and the development of CER-209 for the treatment of patients suffering from Non-Alcoholic SteatoHepatitis who are at very high risk of a cardiovascular event.*

*Cerenis still has a long way to go before it can commercialize CER-001. Its distribution can only occur after successfully completing the different clinical phases and obtaining Market Authorization (MA).*

*At present, Cerenis plans to distribute CER-001 directly as a treatment for the orphan disease FPHA in Europe.*

*At the date of this Registration Document, the Company has not signed any licensing contract with a pharmaceutical lab.*

*Consequently, Cerenis draws the attention of readers to the risks of not generating any revenue before commercialization of CER-001 for FPHA, which could occur during fiscal 2018 and to the risks inherent in the results of the clinical trials.*

*Finally, Cerenis stresses that there are inherent risks associated with the Company's purpose. By nature, the Company engages in research programs that have uncertain outcomes. Thus while the CARAT did confirm the safety and tolerance profile of CER-001, it did not achieve its main objective, namely, the reduction of atheroma plaque in the coronary arteries, which is measured with IVUS imaging. The consequences of this situation are discussed in paragraphs 12.1 and 12.2.*

#### **4.1. Risks relating to the Company products and market**

##### **4.1.1. Products that the Company is currently developing may entail costly, stringent and highly regulated pre-clinical and clinical trials whose number, duration and outcomes remain uncertain**

The Company conducts pre-clinical and clinical programs<sup>1</sup> mainly intended to develop and distribute therapeutic solutions to treat cardiovascular and metabolic diseases. The development of a drug candidate is a long and costly process spread over several distinct trial phases, each of which is expensive and may result in failure or delay in obtaining marketing authorization (MA). Moreover, the regulatory authorities of different countries in which the Company intends to commercialize its products could interpret the results differently to the Company and could request additional tests at their discretion (including as regards to study protocols, patient profiles and numbers, duration of treatment, analytical methods and post-treatment follow-up) or require additional and unforeseen requirements for these trials. The outcome of these studies is therefore highly uncertain from any viewpoint and the Company cannot therefore guarantee that the clinical trials will lead to marketable results or that these clinical trials will be performed within deadlines for profitable commercialization.

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<sup>1</sup> Reminder:

**Pre-clinical phases:** Laboratory tests to assess the main effects of the molecule and its toxicity.

**Phase I:** Study of the behavior of the molecule tested in the body with time (absorption and elimination kinetics) and analysis of safety and tolerance in humans. This phase is conducted on a small number of voluntary and non-diseased persons (healthy volunteers).

**Phase II:** Estimation of efficiency and safety of the molecule and determination of the therapeutic dose of the molecule.

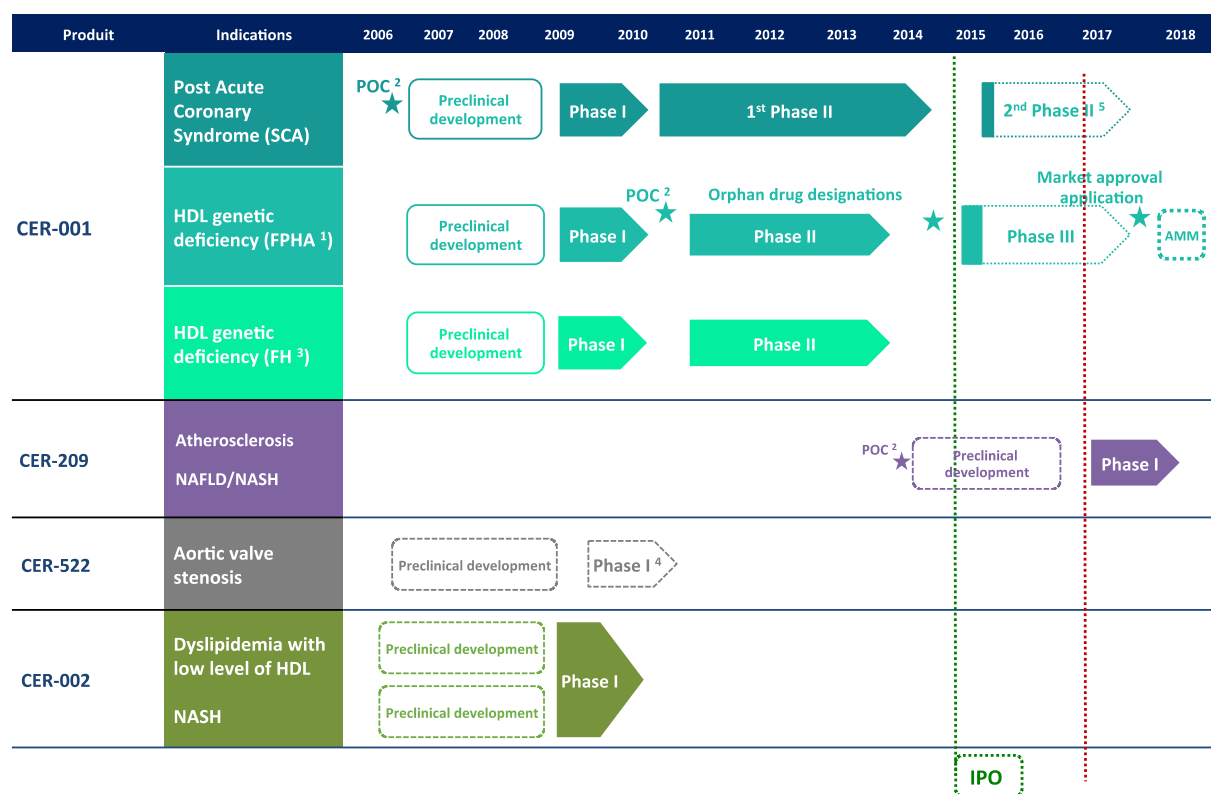
**Phase III:** Comparison of the effectiveness of the new drug with standard treatment. This phase is aimed at a large number of patients. Patients are selected on specific criteria aimed at answering the question of efficiency and benefit of the drug tested as a new treatment standard for that disease.

As a general rule, it takes a long time to develop a drug for human health, approximately 12 to 15 years, from the discovery of the molecule (drug candidate) to delivery of the drug to patients.

In the development of a drug aimed at a broad-based population, the selection and pre-clinical phases may last two to four years: Phase I trials (single and multiple dose studies) may take one to two years, followed by Phase II trials which may last two to four years. These are followed by Phase III studies, which last a total of three to five years and, finally the application for market authorization, which may take one to three years. However, these approximate times vary considerably depending on the nature of the drug candidates (a new chemical entity, a biological product) and on the targeted pathologies (rare diseases or an acute or chronic therapeutic treatment).

In the case of rare diseases, the authorities may decide to curtail the development time of a drug candidate to meet a major unmet medical need.

Since the Company began operating in 2005, it has developed four research programs. The stages already completed by the Company at the date of this Registration Document are as follows:



1. Primary familial hypoalphalipoproteinemia

2. Proof of concept

3. Familial hypercholesterolemia (FH) resulting from a genetic deficiency of the LDL receptor. Please see Section 6.6.1

4. The "Investigational new drug" (IND) was accepted by the FDA in April 2009. CER-522 is ready to enter a Phase I clinical trial. Please see Section 6.6.4.

5. The phase II study CARAT did not meet its primary endpoint. Cf. paragraphs 5.1.5 and 6. The development for the ACS indication has been suspended pending the results of a more detailed analysis to understand the outcome of this study. These are expected at end 2017.

The various studies carried out by the Company regarding these four research programs, and therefore, their stages of completion, have been driven by the Company's strategic choices in terms of products and allocation of resources.

Moreover, the Company may experience difficulties in recruiting and retaining patients to take part in the clinical trials. Once recruited, patients taking part in these trials could, at any time and without having to provide justification, suspend or terminate their participation. If too many patients terminate their participation in a clinical trial, analysis of trial data may not reach statistically significant levels.

The clinical trials designed and coordinated by the Company are performed by medical and hospital centers, otherwise known as *Contract Research Organizations* (CRO), whose work (selection of target populations, measurement of baselines, compliance with protocols/doses/number of administrations/intermediate time intervals, data collection) is crucial to the evaluation and accuracy of the findings.

The Company cannot guarantee that the findings of the clinical trials will demonstrate tolerance, safety (including absence or limitation of adverse side effects or interactions with other drugs or therapeutic solutions) and the efficacy of one or more of its therapeutic products in animals or humans. Any failure or ambiguity in the findings during the various clinical trials with a given indication could delay the development and commercialization of the therapeutic products considered or result in stopping their development. For instance, the CHI SQUARE trial, during which several doses have been tested (3, 6 and 12 mg/kg), did not reach its main objective, i.e. an atherosclerotic plaques reduction with the 12 mg/kg dose compared to the placebo treatment. Although this study has revealed the mobilization of cholesterol by CER-001 at all doses tested (3, 6 and 12 mg/kg) and a good patient safety profile, the reduction in the total atherosclerotic volume vs. placebo at a dose of 12 mg/kg, which was the main objective of the trial, was not achieved. However, the reduction in total atherosclerotic volume vs. baseline (volume at the start of the trial) was statistically significant at 3 mg/kg, evidencing that the product administered in small and multiple doses is more efficient than a single and large dosing.

A further independent analysis by SAHMRI confirmed that the 3 mg/kg dose was optimal and that it could be selected for the subsequent Phase II trial. Therefore, the findings obtained, associated with other clinical trials conducted in parallel (SAMBA and MODE – see Section 6 of this Registration Document), supported the Company's decision to develop CER-001. Indeed, this trial aided in confirming the safety of the drug candidate CER-001, identifying the optimal dose, clarifying the efficacy mechanisms and optimizing the protocol to be applied to future studies. The Company conducted a second Phase II trial for CER-001 to treat post-ACS patients, known as the CARAT study. This trial aimed at confirming the results obtained with the recommended 3 mg/kg dose for 10 administrations, a higher number of administrations than in the previous trial. Although the CARAT study confirmed the safety and tolerance profile of CER-001, it did not meet the primary endpoint (regression of atherosclerosis plaque in the coronaries assessed by the IVUS method). The results were presented on March 18, 2017 at the annual conference of the American College of Cardiology. As a consequence, the development of CER-001 has been temporarily suspended in the indication of secondary prevention in post-ACS patients until a full analysis of the results of CARAT has been made and until the results of the phase III study TANGO are available.

The clinical development of CER-001 is currently being pursued in phase III (TANGO) for the treatment of genetic deficiency of HDL within the framework of two designations of orphan diseases granted by the European Medicines Agency. The TANGO timetable is presented in Section 6 of this Registration Document.

Entry into Phase III or commercialization of certain drug candidates will expose larger population samples to the drug candidate in question, which could reveal safety problems, adverse side effects, inefficacy or interactions not previously anticipated or detected, which could, in extreme cases, lead to death. Moreover, Phase III studies may also trigger or worsen currently unknown pre-existing or



non-pre-existing pathologies, which could slow down or even stop the development of the products concerned. In addition, some clinical trials could require the creation of partnerships with other parties, including conducting an extensive Phase III study, and consequently, the Company will be exposed to the risks described in Sections 4.1.8 and 4.2.3 of this Registration Document.

If any of the aforementioned risks materializes or if the clinical trials on a drug candidate fail or are delayed, drug commercialization may be delayed or remain incomplete, which would have a major negative impact on the Company, its business, prospects, credibility, goodwill, ability to obtain further funding, financial position, cash flow situation or operating income.

#### **4.1.2. All clinical trials must be pre-approved by health authorities**

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All of the Company's products are currently in a pre-clinical or clinical trial stage and none have been subject to a marketing approval application. Consequently, additional clinical trials will be required. All these studies require prior approval from the regulatory authorities in the country in which the studies are planned as well as from various other committees, including Ethics Committees, Management Review Committees or Safety Committees. An authorization denial or negative opinion issued by a committee could suspend or terminate the Company's clinical development program. Once authorization has been granted, the health authorities or the Company could decide to suspend or terminate development of the drug candidate before the completion date. The occurrence of one of these risks could significantly undermine the Company, its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.1.3. Interactions with other drugs could delay or prevent the commercialization of the Company's products**

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The Company's products are intended to be used in combination with other drugs. The Company will conduct studies to assess the risks of interactions between its products and other drugs and treatments administered concomitantly. These studies, by their very nature, cannot cover all possible combinations. Moreover, it cannot be guaranteed that the Company's products will have no negative interaction with other drugs or treatment among populations not covered by the studies or that such interactions will not appear once the products have been released in the market. These interactions could have adverse, unacceptable or undetected side effects or reduce or wipe out the efficacy of the Company's products, which could reduce the sales potential of the Company's products, delay their development and consequently undermine the Company, its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.1.4. Marketing authorizations must be obtained prior to any commercialization of the Company's products**

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The Company exercises its activities in a field highly regulated by health authorities, in particular the American *Food and Drug Administration* ("**FDA**") in the United States and the European Medicines Agency ("**EMA**") in Europe. All drugs developed by the Company require marketing authorizations ("**MA**") for each country in which the drug will be distributed. The Company cannot guarantee that any MA application will be granted by the health authorities for a given country. Failure to obtain MA in a given country will prevent the Company from distributing its products in that country. To this date, the Company has filed no MA applications.

Obtaining MA depends on several factors, some of which fall outside the Company's control. These factors include the Company's ability to continue to develop its drug candidates in preliminary clinical trials or to switch from a pre-clinical phase to a clinical phase or from one clinical phase to the next, the ability of the Company or of its CROs (*Clinical Research Organisations*) to complete the clinical trials

required within the set deadlines and with the human, technical and financial resources planned, to observe best clinical practices followed by the Company, its CROs and its other partners, to demonstrate the efficacy of the drug candidate and to conduct toxicity, morbidity and mortality studies.

A delay or failure to obtain MA in all or some of the Company's markets for a given product could adversely affect the product's development costs, the product's market value and the related intellectual property rights, and the inability to widely distribute the product, all of which could undermine the Company, its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.1.5. MAs could be modified or withdrawn by health authorities**

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If, after obtaining MA, it appears that the Company's drug(s) cause side effects or undesirable or undetected interactions during the clinical trials period, including as a consequence of interactions with other drugs once commercialized (please refer to Section 4.1.3 above), MAs could be modified or even withdrawn and it could then be impossible for the Company to continue to commercialize its product(s) for all or part of the targeted indications, which could significantly undermine its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.1.6. Commercialization of the Company's products might not be successful**

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Until now, no drug candidate developed by the Company has led to an MA application. If the Company succeeds in obtaining MA for its products, in particular CER-001, it may fail to gain the support of the medical community, care prescribers or third-party payers.

The development of the Company and its ability to generate revenues will depend on the degree to which the market accepts the Company's products. This acceptance depends on several factors:

- Product efficacy and perception of its therapeutic benefit by prescribers and patients;
- Absence of product side effects or undesirable drug interactions;
- Product's ease of use, mainly related to its administration route;
- Cost of treatment;
- Reimbursement policies from governments and other third-party payers;
- Effective implementation of a scientific publication strategy;
- Support of opinion leaders in the cardiovascular and metabolic disease field; and
- Development of one or more competitor's product(s) for the same indication.

If one or more of the Company's product(s) are not adopted by the market for one or more of the reasons mentioned above or for any other reason, in one or more countries, this could undermine their profitability or commercial potential, which could considerably undermine the Company, its business, its prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

Moreover, commercialization of the Company's products could require to entering into partnerships (please see Sections 4.1.8 and 4.2.3 below).

**4.1.7. Most of the Company's human, financial and material resources are invested in developing a single drug candidate, CER-001**

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The Company heavily depends on the success of a single drug candidate and is therefore particularly subject to delays in the development and distribution of CER-001 and in the future developments of this drug candidate.

Failure or delay by the Company in developing or commercializing CER-001 could significantly undermine the Company, its business, its prospects, ability to achieve its objectives, financial position, cash flow situation or operating income.

**4.1.8. The Company may decide to conduct its own Phase III clinical trials with CER-001, which would require substantial funding**

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The Company could be in a situation where additional phase III clinical trials would be requested to complement the current TANGO phase III study. These additional clinical trials would require substantial financing.

The Company may decide to conduct Phase III clinical trials on its own or to enter into partnerships for the purposes of Phase III clinical trials (please see Section 4.2.3 below). Such clinical trials will require substantial financial resources that the Company may not have. The Company's ability to harness such resources will therefore depend on its ability to obtain adequate funding.

Any delay, failure or inability to obtain such funding at an acceptable cost could delay or prevent Phase III clinical trials for CER-001 in the country or countries concerned and could therefore considerably undermine the Company, its business, its prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

**4.1.9. There are many competitors in the field of treatment for cardiovascular and metabolic diseases**

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The Company operates in a highly competitive field in which there are many competitors, in particular pharmaceutical laboratories, biotechnology companies, institutions, universities and other research institutions which are actively engaged in the discovery, research, development and distribution of treatments for cardiovascular and metabolic diseases. Some of the Company's competitors benefit from greater resources and know-how than the Company in all respects (please see Section 6.8 of this Registration Document). The competition mainly focuses on therapies that aim to reduce LDL-C. The competition regarding HDL therapies is less fierce, particularly in the HDL mimetics segment in which the Company specializes (please see Section 6.8).

The Company cannot guarantee that competitors will not develop alternative products that successfully compete with the Company's products in terms of efficacy, mode of action, price or distribution, or which are regarded by the market as being of similar or greater quality than those of the Company or which render them obsolete. Moreover, the Company cannot guarantee that competitors will not obtain MA for their products before the Company is in a position to commercialize its own products.

In addition, the Company cannot guarantee that its competitors will not deploy superior resources in order to reduce or limit the Company's prospects or its products. Occurrence of one of these risks could significantly affect the Company's ability to generate profits from its products, which could ultimately considerably undermine the Company, its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.1.10. The sales performance of the Company's products will depend on its ability to set prices that ensure sufficient profitability**

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The sales performance of the Company will partly depend on its ability to set the sales price of its products, whether paid by private individuals or by third-party payers such as insurance companies, certified public institutions or social organizations. In the current context of control of healthcare costs and budget deficits in countries that are part of the Company's main markets, pressures to control and reduce the sales price of drugs and reimbursement levels are increasing and are bound to increase in the future.

The sales price and reimbursement levels of the Company's products will be negotiated on a country by country basis, with regard to the perceived and actual safety and efficacy of each product. If the Company (or its partners) does not satisfactorily negotiate the sales prices and levels of reimbursement, this could significantly undermine the Company, its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.1.11. The legal and regulatory framework related to the Company's products could evolve**

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The Company operates in a highly regulated market. This regulatory framework could change in the main markets in which the Company operates, in particular in the United States, Europe, India, China and Japan. These changes could limit the indications for which the Company could commercialize its products or prevent commercialization altogether. The costs for complying with existing rules and regulations are high and growing. If this trend continues, it could reduce the market value of the Company's products.

For example, certain health authorities, in particular the FDA, have laid down increasingly stringent requirements in terms of the volume of data required to demonstrate efficacy and safety of a drug candidate. These requirements have reduced the number of drug candidates that meet the eligibility criteria for issuing a *New Drug Application* or MA and the number of approved products. The risk/benefit ratio for commercialized products is also regularly re-assessed after their MA has been granted. Late discovery of issues not detected at the research stage may lead to restrictions on the commercialization of products or on suspension or withdrawal and to a greater risk of legal action.

If the Company fails to comply with such rules and regulation or with their amendments, it could be exposed to major sanctions, in particular fines, product recalls, restrictions on sales, temporary or permanent suspension of its activities and criminal or civil prosecution. The occurrence of one of these risks could significantly undermine the Company, its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.1.12. The Company is liable for the development and distribution of its pharmaceutical products**

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The Company's liability is and will be exposed during clinical development, manufacture and commercialization of its products. Its liability could therefore be invoked by patients participating in clinical trials in case of unexpected side effects. In addition, the Company's liability could be engaged owing to undetected side effects caused by the interaction of one of its products with other drugs following its release on the market. Criminal proceedings or legal action could also be brought against the Company by patients, regulatory agencies, pharmaceutical companies or any other third party that uses or distributes its products. To this date, no such action has been taken against the Company. Such criminal or legal proceedings may be brought from acts by its partners, licensees and sub-contractors over which the Company has little or no control (please see Section 4.2.8 of this Registration Document). If the Company's liability with regard to its products is invoked, its goodwill

and commercialization of its products could be seriously affected, which could considerably undermine the Company, its business, its reputation, prospects, ability to raise further funds, ability to reach its objectives, financial position, cash flow situation or operating income.

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**4.1.13. Alternative treatments, which are currently at different stages of development, could cause the Company's potential market to shrink**

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Certain alternative treatments or surgical procedures to combat cardiovascular and metabolic diseases are under investigation and are at different stages of development. If these solutions prove to be effective and/or reliable, they could reduce the potential market for the Company's products, which could therefore considerably undermine the Company, its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

**4.2. Risks relating to the Company activities**

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**4.2.1. Since it was founded, the Company has posted losses every year and has not generated any sales in the last two financial years. It will probably experience further losses in future financial years linked to financing its development**

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Since it was founded in 2005, the Company has posted operating losses every year. The Company's cumulative net losses over the last two fiscal years amount to approximately €42 million. These are the result of internal and external research and development costs in connection with multiple pre-clinical and clinical trials, for the most part related to the development of CER-001. The Company could incur further losses in the forthcoming years linked to the financing of its development as its R&D activities continue and gain pace or following the purchase of new technologies, products or licenses. The Company cannot guarantee that it will generate enough revenue in the future to offset previous, current or future losses and reach its profitability threshold, which could affect the Company's ability to continue its business. In addition, even if the Company reaches a satisfactory threshold, such profitability could prove to be non-lasting. The inability to generate sustainable profits could seriously undermine the Company, its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

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**4.2.2. The Company relies on a small number of vendors and service-providers**

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The Company depends on third parties for the supply of various raw materials used in the manufacture of its products and clinical batches required to conduct its clinical and pre-clinical trials. Failures or delays on the part of these third parties could affect the duration, cost or continuation of the clinical trials and quality of the data, which must meet strict standards (Good Laboratory Practices, Good Clinical Practices and Good Manufacturing Practices), imposed by the regulatory and control authorities, and hence delay commercialization of the Company's products.

In this regard, the stem/progenitor cells used in the manufacture of CER-001, over which Cerenis has full ownership rights, is stored in several vials kept at two different sites managed by Catalent. However, the Company might work with other providers provided they comply with the standards imposed by the regulatory authorities.

Any failure by any of the Company's vendors or service-providers could considerably undermine the Company, its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### 4.2.3. Failure of sub-contractors (particularly of those to whom clinical trials and manufacture of products are outsourced) could place the Company at risk

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The Company relies on sub-contractors for the development of CER-001 (for manufacture of drug batches and for conducting clinical trials). It entrusts the manufacture and development of complex processes, which must be closely monitored, as well as the conduct of clinical trials, to sub-contractors. The Company therefore depends on third parties to conduct clinical trials and to manufacture its products.

##### Sub-contracting of product manufacture

The Company has signed a sub-contracting agreement to produce CER-001 with NOVASEP, as described in Section 22.8 of this Registration Document. This enables the Company to produce the batches necessary to conduct clinical trials. In addition, the Company may have to sign further agreements with NOVASEP or with other sub-contractors if production requirements increase, in particular to meet pharmaceutical standards during commercialization of CER-001.

Any interruptions in the supply of products by its main sub-contractors for any reason, including the inability to retain the necessary regulatory authorizations or to meet manufacturing and test requirements, could delay or halt the Company's clinical and pre-clinical trials, which could therefore impact the manufacturing and commercialization of the Company's products.

In the event of an interruption in the supply chain, the Company may not find other sub-contractors able to supply products and services in sufficient quantities and with sufficient quality or at a reasonable cost.

If the Company were to change manufacturer for its products, the new manufacturer would be asked to re-approve the manufacturing process and procedures in keeping with current Best Manufacturing Practices. Such re-approval would be costly and time-consuming and require highly qualified personnel within the Company. If re-validation were to be refused, the Company could be forced to seek another vendor, which could delay production, development and commercialization of its products and increase their manufacturing costs.

Moreover, the use of sub-contractors entails additional risks that the Company would not face if it produced its own products, i.e.:

- Non-compliance by these third parties with regulatory standards and quality control requirements;
- Violation of the agreements by these third parties; and
- A termination or non-renewal of these agreements for reasons outside its control.

If products manufactured by other vendors were to fail to comply with applicable regulatory standards, sanctions could be imposed on the Company. These sanctions could include fines, injunctions, civil penalties, refusal by regulatory authorities to authorize clinical trials or grant MA for its products, delays, suspension or withdrawal of authorizations, termination of licenses, seizure or recall of its products, operating restrictions or criminal prosecution. All such measures could have a considerable negative impact on the Company's activities.

Moreover, contracts signed with sub-contractors usually contain limitation of liability clauses in their favor, which means that the Company may not obtain full compensation for any losses it may incur in the event of breaches of their commitments by the sub-contractors concerned.

The occurrence of one of these risks could significantly undermine the Company, its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

In order to limit these risks, the Company attaches great importance to the relationship with and the monitoring of its sub-contractors. In this regard, the Company has formed a joint steering committee with NOVASEP, which meets regularly during the production phase to verify that it runs smoothly and according to plan. Furthermore, the Company ensures the quality of the batches before accepting delivery.

Moreover, the sub-contractors are assessed and subject to stringent audits by the regulatory agencies and by the Company.

#### Sub-contracting of clinical trials

The Company sub-contracts clinical trials and the analysis of clinic trial data to specialized scientific institutions (*Contract Research Organizations* or CRO) on the basis of a clinical protocol (including selection and recruitment of patients based on defined eligibility criteria) for each trial and therefore depends on the fulfillment and compliance by the CROs with respect to their obligations.

Any failure or delay by these CROs in fulfilling their obligations (including data analyses) could impact the results of the clinical trials and consequently the Company's business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.2.4. The tax status of the Company could be subject to re-appraisal**

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The Company has been classified as an SME (small and medium-sized enterprise) by the European Medicines Agency. The status of SME, aimed at promoting innovation and development of new drugs in human and veterinary medicine, was adopted by the European Commission on December 15, 2005 through specific provisions. The incentive measures associated with this status include administrative aid, assistance in procedures as well as various reductions, exonérations or deferments of costs and social security contributions.

The loss of the Company's SME status for any reason, including in the event of non-compliance with one of its granting criteria, could negatively impact the Company, its business, prospects, and ability to reach its objectives, financial situation, cash flow situation or operating income.

SME status is obtained when the following requirements are met:

- A workforce under 50 employees;
- Revenue or a total balance-sheet income less than or equal to €10 million;
- No shareholders hold more than 25% of the share capital.

#### **4.2.5. Risks relating to the Company's dependency on key employees**

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Given the Company's development stage and the innovative nature of its products, it could lose key employees and be unable to attract new qualified staff.

The Company's success largely depends on the engagement and expertise of its managers and qualified scientific personnel, in particular Jean-Louis Dasseux, the Company's CEO, in relation to whom a key person insurance has been taken out by the Company (refer to Section 4.5 "Insurance and risk coverage").

Although the Company has introduced know-how management and transfer programs since it was founded, thereby building an expertise base independent of key individuals, the simultaneous departure of several key managers and supervisors in its R&D and development teams could undermine the Company's ability to reach its objectives.

The Company has included special provisions in its employment contracts with managers and executive grade personnel, as provided under applicable labor law, such as the transfer of intellectual property rights and confidentiality clauses.

The Company has also introduced incentive and loyalty retention programs for its personnel, including for key Company officers, in the form of a variable salary scheme and/or allocation of shares providing access to the Company's share capital (stock options, share purchase warrants, business creation subscription warrants and free shares) according to performance criteria.

The Company's inability to attract and retain these key Company officers could prevent it from reaching its objectives and hence considerably undermine its business, income, development and future prospects.

#### **4.2.6. The Company's development strategy could depend on its ability to manage internal development**

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As part of its development strategy, the Company plans to recruit managers, scientific personnel and other personnel to develop its operating capacities to meet its future needs in clinical research.

Such recruitment will lead to an increase in the Company's pay roll costs. To manage such development and ensure that newly recruited individuals successfully integrate in the Company, the Company must develop systems to manage a growing number of employees (including IT, financial and existing management systems), train and retain these employees and sufficiently anticipate related expenses as well as related financing requirements. The Company's inability to generate growth or overcome unexpected difficulties encountered during its expansion could considerably undermine its business, prospects, ability to reach its objectives, financial situation, cash flow situation or operating income.

#### **4.2.7. The Company may not be adequately insured against certain risks**

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The Company is exposed to liability risks during the development, manufacture and distribution of its products. Other potential risks include the occurrence of side effects or unexpected interactions that may result in legal proceedings, and disputes related to the Company's intellectual property could invoke its liability for uncovered damages or for damages that exceed the guaranteed amount specified in its insurance policies. The Company cannot guarantee that it will always be able to maintain and, where necessary, obtain insurance coverage at an acceptable cost (please see Section 4.5 of this Registration Document, which lists insurance policies currently contracted). If the Company is unable to maintain such coverage, this could considerably undermine its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

Additionally, any losses that the Company could incur owing to the unavailability of senior managers might not be sufficiently covered by its current insurance policies regarding "key officers."

#### **4.2.8. The Company's liability could be invoked via its partners and sub-contractors**

---

The Company uses and will continue to use partners and sub-contractors for all aspects of its business. This exposes it to potential claims filed regarding their activities and compliance with their obligations over which the Company has little or no control. For example, its partners and sub-contractors use



certain regulated materials in the context of their contract with the Company. If they do not handle these materials in an appropriate and safe manner, the Company's liability could be invoked. Similarly, the Company could be held liable for all or part of the losses, physical injuries or death resulting from an accident involving a partner or sub-contractor. The liability invoked could exceed the coverage threshold specified in the insurance policies subscribed by the Company, or not be covered at all. Invoking the Company's liability, whether or not it is covered by insurance policies, could therefore considerably undermine its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.3. Regulatory and legal risks**

Legal and arbitration proceedings are detailed in Section 20.7.

##### **4.3.1. The protection offered by patents and other intellectual property rights is uncertain and for a limited time period**

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The commercial success and viability of the Company will depend, at least in part, on its ability to develop products and technologies protected by valid patents held by the Company or under licenses that it benefits from in its main markets, including Europe, the United States and Japan and which do not infringe patents held by third parties. The Company's current strategy and its future prospects particularly depend on its portfolio of patents, including patents related to CER-001.

Moreover, the Company intends to pursue its policy to protect its intellectual property rights by filing further applications for patents at times that it deems appropriate. In particular, the Company plans to file and defend new applications for patents, applications to extend existing patents and, where necessary, to apply for Supplementary Protection Certificates ("SCP") in order to extend the protection of its patents beyond their initial expiry date. An SCP is based on the original patent covering the drug and/or its use and the marketing authorization (MA) for such drug and may, under certain conditions, extend the protection period for up to a maximum of five years in Europe. Possibilities exist to obtain a similar extension in the United States and in other countries.

However, the Company is notably subject to the following risks regarding patents and other intellectual property rights. Moreover, it cannot be ruled out that:

- The Company may fail to develop or produce patentable inventions which would therefore significantly reduce the value and market share of its products;
- The Company may fail to obtain new patents or other intellectual property rights in France or in other countries that would adequately protect its drug candidates, methods, products, manufacturing processes, applications, sales offerings, commercialization or imports;
- The Company may fail to maintain protection of its current patents or other intellectual property rights;
- The Company may fail to obtain the issue of patent extensions, in particular SCPs, which could limit the protection period and the value of patents granted to the Company;
- The Company's patents may be disputed or regarded as invalid by a qualified authority or a court;
- The Company's patents may not prevent the issue in France or elsewhere of patents to third parties, relating to similar or competitor drug candidates, methods, products, manufacturing processes, applications, sales offerings, distribution or imports;
- The Company may fail to adequately enforce its patents or other intellectual property rights in France or in other countries;

- The Company may be exposed to claims filed by third parties who challenge the granting or scope of licensing rights, who dispute the fees charged for such licensing rights or who seek to obtain an injunction restricting the use by the Company of its patents or other intellectual property rights, whether or not such claims are founded;
- The scope of the protection granted by the Company's patents and other intellectual property rights may be inadequate in France and in other countries against appropriation or counterfeit goods by one or more third parties;
- The Company may have to incur substantial expenses in attempting to protect and defend its patents and other intellectual property rights. Moreover, it cannot be guaranteed that these expenses will enable the Company to win litigation cases or to force one or more third parties to cease competing with the Company or to obtain adequate compensation for the prejudice it suffers;
- The extent, validity and life of the Company's patents and other intellectual property rights may be interpreted differently depending on the country, which could reduce the protection granted by such rights;
- The Company's patents and other intellectual property rights may be impossible to protect or defend in France or in other countries;
- The Company's employees, partners, sub-contractors or other parties may claim property rights over the Company's patents or other intellectual property rights or request remuneration in return for patents or other intellectual property rights to the creation of which they claim to have contributed despite the Company's efforts to take measures to prevent such a risk.

Given the importance of intellectual property rights for the Company's business and viability, the occurrence of one or more of the risks above could considerably undermine the Company, its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.3.2. Infringement of the Company's patent rights may lead to costly disputes the outcome of which is uncertain**

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The Company's competitors may infringe the Company's patent rights in France and in other countries. In order to protect its patents, the Company may have to initiate long and costly legal proceedings. The Company cannot guarantee that it will win law suits filed against it or that it will be able to adequately protect its patent rights in France or other countries. If the Company fails, this could considerably undermine its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.3.3. The Company could find itself in breach of intellectual property rights held by third parties**

---

The growth of the biotechnologies industry and the associated increase in the number of granted patents raises the risk that one or more third parties regard the Company's products or technologies as infringing their own intellectual property rights and the risk that one or more third parties sue the Company in order to protect their intellectual property rights.

Moreover, in accordance with applicable legislation in the United States before March 2013, patents were granted to the first inventor of a new concept. Since March 2013, the United States has adopted a "first to file" system that may raise doubts at the *United States Patent and Trademark Office* (USPTO) or in the American courts as to the patentability or validity of inventions covered by patent applications or American patents.

The Company cannot guarantee in France or in other countries:

- That its drug candidates, methods, products, manufacturing processes, applications, sales offering, commercialization or imports do not breach or infringe any patent or other intellectual property rights held by one or more third parties;
- That one or more third parties were not the first to invent or file patent application for inventions also covered by the Company's own patent applications or granted patents;
- That a third party who holds patents or other intellectual property rights covering the Company's drug candidates, methods, products, manufacturing processes, applications, sales offering, commercialization or imports will grant the Company a license;
- That one or more third parties will not bring legal action against the Company even if such action is malicious and groundless; and
- That there are no trademark rights or other prior similar rights held by a third party which could lead to infringement proceedings being brought against the Company or that they could restrict or prevent the Company from using its trademarks or domain names or from exercising other similar rights.

Any claim against the Company related to its patents or other intellectual property rights or to those of one of more third parties, whatever the outcome, could result in major costs and use of resources for the Company, could require substantial management involvement and undermine the Company's goodwill and its financial situation. Some competitors with substantially more resources than the Company may be in a better position to bear the costs resulting from such procedures and undertake action to obtain a substantial market edge, which could considerably undermine the Company, its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.3.4. If the Company fails to win litigation cases on patent or other intellectual property rights held by third parties, the continuation of its business could be in jeopardy**

---

If the Company is unable to adequately defend itself against a lawsuit that seeks to demonstrate that it breaches or infringes patents or other intellectual property rights held by one or more third parties, the Company could be forced to:

- Cease developing, formulating, using, selling, distributing or importing its drug candidates, products or methods in France or in other countries;
- Develop or obtain alternative technologies, review its design or, in the event of disputes regarding registered trademarks, rename its products; and
- Apply for a license from the holder of intellectual property rights that it would not be possible to obtain or only at economically unfavorable terms or at terms unacceptable to the Company.

The occurrence of one or more of these events could considerably undermine the Company, its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.3.5. The Company shares certain confidential information with third parties, the level of protection and confidentiality of which and the ability to keep it protected and confidential are outside the control of the Company**

---

In addition to its patented or patentable intellectual property rights, the Company holds certain information such as commercial secrets, in particular technologies, processes, know-how or non-patentable and/or non-patented data. Under partnership or confidentiality agreements between the Company and researchers from academic institutions as well as with other public or private entities, sub-contractors or any third party, some of this confidential information, in particular data related to its methods, products and drug candidates may be disclosed to them in order to, for example, conduct certain pre-clinical or clinical trials.

The Company cannot guarantee that its partners will protect its intellectual property rights and commercial secrets or will comply with their commitments under confidentiality agreements. Moreover, there is no guarantee that the Company will succeed in enforcing confidentiality agreements or any other similar agreements or, if it does succeed, in obtaining an injunction or adequate compensation for the prejudice it suffers in case of a breach of said agreements, nor can the Company guarantee that it has introduced suitable solutions and safeguards against the disclosure of its commercial secrets.

If the Company or its partners fail to maintain confidentiality of information to third parties or to obtain satisfactory repair for the prejudice it suffered following a breach of the aforementioned agreements, this could considerably undermine the Company, its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.3.6. The exercise of certain intellectual property rights is based on licenses**

---

Some of the Company's intellectual property rights are based on licenses granted to the Company (please see Section 22 of this Registration Document). These licenses are granted for long periods, but the Company runs the risk of losing the benefit of these licenses in the event of a breach of contract. In particular, the license granted to CATALENT, as described in Section 22.1 of this Registration Document, concerns the production of co-developed cell lines enabling the production of the protein needed to manufacture CER-001. If this license is terminated, the Company will need to develop a new cell line expressing the A-1 apolipoprotein with a new CRO using a different expression system, which will cause significant delays on the development schedule of CER-001 and CER-001 market access, as well as additional costs.

If the Company or its partners fail to maintain these licenses, this could considerably undermine the Company, its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.3.7. Intellectual property rights, including the life of patents, may evolve**

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Laws and regulations and resulting rights applicable to patents and other intellectual property rights are subject to changes, variations, reductions or other changes in France or in other countries without notice or payment of indemnities to the Company. If property rights vary, are reduced or modified, in particular as regards the life of patents, the Company could suffer a decrease in the value of its patents and other intellectual property rights which would therefore considerably undermine the Company, its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

## **4.4. Financial risks**

### **4.4.1. The Company may need to increase its equity capital or to draw on additional financing to ensure its development**

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Since it was founded, the Company has not generated any sales turnover. It has incurred major losses and has had to finance its development through successive rights issues, reimbursable advances obtained from OSEO and grants, and through the reimbursement of research tax credit (Crédit Impôt Recherche, "CIR") receivables (please see Section 4.4.2 below).

Given its current stage of development and its risk profile, the Company does not currently have access to bank funding in the form of bank loans and may not have access to such funding in the short or mid-term.

The R&D costs and expenses related to the Company's products and the continuation of its clinical development program are partly out of the control of the Company, in particular owing to its use of sub-contractors, and will continue to require major funding in the future. The Company could find itself unable to obtain such funding or at least on satisfactory economic terms or it could have to seek funding itself through new rights issues, which would result in the dilution of the stock held by its shareholders. In addition, debt financing, where possible, could impose certain constraints on the Company that could affect its business, its ability to find future funding or pay out dividends to its shareholders.

If the Company fails to obtain adequate funding, this could delay, reduce or eliminate the number or scope of its projects or products, in particular its pre-clinical and clinical trials programs, or force it to grant licenses for its technologies to partners or third parties or to sign new partnership agreements at less favorable terms than it could have obtained in a different context.

The occurrence of one or more of these risks could considerably undermine the Company, its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income (please see Section 4.4.8 below).

### **4.4.2. The Company receives the Research Tax Credit (CIR) granted by the French government**

---

The Company receives the Research Tax Credit or "CIR" (Crédit Impôt Recherche) which offers French companies tax inducements to enable them to develop scientific and technical research. Research expenses eligible for CIR include and are subject to certain conditions: salaries and wages of researchers and technicians, amortizations of fixed assets allocated to research activities, services sub-contracted to certified research organizations (public and private) and patent registration and maintenance costs.

The amounts received by the Company under CIR are as follows:

- The Company received a CIR reimbursement in fiscal 2015 totaling €2,095,984 on July 5, 2016;
- The Company received a CIR reimbursement in financial year 2014 totaling €1,176,779 on May 27, 2015;
- The Company received a CIR reimbursement in financial year 2013 totaling €1,933,433 on June 30, 2014.

In 2017, the Company is expected to receive a reimbursement of €3,584,589 in connection with CIR for fiscal 2016.

At the request of the tax authorities, companies may be required to justify the amount of CIR receivables and the eligibility of activities taken into account to benefit from them.

Financial years prior to 2012 have been investigated by the tax authorities and have not led to any tax adjustments. For financial years after 2012, it cannot be ruled out that the tax authorities will question the methods that the Company used to calculate its R&D costs to determine the CIR amount for which the Company is eligible. Similarly, it cannot be ruled out that a change in applicable regulations will reduce future CIR benefits and will no longer enable the Company to benefit from it.

The Company benefits from an early reimbursement of CIR (immediately and not 3 years after the request). If the Company no longer receives sums under CIR or its status or its calculations were to be revised, this could considerably undermine its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.4.3. The Company could be unable to carry forward future tax losses**

---

In fiscal 2016, the Company posted a tax loss of €22,119,242 and recorded tax deficits carried forward of €148,278,704, i.e. total losses carried forward of €170,397,945 as at December 31, 2016.

To this date, the Company has not accounted for any deferred tax assets related to its tax deficits carried forward.

In France, for financial years after December 31, 2012, charging these deficits is capped at €1 million, increased by 50% of the fraction of profits exceeding this threshold. The unused balance of the deficit remains carried forward to future years and is chargeable under the same conditions without any time limitation.

It cannot be ruled out that future tax changes will call these measures into question by limiting or eliminating the possibility to forward charge tax deficits, which could considerably undermine the Company's business, prospects, ability to reach its objectives, financial situation, cash flow situation or operating income.

#### **4.4.4. The Company has benefited from reimbursable advances that may have to be reimbursed early**

---

During the last three financial years, the Company has been granted reimbursable aid from Bpifrance (formerly OSEO) totaling €1,500,000 of which €500,000 were received at the date of this document. Moreover, in 2010, the Company obtained reimbursable aid from Bpifrance under an ISI (Industrial Strategic Innovation) partnership project totaling €6,384,000, of which €4,602,000 had been received at December 31, 2016. As of now, the Company has fully repaid the reimbursable aid it received in 2009.

A summary table of all the aid received by the Company since its incorporation is presented in Section 10.1.3.

In the event that the Company ceases to meet the established reimbursement schedule (please refer to Note III.M of Section 20.1 of this Registration Document) in reimbursable advances agreements signed, it may have to reimburse the advanced sums early. This situation could force the Company to seek financing solutions or delay or terminate some of its R&D projects, which could considerably undermine its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.4.5. The Company's share capital could be diluted**

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Since its incorporation, the Company has issued or granted stock options, warrants ("BSA"), founders' warrants ("BCE") and free shares; see Section 21.1.4 for more details. At the date this Registration Document, the full exercise of all instruments granting access to the capital granted or in circulation up to this date would enable the issue and subscription of 802,598 ordinary new shares (see Section 21.1.4), causing a dilution equivalent to 4.20% of the Company's share capital on a fully diluted basis.

As part of its incitement policy for executive and non-executive personnel and in order to attract additional talent, the Company could issue or allocate shares or new financial instruments in the future, granting access to the Company's share capital, thereby resulting in further and a potentially significant dilution of the stock held by the Company's current and future shareholders. The dilution could cause the Company's share price to fall.

#### **4.4.6. The Company is exposed to foreign currency risks which could grow in the future**

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The Company compiles its accounts in euros and uses the euro as the currency for its current transactions.

From time to time, the Company may incur expenses in US dollars, Australian dollars, pounds sterling or in another currency.

In order to protect its operations against currency fluctuations, the Company has several accounts in US dollars totaling USD 2,631,000, of which USD 9,000 is held in the bank account of its American subsidiary Cerenis Therapeutics Inc.; the Company also has AUD 1,328,000.

The exchange risk is considered as non-significant as the amounts held cover the most part of commitments of the Company for 2017.

However, and although the Company plans to use the euro in its signed contracts, it is not always in a position to do so. Signing of contracts not denominated in euros will increase in number and amount owing to the development of the Company's products for distribution and their expansion on new markets. This will result in greater exposure to foreign currency risks and consequently the Company will be exposed to movements in the exchange rates between the euro and related foreign currencies; this could considerably undermine its business, prospects, ability to reach its objectives, financial position, cash flow situation or operating income.

#### **4.4.7. Interest rate risk**

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The Company has no exposure to the risk of interest rates in the assets recorded in its balance-sheet accounts in so far as:

- Investment marketable securities are made up of short-term monetary SICAVs (unit trusts);
- Available cash is only in bank accounts;
- Non-current financial assets include futures accounts;
- No variable rate debts have been subscribed for.

To this date, the Company has not subscribed for any financial instrument for speculative purposes.

Given the low level of current returns on the Company's investments, the Company believes that a shift of +/- 1% could have a non-significant impact on its net income in the light of the amount of its operating losses.

#### 4.4.8. Liquidity risk

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Since its incorporation, the Company has funded its development by increasing its capital equity through successive rights issues and by reimbursement for Research Tax Credit (CIR) receivables, but has never taken out bank loans. The Company is not therefore exposed to a liquidity risk resulting from the early repayment of such loans.

Moreover, the Company has a policy of prudent investment in immediately available assets.

Substantial R&D efforts and expenses related to pre-clinical and clinical trials have been undertaken since the start of the Company's activities, generating cash flows totaling €(13,711,000) and €(19,197,000) respectively for the fiscal years ended December 31, 2015 and 2016.

Having available cash of €24,675,000 as at December 31, 2016, the Company will continue to require major financing to develop its technology, manage and protect its industrial property rights, continue its clinical research development program and produce and commercialize its products, the degree and scheduling of which depend on factors largely outside the control of the Company, such as:

- Slower than expected progress in its R&D programs and clinical trials;
- Costs of preparing, filing, defending and maintaining its patents and other intellectual property rights;
- Longer than expected times for obtaining MA for its products as well as their authorizations for reimbursement, including the time for drafting filing applications with qualified authorities; and
- New opportunities to develop new products or acquire technologies, products or companies.

The Company could fail to obtain additional capital when it is needed, or this capital might not be available on terms that are acceptable to the Company. If the funds required are not available, the Company may have to:

- Delay, reduce or cancel the number or scope of its pre-clinical and clinical trials program;
- Grant licenses for its technologies to partners or to third parties, and/or sign new partnership agreements at terms that are less favorable to the Company than those that might be obtained if the context were different.

If the Company raises capital through the issue of new shares, the stock held by its shareholders could be diluted. In addition, debt financing, where available, could impose certain constraints on the Company and its shareholders.

The occurrence of one or more of these risks could seriously undermine the Company, its business, financial situation, operating income, development and prospects.

The Company has conducted a specific review of its exposure to liquidity risk and considers that it is able to meet its future obligations over the next 12 months.



## 4.5. Insurance and risk coverage

The Company is insured against major risks for guaranteed sums that it estimates in keeping with the nature of its business.

Summary table of insurance policies subscribed by the Company:

Country/Purpose	Insurer	Period covered	Amount covered
<b>Clinical trials</b>			
Hungary	Allianz	07/01/2015 - 11/30/2016	EUR 1,000,000
Netherlands	Allianz	07/01/2015 - 11/30/2016	EUR 3,500,000
Australia	Allianz	07/01/2015 - 11/30/2016	AUD 20 000 000
USA	Allianz	07/01/2015 - 11/30/2016	USD 5,000,000
Netherlands	CHUBB	11/01/2015 - 12/31/2018	EUR 650,000 per claim EUR 5,000,000 for the clinical trial
Canada and USA	CHUBB	11/01/2015 - 12/31/2018	EUR 1,000,000 per claim EUR 6,000,000 for the clinical trial
Italy	CHUBB	04/01/2016 - 12/31/2018	EUR 1,000,000 per claim EUR 5,000,000 for the clinical trial
France	CHUBB	04/01/2016 - 12/31/2018	EUR 1,000,000 per claim EUR 6,000,000 for the clinical trial
Belgium	CHUBB	05/01/2016 - 12/31/2018	EUR 650,000 per claim EUR 3,500,000 for the clinical trial
Israël	CHUBB	07/01/2016 - 12/31/2018	USD 3,000,000 per claim USD 3,000,000 for the clinical trial
USA	Medmarc	01/05/2017 - 01/05/18	USD 10,000,000 per claim USD 10,000,000 for the clinical trial
<b>Corporate</b>			
Directors and officers liability	AIG	01/01/2016 - 01/01/2017	EUR 20,000,000
Prospectus insurance	AIG	03/12/2015 - 03/12/2016	EUR 20,000,000
Operational liability	CHUBB	04/01/2016 - 03/31/2017	EUR 5,000,000
Key man	Générali	05/15/2016 - 05/14/2017	EUR 2,209,289
Multirisk Pro, other insurances	AXA, APRIL	automatic yearly renewal	

## 5. INFORMATION ON THE ISSUER

### 5.1. Company history and growth

#### 5.1.1. Company name

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The Company's name is: Cerenis Therapeutics Holding.

#### 5.1.2. Company's registration location and number

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The Company is registered with the Toulouse Companies and Trades Register under number 481 637 718.

The Company's NAF code is 7211Z.

#### 5.1.3. Incorporation date and term

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The Company was incorporated on March 24, 2005 for a term of 99 years, which is due to expire on April 5, 2104 except if the Company is wound up before the expiration date or if its term is extended.

#### 5.1.4. Registered office, legal status and applicable legislation

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The Company's registered office is located at:

265, rue de la Découverte – 31670 Labège

Telephone: +33 (0)5 62 24 97 06

Fax: +33 (0)5 62 19 04 17

Email: [info@cerenis.com](mailto:info@cerenis.com)

Website: [www.cerenis.com](http://www.cerenis.com)

The Company is a limited-liability company with a Board of Directors.

The Company is governed by French law. Its business activities are subject to Articles L. 225-1 et seq. of the French Commercial Code.

#### 5.1.5. Company History

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**2005:** *April:* creation of the Company by its founders (Jean-Louis Dasseux and William Brinkerhoff) as a simplified limited liability company.

**July:** initial fundraising totaling €25 million from Sofinnova Partners, Alta Partners, HealthCap, NIF Japan Capital and EDF Ventures, and conversion of the Company into a limited liability company with board of directors. Jean-Louis Dasseux is appointed CEO.

**2006:** *July:* issue of the first patent for Family 8.

*October:* demonstration of proof of concept of a complex containing apoA-I and negatively charged phospholipids.

**November:** second fundraising totaling €42 million from a long-time investor and from TVM Capital, payable in three installments.

**2007:** *February:* end of research work on the cell line for expression of the apolipoprotein apoA-I (apoA-I) with Catalent.

- 2008:** *November:* first compliant (Best Manufacturing Practices) batch produced from a cell culture in a 200-liter bioreactor.
- 2009:** *April:* first compliant (Best Manufacturing Practices) purified batch of apoA-I.
- May:* first compliant (Best Manufacturing Practices) batch of CER-001 in vial, first complex generation.
- July:* first IND application to enter Phase I with CER-001.
- November:** inclusion of the first patient in the Phase I trial of CER-001.
- 2010:** *July and October:* third fundraising totaling €50 million (€40 million plus €10 million) from Bpifrance, OrbiMed, IRDI and IXO Private Equity, payable in two installments.
- May:** encouraging Phase I results on drug candidate CER-001.
- November:* first compliant (Good Manufacturing Practices) batch of CER-001 in vial, second complex generation produced by Novasep.
- 2011:** *March:* inclusion of the first patient in the CHI-SQUARE clinical trial.
- August:* departure of William Brinkerhoff.
- October:* first compliant (Good Manufacturing Practices) batch of a cell culture in a 1,000-liter bioreactor produced by Novasep.
- November:* inclusion of the first patient in the MODE trial.
- December:* first purified compliant (Good Manufacturing Practices) batch of apoA-I produced at the Novasep facility in 600-liter batches.
- 2012:** *January:* first compliant (Good Manufacturing Practices) batch of CER-001 in vial incorporating all the process optimizations implemented jointly with Novasep.
- February:* inclusion of the first patient in the SAMBA trial (FPHA).
- Issue of the first patent for Family 1.
- 2013:** *January:* issue of the first patent for Family 7.
- February:* issue of the first patent for Family 6.
- 2014:** *January:* announcement of the findings of the CHI SQUARE trial.
- April:* issue of the first patent for Family 2.
- June:** Cerenis announces positive results in two Phase II clinical trials on its HDL mimetic drug, CER-001.
- August:** Cerenis obtains two European orphan drug designations for CER-001 to treat genetic diseases: apoA-I deficiency and ABCA-1 deficiency.

**2015:** *February:* Cerenis announces the appointment of Renée Benghozi as Clinical Research Director and of Christian Chavy, Michael Davidson and Marc Rivière as new Company Directors.

*March:* the Group completes its IPO in compartment B of the Euronext Paris regulated market ("Euronext Paris"), raising €53.4 million through a capital increase.

*September:* Cerenis announces the launch of a Phase II clinical trial (CARAT). This trial will involve 292 patients in four countries: Australia, Hungary, the Netherlands and the United States.

*December:* Cerenis announces the launch of a Phase III trial (TANGO) on the orphan disease FPHA designed to assess the impact of six-month chronic treatment using CER-001 in 30 patients with HDL deficiency.

**2016:** *June:* "LOCATION" clinical trial: On June 2, Cerenis announced in the scientific journal of the European Atherosclerosis Society (EAS) the findings of the LOCATION clinical trial, which demonstrate the functionality of CER-001.

*November:* "CARAT" clinical trial: Patient recruitment was completed in August 2016 and the last patient received the tenth and final administration of CER-001 or a placebo in the fourth quarter of 2016.

*December:* The US Food and Drug Administration (FDA) informed Cerenis Therapeutics that CER-209 could enter into clinical development. This FDA authorization (IND – Investigational New Drug application) is for a Phase I clinical trial for the CER-209 drug candidate.

**2017:** *January:* the Company announced that active recruitment of patients in the TANGO Phase III study was ongoing in fiscal year 2017.

*March:* the Company announced the negative results of the CARAT Phase II study. There was no statistical difference between the treated group and the placebo group. The results were presented at the American College of Cardiology (ACC) 2017 Annual Conference. Consequences of this are outlined in Chapter 4.1.1, 6 and 12 of this document.

*April:* The Company announced the launch of the Phase I clinical trial with CER 209 in NAFLD and NASH.

## 5.2. Investments

### 5.2.1. Main investments made in the last two years

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Cerenis has not made any significant financial, tangible or intangible investments in the last two years.

R&D costs are recognized as expenses when they are incurred. In accordance with standard IAS 38 (Intangible fixed assets), these costs are recognized for the period under "R&D costs." See Note II.G of paragraph 20.1.

### 5.2.2. Main current investments

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None.

### 5.2.3. Main planned investments

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None.

## 6. OVERVIEW OF ACTIVITIES

*To facilitate readers' understanding of this document, a glossary containing the main scientific and technical terms used is included in Section 27 of this Registration Document.*

Founded in 2005, Cerenis Therapeutics is an international biopharmaceutical company dedicated to the discovery and development of innovative HDL-based therapies and the metabolism of lipids for the treatment of cardiovascular and metabolic diseases associated with, for example steatohepatitis.

The crux of the Company's work is to engage in R&D programs that offer innovative therapeutic solutions to patients. These programs inherently carry a certain risk, and their outcome cannot be foreseen.

The start of 2017 was marred by negative results in the CARAT study and the suspension of the indication of secondary prevention in acute coronary syndrome (ACS) patients<sup>2</sup>. It should be noted that the high risk of negative results is specific to the development of a pharmaceutical product. The development of an innovative candidate drug such as CER 001 must deal with the complexity of a living human being, and it proceeds through an approach based on trial and error in order to determine what patient population to treat and the most suitable treatment methods. In order to assimilate this complexity, Cerenis also tests CER 001 on patients with a genetic HDL deficiency. The patients included in the TANGO trial, who have had this illness since birth, are not comparable to those included in the CARAT trial. In addition, the CER 001 dose, the number of administrations, the length of treatment, the vessels analyzed and the imaging method are different.

The CARAT results do not compromise the potential results of TANGO or other R&D programs. Therefore, Cerenis is continuing to implement its strategy, which consists of developing several candidate drugs that are at different stages of development and that work differently.

The Company has a diversified portfolio of candidate drugs, two of which, CER 001 and CER 209, are in the clinical trial phase:

- CER 001 is developed to treat patients with a genetic HDL deficiency.
- CER 209 is developed to treat patients with steatohepatitis, who have a very high cardiovascular risk.

Since it was founded, Cerenis has mainly invested in:

CER-001:

- Development of CER-001, a candidate drug that imitates natural pre-beta HDL particles. It aims to reduce atherosclerotic plaques in the vessel walls and is designed to treat cardiovascular diseases and FPHA (HDL deficiency), an orphan disease, and
- Development of an economically viable manufacturing process in keeping with good manufacturing practices currently applied in the pharmaceutical industry. Cerenis has overcome the challenges of manufacturing ultra pure human apoA-I and homogeneous and

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<sup>2</sup> Cerenis stresses that there are inherent risks associated with the Company's purpose. See Section 4, especially Section 4.1.1. While the CARAT study did confirm the safety and tolerance profile of CER-001, it did not achieve its main objective. The consequences of this situation are discussed in paragraphs 12.1 and 12.2.

functional HDL particles by developing a commercially viable manufacturing process for CER-001.

Administration of CER-001 temporarily increases the number of functional HDL particles and hence increases the reverse cholesterol transport rate, leading to enhanced elimination of cholesterol.

Pre-clinical and clinical data (SAMBA and MODE) generated by Cerenis demonstrate, among other properties, that CER-001 can cause rapid regression of atherosclerotic plaques.

Cerenis has been granted two separate orphan drug designations from the regulatory authorities for the use of CER-001 in the treatment of patients with rare genetic defects.

The TANGO phase III trial for the orphan disease FPHA, designed to assess the impact of chronic treatment for 6 months of 30 patients with HDL deficiency due to rare genetic defects of the coding gene for apoA-I deficiency and/or the coding gene for ABCA1 deficiency is currently underway. This study will support the application in 2018 to obtain marketing authorization of CER-001 to treat patients suffering from genetically defined FPHA.

CER 209:

- Cerenis has designed new P2Y<sub>13</sub>r-specific agonists (stimulators) with the potential to be first-in-class, including a series that contains CER 209. The stimulation of P2Y<sub>13</sub>r activity should promote HDL recognition by the liver, increase the activity of Reverse Lipid Transport (RLT) and promote the elimination of lipids, thus limiting the development of atherosclerosis and steatohepatitis (NAFLD/NASH).
- The Company recently started a Phase I clinical trial with CER 209 using healthy volunteers in the NAFLD and NASH indications, following the acceptance of an IND (Investigational New Drug application) by the US Food and Drug Administration (FDA), the procedure that authorizes this clinical launch.

### **A clear strategy for creating short and medium-term value**

Cerenis strategy is an innovative approach that combines:

- Accelerated development of an indication for rare disease/orphan drug, CER-001 in FPHA, enabling the filing of a market authorization application by 2018;
- The development of CER-209 for the treatment of patients with NASH/NAFLD who are at high cardiovascular risk.  
The development of new products/approaches based on our knowledge of HDL, the production of apolipoprotein A-I and HDL mimetics.

## 6.1. Atherosclerosis and the protective role of HDL

### 6.1.1. Accumulation of cholesterol in the arteries (atherosclerosis) results in cardiovascular diseases, the leading cause of death worldwide

#### 6.1.1.1. Cardiovascular diseases

In 2015, cardiovascular diseases were responsible for the death of 15 million people worldwide, representing approximately one in three deaths.<sup>3</sup> Worldwide, many more people die each year of cardiovascular diseases than from any other cause.

Atherosclerosis is a disease arising from formation of plaque, so-called atherosclerotic plaque, caused by deposits of lipids, especially cholesterol in the vessel wall, which leads to the manifestation of cardiovascular diseases including angina pectoris and myocardial infarction ("heart attack"), all designated by the term acute coronary syndrome (ACS). Atherosclerosis affects the entire vascular system and also leads to several other complications, including ischemic stroke, renal failure and arteriopathy of the lower limbs. Atherosclerosis is the cause of several pathologies as shown below:

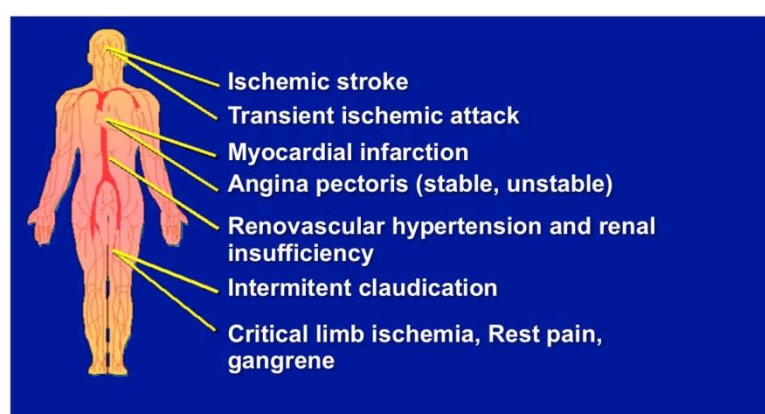


Figure 1: Pathologies caused by atherosclerosis

Cardiovascular diseases have a considerable financial cost in terms of public health but they also have an important impact on quality of life:<sup>4</sup>

- In the United States, the direct annual cost of coronary heart diseases to public health - a large part of which is associated with ACS - was estimated at approximately USD 107 billion in 2010, while the social and economic indirect cost due to loss of productivity, was estimated at approximately USD 97 billion;<sup>5</sup>
- Within the European Union, the cost of cardiovascular diseases for healthcare systems was approximately €110 billion in 2009, including 22 billion for acute coronary syndrome (ACS). Hospitalization of ACS patients accounted for more than half this cost and drug treatment approximately one quarter.<sup>6</sup>

<sup>3</sup> World Health Organization, memorandum no. 317, March 2013. World Health Organization Cardiovascular Disease (CVDs) Fact sheet <http://www.who.int/mediacentre/factsheets/fs317/en/>

<sup>4</sup> Turpie AG. Burden of disease: medical and economic impact of acute coronary syndromes. Am J Manag Care 2006; 12: S430-4.

<sup>5</sup> American Heart Association. Heart Disease and Stroke Statistics: 2014 Update At-a-Glance. 2014; 129: e280-81.

<sup>6</sup> Statistics website from the British Heart Foundation statistic. 2012; <http://www.bhf.org.uk/publications/view-publication.aspx?ps=1002098>

### 6.1.1.2. Cholesterol in the body

The human body is comprised of building blocks called cells. Cells are made mainly of protein, carbohydrate and fat (lipid) molecules. Cholesterol is an essential lipid for the correct functioning of cells. It is an essential constituent of the cell membrane. Our body obtains cholesterol, first, from our food and, second, by manufacturing it in some of our cells and certain organs, particularly the liver. Cholesterol can remain inside the cell or be secreted into the blood to be transported to various organs. In a healthy human, the amount of cholesterol in the body is precisely regulated and excess cholesterol is eliminated in the feces.

Cholesterol cannot circulate alone in the blood because of its lipophilic nature, it must be transported. The main cholesterol transporters in the blood are lipoproteins, especially low-density lipoproteins or LDL particles and high-density lipoproteins or HDL particles.

LDL particles carry cholesterol to organs where it can be used to produce hormones, maintain cells in good health or be transformed/metabolized into other molecules such as, for example, biliary acids. HDL particles (commonly called “good cholesterol”) take excess cholesterol from arteries and tissues and bring it back to the liver by a pathway called “reverse lipid transport” (RLT) for either storage, recycling or elimination as shown in Figure 2 below.

An HDL particle is a nanoparticle containing apoA-I (apolipoprotein A-I) synthesized in the liver or the bowel associated with several kinds of lipids. This complex forms a negatively-charged nascent disc-shaped particle of several nanometers in diameter, also called pre-beta HDL particle. In the circulation, the empty nascent pre-beta HDL particle captures cholesterol and other lipids to transform into a spherical particle that is called mature HDL.

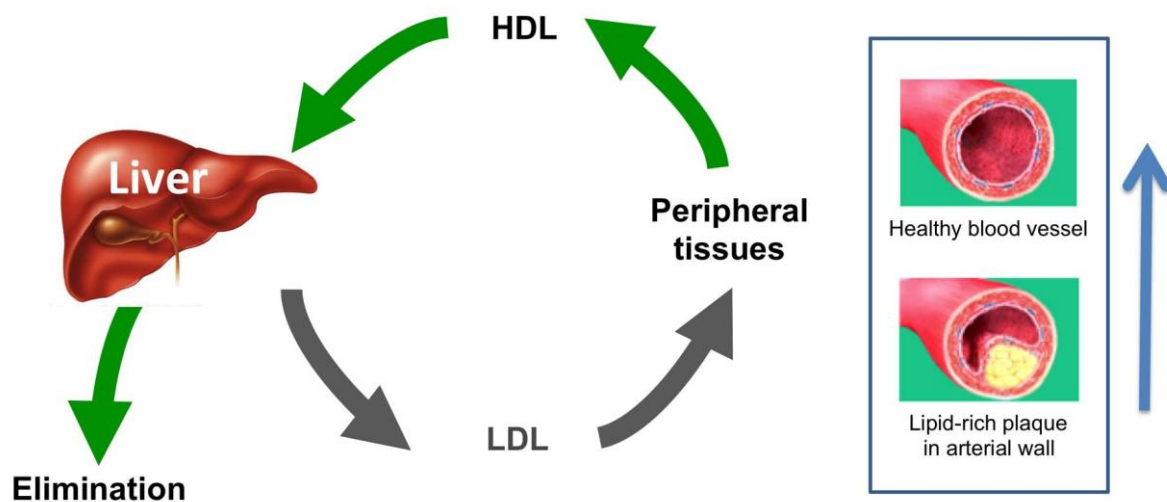


Figure 2: Cholesterol cycle

The reverse lipid transport (RLT) enables the elimination of cholesterol.

The RLT pathway is comprised of four main steps (see Figure 3 below):

- The first step is the exit of cholesterol from the artery wall cells followed by uptake of the cholesterol by pre-beta HDL particles in a process called **cholesterol removal (also called cholesterol mobilization)**. The exit of cholesterol from the cell is performed and controlled by the intermediary proteins ABCA1 and ABCG1 that act as “transporters and sentinels”.
- During the second step, cholesterol is converted by the LCAT (lecithin cholesterol acyl-transferase) enzyme into a new chemical form (the cholesteryl ester), which is more closely



bound to HDL to facilitate transport in the blood; this process is called **cholesterol conversion** or esterification.

- The third step is the transport and delivery to the liver of this converted cholesterol in a process called **cholesterol transport**.
- The fourth step is the transformation and elimination of this cholesterol by the liver in a process called **cholesterol elimination** so that it can ultimately be rejected in the feces.

The RLT pathway is the only natural mechanism capable of transporting cholesterol from the vascular wall plaque to the liver for it to be eliminated from the body and, consequently, lead to a regression in atherosclerotic plaque.

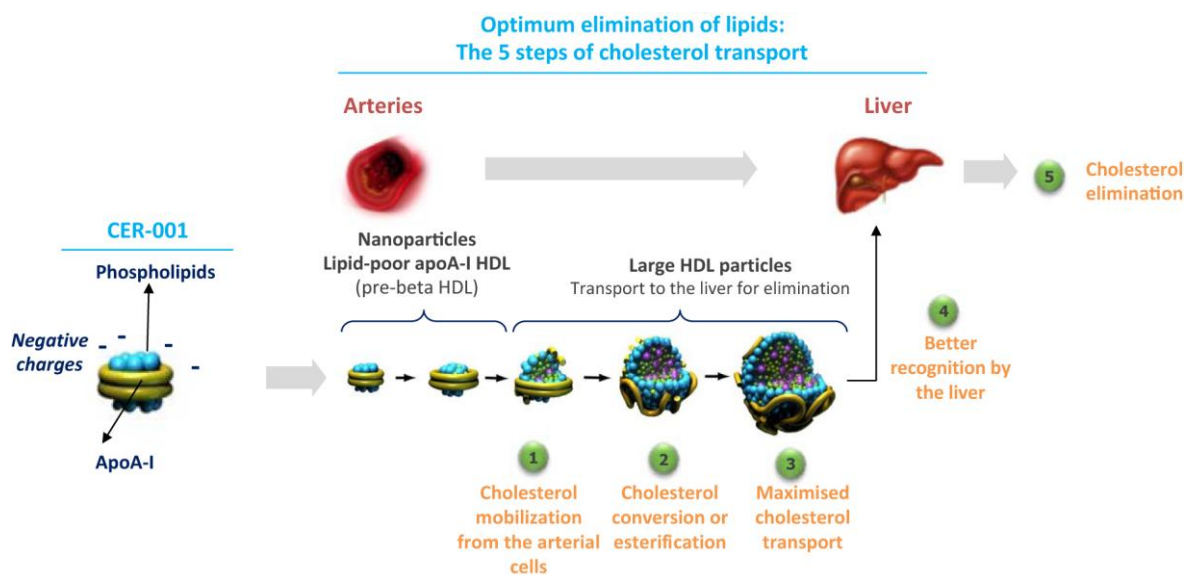


Figure 3: Reverse Lipid Transport mediated by the HDL particles

#### 6.1.1.3. Cholesterol imbalances and formation of atherosclerotic plaques

In a healthy human, the production and elimination of cholesterol are in equilibrium. Over time, however, an imbalance often occurs in our body with an excess level of cholesterol contained in LDL particles (which are consequently called the "bad cholesterol") or a deficiency of cholesterol contained in HDL destined for elimination. Atherosclerosis develops as a result of this imbalance. When a person has high blood levels of LDL cholesterol or low blood levels of HDL cholesterol, the imbalance results in more deposition of cholesterol in the arteries than is withdrawn (see Figure 2 above). This process of cholesterol accumulation takes place over years, even decades, resulting in the formation of atherosclerotic plaques.

This imbalance in cholesterol regulation can also be exacerbated by other factors including, among others, age, gender, hypertension, smoking, diabetes, obesity, genetic factors, physical inactivity or a high-fat diet.

A healthy and low-fat diet, especially low in saturated fats, not smoking, reduced alcohol consumption, physical activity and reduced stress are among public health recommendations to reduce cardiovascular risk.

Excess cholesterol transported in the blood by LDL particles can be deposited all over the body often in the artery walls, and especially the arteries that supply the heart muscle. Excess cholesterol deposits can cause potentially life-threatening complications such as vascular inflammation and the

formation of atherosclerotic plaques which stenoses or narrows the arteries, causing chest pain on effort or even at rest. The unexpected rupture of a plaque can result in sudden obstruction of these arteries, leading to angina pectoris or a heart attack, which may lead to death of the patient.

### 6.1.2. Current treatments for atherosclerosis and their limitations

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**Current medical recommendations for the treatment of excess of cholesterol** (e.g. prescription of statins, bile acid sequestering resins, intestinal cholesterol absorption inhibitors, PCSK9 inhibitors, etc.) **aim to reduce LDL levels in the circulation**, with the long-term aim of limiting or preventing continued accumulation of cholesterol in the vessel walls.

There is indeed no approved medical treatment that suppresses or directly treats the atherosclerotic plaque once it is formed. Consequently, the disease is only treated indirectly by reducing cholesterol levels in the blood.

#### 6.1.2.1. Available treatments

LDL-cholesterol-lowering treatments aimed to reduce cholesterol levels in the circulation include the following drug classes:

- Statins, such as for example Lipitor® (atorvastatin, Pfizer, USD 2.3 billion sales in 2013) and Crestor® (Rosuvastatin, AstraZeneca, USD 5.6 billion sales in 2013).

Statins are the main LDL-cholesterol lowering drugs in use. They act by blocking an enzyme that takes part in cholesterol synthesis in the liver. Several clinical studies have demonstrated that statins reduce cardiovascular risk by one third.<sup>7</sup>

These treatments can result in an increase in certain liver enzymes called serum transaminases. Moreover, rare observations of muscular conditions have been reported, with statins used alone or in association with other LDL-cholesterol lowering agents. We estimate that approximately 30% of patients stop taking statins in the first year, many because of side effects but also because of the “silent” nature of cholesterol build-up (until the occurrence of cardiovascular events).

- Cholesterol intestinal absorption inhibitors, such as Zetia® (ezetimibe, Merck & Co, USD 2.6 billion sales in 2013), the only approved drug in its class.

Intestinal absorption inhibitors have a very specific mechanism of action. Unlike statins that block synthesis of cholesterol in the liver, these drugs target the other source of cholesterol in the body: the intestine. They reduce the entry of cholesterol in the body by preventing its intestinal absorption. This is why doctors regularly highlight that these molecules have a complementary action to that of statins.

- Sequestering resins (bile acid sequestering resins) such as Colestid® (colestipol, Pfizer), Welchol® (Colesevelam, Daiichi Sankyo Group) USD 422 million sales in 2013 or Questran® (cholestyramine, Bristol-Myers Squibb).

Resins interfere with the intestinal absorption of cholesterol, by binding to and eliminating bile acids, which are necessary for cholesterol absorption, resulting in a decrease in LDL cholesterol.

Sequestering resins have the advantage of being poorly absorbed by the body, which is of interest for some population categories such as pregnant women, children or patients

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<sup>7</sup> [http://www.has-sante.fr/portail/upload/docs/application/pdf/2012-02/statine\\_-\\_fiche\\_bum.pdf](http://www.has-sante.fr/portail/upload/docs/application/pdf/2012-02/statine_-_fiche_bum.pdf)

intolerant to statins. However, observed LDL-cholesterol reductions are limited and the current daily dosing is restrictive and unpleasant.

- PCSK9 inhibitors, such as Repatha® (Amgen) and Praluent® (Regeneron/Sanofi) are a newer class of injectable drugs that have been shown to dramatically lower LDL cholesterol levels, by up to 60% when combined with a statin. PCSK9 inhibitors are monoclonal antibodies (MABs), a type of biologic drug. They bind to and inactivate a protein in the liver called proprotein convertase subtilisin/kexin 9 (PCSK9). PCSK9 itself inactivates the needed receptors on the liver cell surface that transport LDL into the liver for metabolism (breakdown). Without these receptors, more LDL (“bad” cholesterol) remains in the blood. So, by inactivating PCSK9 via inhibition, more receptors are available to capture LDL for metabolism and removal from the blood. Inhibition of PCSK9 results in lower LDL cholesterol in the blood. Repatha® or Praluent® injection is indicated for use in addition to diet and maximally-tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH), homozygous familial hypercholesterolemia (HoFH), or clinical atherosclerotic cardiovascular disease (ASCVD), such as a heart attack or stroke, which require additional lowering of LDL cholesterol.

Results from FOURIER, the first cardiovascular outcome trials to evaluate the effectiveness of an anti-PCSK9 antibody (Repatha® and Amgen) were presented at ACC 2017 in March 2017.<sup>8</sup> The primary composite endpoint (cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for unstable angina or coronary revascularization) was met with a reduction of 15% as well as the key secondary composite endpoint (cardiovascular death, non-fatal MI or non-fatal stroke) with a reduction of 20%. Such results will potentially result in new guidelines after review by the regulatory authorities.

Results from ODYSSEY, the outcome trial with Praluent® are expected by 2018.

- Niacins such as Niaspan® (AbbVie)

Niacin, also called nicotinic acid, is vitamin B3. This vitamin taken in large amounts, several grams a day, reduces production of LDL cholesterol by the liver, reduces triglycerides and increases HDL cholesterol (the “good” cholesterol) levels. However, two large clinical studies AIM-HIGH and HPS2-THRIVE have not demonstrated the efficacy of niacin in reducing cardiovascular risk and have shown harmful effects. Niacin is still prescribed in the United States to patients with little or no response to other drugs available on the market despite its difficult-to-tolerate side effects (hot flushes and redness).

In Europe, this class of drugs is very seldom used.

- Fibrates, such as Tricor®/Trilipix® (Fenofibrate, Abbvie, which sold USD 1 billion in 2013 for this class, including Niaspan®) or Lopid® (gemfibrozil, Pfizer).

Drugs from the fibrate family reduce LDL-cholesterol levels and also, in part, blood triglyceride levels. They are used when statins have not been effective or have caused side effects.

Patients who take fibrates must undergo regular medical monitoring of liver and muscle functions.

These different classes of drugs are at sometimes used in combination to maximize the reduction in LDL-C.

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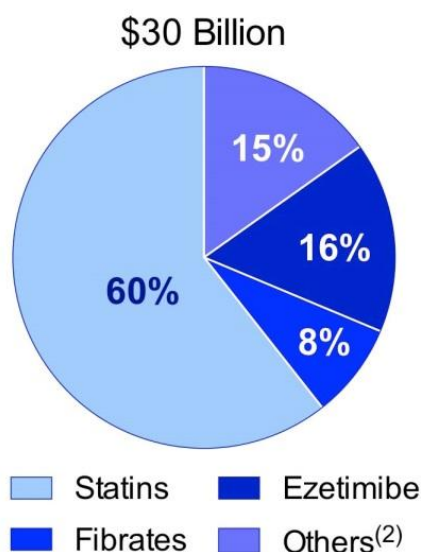
<sup>8</sup> Sabatine et al. NEJM. DOI: 10.1056/NEJMoa1615664

Overall, these therapies for cholesterol management represented a market of USD 30 billion in 2013, due largely to the success of several drugs which have attained a “blockbuster” status with annual sales exceeding USD 1 billion, as shown in the following table.

Drug class	Drug name	2013 Sales in USD billion	Company	Company 2013 Sales
Statins	Lipitor® (atorvastatin)	2.3	Pfizer (USA NYSE)	USD 51.6 billion
	Crestor® (rosuvastatin)	5.6	AstraZeneca (UK, LSE)	£16.45 billion
Intestinal Absorption Inhibitors	Zetia® (ezetimibe)	2.6	Merck & Co (USA, NYSE)	USD 44 billion
Resins	Colestid® (colestipol)	NA	Pfizer (USA, NYSE)	USD 51.6 billion
	Welchol® (colesevelam)	0.4	Daiichi Sankyo Group (Japan, TSE)	JPY 1.118 billion
	Questran® (cholestyramine)	NA	Bristol-Myers Squibb (USA, NYSE)	USD 16.4 billion
PCSK9 inhibitors	Praluent®	NA**	Sanofi/Regeneron	
	Repatha®	NA**	Amgen	
Niacins	Niaspan®	NA	AbbVie (USA, NYSE)	USD 18.8 billion
Fibrates	Tricor®/Trilipix® (fenofibrate)	1*	AbbVie	USD 18.8 billion
	Lopid® (gemfibrozil)	NA	Pfizer	USD 51.6 billion

\* incl. Niaspan, \*\* marketed mid-2015

### Lipid-Lowering Agents<sup>(1)</sup> Worldwide Sales 2013



(1) IMS MIDAS

(2) Niacin, Omega 3 therapies

It is also important to highlight that many patients who have a cardiovascular event present with relatively “normal” LDL-cholesterol levels, because their cholesterol imbalance is caused by a defect in cholesterol elimination by HDL particles rather than by “excess” cholesterol being transported by LDL particles. The therapeutic treatment options are limited for this kind of patient.

The other options available for these patients are mechanically removing the atherosclerotic plaques (rotatory atherectomy) or restoring the artery diameter by placing a stent; however, these invasive methods only treat the disease locally, one area of an artery at a time, without treating other vessels that may be loaded with plaque. These local procedures cannot treat a disease such as

atherosclerosis, which is systemic and marked by accumulation of cholesterol in all vessel walls with multiple plaques in several vascular beds.

#### **6.1.2.2. Outcomes and limitations of treatments aimed at reducing LDL cholesterol**

These preventive strategies to limit plaque accumulation by reducing circulating LDL cholesterol have proved their capacity to reduce cardiovascular events by one third and have become the standard of care recommended by health authorities for the treatment of cardiovascular risk.<sup>9</sup>

An important limitation of LDL therapies is that most patients generally start to receive these treatments around age 30 or 40 when their cholesterol has already accumulated for decades in their vessel walls.

These treatments only have a modest effect on regression of the atherosclerotic plaque in itself<sup>10</sup> and this only when the most potent statins are administered at the highest doses and for several years. Moreover, they are aimed at attaining very low levels of LDL cholesterol (< 70 mg/dl), which are not attainable by all patients either because of increased risk of side effects at higher doses or due to a lack of compliance with treatment in the long term.<sup>11</sup> The results of the clinical trial IMPROVE-IT have also been very instructive in this regard, in that the additional reduction of 15%-20% of LDL cholesterol in patients treated for seven years by the combination ezetimibe/simvastatin compared to that seen with simvastatin alone (69.5 mg/dl) resulted in a reduction in absolute risk of only 2% of the clinical trials primary objective<sup>12</sup> (32.7% and 34.7% respectively).

Due to the modest results obtained from the phase III study IMPROVE-IT, the FDA rejected Merck's request to extend the indication of Zetia® (ezetimibe) and Vitoria® (ezetimibe/simvastatin) to cardiovascular events in patients with coronary artery disease.<sup>13,14</sup>

Therefore, there is a still unmet significant medical need for addressing the remaining two-thirds cardiovascular risk<sup>11</sup>: even patients treated at the highest doses of the best currently available treatments still have a high level of risk of heart attack, stroke and cardiovascular death. This leaves a significant place for the next generation of new therapies that may directly eliminate atherosclerotic plaque and, thereby, attack the cause of the disease.

In March 2017, the FOURIER study showed that Repatha® (evolocumab, Amgen), in addition to statin therapy, led to a statistically significant 15% reduction in the combined primary endpoint (cardiovascular death, Nonfatal myocardium (MI), nonfatal stroke, hospitalization for unstable angina pectoris or coronary revascularization). The study also showed a statistically significant 20% reduction in the combined secondary endpoint (cardiovascular death, non-fatal first MI or non-fatal stroke). However, as with recent studies to reduce LDL cholesterol significantly, no effect on cardiovascular mortality has been observed. As the absolute reduction in cardiovascular risk is 1.5%, new therapies that would act through other mechanisms, different from the lowering of LDL cholesterol, would address the residual cardiovascular risk that remains important.

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<sup>9</sup> Ridker PM The JUPITER trial: results, controversies, and implications for prevention. *Circulation: Cardiovascular Quality and Outcomes*. 2009; 2: 279-285.

<sup>10</sup> Nissen SE, et al REVERSAL investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA*. 2004 Mar 3; 291(9): 1071-80.

<sup>11</sup> Kamal-Bahl SJ et al. Discontinuation of lipid modifying drugs among commercially insured United States patients in recent clinical practice. *AMM. J. Cardiol*. 2007 Feb 15; 99(4): 530-4.

<sup>12</sup> IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (CV death/MI/unstable angina/coronary revascularisation/CVA)

<sup>13</sup> <http://www.reuters.com/article/merck-co-zetia-fda-idUSL3N15U435>.

<sup>14</sup> <http://www.mercknewsroom.com/news-release/prescription-medicine-news/merck-receives-complete-response-letter-us-fda-zetia-ezetim>.

### 6.1.2.3. The protective role of HDL particles

The protective role of HDL particles including cardiovascular diseases has been demonstrated by several epidemiological studies (FRAMINGHAM<sup>15</sup>, MONICA<sup>16</sup>, PROCAM<sup>17</sup>, CANHEART<sup>18</sup>).

Therefore, increasing the number of functional HDL particles represents an important therapeutic approach for the next major step forward in treating atherosclerosis.

Epidemiological studies have demonstrated that the risk of developing a cardiovascular disease is higher in patients with low levels of HDL cholesterol regardless of LDL cholesterol levels, even when these patients are treated with the best available therapies.<sup>19</sup> Other large-scale studies have demonstrated more specifically that the level of apoA-I (the main protein in HDL particles) represents a better predictive factor of cardiovascular events. These reference studies are examples of the large body of clinical data demonstrating the cardioprotective role of HDL and the predictive value of low HDL cholesterol levels to quantify the elevation of cardiovascular risk at the individual patient level.

- The Framingham and PROCAM studies, two broadly recognized epidemiological studies, have demonstrated a strong correlation between levels of HDL cholesterol and the risk of coronary disease. As shown in Figure 4 below, the lower the level of HDL cholesterol, the higher the incidence of cardiovascular events, regardless of LDL cholesterol levels (the “bad” cholesterol).

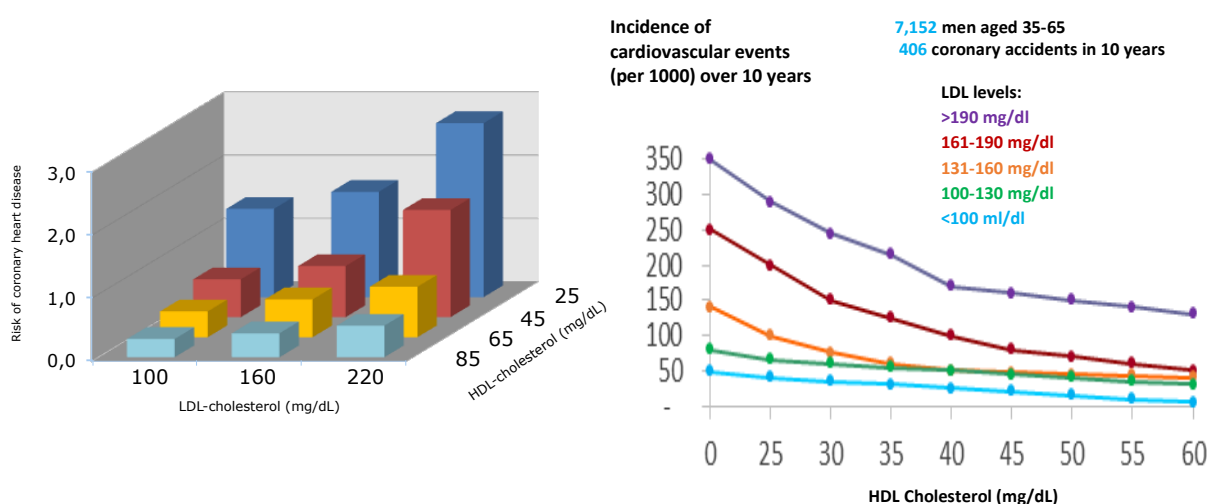


Figure 4: Framingham (on the left) and PROCAM (on the right) studies

- In the AFCAPS/TexCAPS trial, the authors concluded that HDL cholesterol should be included in the risk assessment, even when concentrations of LDL cholesterol are normal. Another epidemiological study conducted over 21 years<sup>20</sup> demonstrated that a low level of HDL cholesterol, even in the absence of high levels of LDL cholesterol, is an independent risk factor for the development of new or recurrent cardiovascular events.

<sup>15</sup> <https://www.framinghamheartstudy.org/index.php>

<sup>16</sup> <http://web.pasteur-lille.fr/fr/recherche/u744/resultat/enqpop.html>

<sup>17</sup> <http://www.assmann-stiftung.de/>

<sup>18</sup> CANHEART HDL Study Ko et al. JACC, vol 68, No. 19, 2016: 2073-83.

<sup>19</sup> Barter et al., HDL-cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N. Engl. J. Med. 2007, 357(13), 2007; 1301-10.

<sup>20</sup> Goldbourt U, et al. Isolated low HDL cholesterol as a risk factor for coronary heart disease mortality. A 21-year follow-up of 8000 men. Arterioscler. ThrombVasc. Biol. 1997; 17: 107-13.

- The Veterans Affairs HDL Intervention Trial (VA-HIT)<sup>21</sup> also supports the importance of HDL cholesterol in the prevention of cardiovascular diseases. This clinical study provided the first clear evidence that an increase in HDL levels significantly reduces the incidence of cardiovascular events.
- The INTERHEART study<sup>22</sup>, a global case-control study conducted over 5 years on more than 10,000 patients confirmed the relevance of apoA-I levels to predict the risk of cardiovascular events. The concentration of apoA-I may be considered, in fact, as an approximation of levels of small HDL particles. Consequently, the study demonstrates the correlation between higher levels of nascent pre- $\beta$  HDL particles that are “empty” transporter particles not yet loaded with cholesterol, and a reduction in cardiovascular risks.
- This conclusion has also been demonstrated in the AMORIS<sup>23</sup> study, a Swedish prospective study of more than 175,000 patients followed for 6 years as well as in the PRIME<sup>24</sup> study in more than 10,000 patients.
- The capacity of the blood to mobilize cholesterol and to increase its cellular efflux (the first step of the reverse lipid transport) was inversely associated with the incidence of cardiovascular events in a cohort of 2,924 adults in the Dallas Heart Study, representative of the population.<sup>25</sup>

Beyond demonstration of the protective role of HDL, two recent studies have demonstrated the importance of the number of HDL particles and their correlation with cardiovascular risk:

- An initial study (MESA) has demonstrated that the highest levels of HDL and, especially, a higher number of HDL particles are directly linked to lower levels of atherosclerosis in addition to a lower incidence of cardiovascular events (myocardial infarction, death from a cardiovascular event and angina pectoris). The best predictor of cardiovascular events (CV) is the number of HDL particles: cardiovascular risk is inversely correlated to the number of HDL particles. The higher the number of HDL particles, the lower the cardiovascular risk (observational clinical study of more than 5,500 men and women, MESA- “Multi-ethnic Study of Atherosclerosis”, Mackey et al., 2012<sup>26</sup>, performed by measuring the intima-media thickness of the carotid or cIMT by ultrasound).
- A second study (JUPITER) has demonstrated the excellent predictive value of the number of HDL particles for cardiovascular events in patients treated with statins. Among subjects from the group receiving rosuvastatin (Crestor®), the number of HDL particles at the start of the study had a statistically significant correlation with cardiovascular disease (JUPITER, a study of placebo-controlled rosuvastatin in more than 17,802 asymptomatic men and women (Mora et al., 2013<sup>27</sup>).

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<sup>21</sup> Rubins, H. B., et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N. Engl. J. Med.*, 1999, 341, 410-418.

<sup>22</sup> Yusuf S, et al. on behalf of the INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004, 364:937-952.

<sup>23</sup> Walidius, G. et al. Rationale for using apolipoprotein B and apolipoprotein A-I as indicators of cardiac risk and as targets for lipid-lowering therapy *Eur Heart J*; (February 2005) 26(3): 210-212, first published online on 15 December, 2004 [doi:10.1093/eurheartj/ehi077](https://doi.org/10.1093/eurheartj/ehi077).

<sup>24</sup> Luc, G. et al. Lipoprotein (a) as a predictor of coronary heart disease: the PRIME Study. *Atherosclerosis*. 2002 Aug; 163(2):377-84.

<sup>25</sup> Rohatgi et al. HDL Cholesterol Efflux Capacity and Incident Cardiovascular Events. *NEJM Epub* November 18, 2014.

<sup>26</sup> Mackey RH, et al. High-Density Lipoprotein Cholesterol and Particle Concentrations, Carotid Atherosclerosis, and Coronary Events MESA (Multi-Ethnic Study of Atherosclerosis) - *J. Am. Coll. Cardiol.* 2012, 60:508-16.

<sup>27</sup> Mora S, et al. HDL cholesterol, size, particle number, and residual vascular risk after potent statin therapy. *Circulation*. 128: publié en ligne le 3 septembre 2013.

### 6.1.3. HDL particles therapy: an innovative cardiovascular disease treatment

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The RLT pathway is responsible for the removal of cholesterol from arteries and its transport to the liver for it to be eliminated from the body. Figure 5 below shows the life cycle of a natural HDL particle. Structurally, HDL is a particle containing apoA-I (apolipoprotein A-I) synthesized in the liver and complexed with several kinds of lipids to form a negatively charged nascent nanoparticle in the form of a disc of a few nanometers in diameter, also called pre- $\beta$  HDL.

The natural population of HDL is comprised of particles of different sizes, according to the amount of cholesterol that each one has mobilized for transport to the liver for elimination purposes. Newly formed pre- $\beta$  HDL particles are essentially “empty” transporters and have the largest capacity for cholesterol removal. These small particles increase in size as they are loaded with cholesterol, becoming mature HDL or alpha HDL particles, which are larger and capable of transporting cholesterol back to the liver to ensure elimination (Figure 5).

ApoA-I is the main constituent of HDL nanoparticles enabling its structure as a particle and ensuring its recognition by different organs. This is a natural protein that supports the biological activity of the HDL particle and in particular enables the particle especially to interact with the enzyme LCAT to ensure cholesterol esterification, the chemical transformation which enables retention of cholesterol within the particle. There are between two and four molecules of apoA-I protein per HDL particle, depending on the size of the particle.

After its synthesis, the pre- $\beta$  HDL nanoparticle leaves the liver and reaches the blood circulation where it collects cholesterol by interacting with cells, especially vessel wall cells. As the particle acquires cholesterol and other lipids, it will become larger and change its morphology to a spherical shape characteristic of a mature HDL.

Pre- $\beta$  HDL nanoparticles only represent approximately 10%<sup>28,29,30,31</sup> of the total HDL circulating in the blood. Therefore, most HDL particles in the circulation are  $\alpha$  HDL particles, of larger size, spherical, already loaded with cholesterol and returning to the liver for cholesterol elimination. They are therefore already saturated to their capacity and cannot collect any more cholesterol.

HDL mimetic therapy is based on administration of small empty and functional pre- $\beta$  HDL particles in order to increase the overall transport capacity for cholesterol, and thereby increase its elimination.

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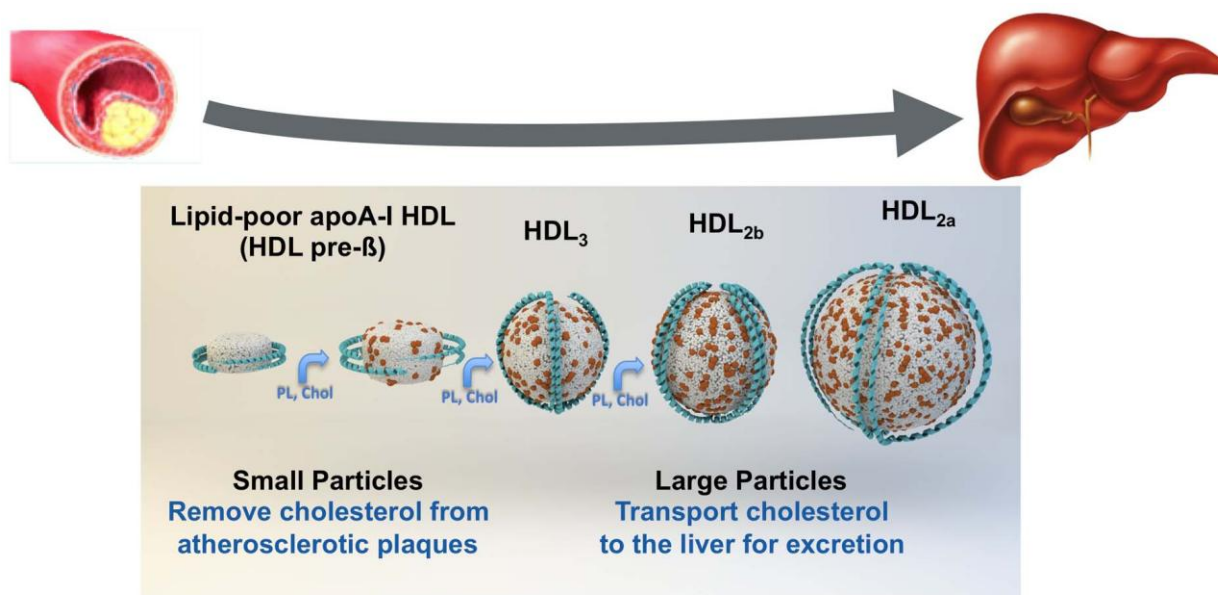
<sup>28</sup> Wang S.P., et al. In vivo effects of anacetrapib on pre-beta HDL: evidence for improvement in HDL remodeling without effects on cholesterol absorption. *J. Lipid Res.* 2013, 54:2858-65.

<sup>29</sup> O'Connor P.M., et al Pre -1 HDL in plasma of normolipidemic individuals: influences of plasma, age, and gender. *J. Lipid Res.* 1998, 39: 670–678.

<sup>30</sup> Watanabe H., et al Decreased High-Density Lipoprotein (HDL) Particle Size, Pre $\beta$ -, and Large HDL Subspecies Concentration in Finnish Low-HDL Families: Relationship With Intima-Media Thickness. *Arterioscler Thromb Vasc Biol.* 2006, 26:897-902.

<sup>31</sup> Söderlung S., et al Hypertriglyceridemia is associated with pre  $\beta$ -HDL concentrations in subjects with familial low HDL. *J. Lipid Res.* 2005, 46: 1643–1651.





**Figure 5: HDL life cycle**

Three key steps are necessary to produce a functional HDL mimetic: production of ultra-pure human apoA-I, optimization of lipid composition and assembly in a homogeneous population of stable particles.

During the last two decades, several attempts have been made by various pharmaceutical companies to develop an HDL mimetic capable of causing regression of atherosclerotic plaques.

Cerenis has developed CER-001, a pre-beta HDL particle containing human recombinant apolipoprotein A-I (apoA-I) designed by bioengineering, which acts like a natural HDL.

## **6.2. CER-001, the only particle acting as a natural HDL**

In the research for solutions that cause regression of atherosclerotic plaques and reduce cardiovascular diseases, the mission of Cerenis, since its creation, is to produce and develop a synthetic lipoprotein that best imitates the structure and functions of a natural high-density lipoprotein (HDL) to improve the reverse lipid transport. Toward this end, Cerenis is committed to developing CER-001, a complex containing the natural human protein of HDL, apolipoprotein A-I (apoA-I) and phospholipids, whose composition has been optimized to obtain a negatively charged discoidal nanoparticle closely resembling a natural pre-beta HDL particle.

This treatment approach, which we can designate “HDL mimetic therapy” consists of several intravenous administrations of an HDL mimetic such as CER-001, enabling regression of atherosclerotic plaques in the arteries and re-establishing a balanced cycle of cholesterol metabolism (in patients at high risk for cardiovascular disease, HDL deficiency or having already experienced an acute coronary syndrome [ACS] event such as angina pectoris or heart attack).

All preclinical studies have demonstrated that CER-001, a bioengineered pre-beta HDL nanoparticle, has all the known biological properties of natural HDL including the capacity to regress atherosclerotic plaque. CER-001 affects all steps of the reverse cholesterol transport pathway, as does a natural HDL thus validating the design, functionality and assembly of the particle during the manufacturing process:

- In cellular models, CER-001 was shown to be an effective acceptor of cholesterol. CER-001 favors the removal of cellular cholesterol (first step of reverse cholesterol transport).
- CER-001 mobilizes cholesterol as shown by the increase in HDL cholesterol. Mobilization of cholesterol is proportional to the dose administered. CER-001 is 20-25 times more potent for cholesterol mobilization than ETC-216, the HDL mimetic containing apoA-I<sub>Milano</sub> that was initially developed by Esperion and more recently by The Medicines Company<sup>32</sup> under the new code MDCO-216. In November 2016, The Medicines Company decided to discontinue development after inconclusive results obtained by the IVUS imaging method in the MILANO-PILOT trial<sup>33,34</sup> (see paragraph 6.8.1.1). These results contradicted those obtained in 2003 with the same IVUS imaging method.<sup>35</sup>
- CER-001 activates the LCAT enzyme resulting in increased esterification of cholesterol (second step of reverse cholesterol transport).
- CER-001 increases elimination of cholesterol in the feces.
- As shown in the validated preclinical models:
  - CER-001 prevents atherosclerosis progression.
  - CER-001 promotes regression of atherosclerosis.
- CER-001 specifically mimics the behavior of a natural pre-beta HDL as shown by the similar dependence of the atherosclerosis regression on the administered dose for both CER-001 and a natural pre-beta HDL. This identical behavior shows that CER-001 modulates ABCA1 and ABCG1, the two “sentinel/transporter” proteins controlling removal of cholesterol from the cell, in the same manner as natural pre-beta HDL.



**A schematic model of CER-001 representing the apoA-I complex (blue band) and phospholipids**

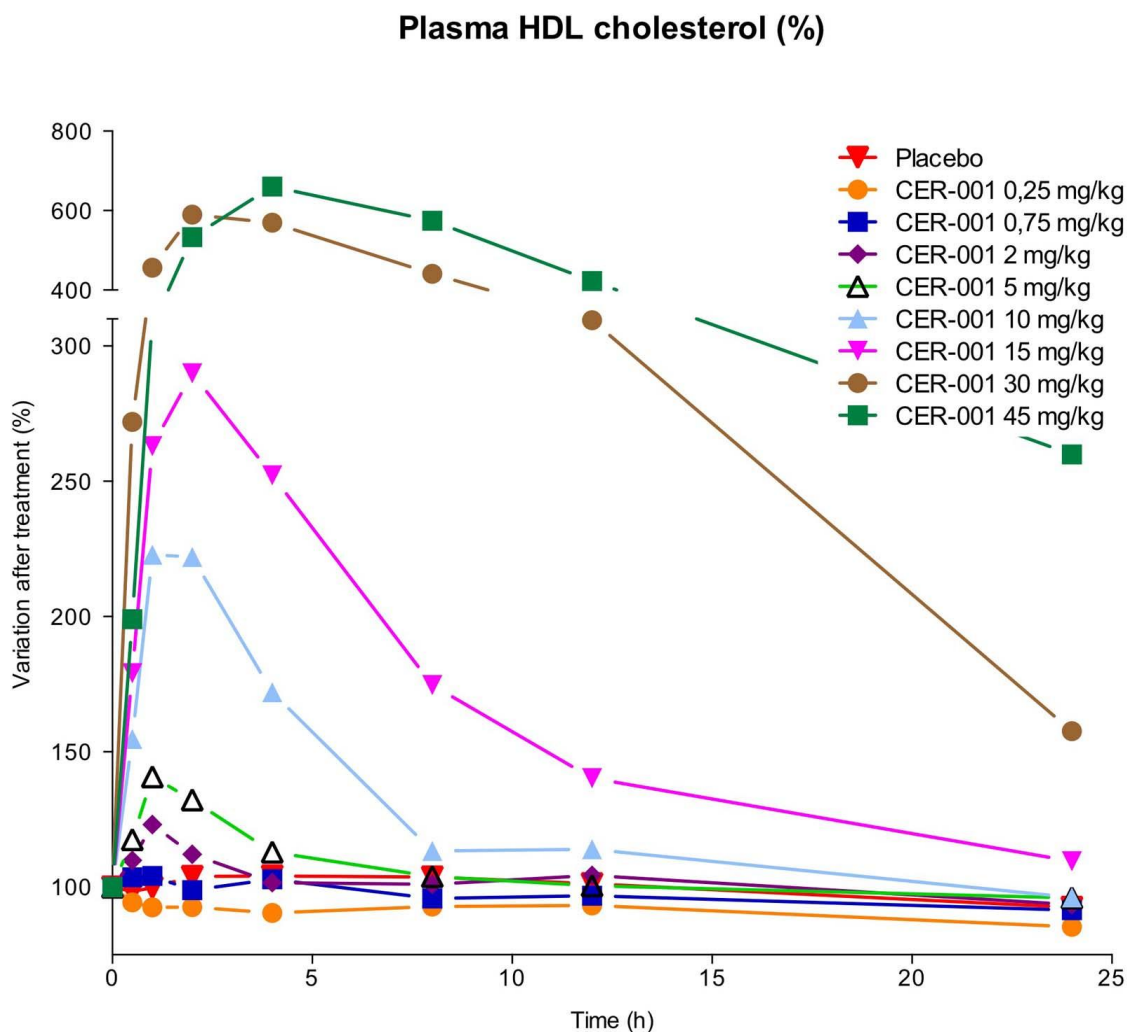
The Phase I clinical study (single administration), which explored doses from 0.5 to 45 mg/kg in humans, has demonstrated that the administration of CER-001 resulted in a significant mobilization of cholesterol in the HDL fraction. The mobilization of cholesterol translated into a 700% increase of HDL cholesterol at the dose of 45 mg/kg. Mobilization of cholesterol in HDL is already observed at doses as low as 2 mg/kg, thus demonstrating the potency of CER-001. The behavior of CER-001 in humans is comparable to what has been observed with natural HDL in clinical and preclinical models.

<sup>32</sup> Marchesi M. et al. Apolipoprotein A-I Milano and 1-palmitoyl-2-oleoyl phosphatidylcholine complex (ETC-216) protects the in vivo rabbit heart from regional ischemia-reperfusion injury. *J Pharmacol Exp Ther*. 2004, 311(3): p. 1023-31.

<sup>33</sup> <http://www.themedicinescompany.com/investors/news/medicines-company-discontinues-development-mdco-216-its-investigational-cholesterol>.

<sup>34</sup> [www.clinicaltrialresults.org/Slides/AHA2016/Nicholls\\_MILANO-PILOT.pdf](http://www.clinicaltrialresults.org/Slides/AHA2016/Nicholls_MILANO-PILOT.pdf)

<sup>35</sup> <http://jamanetwork.com/journals/jama/fullarticle/197579>.



**Figure 6: CER-001 mobilizes cholesterol in HDL: a Phase I study at a single ascending-dose**

Furthermore, this Phase I clinical study demonstrated that there were no significant side effects related to the drug in humans regardless of the dose administered. This confirms the quality of CER-001 compared to other HDL therapies developed to date that have encountered safety problems in their development. CER-001 mobilizes 7 times more cholesterol without causing liver dysfunction or toxicity.

The SAMBA Phase II study in HDL-deficient patients demonstrated the proof of concept for CER-001 in humans: mobilization and elimination of cholesterol leading to plaque regression.

In addition, Cerenis has provided a proof of concept at the other end of the cholesterol homeostasis spectrum, in a rare genetic disease characterized by extremely high LDL-cholesterol levels, and has demonstrated in humans that HDL mimetic treatments can supplement LDL-cholesterol lowering treatments (MODE study describe in section 6.6.1 of this Registration Document).<sup>36</sup>

These various results support the HDL mimetic therapeutic approach taken by Cerenis.

<sup>36</sup> Hovingh, G. K., et al.. "The effect of an apolipoprotein A-I-containing high-density lipoprotein-mimetic particle (CER-001) on carotid artery wall thickness in patients with homozygous familial hypoalphalipoproteinemia.

### 6.2.1. SAMBA, demonstration in humans that CER-001 performs all the steps of the RLT pathway

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The demonstration of reverse lipid transport in humans has eluded scientists for decades because endogenous HDL particles already present in normal individuals tend to mask experimental results. Cerenis has used a novel approach to perform a clinical trial that definitively validates the concept by testing CER-001 in HDL deficient patients. This study has also demonstrated that CER-001 particles carry out all the steps of reverse lipid transport in humans.

#### 6.2.1.1. Presentation of the SAMBA study

With the assistance of researchers-clinicians from the Netherlands and Brazil, Cerenis has identified a group of patients with an extremely rare and life-threatening severe HDL deficit syndrome. This syndrome is caused by various genetic defects resulting in the total absence or extremely low blood levels of HDL particles. The effects of pre- $\beta$  CER-001 particles have therefore been examined without any interference that could be caused by endogenous HDL particles.

The SAMBA study was performed by Prof. Eric Stroes (principal investigator) and Prof. John Kastelein (program consultant) at the Academic Medical Center in Amsterdam on 7 patients with confirmed genetic defects in at least one of three genes responsible for synthesis or maturation of HDL particles. Each of these genetic defects in one of the genes coding for apoA-I, ABCA1 or LCAT result in patients with extremely low levels or total absence of HDL particles.

The study's predetermined endpoints measured the mobilization of cholesterol in the blood in addition to its subsequent modification and elimination in the feces.

Because these patients are extremely rare and suffer from accelerated atherosclerosis in spite of following an optimized LDL-cholesterol lowering treatment prescribed by the general practitioner following current medical recommendations, the study was performed as “open-label” and was not controlled with placebo. Prior to starting treatment with CER-001, a full baseline evaluation was performed on each recruited subject, including a lipoproteins profile at baseline and analysis of atherosclerotic plaque in the carotid and aorta by nuclear magnetic resonance imaging (MRI), because an invasive procedure (like IVUS) is not indicated for these patients with no acute or emergency events such as ACS, for example. In general, these patients suffer from an exaggerated accumulation of cholesterol throughout the whole body, especially in the vascular system because of the absence of an endogenous functional pathway for reverse lipid transport.

The study design is shown in Figure 7: in an intensive “induction phase”, each patient was administered 9 doses of CER-001 8 mg/kg over four weeks, while continuing to follow, in accordance with current medical recommendations, an optimized LDL-cholesterol lowering treatment prescribed by their doctor. After this induction phase, the study subjects were reassessed by a lipoprotein profile analyses and MRI. Subsequently, the study subjects continued to be treated once every two weeks for 20 weeks, i.e. a total duration of treatment of 6 months. At the end of the second phase, the lipoprotein profile analyses and MRI were repeated.

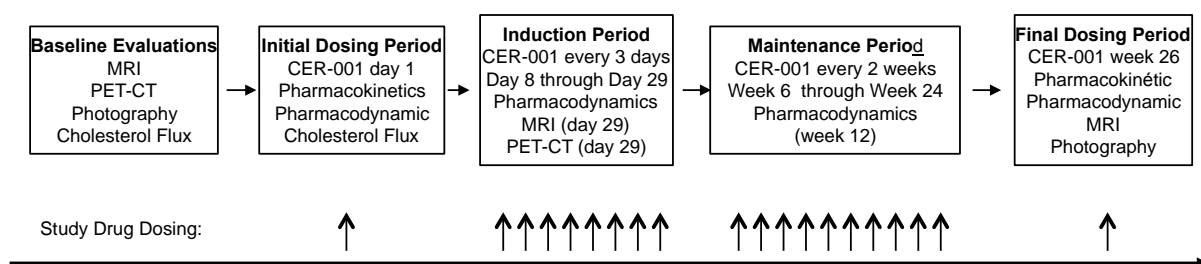


Figure 7: SAMBA study

#### 6.2.1.2. SAMBA: proof of concept for reverse cholesterol transport

The results demonstrate that the four characteristic steps of reverse cholesterol transport are re-enabled after administration of CER-001:

Step 1 – Cholesterol loading of the pre- $\beta$  CER-001 particle and reconstitution of the population of mature HDL- $\alpha$  particles:

As shown by the example of the homozygous patient (a patient with a genetic defect that affects both homologous chromosomes) with total apoA-I deficiency and, consequently, virtually no HDL particles in the circulation (Figure 9), administration of CER-001 resulted in the appearance of HDL cholesterol. As the lipoprotein profile shows, HDL particles are significantly increased. This confirms that administering CER-001, in other words pre-beta HDL particles, achieves the first step of the RLT pathway, removal and mobilization of cholesterol from peripheral tissues to load the particles. An increased level of HDL cholesterol after administration of CER-001 has also been observed in the other 6 patients with homozygous or heterozygous mutations (a mutation that only affects one of the homologous chromosomes) in different genes affecting HDL metabolism.

Important to note: cholesterol loading only occurred in HDL particles; LDL or VLDL “very low-density lipoprotein”) remained unchanged - demonstrating that CER-001 is stable in the blood circulation and behaves like a natural HDL.

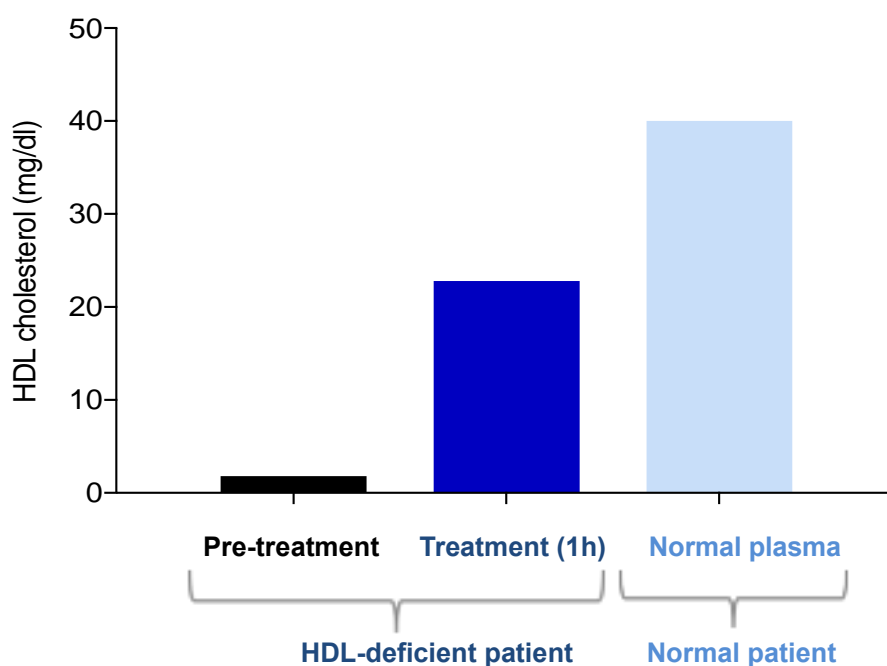
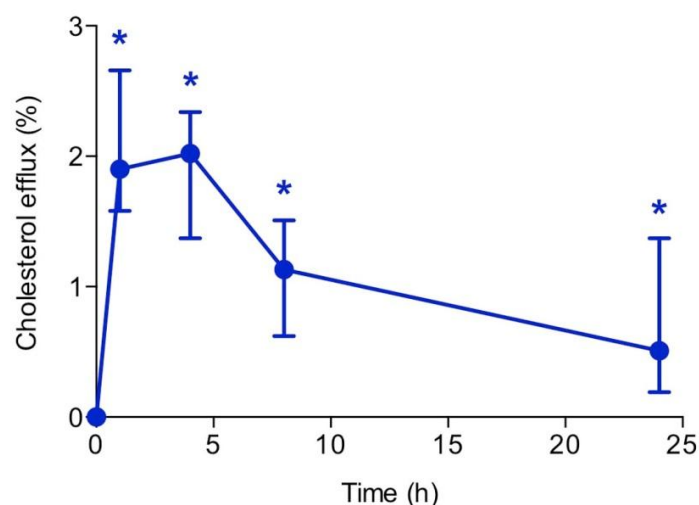


Figure 8: Loading in cholesterol of the pre-beta CER-001 HDL particle

The administration of CER-001 in these patients re-establishes the capacity of the blood to mobilize cellular cholesterol as shown in Figure 11. The curve shows the capacity of the blood to mobilize cholesterol over time following administration of CER-001. CER-001 increases ( $P = 0.018$  vs reference) the removal of cellular cholesterol by 44%.

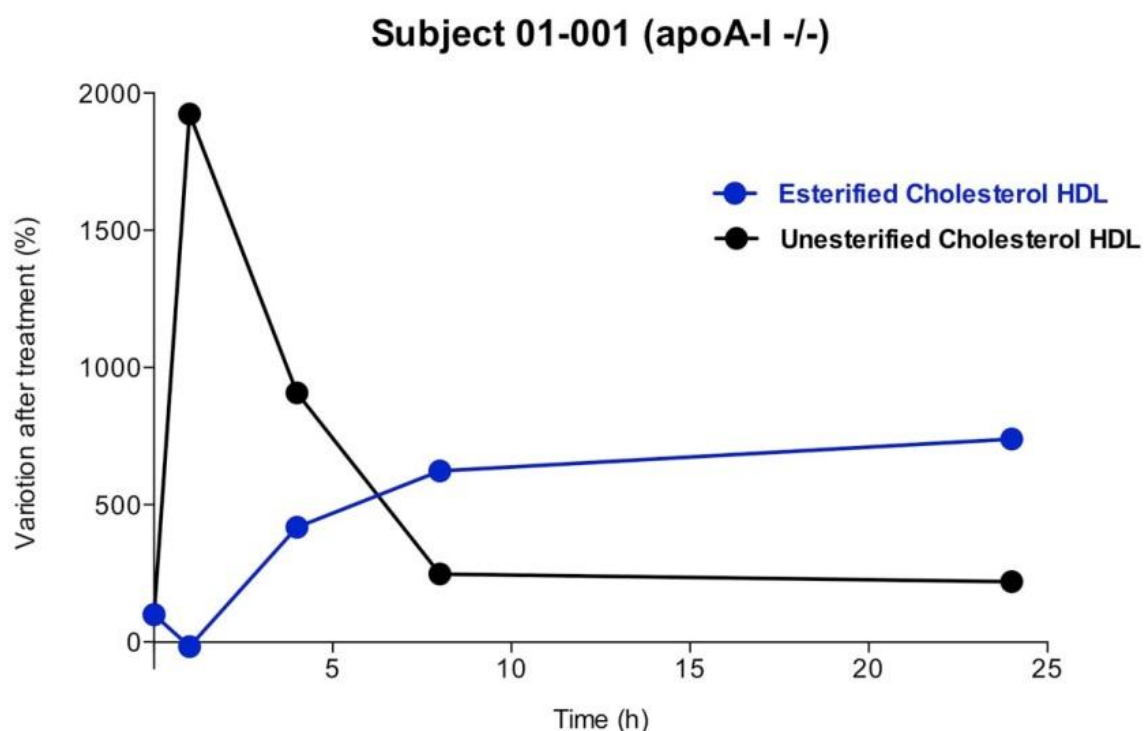


**Figure 9: Removal of cellular cholesterol in excess of the reference value after the first injection**

Step 2 – Cholesterol esterification: the cholesterol loaded in the CER-001 particle is esterified by the LCAT enzyme:

The analysis of esterified HDL-cholesterol levels demonstrates that CER-001 performs the second step of the RLT pathway, i.e. the esterification of cholesterol by the LCAT enzyme, using apoA-I contained in the composition of CER-001, as a cofactor. As shown below, again for the homozygous patient characterized by the absence of natural apoA-I, LCAT causes conversion of cholesterol, recently mobilized, into cholesteryl esters, thereby retaining it as a less mobile form within the CER-001 particles. The cholesterol is trapped within the CER-001 particle, which fills up and transforms into mature HDL ready for subsequent delivery of cholesterol to the liver. CER-001 therefore acts like the natural nascent HDL particles (Figure 10). A similar increase in esterified cholesterol levels has also been observed in patients with other genetic abnormalities in the study.

LCAT is the only enzyme responsible for cholesterol esterification in plasma, and its action requires presence of apoA-I in a defined configuration, interacting with the LCAT enzyme to activate it. ApoA-I is LCAT's cofactor.



**Figure 10:** The cholesterol mobilized by CER-001 is then “locked” inside the particle by the action of LCAT that transforms the cholesterol into a less mobile form, cholesteryl esters. (Subject 01-001 with apoA-I deficiency)

*Result:* The activation of LCAT by CER-001 therefore demonstrates the very high purity and correct configuration of apoA-I produced by the manufacturing process of CER-001 particles developed by Cerenis.

#### Steps 3 and 4 – Recognition of the particle by the liver and elimination of cholesterol from the body:

Although it is not possible to directly measure the recognition of HDL particles by the liver, the effect of this recognition can be measured by the elimination of cholesterol from the body in the feces by performing studies using labeled cholesterol as a marker. In selected subjects, a baseline value for the elimination of cholesterol before treatment was defined by collecting a series of feces samples. Samples were then collected for an additional week after administration of one dose of CER-001 in order to measure the total amount of cholesterol eliminated over one week post-dose.

*Result:* A total net increase from 0.4 to 1.9 g of cholesterol was eliminated (in the form of cholesterol or degradation product such as bile acids) by the body in the feces and was observed over 8 days following administration of a single dose of CER-001 (Figure 11) relative to the pretreatment amount. The amounts of cholesterol eliminated after the first and ninth dose administered are similar and thus demonstrate that the efficacy of the elimination is not reduced over time.

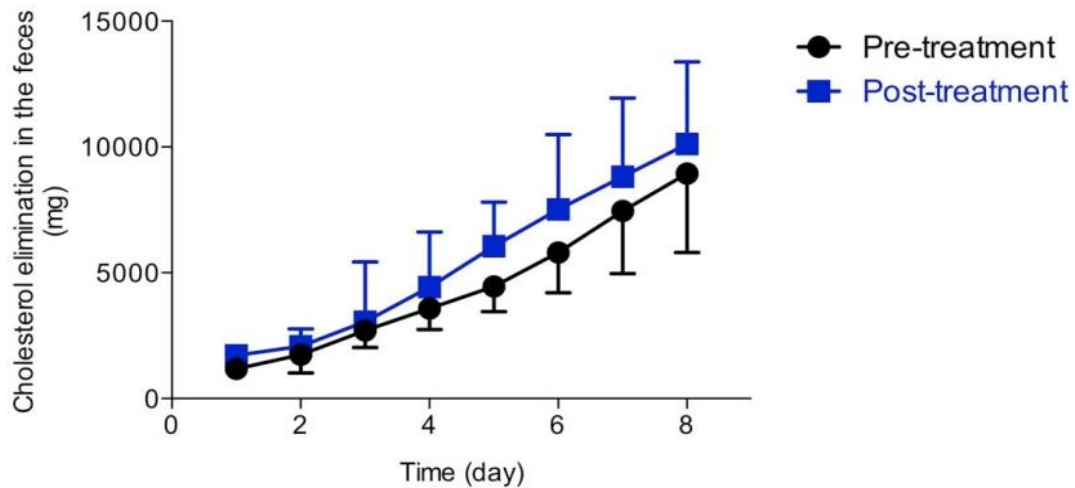


Figure 11: Elimination of cholesterol from the body by CER-001

#### 6.2.1.3. Clinical benefits demonstrated by the SAMBA study: regression of atherosclerotic plaque and reduced inflammation of the vessel wall

In order to demonstrate the clinical importance of cholesterol elimination of this magnitude by the body, a series of nuclear magnetic resonance imaging analyses (MRI) was performed: before treatment (value upon inclusion in the study), at one month (after the induction phase) and at 6 months (after the treatment maintenance phase). Among the parameters measured to evaluate atherosclerosis, variation in the area of the vessel wall of the aorta and carotid arteries, based on a blinded analysis, is represented in Figure 12.

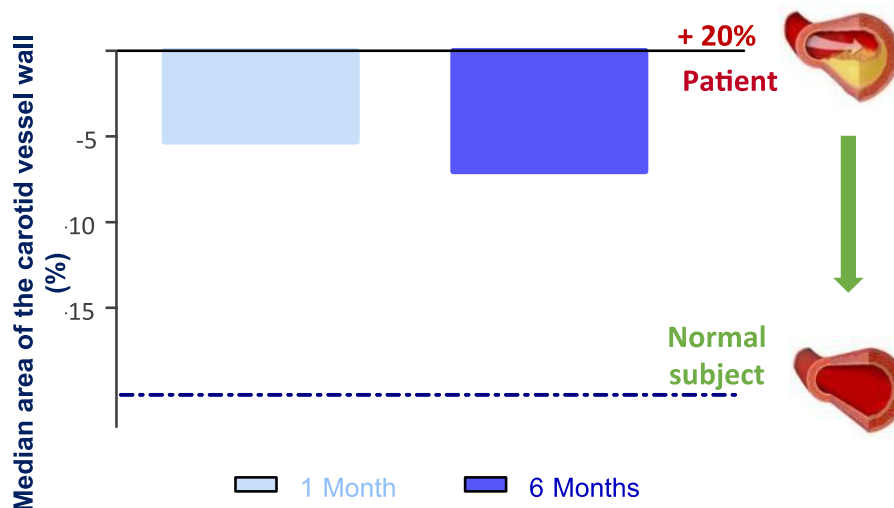


Figure 12: Regression of the median area of the vessel wall of the aorta and carotid after treatment for 1 and 6 months [MRI; n=7]

**Result:** Evaluation of sections obtained by MRI imaging has enabled establishing that the median vessel wall area (MVWA) of the carotid was reduced by 5.4% and the MVWA of the aorta was reduced by 5.0% after 1 month treatment and by 6.9% and 6.1% after treatment for 6 months, respectively



Evaluation of sections obtained by PET-FDG imaging demonstrated that repeated infusions of CER-001 also have a significant anti-inflammatory effect on the vessel wall, a finding which is consistent with the reduction of the anatomic atherosclerosis lesion observed on MRI images. A significant average reduction of 8.9% in TBRmax was observed in the arterial wall (reduced 18F-FDG uptake) of the index carotid artery ( $p=0.046$ ), measured by PET-CT imaging after the induction period (Figure 13) when compared to the baseline levels,

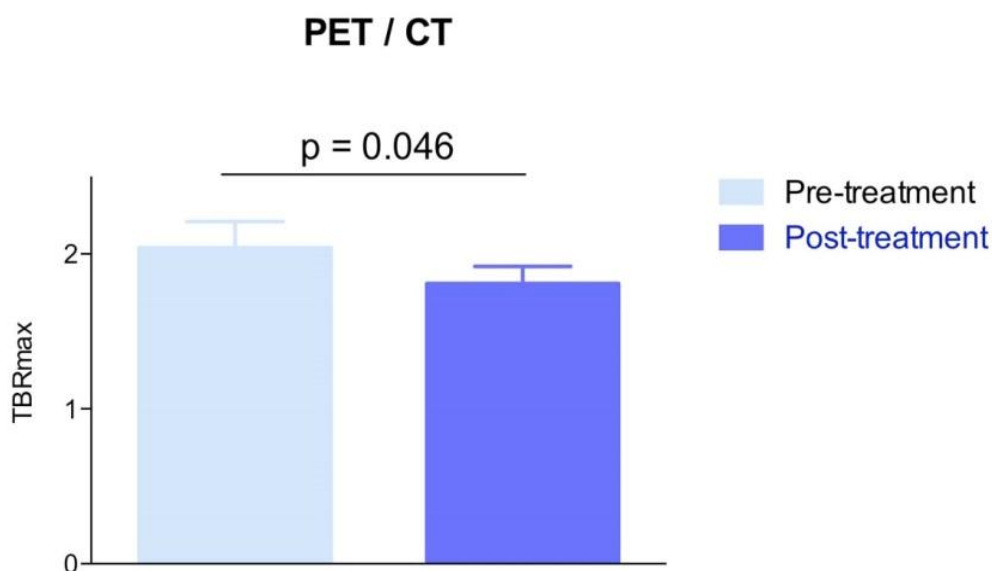


Figure 13: Reduction of carotid vessel wall inflammation (induction phase) [PET-CT; n=7]

For the entire study population, considering the baseline atherosclerosis, a 5% regression in carotid mean vessel wall area (MVWA) observed after only 1 month of CER-001 treatment represents approximately one fourth of the maximum theoretical amount that would be attainable long term (predicted based on age-matched controls).<sup>37</sup>

**Important to note, the rapid, persistent and cumulative benefits of twice weekly CER-001 treatment observed in the two vascular beds (carotid and aorta) were observed on top of any effects due to optimal LDL-cholesterol lowering treatments already prescribed by the general practitioner and allowing optimal lipid management in accordance with current medical recommendations.**

Also note that the largest effect was observed in the two subjects with homozygous genetic defects (complete apoA-I deficiency or ABCA1 deficiency). They showed persistent and cumulative increases in carotid mean vessel wall thickness (MVWT) with reductions of 10% or more.

To date, effects of this magnitude have never been achieved by any other currently available clinical treatment, especially after such a short initial treatment period (1 month). By comparison, Corti et al, 2002<sup>38</sup>, showed an 18.2% reduction in carotid MVWA with simvastatin; however, two years of treatment were required (Figure 14). Moreover, the simvastatin effect in the study was demonstrated in naive patients, i.e. patients who had never been treated by statins, while the effect of CER-001 in this trial was observed in addition to long-term, often multi-drug LDL-cholesterol

<sup>37</sup> Duivenvoorden, R. et al. In vivo quantification of carotid artery wall dimensions: 3.0-Tesla MRI versus B-mode ultrasound imaging. *Circ Cardiovasc Imaging*. 2009, 2; 235-249.

<sup>38</sup> Corti, R., et al. Lipid Lowering by Simvastatin Induces Regression of Human Atherosclerotic LesionsTwo Years' Follow-Up by High-Resolution Noninvasive Magnetic Resonance Imaging *Circulation*, 2002, 106:2884-2887.

lowering therapy already prescribed by the family doctor, maximizing LDL reduction in accordance with current medical recommendations.

#### **6.2.1.4. Conclusions of the SAMBA study**

The analysis and results of the SAMBA study are the first objective demonstration in humans of the reverse lipid transport mechanism, already broadly assumed by the medical scientific community.

Furthermore, CER-001 behaves in the body as a natural pre-beta HDL capable of performing the four key steps of the RLT pathway, removing cholesterol from the artery wall and eliminating it from the body, which results in atherosclerosis regression:

- CER-001 activates reverse cholesterol transport,
- It effectively mobilizes cholesterol which is then excreted by the body in the feces,
- It rapidly reduces plaque and inflammation in the arterial walls,
- No safety issues have been identified which could hinder the development of CER-001 for chronic treatment.

Moreover, these advantages have been observed rapidly and while patients were already following a standard LDL-cholesterol lowering treatment, optimized by their general practitioner and according to current medical recommendations.

The data were recently presented in the “Late Breaking Clinical Trials” session at the European Atherosclerosis Society (EAS) Congress in Barcelona, Spain in June 2014 and have been published in an international journal.<sup>39</sup>

#### **6.2.2. Designations of orphan drug by the European Medicines Agency (EMA)**

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In addition to the scientific demonstration of the reverse cholesterol transport mechanism in humans, these data have enabled the granting of two orphan drug designations by the European Medicines Agency (EMA) to Cerenis in August 2014, for the use CER-001 to treat patients with genetic deficiencies affecting the synthesis and maturity of HDL particles, particularly apoA-I deficiency and ABCA1 deficiency (homozygous ABCA1 deficiency is commonly called Tangier disease).

These two gene defects represent a subpopulation of familial primary hypoalphalipoproteinemia (FPHA), a rare disease encompassing several genetic defects in HDL synthesis and maturation, and characterized by a low number of HDL particles and a significant increase in the risk of premature cardiovascular events (see section 6.4 FPHA).

FPHA comprises patients with various genetic defects, some of which have been identified such as deficiencies in apoA-I, ABCA1 or LCAT and many others, which remain to be identified. New designations could therefore be granted in the future.

These orphan drug designations are proof of the already-demonstrated potential clinical advantages of CER-001 for a poorly-served population with significant unmet medical needs.

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<sup>39</sup> Kootte Rs, et al Effect of open-label infusion of an apolipoprotein A-I-containing particle (CER-001) on reverse cholesterol transport and artery wall thickness in patients with familial hypo-aphalipoproteinemia J Lipid Res. 2015 Jan 5. ePub

These designations by the EMA are an important step in the development of CER-001 for orphan diseases and FPHA. Moreover, this represents a validation of the potential interest in CER-001 for treating post-ACS patients.

#### **6.2.3. Support of internationally renowned scientists**

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CER-001 is strongly supported by eminent international scientists in the field of cholesterol and cardiovascular diseases, as evidenced by consultants associated with the company, the composition of the scientific board and of the steering committees for performed and scheduled Phase II and Phase III studies that include global leaders in the development of cardiovascular products and including for example Prof. John Chapman (INSERM, French Institute for Health and Medical Research, Paris), Prof. Bryan Brewer (MedStar Research Institute, Washington DC, US), Dr. Norman Miller (Honorary Member Magdalen College, University of Oxford, London, UK) and Prof. John Kastelein (Department of Vascular Medicine of the University of Amsterdam, Netherlands).

The steering committees for the current or planned Phase II and Phase III studies include global leaders in the development of cardiovascular products including for example Prof. Stephen Nicholls of the South Australian Health and Medical Research Institute (SAHMRI) in Adelaide, Australia, Prof. Steve Nissen (Chairman of the Robert and Suzanne Tomsich Department of Cardiovascular Medicine at Cleveland Clinic's Sydell and Arnold Miller Family Heart & Vascular Institute), and Prof. Erik Stroes, from the Department of Vascular Medicine of the University of Amsterdam, Netherlands (see sections 6.9.2. and 6.9.3).

#### **6.2.4. CER-001 indications targeted by Cerenis**

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Cerenis has established a clinical development plan for CER-001 for several indications, mainly:

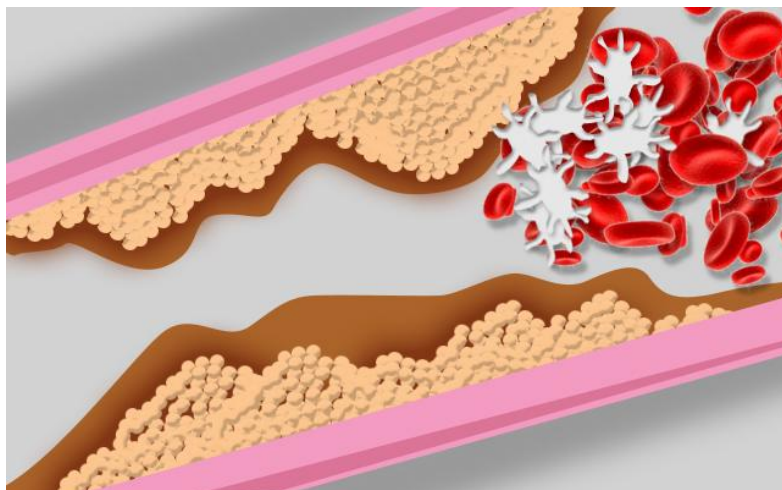
- Secondary prevention (prevention of recurrence) in patients who have already experienced an ACS event (post-ACS). The CARAT study confirmed the safety and tolerability profile of CER-001, however, the primary objective of the study was not achieved (reduction of the atheroma plaque within the coronary arteries evaluated by the IVUS imaging method). Other analyses such as virtual histology of coronary arteries are underway. An analysis of all the results will take several months.
- Treatment of patients with hereditary genetic abnormalities in HDL-cholesterol metabolism (familial primary hypolipoproteinemia, FPHA), for which two different orphan drug designations were granted by the European Medicines Agency (EMA): apoA-I deficiency and ABCA1 deficiency (commonly referred to as Tangier disease).

CER-001 is currently in Phase III of clinical development for FPHA treatment, with a TANGO study ongoing.

### 6.3. Principal indication FOR CER-001, the secondary prevention of cardiovascular events post acute coronary syndrome

#### 6.3.1. Atherosclerosis and acute coronary syndrome occurrence, unmet medical needs

CER-001 could become an important treatment for patients who survived an acute coronary syndrome event and remain high cardiovascular risk patients. These patients remain under long-term drug treatment.



**Rupture of an atherosclerotic plaque leads to blood clot formation**

Acute coronary syndrome (ACS) is a general term to describe situations in which blood flow to the heart muscle has been suddenly reduced or blocked. When an atherosclerotic plaque detaches in a coronary artery, an ACS event occurs. This event is often characterized by the sudden onset of initial symptoms such as chest pain, a feeling of oppression and shortness of breath, which cannot be relieved by rest, or the administration of oral drugs. The ACS event can lead to sudden death resulting from:

- Myocardial infarction (MI, commonly called heart attack):
  - ST-segment elevation MI (STEMI) - occurs in case of sudden occlusion of the coronary artery, which generally results in a large muscular injury. This type of heart attack is considered the most serious and patients usually experience severe and sudden symptoms when the attack starts.
  - Non-ST-segment elevation MI (NSTEMI) - occurs in case of sporadic and partial blockade (occlusion) of the coronary artery, severe enough to cause a heart muscle lesion.
- Angina pectoris or unstable angina:

Angina pectoris or unstable angina occurs when a blood clot forms in a coronary artery and almost completely blocks it. This occlusion reduces blood flow within the heart muscle and causes chest pains - even when the patient is at rest.<sup>40</sup> Angina pectoris or unstable angina can progress to a myocardial infarction if the interruption in blood flow to the heart muscle persists and becomes more severe, causing irreversible lesions to the heart muscle.

Pathologies arising from the same basic event: rupture of an atherosclerotic plaque in a coronary artery

<sup>40</sup> Bassand JP et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007, 28:1598-660.

There is a continuum from angina pectoris to NSTEMI or STEMI: these are pathophysiological consequences of the same underlying event, i.e. occlusion of the coronary artery usually caused by rupture of an atherosclerotic plaque and partial or total thrombosis that it generates in the artery responsible for the infarct.

These events only differ by the magnitude of the disturbance to blood flow (i.e. the extent of the ischemia). The risk of complications is proportional to the magnitude of the myocardial lesions. An angina pectoris or unstable angina implies a high risk of myocardial infarction recurrence and is therefore managed in the same way.

#### *Treatments and cost in case of ACS event*

An ACS event requires immediate transport and emergency care, followed by hospital admission. The priority is to stabilize the patient according to applicable medical directives and to treat the coronary obstruction with drugs, which is usually followed by:

- Diagnosis confirmation, then
- Definitive treatment such as angioplasty or stent implantation in the cardiac catheterization laboratory, often following intravascular ultrasound (IVUS) of coronary arteries
- After stabilization, the post-ACS patient is discharged home, generally under chronic medical treatment aimed at reducing the cardiovascular risk in the long-term, which is also referred to as “secondary prevention”. This treatment is mainly comprised of LDL-cholesterol lowering treatments (statins, cholesterol intestinal absorption inhibitors, etc.) in combination with other drugs, e.g. hypertension treatments.

The costs of hospitalization and for treatments administered in acute settings for an ACS event in the United States range between USD 20,000 (stent implantation only) and USD 60,000 (coronary artery bypass) per patient.<sup>41</sup>

#### **6.3.2. Risk of post-ACS recurrence, a high probability in the months following a cardiac event**

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In spite of secondary prevention measures, the persistent risk of recurrence of a heart attack for patients who already experienced an ACS event remains very high and represents a significant and unmet medical need.

A high percentage of post-ACS patients (approximately 12%) experience a recurrent cardiovascular event within one year after the ACS.<sup>42</sup>

- A total of 19% of men and 26% of women aged over 45 who experienced a first myocardial infarction will die within one year due a second cardiovascular event related to atherosclerosis; these mortality rates rise to 36% for men and 47% for women in the five years following the initial event.<sup>43</sup>
- The rate of myocardial infarct or fatal coronary disease recurrence in the five years following a first myocardial infarction varies from 15% in men aged 45-64, to 22% in men aged 65 or older and women aged 45 or older<sup>39</sup>.

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<sup>41</sup> National Healthcare Cost and Utilization Centers for Medicare and Medicaid Services.

<sup>42</sup> Cornel, J. et al., for the PLATO study group. Prior smoking status, clinical outcomes, and the comparison of ticagrelor with clopidogrel in acute coronary syndromes-insights from the PLATelet inhibition and patient Outcomes (PLATO) trial. Am Heart J 2012, 164, 3, 334–342.e1.

<sup>43</sup> Go, A.S. et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation 2013, 129:e28-e292.

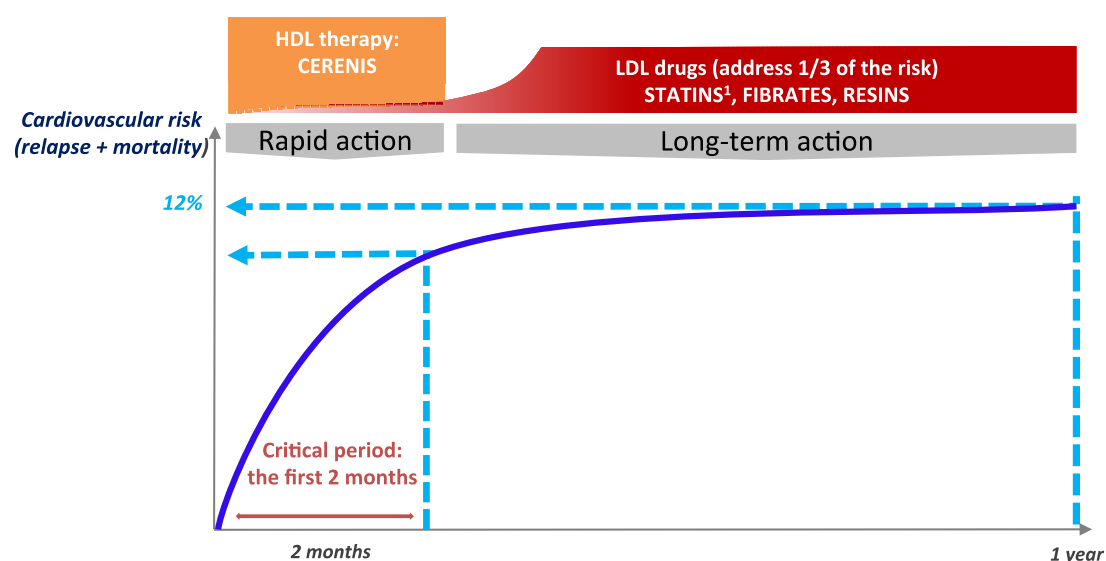


Figure 14: post-ACS cardiovascular risk

The risk of recurrence is especially high during the first two months following an ACS event thus making this period very critical. Moreover, atherosclerosis is a systemic pathology that can manifest itself by an ACS event following an initial event in another vascular setting (stroke or arteriopathy of the lower limbs).

Risk of ischemic events for patients suffering from atherosclerosis and other cardiovascular diseases<sup>44</sup>:

		Increased risk compared to the overall population	
		Myocardial Infarction	Stroke
Primary ischemic event	Prevalence		
Myocardial Infarction	4.4 million	5-7 times	3-4 times
Stroke	7 million	2-3 times	9 times
Arteriopathy of the lower limbs	9 million	4 times	2-3 times

Considering this substantial unmet medical need, CER-001, by enabling fast regression of atherosclerotic plaques, provides a unique opportunity to reduce the risk of recurrence over the first few months following occurrence of an ACS event. CER-001, in addition to long-term LDL-cholesterol lowering treatments, could result in an additional reduction in mortality and morbidity rates and become the new standard of excellence to treat ACS patients (cf. figure 14).

<sup>44</sup> National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II) Circulation. 1994; 89:1333-1363.  
Kanel, WB. Risk factors for atherosclerotic cardiovascular outcomes in different arterial territories J Cardiovasc Risk. 1994, 1:333-339.  
Wilterdink, JI, et al. Vascular event rates in patients with atherosclerotic cerebrovascular disease. Arch.Neurol. 1992, 49:857-863.  
Crique, MH, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992, 326:381-386.

### 6.3.3. Interest in short term CER-001 treatment in post-ACS patients

HDL mimetic therapy in post-ACS patients should improve cholesterol transport via the RLT pathway, by providing an additional capacity to eliminate cholesterol in the form of pre- $\beta$  HDL particles and thus reduce atherosclerotic plaques throughout the body.

The elimination of cholesterol accumulated in the vessel wall should reduce plaque size and associated inflammation, especially during the period of increased vulnerability to cardiovascular recurrence and thus reduce recurrence rates.<sup>45</sup>

Despite secondary prevention measures including drugs such as aspirin and other antiplatelet agents, beta-blockers, angiotensin converting enzyme (ACE) inhibitors and statins, the recurrence rate in post-ACS patients remains particularly high and the unmet medical need very considerable.

The window of broadest vulnerability for post-ACS patients is within the first few weeks after their cardiac event; these patients would especially benefit from HDL mimetic treatment immediately after the cardiac event, resulting in a rapid and significant reduction in atherosclerotic plaque and stabilization of the lesions.

In these patients, treatment with CER-001 is designed in the form of one cycle of a series of weekly administrations soon after the cardiac event. This cycle could be repeated after an interval of several months or years in case of cardiovascular recurrence.

Since two-thirds of recurrent cases are observed during the first two months following an ACS event, the next clinical studies of CER-0001 in post-ACS patients will consist of multiple administrations of CER-001 following the primary event (Figure 15) during the first weeks, once or several times a week to concentrate treatment during this window of maximum clinical opportunity (10 administrations for the first 9 weeks in CARAT).

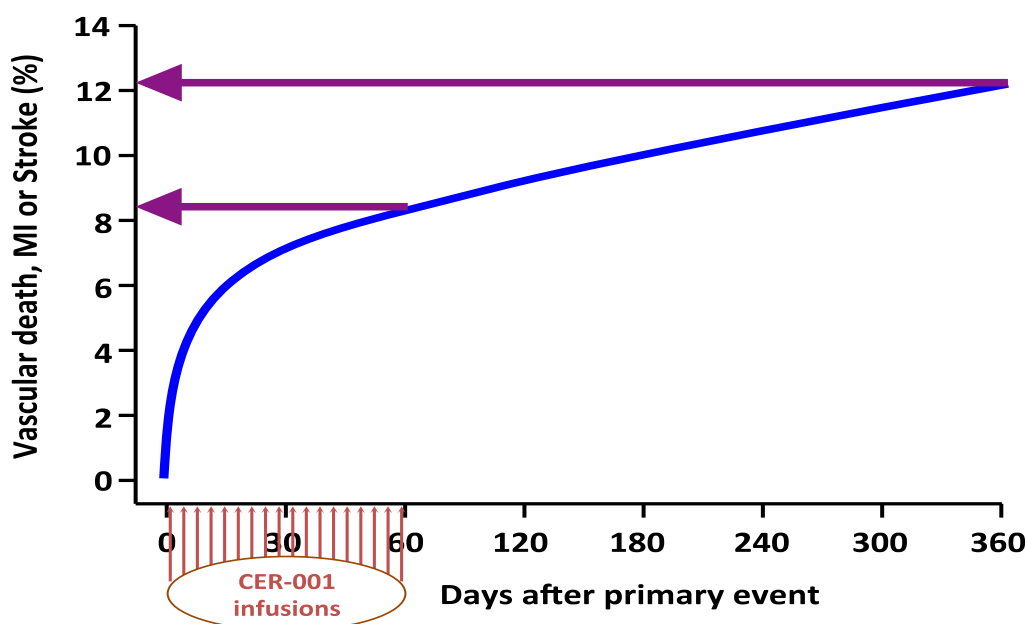


Figure 15: Patients who experience a CV event are at high risk of recurrence<sup>46</sup>

<sup>45</sup> Rader et al NEJM 2014, cited in Section 1.

<sup>46</sup> Cornel, J. et al., for the PLATO study group. Prior smoking status, clinical outcomes, and the comparison of ticagrelor with clopidogrel in acute coronary syndromes-insights from the PLATelet inhibition and patient Outcomes (PLATO) trial. Am Heart J 2012, 164, 3, 334–342.e1.

#### 6.3.4. The addressable market for CER-001 as treatment for secondary prevention post-ACS

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Post-ACS hospital discharges (discharges following a myocardial infarction and angina pectoris) amounted to approximately 1.1 million patients in 2010 in the United States.<sup>47</sup>

Assuming prevalence rates in Europe and Canada similar to those observed in United States, Cerenis estimates that there are approximately 1.4 million patients who experience an ACS event in Europe and 0.2 million in Canada each year.

In total, the population of post-ACS prevention target patients for CER-001 is estimated at approximately 2.8 million patients per year for North America and Europe.

#### 6.3.5. Clinical development program for post-ACS patients

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Clinical results obtained in patients with genetic defects affecting HDL synthesis or maturation have validated the mechanism of action of CER-001 by demonstrating that CER-001 administration transiently increases the number of functional HDL particles and, therefore, increases the rate of transport through the RLT pathway, leading to greater significant cholesterol elimination (SAMBA study).

The CHI SQUARE Phase II study was conducted between March 2011 and January 2014 on 507 subjects immediately after an ACS event, with 6 administrations of CER-001 or placebo. The data from this study enabled selection of a dose (3 mg/kg) for which we observed a statistically significant reduction compared to placebo for total atheroma volume of the coronary artery, measured by intravascular ultrasound (IVUS) in the subpopulation who most closely followed the study protocol. These analyses show the interest in continuing clinical studies to demonstrate the efficacy of CER-001 as a short-term treatment for atherosclerosis.

- A phase II, placebo-controlled study, CARAT (CER-001, Atherosclerosis Regression ACS Trial) was recently completed and the full analysis of the results should be available during the second semester of 2017. Its objective was to maximize the therapeutic efficacy of CER-001 by increasing the number of 3 mg/kg doses in post-ACS patients. A total of 301 post-ACS patients were included and allocated at random in a 1:1 ratio to the placebo group or the group treated with CER-001, and who received 10 administrations over 9 weeks, one administration per week. The primary objective of the clinical study was the reduction in the percent atheroma volume (PAV) measured by coronary artery IVUS imaging. The CARAT study confirmed the safety and tolerability profile of CER-001, however, the primary objective of the study was not achieved (reduction of the atheroma plaque within the coronary arteries evaluated by the IVUS imaging method). Other analyses such as virtual histology of coronary arteries are underway.

Should the efficacy of CER-001 be confirmed in the TANGO clinical study for the treatment of patients suffering from HDL deficiency, it could be envisaged to assess the interest of a phase III study of secondary prevention of cardiovascular events, CALMS.<sup>48</sup>

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<sup>47</sup> 2015 Update of the Heart Disease and Stroke Statistics, published by the American Heart Association - <http://circ.ahajournals.org/content/early/2017/01/25/CIR.0000000000000485>.

<sup>48</sup> CALMS: CER-001, ApoA-I containing HDL mimetic, Lowering Morbidity/Mortality Study », study of decreasing morbidity and mortality through CER – 001, a mimetic of HDL containing apoA-I.



### 6.3.5.1. Completed dose-response study: CHI SQUARE

CHI SQUARE was the first multidose study with CER-001, a multicenter, Phase II clinical study performed in the United States of America, Canada, the Netherlands and France to evaluate the effect of CER-001 on the atherosclerotic plaque burden in post-ACS patients.

The aim of this study was to evaluate the impact of 6 administrations of 3, 6 or 12 mg/kg of CER-001 or placebo administered on a weekly basis, on the volume of the atherosclerotic plaque in subjects who experienced an ACS event. This impact was measured by coronary IVUS imaging.

A total of five hundred and seven (507) subjects were included and randomly allocated in each group of this multicenter, double-blind study. The subjects were treated in three sequential cohorts, each cohort receiving increasing doses of CER-001 and compared with placebo (Figure 16). For each patient, a series of six doses was administered at an interval of at least seven days between doses.

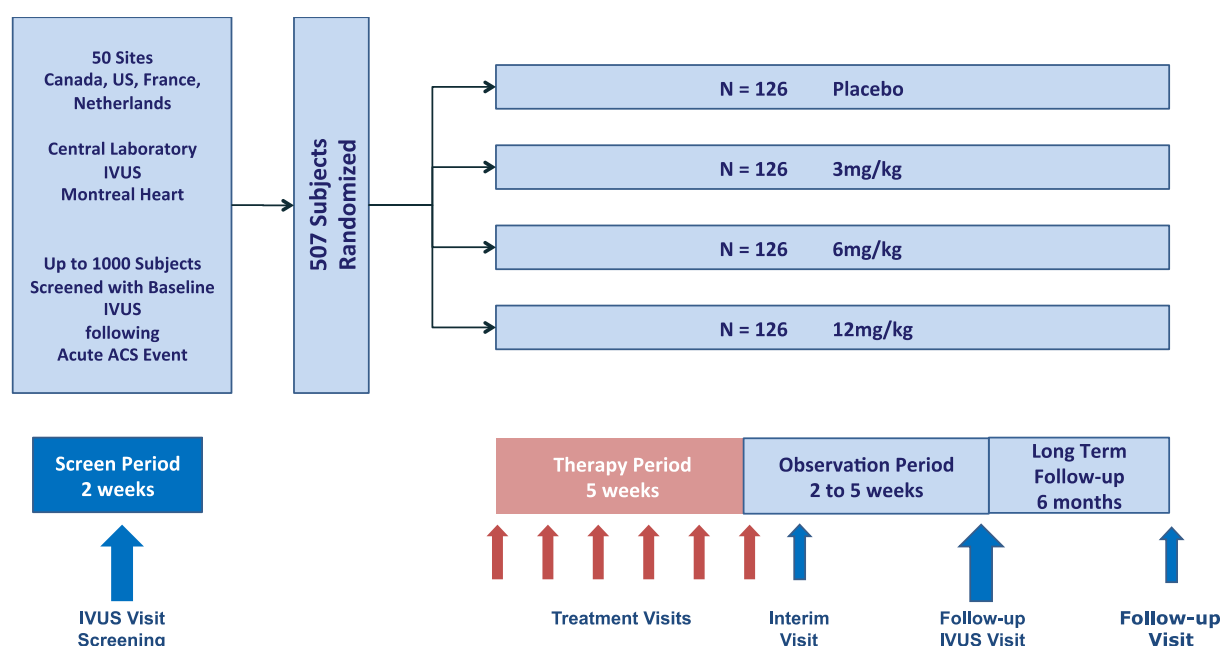


Figure 16: CHI SQUARE study

The biochemical results show that CER-001 increases total cholesterol, non-esterified cholesterol, phospholipids and apoA-I levels, when measured one hour after the end of each administration. These levels were significantly different from those observed with placebo. The effect of the treatment was maintained up to the sixth administration; no attenuation of efficacy was indicated over time.

An initial analysis of the CHI SQUARE study, during which three different doses, 3, 6 and 12 mg/kg, were tested, was performed by the Montreal Heart Institute (Jean-Claude TARDIF, MHI, Canada<sup>49</sup>) and did not reach statistical significance for the primary endpoint of the study as defined as a reduction of total atheroma volume at 12 mg/kg vs placebo. However, this study showed cholesterol mobilization by CER-001 at every dose tested (3, 6 and 12 mg/kg) as well as a good patient safety profile. Nonetheless, reduction in total atheroma volume vs. baseline proved to be statistically significant at 3 mg/kg demonstrating that CER-001 was more efficacious when given at low dose several times rather than given at high dose.

<sup>49</sup> Tardif, J-C., et al. Effects of the high-density lipoprotein mimetic agent CER-001 on coronary atherosclerosis in patients with acute coronary syndromes: a randomized trial. Eur. Heart J. 2014, 43, 1-10.

This study was therefore supplemented by an independent and blinded analysis of the same raw data by the South Australian Health and Medical Research Institute (Dr. Stephen Nicholls, SAHMRI in Adelaide, Australia<sup>50</sup>) by following a methodology developed and validated for statins. These two analyses taken together enabled defining an optimal dose (3 mg/kg), resulting in a marginally significant change in PAV, and demonstration of a similar safety profile for CER-001 and placebo.

To elaborate, SAHMRI undertook its analysis independently and in a blinded manner from the same full set of raw IVUS images for each patient (using the analysis technique implemented by Dr. Steve Nissen in the Cleveland Clinic and validated in the statin clinical trials<sup>51</sup>).

For this analysis, the lowest dose of 3 mg/kg attained statistical significance versus placebo for the change in total atheroma volume (TAV) in the modified per protocol population (mPP) (Table 1). At the same dose of 3 mg/kg, the change in percent atheroma volume (PAV) versus placebo was marginally significant (Table 2). The statistical significance of differences in TAV or PAV versus placebo was not demonstrated for the mid- and high-dose groups of CER-001. Moreover, in patients for whom baseline PAV was equal or superior to 30, the lowest dose of 3 mg/kg had obtained statistical significance versus placebo for the change in total atheroma volume (TAV) and the change in percent atheroma volume (PAV) for all patients (mITT) (Table 3, Figure 17).

**Table 1: Change in total atheroma volume (TAV) - CHI SQUARE: modified per protocol population.**

Parameter	Placebo N = 75	3 mg/kg N = 73	6 mg/kg N = 78	12 mg/kg N = 70
Baseline TAV (mm <sup>3</sup> ) (median)	151.9 (106.9 – 189.8)	122.4 (96.7 – 160.3)	137.1 (105.7 – 177.6)	146.0 (99.3 – 167.4)
Change in TAV (mm <sup>3</sup> )	-3.17	<b>-5.62</b>	-3.10	-1.73
p-value vs. baseline	0.089	< 0.001	0.009	0.302
p-value vs. baseline (RNK)		<b>0.04</b>	0.41	0.71

Abbreviations: RNK = ranked p-value for non-parametric test, TAV = total atheroma volume

**Table 2: Change in percent atheroma volume (PAV) - CHI SQUARE: modified per protocol population.**

Parameter	Placebo N = 75	3 mg/kg N = 73	6 mg/kg N = 78	12 mg/kg N = 70
Baseline PAV (%) (median)	37.2 (30.4 – 42.4)	34.2 (28.9 – 39.6)	37.6 (28.9 – 43.0)	36.8 (29.4 – 42.8)
Change in PAV (%)	-0.11	<b>-0.69</b>	-0.31	0.33
p-value vs. baseline	0.962	0.025	0.231	0.246
p-value vs. baseline (RNK)		<b>0.05</b>	0.28	0.48

Abbreviations: RNK = ranked p-value for non-parametric test, PAV = percent atheroma volume

<sup>50</sup> Presentation at the 2014 Annual Scientific Meeting of the International Society of Cardiovascular Pharmacotherapy, Adelaide, Australia

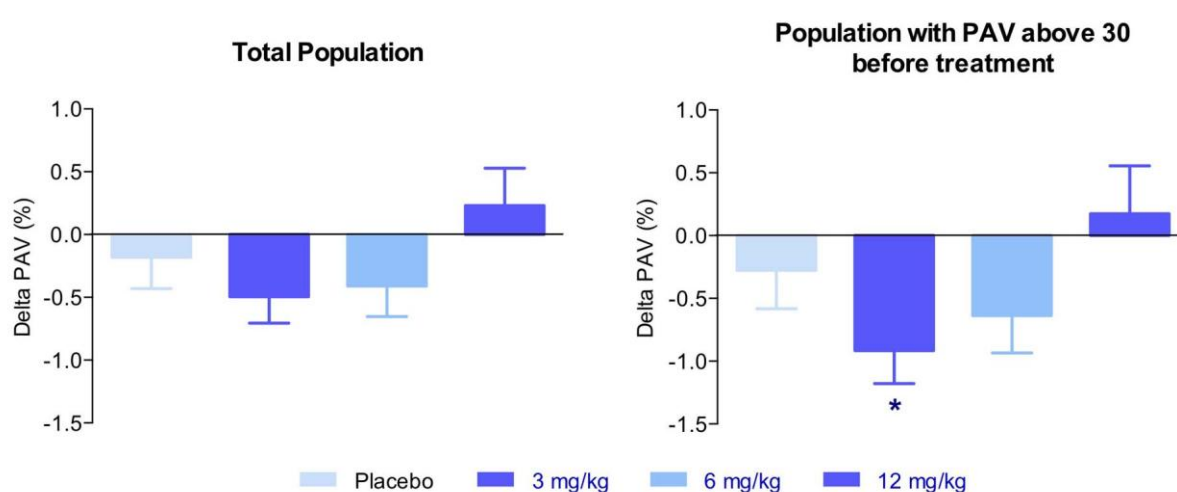
<sup>51</sup> Kataoka, Y., et al. Greater Regression of Coronary Atherosclerosis With the Pre-Beta High-Density Lipoprotein Mimetic CER-001 in Patients With More Extensive Plaque Burden. 2015. [AHA](#) Orlando, FL USA, Circulation. 132. A12156

**Table 3: Change in percent atheroma volume (PAV) and total atheroma volume (TAV) in patients with a baseline PAV greater or equal to 30 – CHI SQUARE: mITT population, N=271.**

Parameter	Normality Test		Averages LS and p-value according to ANCOVA model						
	W	p-value	Placebo (n=69)	3 mg/kg (n=58)	p-value†	6 mg/kg (n=78)	p-value†	12 mg/kg (n=66)	p-value†
PAV	0.927	< 0.0001	-0.259	<b>-0.963</b>	<b>0.038*</b>	-0.619	0.287	+0.177	0.587
TAV	0.986	0.009	-2.744	<b>-6.258</b>	<b>0.035*</b>	-3.429	0.500	-2.726	0.927

† Non-parametric ANCOVA model based on data classification using baseline values as covariate. The non-parametric test was used because the Shapiro-Wilk normality test has a p-value < 0.05.

\*Statistically significant result



**Figure 17: PAV graphical representation from Table 3**

### *Dose-response mechanism*

Preclinical experiments performed by Cerenis have demonstrated that an inverse dose-response curve mechanism exists (a higher dose can be less effective by hindering response) and is due to down-regulation of ABCA1 at high drug doses.

This mechanism, reduced response with higher doses was also observed in the CHI SQUARE study and other atherosclerosis regression clinical studies performed with HDL mimetics: ABCA1 acts as a “Sentinel/transporter” controlling the outflow of cholesterol from macrophages loaded with cholesterol in the plaque and is well known for its role in plaque regression (see Figure 18 below):

## Percent of regression of atheroma plaques in carotids

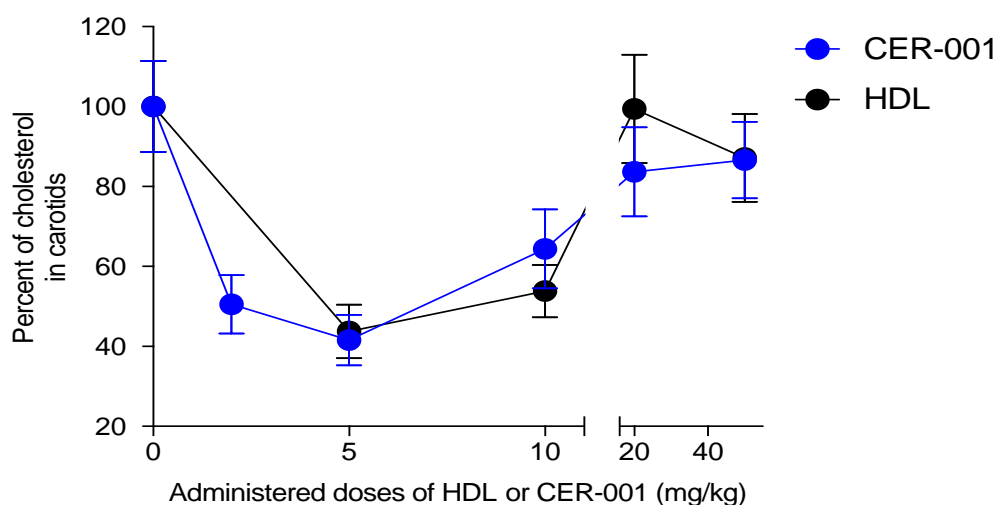


Figure 18: Percent regression - CER-001 behaves like a natural HDL

Data from the preclinical model subject of a scientific publication<sup>52</sup> and a pending patent application, demonstrated that high doses of CER-001 lead to significant and rapid negative regulation of ABCA1 both *in vitro* and *in vivo*. The intensity of the negative regulation has a direct consequence on the reduction of plaque size in the preclinical model. Therefore, for a natural HDL particle or an HDL mimetic such as CER-001 to have a full and effective action on cholesterol removal from the vessel wall, we considered it necessary to limit the dose (3 mg/kg of CER-001 in the clinic for post-ACS patients) in order to maximize the regression of atherosclerotic plaque by minimizing down-regulation of ABCA1.

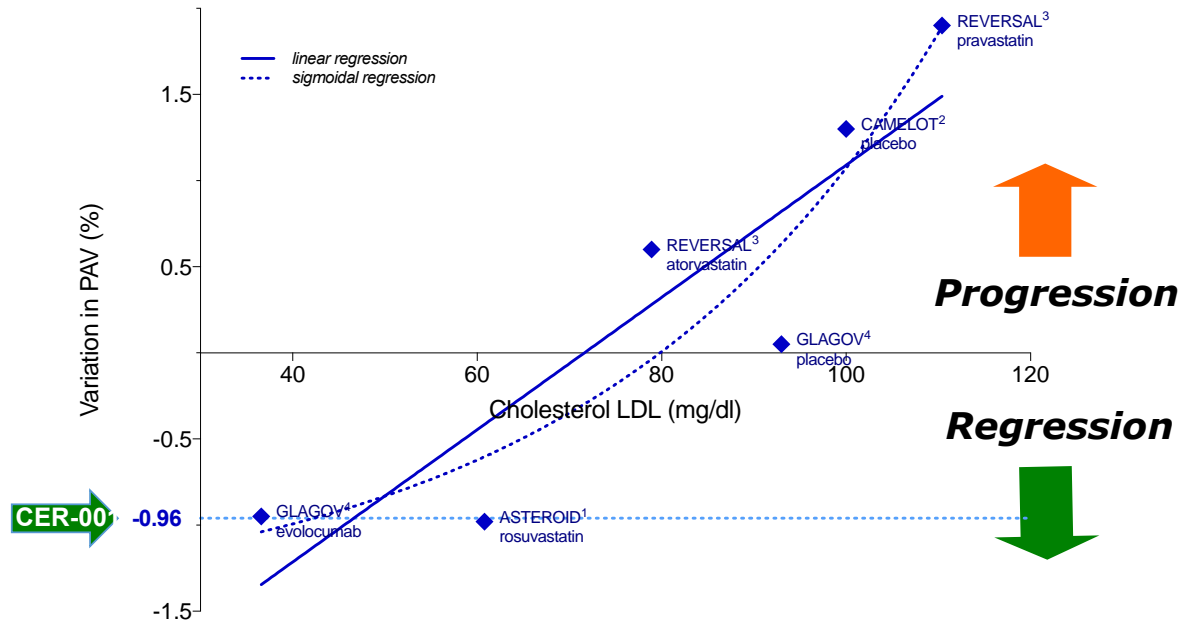
Significant lessons were drawn from CHI SQUARE and validated the clinical relevance of CER-001:

- The dose of 3 mg/kg was the best dose of the three doses tested in the CHI SQUARE study; these data provided a path to follow for CER-001 in secondary prevention post-ACS applications.
- The result on TAV confirmed and exceeded the results on efficacy of plaque regression observed in the Esperion trial with apoA-I<sub>Milano</sub>.<sup>53</sup> In that trial, a 4.2% TAV reduction versus baseline had been observed; this reduction was statistically significant versus baseline, but not versus placebo, likely because of the small study size. The 4.6% reduction in plaque volume versus baseline, observed with the 3 mg/kg CER-001 dose in the mPP population was statistically significant not only versus baseline but also versus placebo. Therefore, in CHI SQUARE the extent of TAV reduction versus baseline in patients treated with CER-001 in the mPP population was comparable to the percentage observed with ETC-216, and is also statistically significant versus placebo – **a result that confirmed and exceeded the results of the study with apoA-I<sub>Milano</sub>**.
- The atheroma volume measured by IVUS is considered as a predictor of the reduction in cardiovascular events in large-size trials (Figure 19). The 0.69% PAV reduction versus baseline in the treatment group at 3 mg/kg of CER-001 was clinically significant with regard to other

<sup>52</sup> Tardy, C. et al. PLOS ONE, 2015 – DOI :10.1371/journal.pone.0137584

<sup>53</sup> Nissen, S.E., et al Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA, 2003,290, 2292-300.

treatments, especially when we consider that these changes were observed in only five weeks, instead of 18-24 months for the statins (as in the Asteroid study) in naive patients (having never received this kind of treatment) and 18 months with Repatha®, a PCSK9 antibody. The 0.69% PAV reduction was observed in patients who were already following maximum statin treatment according to current medical recommendations.



1 Nissen S et al. N Engl J Med 2006; 354:1253-1263. 2 Tardif J et al. Circulation 2004; 110:3372-3377.  
3 Nissen S et al. JAMA 2006;295 (13): 1556-1565. 4 Nissen S et al. JAMA 2004;292:2217-2225.  
5 Nissen S et al. JAMA 2004; 291:1071-1080. 6 Nicholls S et al. JAMA 2016 ; 2373-2384

Figure 19: PAV reduction (CHI SQUARE)

The main conclusions of CHI SQUARE to consider for future development were the following:

- The independent/blind analysis made by SAHMRI has enabled determination of a dose of CER-001, which showed a statistically significant reduction in coronary plaque versus placebo (3 mg/kg).
- Rigorous and regular sampling along the target vessel by the IVUS imaging method was an essential prerequisite for a representative analysis in order to obtain a precise evaluation of efficacy.
- The demonstration of clinical benefit by IVUS despite relatively low baseline volume of plaque was supposed to increase the probability of success of the next clinical trials.
- A dose of 3 mg/kg of CER-001 was clinically (according to IVUS) equivalent (based on PAV) to a dose of 15 mg/kg of ETC-216.
- Mobilization of cholesterol by CER-001 at 3 mg/kg (3%) similar what was observed with ETC-216 at 15 mg/kg (2%) confirmed the 5-7 times higher potency of CER-001 compared to ETC-216 (presentation by Dr. Herman Kempen, at the HDL workshop - Toronto, May 2014)
- Doses of CER-001 higher than 3 mg/kg did not increase efficacy but reduced it.

- This confirmed the observations of the study with ETC-216 by IVUS where the highest dose was found to be less effective.<sup>54</sup>
- CER-001 has enabled identification of the molecular mechanisms of maximizing the effect on the plaque.
- CER-001 was well tolerated at all doses. The data from all clinical studies performed by Cerenis confirmed a significant safety margin for the 3 mg/kg dose.

#### **6.3.5.2. Study aimed at defining the number of administrations: CARAT**

As it is often necessary in clinical development, a Phase II program in two stages permits determination of the dose regimen for the drug candidate, in this case CER-001, to subsequently be used in Phase III clinical trials in post-ACS patients. As indicated above, the first stage, already completed with the CHI SQUARE study, provided several safety data for a range of doses and identified the optimal dose, i.e. 3 mg/kg.

In the second stage, Cerenis hoped to confirm the number of doses to administer to post-ACS patients based on the main lessons drawn from long-term studies (SAMBA and MODE) already performed, i.e. that an intensive administration schedule of more than 6 administrations leads to a more significant clinical benefit.

Thus, Cerenis has completed CARAT, a study to determine the number of administrations using the imaging IVUS method, in order to evaluate the additional benefits that may be gained by increasing the number of CER-001 administrations to 10, instead of the 6 administered in CHI SQUARE.

In this placebo-controlled, two-group study called CARAT in 301 ACS patients, a dose of 3 mg/kg of CER-001, which was shown to reduce atherosclerotic plaque in the CHI SQUARE analysis by SAHMRI, was tested in a treatment regimen of 10 CER-001 administrations over 9 weeks (instead of 6 administrations over 5 weeks used in the CHI SQUARE dose finding study) (Figure 20). The study was conducted in four countries (Australia, Hungary, United States and the Netherlands).

The primary endpoint of the study was the change in percent atheroma volume (PAV) versus placebo in the whole population, as set out in the CARAT protocol, in a statistically significant manner.

Prof. Stephen Nicholls was the principal investigator with a steering committee composed of Prof. Stephen Nissen (Cleveland Clinic, United States), Prof. John Kastelein (Academic Medical Center, Amsterdam, Netherlands), Prof. Kausik Ray (Professor of Public Health, Department of Primary Care and Public Health, Imperial College London, London, United Kingdom), Prof. Gregory Schwartz (Professor of Medicine, University of Colorado, Denver, United States), Prof. Béla Merkely (Cardiac and Vascular Centre, Semmelweis University, Budapest, Hungary) and Prof. Stephen Worthley (CVIU, Royal Adelaide Hospital, Adelaide, Australia).

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<sup>54</sup> Nissen, S.E., et al Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA 2003, 290, 2292-300.

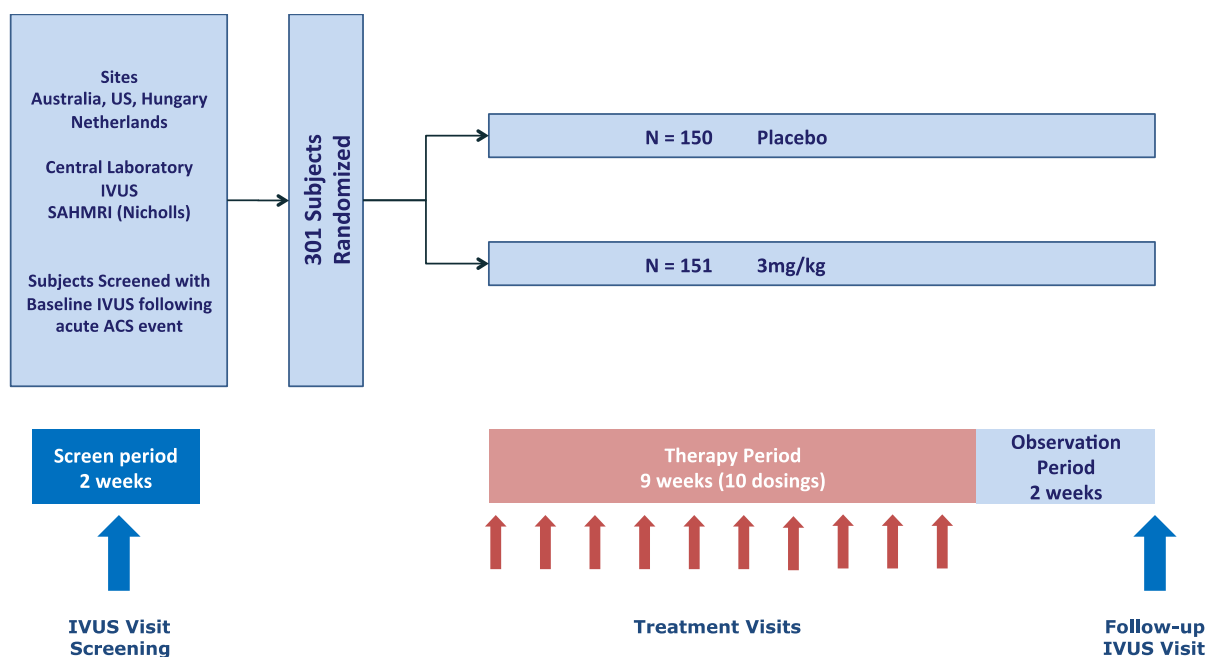


Figure 20: Design of the CARAT study

The major innovations that were included in the design of the CARAT study were the following:

- Recruitment of patients with a high atherosclerotic plaque burden.
  - The selection of a population of patients with a higher plaque volume was supposed to increase the treatment outcome versus baseline, giving more “margin” to show by IVUS regression of the plaque induced by CER-001.<sup>55</sup>
  - It has been demonstrated that a larger baseline plaque volume enables better measurement of the change induced by treatment.<sup>56</sup>

<sup>55</sup> Nicholls, S.J., et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome JACC 2010, 55, 2399-407.

<sup>56</sup> Nicholls, S.J., et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome JACC 2010, 55,2399-407.

- Administration of the optimal dose (3 mg/kg) more frequently.
  - The dose-response curve data indicated that it was preferable to have more administrations at the optimal dose of CER-001, rather than a lower number of administrations at a higher dose.
  - An increase in the number of total administrations from 6 to 10 was intended to sustain the increase of the treatment effect on the primary aim of the study, based on what was observed in SAMBA and MODE.
  - The data on chronic use from the SAMBA and MODE trials suggested the safety of additional doses (data confirmed through the CARAT study).

## 6.4. Treatment of FPHA by CER-001, an opportunity to enter the market in the short-term

### 6.4.1. Molecular and genetic basis of FPHA

Hypoalphalipoproteinemia (“deficiency or absence of HDL”) is a general term defined clinically as a disease where the level of HDL-cholesterol is lower than 40 mg/dl (1.0 mmol/l) in men, or 50 mg/dl (1.3 mmol/l) in women.

In a very small percentage of the population, in particular in patients with the lowest levels of HDL cholesterol, there are patients affected with a genetic defect that changes the elements which are part of the composition of HDL particles, the process of synthesizing pre- $\beta$  HDL particles, the maturation steps to obtain mature HDL particles, or the levels of catabolism (the natural destruction and elimination) of HDL. These are patients with primary familial hypoalphalipoproteinemia, a group of genetic diseases as the adjectives “primary and familial” indicate. Any of these defects, alone or in combination with others, may be the cause of a very low number of circulating HDL particles. These are patients who are at the very highest risk of cardiovascular disease as a consequence of having a virtually absent endogenous RLT pathway.

Patients with FPHA have HDL-cholesterol levels usually below the 1<sup>st</sup> percentile, and have often experienced premature cardiovascular events.

FPHA is defined by:

- A clinical criteria: a level of apoA-I lower than 70 mg/dl compared with a normal concentration of apoA-I of approximately 140 mg/dl<sup>57</sup>; and/or
- a genetic criteria reflected by:
  - either a known defect in one of the genes responsible for synthesis or maturation of HDL particles, and/or
  - a family history of low HDL-cholesterol levels or of early cardiovascular disease.

In the absence of an identifiable metabolic disorder, genetic causes are thought to be the most likely explanation of extremely low apoA-I levels/HDL particle numbers. All of the genetic causes of the deficiency in HDL particles have not yet been fully characterized. Nevertheless, mutations in the

<sup>57</sup> Junger, I. et al., Apolipoprotein B and A-I values in 147576 Swedish males and females, standardized according to the World Health Organization-International Federation of Clinical Chemistry First International Reference Materials. Clin. Chem. 1998, 44, 1641-8.



genes coding for proteins critical for HDL metabolism resulting in a decrease in the number of circulating HDL particles have been identified. These proteins are:

- **apoA-I, the HDL structuring protein:** deficiency in apoA-I is debilitating and chronic because it results in a severe HDL deficiency.
- **ABCA1, the protein controlling the efflux of cellular cholesterol:** mutations in the gene coding for ABCA1 lead to defective or non-functional proteins resulting in severely decreased levels of HDL cholesterol. Tangier disease is the result of a mutation affecting the two homologous chromosomes.
- **lecithin-cholesterol acyltransferase (LCAT) catalyzes esterification of cholesterol:** LCAT enables cholesterol to anchor itself more strongly in the HDL particle; its deficiency prevents HDL particle maturation.<sup>58</sup> A total deficiency in LCAT is called “familial LCAT deficiency” and if it is partial, it is called “fish-eye disease.”

These mutations result in a deficiency in apoA-I and a reduction in the level of circulating HDL particles, causing absent or deficient RLT capacity, and as a result, accumulation of cholesterol in peripheral tissues (which causes development of early cardiovascular diseases regardless of LDL-cholesterol levels<sup>59</sup>).

#### 6.4.2. Epidemiology and prevalence of FPHA in North America and Europe

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The absence of available treatment specifically for FPHA has resulted in limited screening for this deficiency: patients were identified only when they presented with an early cardiovascular event or when a family member who experienced a cardiovascular event was found to have a low number or no HDL particles. Thus, many patients with low numbers of HDL particles remain undiagnosed until a triggering event occurs which brings them to the attention of expert medical professionals.

The NHANES III database provides apoA-I concentration data from 12,869 American subjects, which forms a representative sample of the US civilian population in terms of apoA-I concentration and the number of HDL particles. By grouping all subjects with a phenotype of low number of HDL particles, with the criterion of apoA-I level lower than 70 mg/dl, the prevalence of the subjects affected is 39/100,000 (0.039%) with a similar prevalence determined for the European population.

Consequently, patients grouped under the generic term FPHA represent a population of a rare disease estimated by Cerenis at approximately 100,000-150,000 subjects in the United States and Europe.

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<sup>58</sup> Saeedi R., et al. A review on lecithin: cholesterol acyltransferase deficiency. Clin. Biochem. ePub (2014).

<sup>59</sup> Harchaoui, K., et al. Abstract 1099: Reduced Fecal Sterol Excretion in Subjects with Low HDL Cholesterol Levels. Circulation. 2007;116:II\_220. and Reduced fecal sterol excretion in subjects with familial hypoalphalipoproteinemia. Atherosclerosis; 2009;207:614–6, Glueck, C.J. et al., Familial hypoalphalipoproteinemia. Adv Exp Med Biol. 1986, 201:83-92; Gordon, T., et al., High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study Am J Med.;62:707-14 (1977).

## Number of individuals versus plasma apoA-I concentration

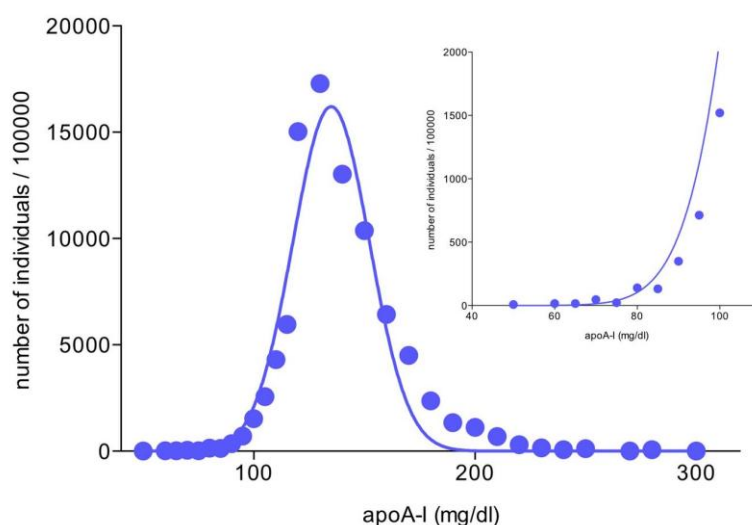


Figure 22: Distribution of ApoA-I concentration in the US population<sup>60</sup>

Within this population, the population corresponding to identified genetic mutations was estimated by the European Medicines Agency (EMA) based on the only existing publications justifying the populations for the two orphan drug designations granted to Cerenis. The prevalence of homozygous/heterozygous apoA-I deficiency ( $<0.01/10,000$ ) is estimated at approximately 500 persons in Europe. Similarly the prevalence of homozygous/heterozygous ABCA1 deficiency ( $<0.01/10,000$ ) is estimated at approximately 500 persons in Europe. Homozygous LCAT deficiency alone (i.e., without heterozygous patients) is estimated at approximately  $0.001/10,000$ , or approximately 50 persons in Europe.<sup>61</sup>

These results support the conclusion that FPHA patients with genetic defects resulting in HDL deficiency, represent a truly unique clinical population with an important unmet medical need.

### 6.4.3. FPHA management

#### 6.4.3.1. Absence of specific treatment

To date there is no specific treatment for apoA-I deficiency, ABCA1 deficiency, or LCAT deficiency. No pharmaceutical product is currently authorized for the treatment of apoA-I deficiency, ABCA1 deficiency, or LCAT deficiency.

In August 2014, Cerenis received two orphan disease designations for the treatment of apoA-I and ABCA1 deficiencies.

CER-001 was shown to benefit LCAT-deficient patients, even in the absence of esterification. Cerenis intends to recruit this type of patients later in a clinical study in order to develop this indication.

<sup>60</sup> National Center for Health Statistics. Data files, documentation and SAS for NHANES III. Centers for Disease Control and Prevention website <http://www.cdc.gov/nchs/nhanes/nh3data.htm>

<sup>61</sup> Reference: EU/3/12/1051

An orphan disease designation (EU/3/12/1051) for the treatment of LCAT deficiency was granted to Alphacore Pharma Limited United Kingdom, on October 10, 2012 by the European Medicines Agency, for the use of recombinant human LCAT (ACP-501, MEDI-6012). However, the development of this product is still in the initial clinical trials stage for LCAT deficiency. Alphacore was acquired in April 2013 by Astra-Zeneca. The product, whose code is now MEDI6012, is currently being developed for the treatment of patients with stable atherosclerotic cardiovascular disease.<sup>62</sup>

Current management of FPHA patients is therefore very limited and focused on diet control and aggressive pharmacotherapy intended to decrease LDL cholesterol. There is no treatment currently available which can directly restore normal and functioning HDL particles.

#### **6.4.3.2. Limited effects of LDL lowering therapies**

As previously indicated, LDL therapies have demonstrated that they can reduce cardiovascular events by one third in populations with generalized atherosclerosis and have therefore become the standard of care in management of cardiovascular risk. Nevertheless, numerous FPHA patients have relatively “normal” levels of LDL cholesterol because their cholesterol imbalance is caused by a defect in cholesterol elimination rather than by an excess in transport of cholesterol by HDL particles. Intensive LDL-cholesterol lowering therapy will thus have a limited effect; consequently, a significant amount of residual cardiovascular risk remains unaddressed and can only be addressed by a specific chronic therapy specifically targeted at HDL, the only way to treat that can respond to HDL deficiencies of genetic origin.

#### **6.4.4. Therapeutic rationale**

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The principle therapeutic premise for the FPHA treatment is that the underlying imbalance in the RLT pathway is treatable by a replacement therapy using pre- $\beta$  HDL particles containing bioengineered human recombinant apoA-I designed by bio-engineering. The rationale for HDL mimetic therapy is that re-establishment of cholesterol flow through the RLT pathway should lead to elimination of cholesterol accumulated in the vascular walls and reduction in cardiovascular events as well as other deficiency symptoms.

#### **6.4.5. Two orphan drug designations were granted by EMA**

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In Europe, two orphan drug designations were granted to Cerenis for the use of CER-001; one is for the treatment of patients with ABCA1 deficiency and the other for those with apoA-I deficiency.<sup>63</sup>

Obtaining these orphan drug designations for Europe enables the Company to continue its research and benefit from financial advantages, help in defining the clinical studies protocols by the European Medicines Agency, and market exclusivity for a 10-year period once the drug is approved.<sup>64</sup>

If additional positive clinical data are obtained for LCAT deficiency, Cerenis could receive a third orphan drug designation.

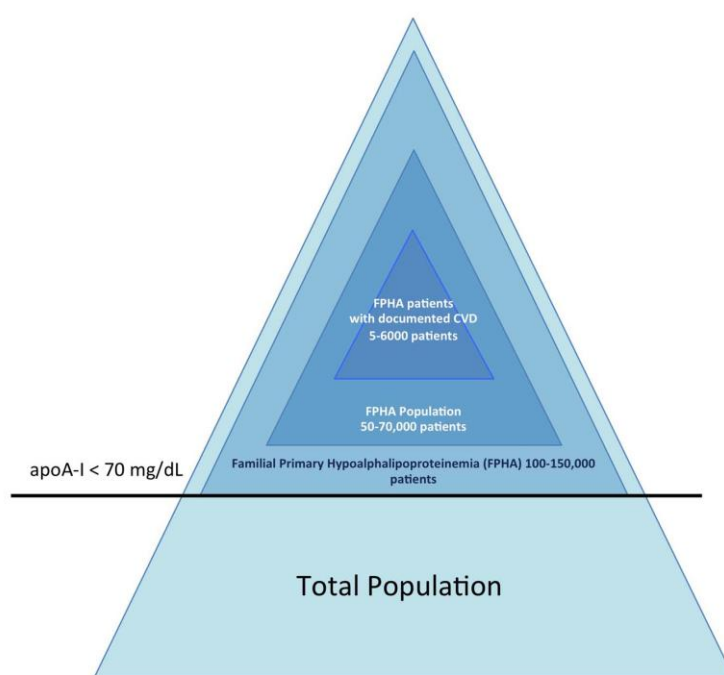
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<sup>62</sup> <https://clinicaltrials.gov/ct2/show/NCT03004638?term=MEDI-6012&rank=1>

<sup>63</sup> EMA/OD/063/14 and EMA/OD/064/14

<sup>64</sup> [www.emea.eu.int](http://www.emea.eu.int)

The nested sub-groups of FPHA patient populations are represented below:



**Figure 23: Ascertainable FPHA population**

Of the total population estimated by prevalence, i.e. 100-150,000 persons, the FPHA population, characterized by a deficiency in apoA-I and genetic defects, is estimated at 50-70,000 patients for Europe and North America (*“Assessment of CER-001 in FPHA”* study, performed by DefinedHealth in June 2014 at 40 specialized sites in the United States), with the understanding that not all genetic defects have been identified to date.

On the basis of this same study and the data communicated by the interviewed specialists, a population of 5-6,000 patients (including 60% in North America and 40% in Europe) with a genetic defect in the genes coding for apoA-I, ABCA1 and/or LCAT, was estimated and, to date, forms the first patients who have already been identified and who can be treated once approval is granted.

#### **6.4.6. Clinical development and approval strategy for FPHA**

Cerenis is developing CER-001 to treat patients with defects in HDL particle synthesis or maturation (FPHA). To accelerate the initial approval of CER-001, Cerenis is seeking approval in a narrow, targeted, genetically-confirmed FPHA population with a known history of coronary disease.

To date, the development program of CER-001 for FPHA consists in two completed studies:

- one Phase I study completed in healthy volunteers and
- one proof-of-concept Phase II study (SAMBA) in subjects with known genetic defects in HDL particle synthesis or maturation (see section 6.2.1 of this chapter).

Cerenis is currently conducting TANGO, a phase III study in a larger number of patients with FPHA.

#### 6.4.6.1. Characteristics of the ongoing Phase III study

This Phase III study (TANGO) will support CER-001 approval for treating patients with genetically defined FPHA (apoA-I and ABCA1 deficiencies).

The study is being conducted in the US, Canada, Israel and in Europe. The TANGO trial is a multicenter, double-blind study versus placebo of the effects of chronic use of CER-001 on apoA-I and the vascular wall in 30 subjects with genetically-defined FPHA (apoA-I deficiency and ABCA1 deficiency).

The objective of the study is to assess the impact of 6 months of treatment with CER-001 on the mean vascular wall area (MVWA) of the carotid artery as determined by MRI, when administered to subjects with genetically-defined apoA-I deficiency and ABCA1 deficiency), with a history of coronary heart disease, and evidence of carotid vessel wall thickening.

During the induction phase, subjects receive a placebo or CER-001 (8 mg/kg) once weekly for 8 weeks (total of 9 doses), followed by a 16-week maintenance period of bi-weekly administration. In the safety phase that immediately follows the maintenance phase, subjects will continue bi-weekly administration in the same treatment group for an additional 24 weeks (Figure 24).

Given that the effect of CER-001 on the removal of cholesterol from the periphery is independent and incremental with each dose, administration of the same number of doses as in SAMBA but administered once weekly should be sufficient to achieve the same therapeutic effect during the induction phase. The bi-weekly regimen for the maintenance phase in this study is identical to that employed in SAMBA, which showed a persistent and cumulative benefit from the additional doses.

Cerenis will use 3 Tesla Magnetic Resonance Imaging (3TMRI) to investigate changes in atherosclerotic plaque, using quantitative measurements in the carotids.

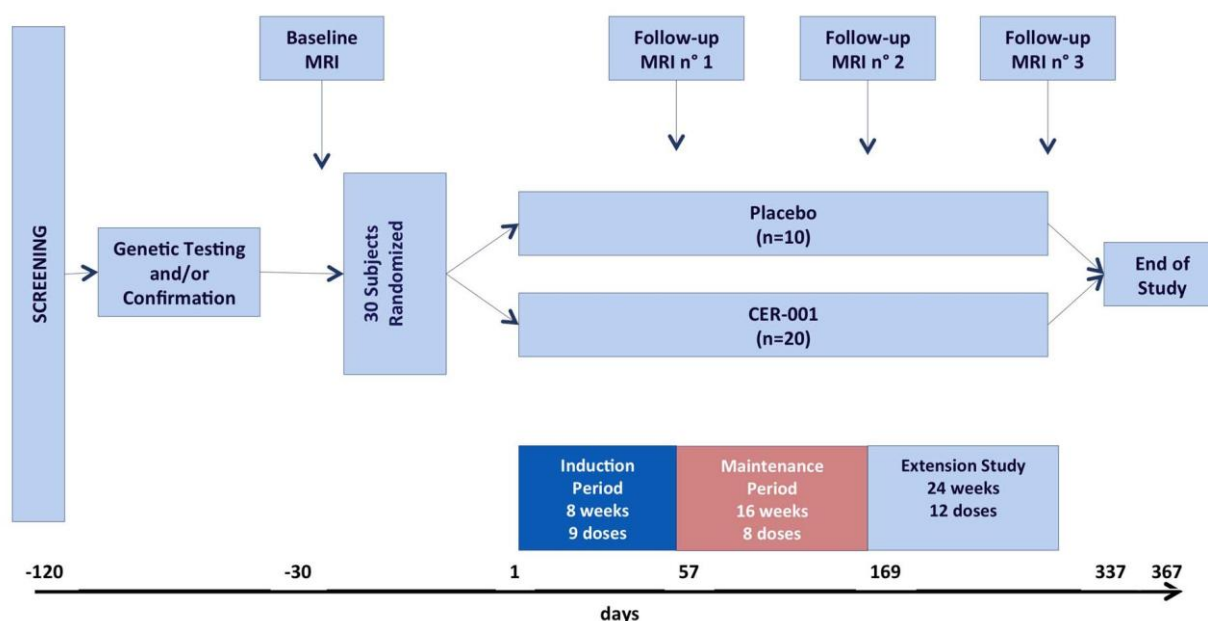


Figure 24: Design of the TANGO study

The design of the study was established in close collaboration with the main experts in the field, namely Profs. John Kastelein and Erik Stroes (Academic Medical Center, Amsterdam, the Netherlands) and during meetings with the scientific councils of various European regulatory agencies. The challenges in recruiting patients with these rare conditions were well recognized,

and it was confirmed that a cardiovascular morbidity and mortality study in FPHA is not possible with CER-001 in these patients because of the small FPHA patient population.

The enrollment of the first patient occurred in December, 2015. The primary endpoint should be available by the end of 2017.

#### 6.4.6.2. Safety and tolerability profile

Although in TANGO the efficacy assessment of CER-001 is based on a small sample size (because of the small number of patients), a large safety database is available, that includes all patients already treated in the clinical studies conducted to date by Cerenis<sup>65</sup>:

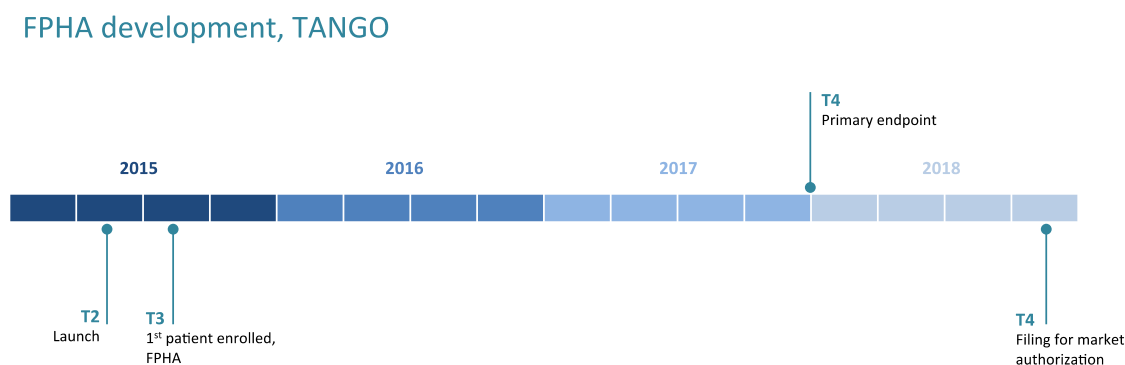
- 591 subjects in total have received at least one dose of CER-001 (out of TANGO which is on-going and blinded);
- more than 4,000 doses of CER-001 have been administered during the phase II studies (not including TANGO, which are ongoing blinded studies);
- CER-001 was generally well tolerated at all doses, in all subjects, with a profile of adverse events similar to placebo;
- no safety issues that would prevent continued development have been identified during examination of the currently available data.

The available safety database is considered sufficiently robust to support the chronic treatment of FPHA.

#### 6.4.7. Project schedule

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The timeline of the TANGO study that the Company is prepared to conduct in orphan diseases is as follows:



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<sup>65</sup> Poster presented at European Society of Cardiology congress in Rome, 2016 Clinical tolerability and safety of CER-001, a novel bio-engineered pre-beta HDL-mimetic, across the clinical development programme. A. Corsini et al.

## 6.5. Sale and marketing strategy

Cerenis' strategy is based on an innovative approach which relies on the accelerated development of an indication for an orphan/rare disease, FPHA, enabling a faster approval, and in parallel, development of the main indication, representing a considerable market, post-ACS prevention (post-cardiovascular event treatment, angina pectoris or myocardial infarction).

### *Direct market access for orphan diseases*

At the present time, Cerenis plans to market CER-001 directly for rare diseases in Europe. This marketing strategy is realistic and reasonable taking into account the position of CER-001, which initially targets orphan diseases (apoA-I deficiency and ABCA1 deficiency) and thereafter all FPHA patients, and indications managed by specialists. These specialists are identified, which only requires a relatively modest sales force to interact with them compared to what would be required for the primary care market (i.e. general practitioners).

Cerenis will be in a position to master pre-launch and launch activities of its first and best-in-class product by a strong and intense preparation of the market. To this end, Cerenis intends to progressively build up its sales force and strengthen its medical and scientific organization in preparation for the market launch for orphan diseases by mid-2018 (assuming that convincing data will translate to an accelerated review by regulatory authorities).

Cerenis has worked with rare disease experts to establish the Company's strategic plan for sales and marketing in Europe.

Cerenis will prepare based on the detailed strategy below:

- First step: recruitment of medical/scientific ambassadors (MSA) to enable contact with physicians from the centers specializing in lipids that treat FPHA patients and to train them on the key role of HDL particles and the RLT pathway in the progression and regression of atherosclerotic plaque.
- Second step: on the registration date of this Registration Document, the Company anticipates that preparation of the disease awareness campaign will be achieved by a team formed from the clinical development, medical and scientific affairs, and marketing departments. The main objective will be consolidation of the scientific and marketing message and subsequent preparation of promotional and presentation material, based on data from clinical studies and profile of the target product.
- Third step: create advisory councils in order to introduce key scientific leaders to the concept of reverse lipid transport as a therapeutic strategy in order to reinforce the positioning of CER-001 as "first and best-in-class".
- Fourth step: hire the first sales representatives within six months prior to the FPHA launch.
- Fifth step: Cerenis will evaluate opportunities for the North American market with a potential partner or through its own commercial organization, based on the regulatory strategy with FDA that will unfold going forward.

The global strategy bringing CER-001 to market for FPHA will therefore leverage the organization created for its marketing:

- First step: by proposing the first HDL-directed therapy to reach the market, Cerenis will bring an innovative therapeutic breakthrough in a domain devoid of specific therapies.
- Second step: Cerenis has conducted initial market research with prescribers, medication reimbursement authorities and payer organizations to help guide the assumptions used in its initial financial models and sales forecasts. Cerenis intends to build a team of pharmacoepidemiologists and pharmacoeconomists who will engage proactively with pricing and reimbursement authorities worldwide in order to demonstrate the value of CER-001 in cardiovascular disease to payers and authorities and to negotiate sales prices and reimbursement rates.

The application for market authorization of CER-001 for the treatment of orphan disease is planned for the second half of 2018 in Europe. Cerenis will work in parallel on the development for the North American market based on the discussions that have taken place with the FDA until then. In total, the target population for CER-001 is estimated at approximately 5,000 to 6,000 patients for Europe and North America, out of which 40% are in Europe.

In most countries, Cerenis expects market penetration of its product will be very rapid, given that these patients are identified by specialized lipid clinics at an early age (often with additional family members), and that their physicians, specialists in the field, are often the first to adopt new treatments due to the high intrinsic cardiovascular risk associated with this disease.

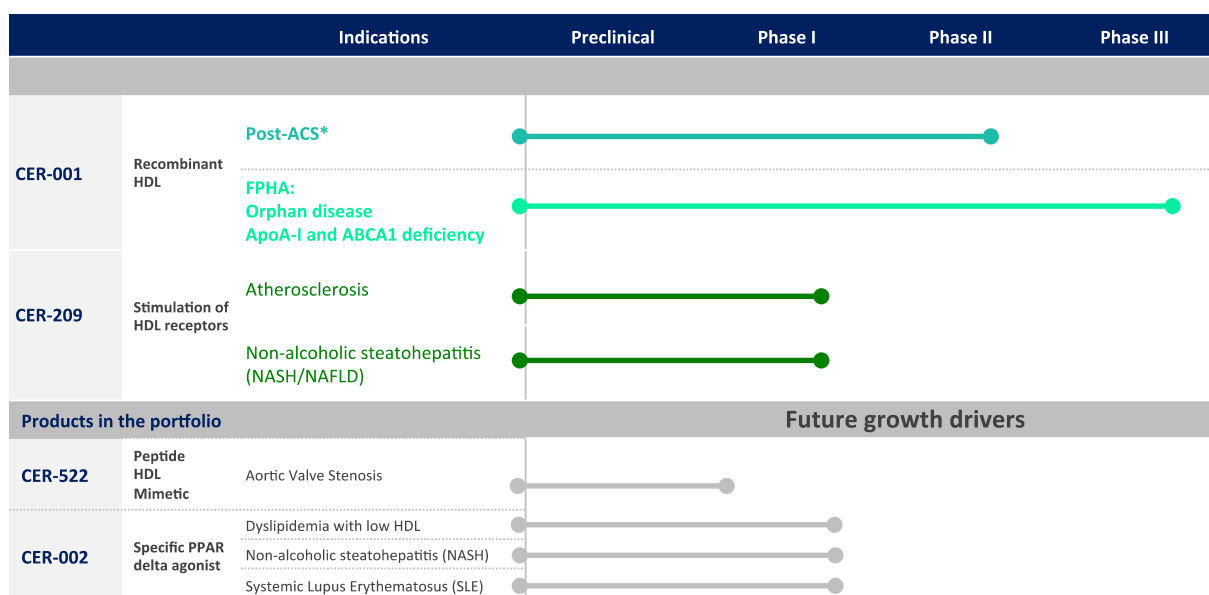
#### **6.6. A rich portfolio of innovative RLT THERAPIES**

Cerenis has developed a rich portfolio of innovative products with different mechanisms of action based on the RLT pathway that are at various stages of development.

These products under development address the treatment of cardiovascular diseases as well as the treatment of associated metabolic diseases such as non-alcoholic steatohepatitis (NASH).

The Company will focus its efforts on the success of CER-001 in the treatment of FPHA as well as on the clinical development of CER-209 following regulatory approval to initiate a Phase I clinical study of its P2Y<sub>13</sub> receptor agonist drug candidate (CER-209) in healthy volunteers for the clinical investigation of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). The programs will thereafter be enlarged thanks to the Company's product portfolio (cf. figure below).





\* The phase II study CARAT did not meet its primary endpoint (cf. to paragraph 5.1.5 and chapter 6). Thus the development for the ACS indication has been suspended until a full and detailed analysis is done in order to get a better understanding of the results obtained.

- CER-001:

- Familial hypercholesterolemia:

Another Phase II study (MODE) validated another potential use of CER-001, this time from the other end of the spectrum of cholesterol regulation mechanisms, namely for familial hypercholesterolemia (FH), a hereditary orphan disease characterized by a markedly elevated level of LDL cholesterol. Familial hypercholesterolemia is due to a genetic defect of LDL receptors resulting in accumulation of cholesterol in tissues, premature cardiovascular diseases, as well as a very elevated cardiovascular risk. This study met its primary endpoint, demonstrating a statistically significant reduction in carotid artery atherosclerosis after 6 months of chronic bi-weekly treatment.

- CER-522 is a peptide-based apoA-I analogue HDL mimetic and is being evaluated for the treatment of aortic valve stenosis.
- CER-209 is the first drug candidate in its category, oral P2Y<sub>13</sub> receptor agonists. Preclinical studies have shown that CER-209 acts on the last step of the RLT pathway, increasing HDL recognition by the liver and facilitating elimination of lipids in the feces, ultimately leading to regression of atherosclerotic plaque. Because of the favorable metabolic effects observed in the liver in preclinical experiments, CER-209 may also offer a new mechanism for the treatment of non-alcoholic steatohepatitis (NASH).
- CER-002, a selective PPAR-delta agonist, demonstrated its capacity to increase HDL levels in preclinical studies. CER-002 proved its excellent pharmacokinetic and safety profile in Phase I. Potential target diseases include metabolic syndrome, mitochondrial diseases, as well as systemic lupus erythematosus.

#### 6.6.1. CER-001: proof of concept in patients with familial homozygous hypercholesterolemia (FH)

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The absence or gross malfunction of the LDL receptors due to genetic defect impairs normal metabolism of circulating LDL (“bad cholesterol”), leading to severe elevations in total cholesterol and LDL cholesterol. The elevated LDL-cholesterol level from birth causes early narrowing of arteries due to the severe and generalized accumulation of atherosclerotic plaques. All of the major artery beds, in particular the carotid, coronary, iliac and femoral arteries, are affected. Familial hypercholesterolemia is characterized by premature occurrence of cardiac diseases.

Current management includes diet control and aggressive pharmacotherapy, primarily with statins, MPT inhibitors (microsomal triglyceride transfer protein) or PCSK9 inhibitors (antibodies against proprotein convertase subtilisin/kexin 9). Patients who present with very high LDL-cholesterol levels despite LDL-cholesterol lowering treatments (or who cannot tolerate them due to the side effects) are treated by LDL apheresis. This procedure filters the patient's blood through a machine (for 4 hours or more), separates the lipids from the other blood components and re injects the lipid-free blood into the patient, following a process similar to dialysis for renal diseases.

The MODE clinical study (Modifying Orphan Disease Evaluation, an evaluation of the change in an orphan disease) completed at the start of 2014 was a multicenter, open-label, Phase II pilot study intended as a proof of concept that CER-001 could regress atherosclerosis in homozygous FH patients.

Due to the anticipated need for chronic treatment in this population, a different dosing schedule from studies of post-ACS patients was chosen. The primary endpoint was the change in carotid artery mean vascular wall area (MVWA) after twelve IV infusions of 8 mg/kg CER-001, at biweekly intervals over 6 months, as measured by 3T MRI. 23 subjects were enrolled in the study.

The MODE study achieved its primary endpoint, demonstrating a statistically significant reduction in carotid artery atherosclerosis after 6 months of bi-weekly treatment. Considering a 10% greater level of plaque in patients compared to the normal population, the mean 2.53% reduction in the mean vascular wall area (MVWA) represents approximately 20% of the theoretical maximum that may be achieved long-term, which is clinically significant. Importantly, the cumulative benefits of twice weekly treatment with CER-001 were observed on top of LDL-lowering therapies, already being administered, allowing optimal management of lipids according to current medical recommendations, including LDL apheresis.

A scientific presentation of these results was recently made in the *Late Breaking Clinical Trials* section at the meeting of the European Atherosclerosis Society in Barcelona, Spain, in June 2014. The overall results are included in a publication entitled (*“The effect of an apolipoprotein A-I containing HDL mimetic particle (CER-001) on carotid artery wall thickness in patients with homozygous familial hypercholesterolemia”*) in the *American Heart Journal*.<sup>66</sup>

**In conclusion, CER-001 has demonstrated proof of concept in a disease at the other end of the spectrum of cholesterol regulation, namely a rare genetic disease causing extremely high LDL cholesterol levels, and demonstrated that HDL mimetic treatments can be complementary to LDL-cholesterol-lowering treatments.**

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<sup>66</sup> Hovingh, G. K. et al., The effect of an apolipoprotein A-I-containing high-density lipoprotein-mimetic particle (CER-001) on carotid artery wall thickness in patients with homozygous familial hypercholesterolemia: The Modifying Orphan Disease Evaluation (MODE) study *Am Heart J*. 2015 May; **169**(5):736-742.e1. doi: 10.1016/j.ahj.2015.01.008. Epub 2015 Jan 28.

CER-209 offers a new mechanism of action in the treatment of certain types of hepatitis.

#### **6.6.2.1. Background**

The discovery of F1-ATPase and P2Y<sub>13</sub> receptor (P2Y<sub>13</sub>r) in the liver that regulates elimination of HDL cholesterol improved the understanding of HDL metabolism and opened new pathways for the development of therapeutic approaches.<sup>67</sup> The P2Y<sub>13</sub> receptor is a well-known member of the family of the P2Y receptors including the P2Y<sub>12</sub> receptor, target of successful drugs such as the anti-thrombotic agent clopidogrel (Plavix®).

#### **6.6.2.2. Rationale**

By stimulating the activity of HDL receptors in the liver, elimination of cholesterol can be increased.

The stimulation of P2Y<sub>13</sub>r activity should promote HDL recognition by the liver and increase the activity of reverse lipid transport (RLT), and thus have an impact on atherosclerosis development. Thus, instead of “pushing” the cholesterol to the liver by increasing the number of HDL particles transporting cholesterol as Cerenis is doing with HDL mimetics, an increase in P2Y<sub>13</sub>r activity would result in better “traction” of HDL cholesterol being “pulled out” of the body by the increased activity of the liver receptors. Cholesterol removed from the bloodstream would then be eliminated from the body in the feces by the liver, leading to potential reductions in atherosclerosis.

Another potential benefit of this increase in P2Y<sub>13</sub>r activity would be an improvement in overall liver metabolism, given that the increased cholesterol flow to the liver would be accompanied by an increase in gallbladder secretion of cholesterol and lipids. This would result in a “healthier” liver.

#### **6.6.2.3. CER-209 a new “first in class” compound**

Cerenis has designed new P2Y<sub>13</sub>r-specific agonists (stimulators) with the potential to be first-in-class, including a series that contains CER-209 as well as other compounds. In toxicology studies, no sign of toxicity was identified in the preclinical studies at doses ranging up to 800 mg/kg/day. This result gives a favorable therapeutic index, because the pharmacological effects were observed at very low doses (less than 1 mg/g/day).

*In vitro* and *in vivo* tests demonstrated the increased recognition of HDL cholesterol by liver cells (hepatocytes).

Recognition by the liver causes a decrease in the HDL-cholesterol levels (mature HDL particles loaded with cholesterol) and is accompanied by a steady increase in gall bladder secretions, which in turn translates to a decrease in triglycerides and cholesterol levels of in the serum and in the liver.

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<sup>67</sup> Martinez, L. O., et al. Ectopic beta-chain of ATP synthase is an apolipoprotein A-I receptor in hepatic HDL endocytosis. *Nature* 2003, 421: 75-79; Jacquet, S., et al. The nucleotide receptor P2Y<sub>13</sub> is a key regulator of hepatic high-density lipoprotein (HDL) endocytosis. *Cell Mol Life Sci* 2005 62: 2508-2515.

#### 6.6.2.4. Indications

With proof of concept being established, two main independent indications are foreseen to be developed in parallel: atherosclerosis and non-alcoholic steatohepatitis (NASH).

##### 6.6.2.4.1. Atherosclerosis

The anti-atherosclerotic properties of CER-209 have been demonstrated in a preclinical atherosclerosis model.<sup>68</sup>

The agonist activity of CER-209 on the liver P2Y<sub>13</sub> receptor facilitates elimination of mature HDL particles loaded with cholesterol and is accompanied by compensation in the synthesis and an increase in the number of small circulating HDL particles. The increased recognition of mature HDL particles by the liver causes an increase in the secretion of bile acids, cholesterol and phospholipids by the gall bladder, causing an increase in elimination of cholesterol through the feces, which ultimately results in atherosclerosis regression. This concept was further validated by the demonstration *in vivo* of CER-209 specificity for the P2Y<sub>13</sub>r pathway using a validated preclinical model of atherosclerosis (Figure 25).<sup>69</sup>

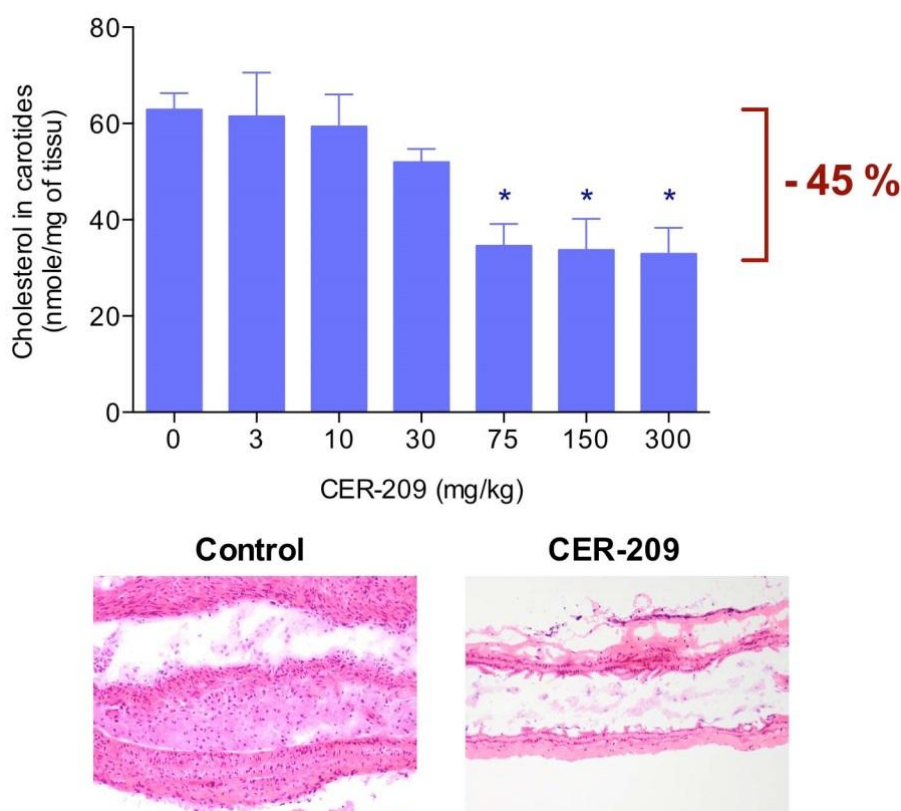


Figure 25: Plaque regression by CER-209 (validated preclinical model)

<sup>68</sup> Cerenis US Patent 8,349,833 (2013)

<sup>69</sup> Goffinet, M., et al. P2Y<sub>13</sub> receptor regulates HDL metabolism and atherosclerosis in vivo. PLoS ONE 2014 9(4): e95807.

#### 6.6.2.4.2. NAFLD/NASH

Cerenis has demonstrated that CER-209 reduces steatosis in the liver, thus identifying a new mechanism of action for treating non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).<sup>70</sup>

The increase in the number of patients suffering from NAFLD and NASH is the result of the growing epidemic of obesity worldwide. NAFLD is the most prevalent chronic liver disease, affecting 20%-40%<sup>71</sup> of the global population. It is a form of fatty infiltration into the liver independent from alcohol intake. Approximately one third of patients with NAFLD will progress to NASH, and 15% of patients will progress to cirrhosis or hepatocellular carcinoma. It is important to highlight that patients suffering from NAFLD present an elevated risk of cardiovascular morbidity and mortality. NAFLD patients have a higher risk of cardiovascular disease than of liver complications. However, it is hard to know if NAFLD is associated with CVD because of the co-existence of multiple CVD risk factors or if NAFLD independently confers an elevated risk for CVD, acting as a pro-atherogenic stimulus. Most of the patients suffering from NAFLD are obese or overweight and many of them suffer from hypertension, diabetes and dyslipidemia, hallmarks of metabolic syndrome. In consequence, NAFLD is considered to be a hepatic expression of metabolic syndrome

#### *Rationale*

Although no specific treatment is yet available, the recent guidelines from the *American Association for the Study of Liver Diseases*, recommends weight loss, a change in lifestyle in order to include more physical activity, control of hyperglycemia and hyperlipidemia treatment.

Dyslipidemia (excess of lipids) is frequently observed in patients with non-alcoholic fatty liver disease, and treatment of dyslipidemia plays a critical role in the overall management of these patients. Statins are effective lipid-lowering agents and reduce the risk of cardiovascular events. However, one of the side effects of statins is increase in liver enzymes, so statins only have limited benefits for treating NASH in patients where liver pathology is already present. The usefulness of statins for the treatment of NASH is still a matter of debate and awaits randomized clinical trials of adequate size and duration.

Instead of attempting to inhibit the LDL metabolic pathway, an alternative and perhaps more fruitful approach for NASH, would be to increase elimination of cholesterol from the liver by means of the reverse lipid transport pathway (RLT), specifically by increasing HDL metabolism. A therapeutic strategy of increasing fecal excretion of bile acids and cholesterol and consequently, the liver, through increased HDL activity had not previously been considered for NAFLD and NASH pathophysiologies. Indeed, Cerenis hypothesizes that overall improvements in lipid elimination by the liver (as previously observed with CER-209 treatment) could favorably impact NAFLD and NASH observed in patients while reducing the cardiovascular risk.

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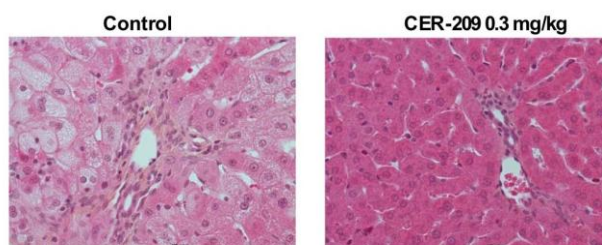
<sup>70</sup> Torres, D.M. et al. Diagnosis and therapy of nonalcoholic steatohepatitis *Gastroenterology* 2008 134:1682-98; Chalasani N., et al. The diagnosis and management of non-alcoholic fatty liver disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* 2012, 55:2005–23.

<sup>71</sup> Wree A., et al. From NAFLD to NASH to cirrhosis-new insights into disease mechanisms *Nat Rev Gastroenterol Hepatol*. 2013, 10(11): 627-36. (2013); Tateishi R., et al. Clinical characteristics, treatment, and prognosis of non-B, non-C hepatocellular carcinoma: a large retrospective multicenter cohort study. *J of Gastroenterol*. 2014 Jun 15. ePub.

### *Proof of concept for NASH*

A preliminary proof of concept study was performed in a preclinical model.

After initiation of CER-209 treatment, a significant decrease in lipid content (cholesterol and triglycerides) of the liver was observed. Liver histology further demonstrated a significant decrease in steatosis, resulting in a trend towards normalization of liver physiology.



### **Competitive advantages of CER-209**

*P2Y13r is a new therapeutic target with a new mechanism of action.*

CER-209 is the first in its class and, as sole player, it offers an excellent profile in the competitive landscape. Due to the specific targeting of pathways for cholesterol elimination, and the absence of multiple effects exhibited by medications that function through nuclear receptors, such as PPAR and FXR agents, it is anticipated that CER-209 will differentiate itself from its competitors for the treatment of NASH pathophysiology. Finally, the double positive effect of CER-209 observed in hepatic pathology and in atherosclerosis has a major advantage, since the vast majority of patients with NASH/NAFLD also have symptoms related to atherosclerosis and heightened cardiovascular risk, represented by high cardiovascular mortality.

### *CER-209 development plan*

Exploratory biology and pharmacology experiments to date have provided preclinical proof of concept for CER-209.

In December 2016, after completing all IND-enabling preclinical studies, Cerenis has received regulatory approval to initiate a Phase I clinical study of its P2Y13 receptor agonist drug candidate (CER-209) in healthy volunteers for the clinical investigation of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). Phase I single dose tolerance clinical study will be conducted over 2017. After reviewing phase I single-dose tolerance and multiple-dose tolerance results, Cerenis intends to initiate a proof of concept study for NASH and atherosclerosis.

Other indications could also be considered, such as chronic idiopathic constipation, progressive intrahepatic familial cholestasis (PIFC) and primary biliary cirrhosis (PBC).

### *Competitive landscape for NAFLD and NASH*

Clinical studies are already under way for these pathologies using different approaches.

Insulin sensitizers (anti-diabetics) such as thiazolidinediones have been extensively tested, showing a significant reduction in liver inflammation and steatosis but unfortunately only modest efficacy in controlling liver fibrosis in NASH patients.

Targeting the farnesoid X receptor (FXR), a member of the nuclear receptor super family which regulates a wide set of target genes involved in bile acid synthesis and transport, lipid metabolism and glucose homeostasis, seems to be a promising strategy. Obeticholic acid, developed by the company Intercept, is currently in Phase III clinical trials for NASH (REGENERATE<sup>72</sup>, Phase III study). Nevertheless, a recent study led by Intercept in Japan did not meet its primary endpoint, thus questioning the interest of this approach.<sup>73</sup>

A double PPAR (peroxisome proliferator activated receptor) agonist, GFT505 (developed by Genfit) has also targeted NASH pathology by its numerous effects on metabolic syndrome. The primary clinical endpoint was not met in GOLDEN, a Phase II clinical trial. However, positive results in subgroup analysis were considered supportive to initiate RESOLVE-IT, a Phase III clinical trials for treatment of NASH.<sup>74,75</sup>

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<sup>72</sup> <http://www.nash-study.com>

<sup>73</sup> (JapicCTI-121993 - <http://ir.interceptpharma.com/releasedetail.cfm?ReleaseID=938853>)

<sup>74</sup> <http://www.genfit.com/wp-content/uploads/2015/11/2015.11.16-PR-GENFIT-Ph3-Elafibranor.pdf>

<sup>75</sup> <http://www.genfit.com/wp-content/uploads/2016/03/2016.10.03-PR-GENFIT-First-patient.pdf>

### List of molecules currently in development for NASH treatment

Company	Molecule	Therapeutic target	Clinical status
Albireo	A-4250	IBAT	Phase I
Arisaph	ARI-3037MO	Niacin	Phase II
Astra-Zeneca	AZ cmpd	NA	Phase II
Astra-Zeneca / Regulus	AZD-4076	miR-103/107	Phase I
Betagenon	O-304	AMPK	Phase I
Avolynt	Remoglifozin	SGLT-2	Phase II
BI / Pharmaxis	PXS-4728A	SSOA / VAP-1	Phase I
Bird Rock Bio	Namacizumab	CB1	Phase I
BMS	BMS-986171	FGF-21	Phase I
	BMS-986036	FGF21	Phase II
	BMS cmpd	Galectin-3	Phase I
Can-Fite	Namodenoson (cf-102)	Adora-3	Phase II
Catabasis	CAT-2054	SREBP	Phase I
Cempra	Solithromycin	Ketolide	Phase II
Conatus	Emricasan	Caspase	Phase II
Daewoong	DWP-10292	NA	Phase I
Durect	DUR-928	NA	Phase I
Galectin	GR-MD-02	Galectin-3	Phase II
Galmed	Aramchol	SCD-1	Phase II
Genfit	Elafibranor	PPAR $\alpha$ / $\delta$	Phase III
Gilead	GS-9674	FXR	Phase I
	GS-4997	ASK1	Phase II
	Simtuzumab	LOXL2	Phase II
Immune Pharm	Bertilimumab	Eotaxin-1	Phase I
Immuron	IMM-124E	IgG	Phase II
Intercept	INT-767	FXR / TGR5	Phase I
Intercept / Sumitomo	OCA	FXR	Phase II
IONIS	IONIS-DGAT2 <sub>Rx</sub>	DGAT2	Phase I
Inventiva	IVA-337	Pan-PPAR	Phase II
Lilly	LY-3202328	DGAT2	Phase I
Madrigal	MGL-3196	THR-bêta	Phase II
MediciNova	MN-001	5-LO/LT	Phase II
Mitsubishi	MT-3995	Mineralcorticoid	Phase II
Naia	NC-101	NA	Phase I
NGM	NGM-282	FGF19	Phase II
NGM/Merck	NGM-313	KLB-FGFR1c	Phase I
Nimbus	NDI-010976	ACC	Phase I
Nitto Denko	ND-L02-s0201	HSP47	Phase I
Nordic Bioscience	KBP-089	DACRA	Phase I
Novartis	LJN-452	FXR	Phase II
	LMB-763	Na	Phase II



Company	Molecule	Therapeutic target	Clinical status
Novartis/Conatus	Emricasan	Caspase	Phase II
Novo Nordisk	Semaglutide*	GLP-1	Phase II
	Liraglutide#	GLP-1	Phase II
Octeta	MSDC-0602K	mTOT	Phase II
Pfizer	PF-05221304	NA	Phase I
Shire	SHP-626	IBAT	Phase I
Tobira	Cenicriviroc	CCR2 / CCR5	Phase II
	Evogliptin	DPP-4	Phase I
Viking	VK-2809	TRbêta	Phase I
ViroBay	VBY-376	Cathepsin B	Phase I

### 6.6.3. CER-002

CER-002 was developed from new chemical entities that are specific agonists for human PPAR $\delta$ , a multifaceted therapeutic target with broad potential for the treatment of cardiovascular and metabolic diseases. It was selected for clinical development from a series of small molecule compounds available to Cerenis through a licensing agreement with Nippon Chemiphar Co., Ltd.

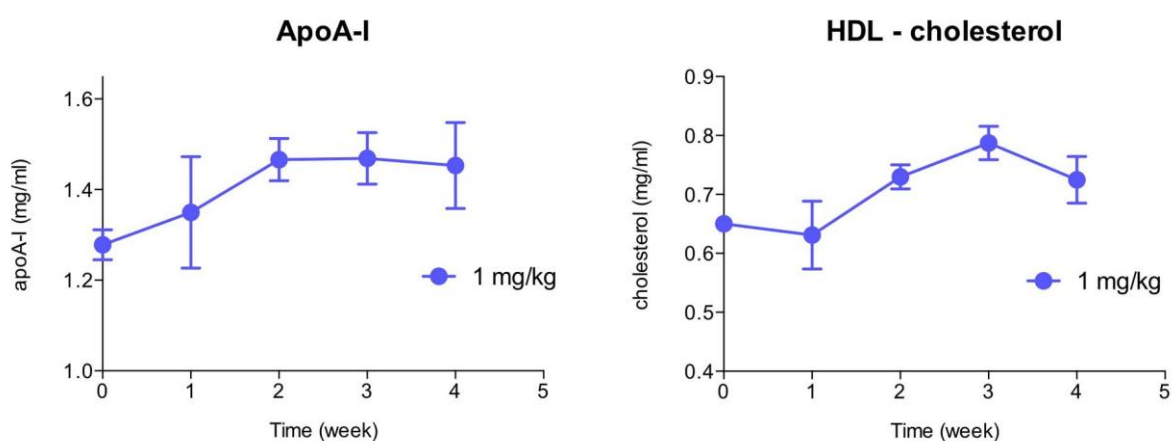


Figure 26: Increase in levels of HDL cholesterol and apoA-I with CER-002 in a preclinical model

In preclinical models, CER-002 demonstrated strong efficacy in elevating HDL and apoA-I and in halting atherosclerosis progression (Figure 26).

CER-002 proved its excellent pharmacokinetic and safety profile in Phase I. In addition, CER-002 demonstrated favorable effects on gamma-glutamyl transferases (GGT) and the lipid profile in subjects with metabolic syndrome, supporting further investigation of metabolic syndrome and NASH (Figure 27).

### Effect of 28 days of CER-002 on GGT

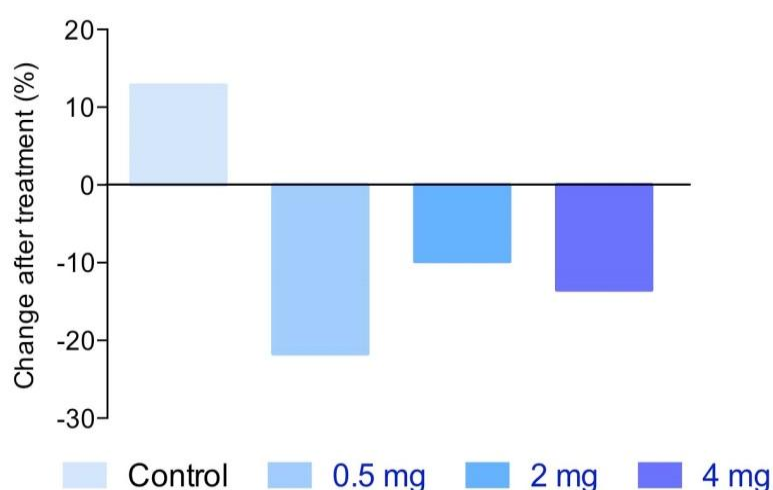


Figure 27: Changes in  $\gamma$ GT in subjects with metabolic syndrome

Other potential target diseases for further Phase II development include rare diseases such as mitochondrial diseases as well as systemic lupus erythematosus. In a preclinical model of systemic lupus erythematosus, treatment with CER-002 resulted in marked reduction in renal necrosis in the biopsies of previously existing pathologies (Figure 28).

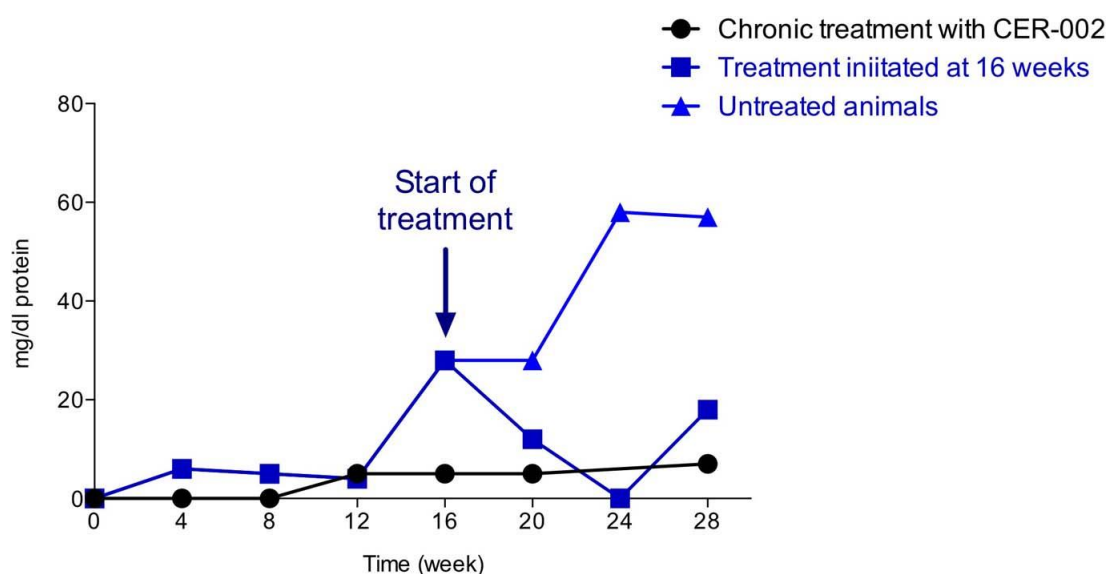


Figure 28: Prevention or reversal of SLE kidney disease with CER-002

#### 6.6.4. CER-522, an HDL mimetic for the treatment of aortic valve stenosis

CER-522 is a complex HDL mimetic under evaluation for the treatment of aortic valve stenosis (AVS), but which also can be developed as an alternative (*“back up”*) to CER-001 in secondary prevention post-ACS.

AVS is the most common valvular disorder in developed countries. Its prevalence increases with age; it affects 2%-4% of adults over age 65. It is a progressive disease and the replacement of the aortic valve remains the only definitive treatment. AVS is considered an active disease process with

similarities to atherosclerosis based on the histopathology of calcified aortic valves that show atherosclerotic-like plaques. Cerenis performed preclinical studies that demonstrated the efficacy of CER-522, in particular in slowing and regression of aortic valve stenosis.

CER-522 is an HDL mimetic based on a peptide analogue of the apoA-I protein complexed with phospholipids. It belongs to a proprietary series of 22 amino acid peptides developed by Cerenis. Initially developed as a possible back up to CER-001, CER-522 forms complexes with phospholipids that have numerous properties of the natural apoA-I protein.

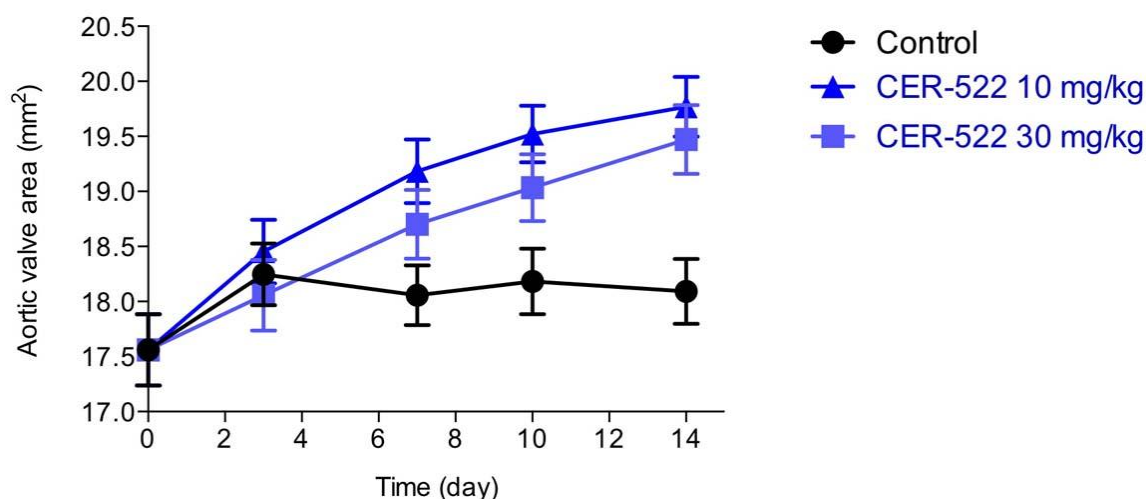


Figure 29: CER-522 decreases aortic valve stenosis as demonstrated by the increase in valve area in a preclinical model

Because the LDL-cholesterol lowering therapies available on the market have failed to slow AVS progression, there is great hope in the possibility that HDL mimetics may have therapeutic value in reducing the need for surgical aortic valve replacement.

CER-522 is ready to enter in Phase I clinical development.

## 6.7. Manufacturing

### 6.7.1. CER-001 manufacturing: the ultimate success in creating pre-beta HDL particle mimetics

Cerenis has overcome significant historic challenges in manufacturing a pre-beta HDL particle and has already developed an exclusive **commercially viable** process for manufacturing CER-001. This process integrates the three key steps necessary for manufacture of a functional HDL mimetic: production of **ultra pure human apoA-I**, **optimization of the particle phospholipid composition**, and assembly to create a **homogeneous population of stable discoidal particles**.

#### 6.7.2. Cerenis has developed a process to manufacture ultra pure recombinant human apoA-I on a commercial scale

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Cerenis has succeeded in producing large quantities of ultra pure, biologically active, recombinant human apoA-I with high yields. The Company has developed a methodology that is different from the classical approaches relying on *E. coli* bacteria to produce apoA-I. This manufacture is based on a mammalian cell expression system, which by definition does not produce endotoxins currently present in certain bacterial systems that are traditionally used.

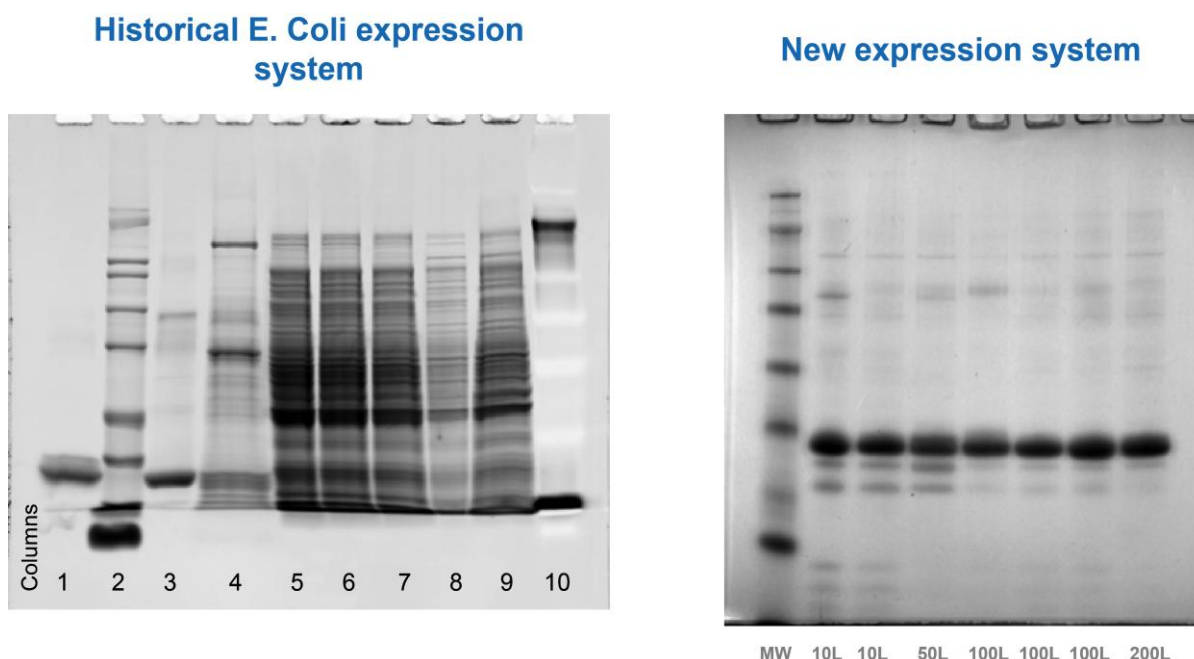
The classical approach for manufacturing recombinant proteins in *E. coli*, a widely used bacterial expression system, encounters problems in terms of optimization, contamination and the risk of impurities. The production of apoA-I in bacteria of a quality sufficient for intravenous (IV) infusion at gram-doses according to good manufacturing practices (GMP) required multiple steps of purification, ultimately resulting in very poor yields and prohibitive production costs.

In the Company's manufacturing process, apoA-I is expressed in the form of pro-apoA-I, a natural precursor allowing secretion of mature apoA-I protein in the culture medium, which facilitates collecting the protein and entails fewer purification steps thereafter. These factors combine to increase the final output of the highly purified protein, well beyond expression systems based on *E. coli* bacteria.

Through the use of a genetic engineering technology for which Cerenis holds exclusive rights, the Company created a strain of mammalian cells integrating the human apoA-I gene, which expresses and secretes the protein. This unique, innovative strain is the property of the Company.

During their culture, the cells multiply and secrete human apoA-I, which is found in the culture medium (supernatant). Over time, this culture medium is enriched in recombinant human apoA-I, making it unnecessary to break the cells in order to extract the apoA-I; this avoids contamination of the culture medium by the cell's own proteins. This remarkable advance greatly simplifies the subsequent steps of purification, improving the overall yield and enhancing final product purity. The cell culture conditions were successfully optimized on a global scale from 10 liters to 1,000 liters, suitable for conducting clinical studies. The data obtained indicate that a culture on a commercial scale of 5,000-30,000 liters is possible.

As illustrated in the figure below, Cerenis' manufacturing process results in very pure forms of apoA-I.



**Figure 30: Cerenis' exclusive expression system overcomes the traditional apoA-I production problems and enables commercially viable production of highly purified apoA-I**

This Figure 30 shows two electrophoresis gels that separate the components of a sample based on their size.

The figure on the left shows the high level of protein heterogeneity obtained from the traditional expression system in *E. coli*. For the sake of comparison, the first and third columns of the gel show a single band (black horizontal line) of the reference human apoA-I, on each side of the size standards column (column 2).

The other columns contain raw material extracted from the expression system in *E. coli*. Many proteins other than recombinant apoA-I are clearly visible (the dark bands above and below the apoA-I band). These contaminating bacterial cell products, which are present in greater proportion than the recombinant apoA-I, must be eliminated by a subsequent series of purification steps, adding a significant degree of complexity to the process of obtaining pure apoA-I and diminishing overall yields.

By contrast, the right-hand gel demonstrates the vast improvement provided by the new Cerenis expression system. The columns of the right gel contain the crude material from the mammalian system culture medium obtained without breaking the cells.

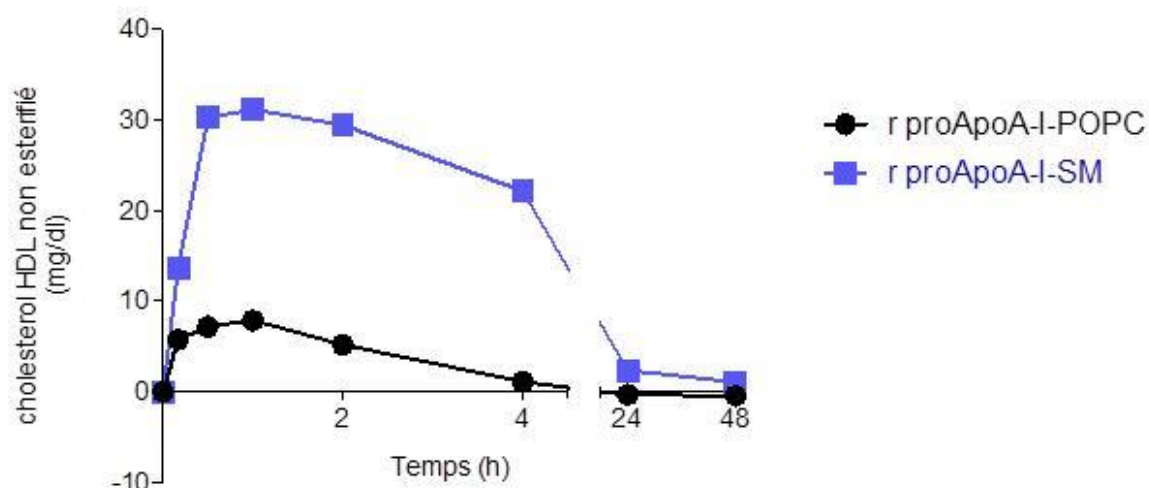
### 6.7.3. The phospholipid composition of CER-001 has been optimized to most closely resemble natural HDL

The phospholipid composition of CER-001 HDL particles has been optimized to maximize cholesterol transport capacity and facilitate their recognition by the liver so that they may be eliminated in the same manner as natural HDL.

Cerenis has optimized the phospholipid composition of CER-001 by incorporating phospholipids that have been selected based on the composition and electrical charge of natural HDL. The natural pre-beta HDL particles are composed of apoA-I and phospholipids, some of which are neutral and others negatively charged, which gives them their biological properties and prevent the particle from being degraded and eliminated too rapidly by the kidneys.

Sphingomyelin is a phospholipid characteristic of natural HDL particles. Sphingomyelin has a better affinity for cholesterol than lecithin and contributes to the efflux of cellular cholesterol by providing a medium that facilitates its capture at the core of the HDL particle.<sup>76</sup>

Cerenis has developed an innovative process of synthesizing sphingomyelin, which is object of a patent application and allows cost reduction for this critical ingredient in CER-001 composition.<sup>77</sup>



**Figure 31: Phospholipid composition is critical for increasing potency. This graph shows better cholesterol mobilization with apoA-I complexes made with sphingomyelin (SM) compared to apoA-I made with lecithin (POPC).**<sup>78</sup>

The other HDL mimetics have been made primarily with lecithin, an uncharged lipid derived from egg or soybeans which differs significantly from the charged mixture of phospholipids found in natural HDL particles (i.e. neutral and charged phospholipids). Cerenis is, to the best of its knowledge, the sole company with a patent covering negatively charged lipoprotein complexes which prevents all potential competitors from developing a true pre-beta HDL mimetic with any other apolipoprotein such as apoA-I<sub>Milano</sub> or apoA-I peptide mimetics.

As a result, the composition of neutral phospholipids and negatively charged phospholipids selected by Cerenis gives CER-001 a structure and efficacy that emulates natural HDL particles better than previous HDL mimetics and those currently being developed (Figure 31).

Product	Protein	Phospholipids (PL)			Ratio PL/Protein (weight/weight)	Phospholipid net charge
CER-001	Recombinant human apoA-I		Sphingomyeline (Sph)	Dipalmytoyl Phosphatidylglycerol (DPPG)		Negative
CSL-112 (1)	Purified apoA-I from human plasma	1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC)			55 molar ratio (about 1/1 weight/weight)	Neutral
MDCO-216 (2)	apoA-I <sub>Milano</sub> dimer	1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC)			≈1/1 (weight/weight)	Neutral

1) <https://doi.org/10.1161/ATVBAHA.113.301981> Arteriosclerosis, Thrombosis, and Vascular Biology. 2013;33:2202  
2211[http://atvb.ahajournals.org/content/atvbaha/suppl/2013/07/18/ATVBAHA.113.301981.DC1/ATV201944\\_Supplemental\\_Material1.pdf](http://atvb.ahajournals.org/content/atvbaha/suppl/2013/07/18/ATVBAHA.113.301981.DC1/ATV201944_Supplemental_Material1.pdf)

2) Eur Heart J Cardiovasc Pharmacother. 2016 Jan;2(1):23-9. doi: 10.1093/ehjcvp/pvv041. Epub 2015 Dec 11

<sup>76</sup> Int. J. Mol. Sci. 2013, 14, 7716-7741; doi:10.3390/ijms14047716

<sup>77</sup> Methods for the synthesis of sphingomyelins and dihydrosphingomyelins, patent applications US 2014/0316154

<sup>78</sup> Extracted from the patent application: Methods of treating dyslipidemic disorders. JL Dasseux et al. US2004/0067873

#### 6.7.4. Cerenis has a proprietary large-scale manufacturing process to produce homogeneous HDL particles

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Finally, apoA-I must be combined with phospholipids to create a homogeneous population of discoidal particles (namely pre-beta HDL particles), which are organized into the specific spatial conformation required to function properly.

Cerenis has demonstrated that apoA-I must be appropriately directed and integrated with phospholipids as to create a charged discoidal particle so that an HDL mimetic can successfully go through all steps of the RLT pathway.

The elegant manufacturing process developed by Cerenis for the assembly of disks is patented.<sup>79</sup> It leverages the behavior of phospholipids based on the temperature to combine apoA-I and phospholipids naturally, in order to spontaneously create a homogeneous and stable population of charged discoidal HDL particles. This process can be easily adapted to a larger scale for commercial production by employing commonly used manufacturing equipment.

Several HDL manufacturing methods have been explored without success in recent decades:

- ultrasound, extrusion and homogenization, techniques which are not easily applicable to batches of several hundred kilograms;
- solubilization with detergent is an effective method, but traces of detergent always remain and are difficult to remove, which can cause toxicity problems.

In the past, phospholipids were generally considered as excipients for solubilizing and protecting apoA-I (Figure 32). Today, it has been demonstrated that apoA-I must also be oriented in an appropriate manner when it associates with phospholipids, in order to form a functional HDL mimetic.

The active substance is not apoA-I alone or phospholipids alone, but rather the complex as a whole, i.e. the lipoprotein. This specific assembly guarantees that apoA-I will have the appropriate conformation, and that phospholipids will participate in the solubilization of cholesterol so that these two critical ingredients will act together to properly carry out reverse cholesterol transport.

Cerenis' discovery that the lipoprotein itself, in its entirety, forms the active substance allowed it to obtain the only patent for *composition of matter* in the domain, covering the definition of negatively charged lipoproteins including all forms of apolipoproteins associated with phospholipids.

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<sup>79</sup> US Patent n° 9,187,551

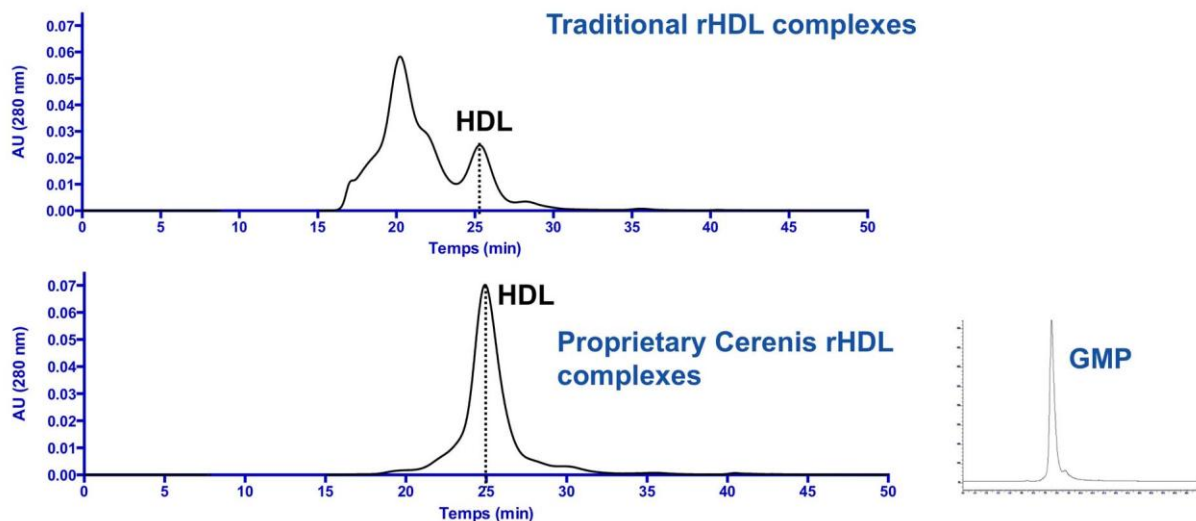


Figure 32: CER-001 A homogeneous drug

Size exclusion chromatography profiles (a technique that separates the populations of molecules or particles based on their size) above demonstrate the significant advances made by Cerenis in homogeneity of the particles: the upper figure shows several populations with particles of different sizes present in the traditional preparation of HDL complexes. The bottom figure shows the single homogeneous population of ultra pure HDL complexes obtained through the Cerenis manufacturing method.

The chart below provides an overview of the entire production process.

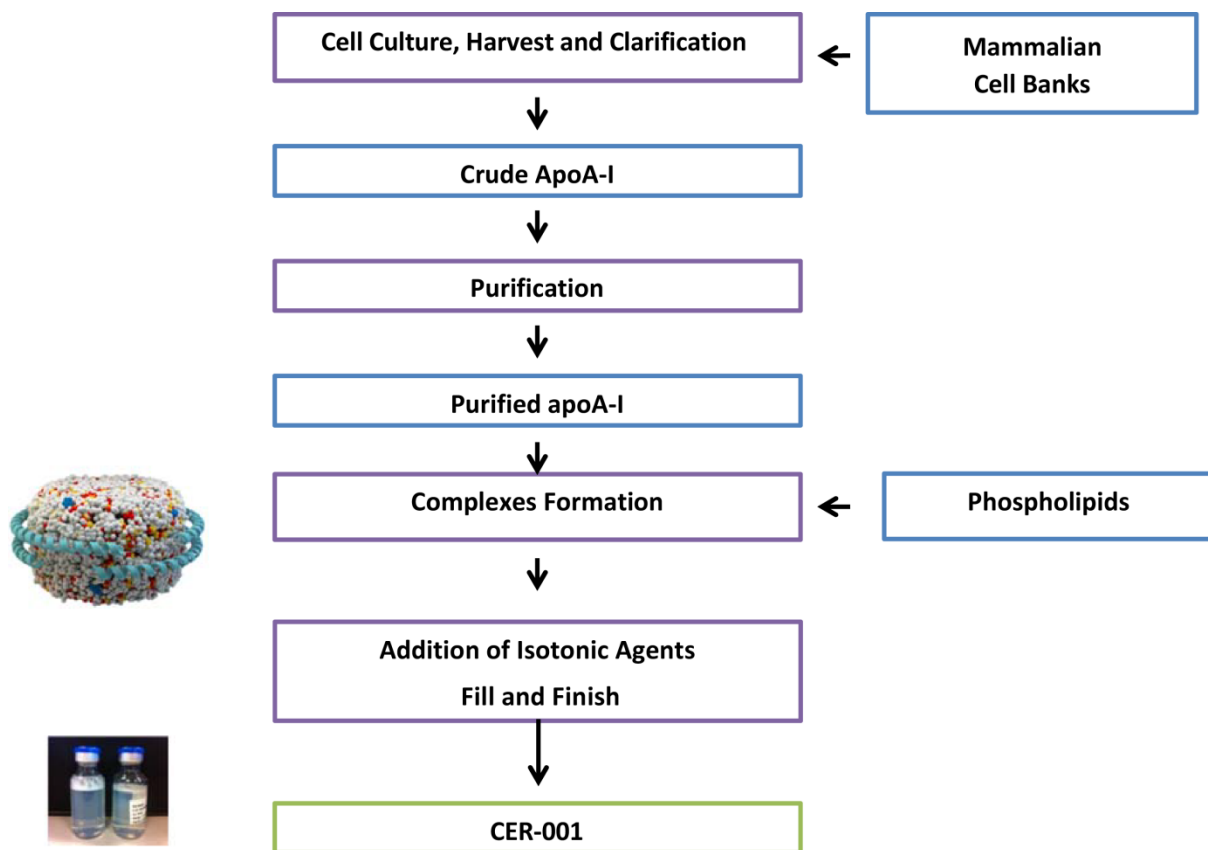


Figure 33: Production process of CER-001



In summary, Cerenis succeeded in producing CER-001 with a simplified, scalable process enhanced with several exclusive and proprietary technologies.

The purity and stability of the formed HDL complexes and the scalability of the manufacturing process have been true manufacturing challenges, which have hindered the clinical development of previous HDL mimetics. To date, Cerenis has managed to produce large amounts of CER-001 using an exclusive commercially viable process, fully validated according to Good Manufacturing Practices.

The Company's production process has allowed it to fully support the largest clinical development program conducted to date for an HDL mimetic. This process is fully scalable to support Phase III development and product commercialization.

Cerenis collaborates with Novasep, one of the leading *contract manufacturing organizations* (CMO), for the implementation and scaling of the CER-001 manufacturing process. Importantly, Cerenis holds all intellectual property rights relating to manufacturing, including know-how, which gives it great freedom in managing the production process.

Phospholipids are provided directly by one or more manufacturers, while production of apoA-I is performed under contract with Novasep.

#### *Production cost*

Since 2010, Cerenis and the CMO (Novasep) have implemented several measures that optimize the manufacturing process and reduce production costs. By increasing production volumes, economies of scale are achievable (i.e., higher volume bioreactors and larger batch size for purification), thereby further reducing the total cost of production.

## **6.8. Competitive landscape**

### **6.8.1. HDL Therapies**

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Cerenis has demonstrated that the administration of CER-001, its HDL mimetic, temporarily increases the number of functional HDL particles and thus the rate of flux through the RLT pathway, leading to enhanced removal of cholesterol. Cerenis has also demonstrated<sup>80</sup> that CER-001 behaves like natural pre-beta HDL particles, mobilizing and transporting cholesterol to the liver so that it is eliminated (RLT pathway). Cerenis' data show that CER-001 can induce regression of atherosclerotic plaque.

In addition, Cerenis possesses strong industrial property rights protecting CER-001, its manufacturing process, and its therapeutic applications. Furthermore, only Cerenis has successfully overcome the significant challenges of manufacturing highly-purified and functional HDL particles, by developing an HDL mimetic, CER-001, that is currently in Phase II and Phase III clinical trials.

Cerenis has identified two categories of experimental therapies that could increase the level of HDL particles or HDL cholesterol: HDL particles obtained by bioengineering and CETP inhibitors. Considering the current evidence demonstrating plaque regression, CER-001 enjoys a strong competitive position as supplemental treatment to standard of care with no equivalent competing product to date and could become *first and best in class*.

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<sup>80</sup> SAMBA Study

#### 6.8.1.1. Comparison between CER-001 and other HDL obtained through bioengineering

The main HDL particles manufactured through bioengineering that are currently under development are detailed here. These products were not as advanced in their development as CER-001 on the registration date of this background document. On the other hand, based on information publicly available, it is Cerenis' view that these products face several challenges in terms of manufacturing, efficacy, and safety.

##### 6.8.1.1.1. MDCO-216

The Medicines Company, listed on NASDAQ, is developing MDCO-216 (formerly ETC-216), an HDL particle based on apoA-I<sub>Milano</sub> (a mutant of apoA-I), under an exclusive license granted by Pfizer in December 2009. Pfizer had acquired ETC-216 as part of the acquisition of the biotechnology company Esperion for approximately USD 1.3 billion in 2004. During tests performed by Esperion at that time, ETC-216 demonstrated a statistically significant decrease in atheroma volume in a clinical trial with 47 post-ACS patients. Because of the small sample size, this study did not reach statistical significance versus placebo.

Thereafter, development was prematurely interrupted in Phase II by Pfizer due to safety problems linked<sup>81</sup> to contaminants, causing Pfizer to redefine a new *E. coli* strain and a new manufacturing process. After so many important changes, The Medicines Company, had to perform a full safety evaluation on MDCO-216, like it would be for a new product. Cerenis estimates that The Medicines Company faces two major obstacles, namely, demonstrating safety of the product and defining the dose to maximize cholesterol mobilization (at least 5-7 times less powerful than CER-001). The Medicine Company announced in July 2016 that data from the MILANO-PILOT trial, a small IVUS study to compare MDCO-216 with historical data obtained with ETC-216, did not show sufficient drug effects on intracoronary atherosclerotic plaque to warrant further development. These results contradict the historic of results obtained with ETC-216.<sup>82</sup>

MDCO-216 is not covered by a patent for *composition of matter*.

##### 6.8.1.1.2. CSL-111 and CSL-112

CSL, an Australian-Swiss company (based in Australia), uses a different technique to manufacture its HDL mimetic. CSL-111 and CSL-112 are complexes of apoA-I protein purified from human plasma samples that have been regrouped and reconstituted into HDL particles by the addition of a phospholipid to the protein, and assembled into complexes by dialysis using a detergent (cholic acid).

CSL-112 is not covered by a patent for *composition of matter*.

The latest CSL-111 IVUS study that has been published<sup>83</sup> gave mixed results and showed hepatic safety issues at the higher dose (80 mg/kg), which had to be dropped from the study. After this study, CSL redeveloped its manufacturing process to decrease the residual level of detergents in CSL-111, resulting in CSL-112.<sup>84</sup> Given the publicly available data, it seems that CSL-112 is 6-10 times less potent than CER-001, and that the kinetics of the complex are not satisfactory. The use of human

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<sup>81</sup> Unexpected long-term effects of ETC-216 (ApoA-I Milano /POPC) on serum lipids and lipoproteins, Herman Kempen.

<sup>82</sup> <http://www.themedicinescompany.com/investors/news/medicines-company-discontinues-development-mdco-216-its-investigational-cholesterol>

<sup>83</sup> Tardif, J-C., et al Effects of Reconstituted High-Density Lipoprotein Infusions on Coronary Atherosclerosis JAMA 200, 1675-82.

<sup>84</sup> Wright, S. W., NJ, US), Imboden, Martin (Münsingen, CH), Bolli, Reinhard (Guemligen, CH), Waelchli, Marcel (Gwatt, CH),. Reconstituted high density lipoprotein formulation and production method thereof. United States, CSL Limited (Parkville, Victoria, AU). 2015. 8999920 <http://www.freepatentsonline.com/8999920.html>

plasma protein involves immune reaction and contamination risks against isoforms of apoA-I and a potential risk of contamination via viruses and/or prions from contaminated donors.

AEGLIS-I, a Phase IIb<sup>85</sup> study in 1258 patients aimed to characterize the safety, tolerability, pharmacokinetics, and pharmacodynamics of CSL112 in patients with a recent acute myocardial infarction showed that 4 administrations of CSL112, at doses of 2 and 6 grams, were well tolerated, and not associated with any significant alterations in liver or kidney function or other safety concern. Even though this Phase II safety study was underpowered to assess efficacy (reduction of major adverse cardiovascular events) and was not designed to test for efficacy, no trend of efficacy was observed.

In the "Dallas Heart Study", increasing plasma capacity to promote cellular cholesterol efflux, a marker for the return of cholesterol, was associated with a 67% risk of major cardiovascular event compared to a low capacity of efflux of the cellular cholesterol, independent of the concentration of HDL cholesterol. According to CSL, although different products have increased HDL cholesterol in clinical trials, these have had little effect on the efflux of cellular cholesterol, which may explain why these products have not led to reducing cardiovascular events ("Major Adverse Cardiovascular Events", MACEs). On the other hand, after treatment with CSL-112 (4 administrations of 6 g of CSL-112, one per week) the plasma capacity to promote the efflux of cellular cholesterol is multiplied by three.

It should be noted that ERASE, the study using the IVUS methodology, did not demonstrate the efficacy of the CSL-developed HDL mimetic on plaque volume and percent of atheroma volume.

Despite this negative result, CSL intends to start a Phase III study end of 2017 beginning of 2018 on post-SCA patients.<sup>86</sup>

#### 6.8.1.1.3. CER-001

The CER-001 particle, on the other hand, contains recombinant human apoA-I, rendering immune responses much less likely.

The charged phospholipid content and complexation into a homogeneous population of discoidal particles results in the same pharmacokinetics profile for apoA-I and mobilized cholesterol, indicative of significantly higher particle integrity and stability. Finally, Phase I data demonstrate that cholesterol mobilization in the HDL fraction is 10 times higher than observed with HDL mimetics of the previous generation, but without signs of increased hepatic toxicity (in Phase I up to 45 mg/kg, in the CHI SQUARE Phase II study in 507 patients, and in both the SAMBA and MODE studies of chronic treatment over 6 months). This indicates that if a homogeneous population of particles similar to pre-beta discoidal HDL (such as CER-001 particles) is administered, a large amount of cholesterol can be mobilized and safely eliminated by the liver without apparent hepatic problems.

#### 6.8.1.1.4. Others

Other companies such Cardigant, Esperion Therapeutics, and Artery are developing HDL mimetic strategies (e.g., oxidation resistant apoA-I, trimeric apoA-I) but are still in the early preclinical phase.

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<sup>85</sup> AEGIS phase 2b Study of CSL112 in Subjects With Acute Myocardial Infarction, ClinicalTrials.com, September 2014.

<sup>86</sup> <http://www.csl.com.au/docs/645/950/RD%20Investor%20Briefing%202016.0.pdf>

Finally, HDL Therapeutics<sup>87</sup> is developing a new HDL technology consisting of administering weekly infusions of delipidated<sup>88</sup> autologous HDL particles (using an exclusive device developed by Lipid Sciences) also in post-ACS patients. It is a technology as constraining as kidney dialysis for patients.

#### **6.8.1.2. Resverlogix: an approach by a small molecule can theoretically induce the synthesis of apoA-1**

Resverlogix is a biotechnology company listed on the Toronto Stock Exchange.

The 299-patient Phase II study, ASSERT, in which RVX-208 was administered over 12 weeks, failed to meet its primary endpoint and did not increase HDL to the magnitude expected. The highest dose of RVX-208 (300 mg/day) only increased apoA-I by approximately 4.5% and HDL by approximately 7%.

In addition, a number of treated patients experienced elevations in transaminase, a marker of liver injury, at least three times higher than the upper limit of normal, compared to no rise in the placebo group.

The Resverlogix compound does not appear to cause regression of atherosclerotic plaque. Resverlogix recently reported the results of its Phase IIb<sup>89</sup> trial, ASSURE, that examined the effect of RVX-208 on plaque regression in 324 high-risk cardiovascular patients over 6 months.<sup>90</sup> The study did not meet its primary endpoint, which was stipulated to be a 0.6 % change in percent atheroma volume (PAV) as determined by intravascular ultrasound (IVUS).<sup>91</sup>

Resverlogix subsequently announced in a press release data from additional *post-hoc* analyses of the ASSURE study:

- Resverlogix stated that regression of atherosclerotic plaque was observed in patients with high levels of high-sensitivity C-reactive protein (hs-CRP) treated with RVX-208, as measured by the percent atheroma volume (PAV - 0.75%) and the decrease in total atheroma volume (TAV - 6.3 mm<sup>3</sup>) compared to baseline. The comparison with placebo was not reported.

When MACE (*Major Adverse Cardiovascular Events*) data (n=499) from both SUSTAIN and ASSURE trials were combined, the company reported that treatment with RVX-208 led to a significant reduction in MACE. The patients treated with RVX-208 (n=331) had fewer cumulative events: 6.74% MACE versus 15.09% in the placebo group (n=168). Furthermore, in patients who had elevated hs-CRP greater than 2.0 mg/d (n=283) the benefit of RVX-208 treatment (n=179) appeared to have been a cumulative 6.42% rate of hs-CRP in the treated group, compared to 0.53% (p=0.007) in the placebo group (n=104).<sup>92</sup> BETonMACE, a Phase III study has recently been launched.<sup>93</sup>

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<sup>87</sup> <http://hdltherapeutics.com/home/>

<sup>88</sup> Waksman, R., et al. A first-in-man, randomized, placebo-controlled study to evaluate the safety and feasibility of autologous delipidated High-Density Lipoprotein plasma infusions in patients with Acute Coronary Syndrome. JACC 2010, 55:2727-35.

<sup>89</sup> Puri R., et al. Effects of an apolipoprotein A-I inducer on progression of coronary atherosclerosis and cardiovascular events in patients with elevated inflammatory markers. J Am Coll Cardiol. 2014, 63, 12\_S.

<sup>90</sup> Nicholls. S.J., et al. ApoA-I induction as a potential cardioprotective strategy: rationale for the SUSTAIN and ASSURE studies Cardiovasc Drugs Ther. 2012 26:181-7.

<sup>91</sup> [http://www.resverlogix.com/media/press-release.html?id=487#.VMQ\\_icZqWhk](http://www.resverlogix.com/media/press-release.html?id=487#.VMQ_icZqWhk) 27 Jun, 2013.

<sup>92</sup> [http://www.resverlogix.com/media/press\\_releases.html#2014](http://www.resverlogix.com/media/press_releases.html#2014) "RVX-208 treated patients have significant lower MACE events in high risk CVD patients" 15 Jan (2014).

<sup>93</sup> [http://www.Resverlogix.com/media/press\\_releases.html#2014](http://www.Resverlogix.com/media/press_releases.html#2014) "RVX-208 treated patients have significant lower MACE events in high risk CVD patients" Jan 15, (2014).

### 6.8.1.3. CETP inhibitors

The activity of the “-cetrapib” class is based on the inhibition of CETP (cholesteryl ester transfer protein), a protein that plays a key role in modulating the exchanges of cholesteryl esters (CE) and triglycerides.

The scientific community is intensely debating whether inhibition of this mechanism, which increases cholesterol content and therefore the size of the HDL particle by enhanced CE transfer via LDL particles, is actually effective in improving the RLT pathway and ultimately in regressing plaque.

Some experts contend that the HDL particles become so overloaded with cholesterol by this mechanism that the “constipated” particles become non-functional and no longer able to unload cholesterol in the liver.

Various products are being developed:

- Torcetrapib was developed by Pfizer to be as a potential successor of Lipitor® to be combined with atorvastatin (Lipitor®, Pfizer). Torcetrapib decreased LDL-cholesterol levels by approximately 15% and increased HDL-cholesterol levels by 50–100% depending on the dose. A critical side effect of torcetrapib was a significant rise in blood pressure. The compound was tested in a large Phase III study, ILLUMINATE<sup>94</sup> (Investigation of Lipid Level Management to Understand Its Impact on Atherosclerotic Events) in order to understand its impact on atherosclerotic events. Despite the increase in HDL cholesterol and the reduction in LDL cholesterol, the combination of atorvastatin with torcetrapib did not prevent the progression of carotid or coronary atherosclerosis more effectively than atorvastatin alone. The trial was stopped before its end due to an excess of cardiovascular events and mortality in the torcetrapib group. Other clinical studies and follow-up analyses clarified that the observed adverse cardiovascular events were compound-specific and that pursuing further clinical development might be possible with other compounds.<sup>95</sup>
- Dalcetrapib was developed by Roche after being acquired from Japan Tobacco. It caused relatively modest effects on the lipid profile in Phase II. On May 7, 2012, Roche announced that it had terminated the development of dalcetrapib following an interim analysis that concluded the futility of the dal-OUTCOMES Phase III trial data, in that it failed to show any efficacy of dalcetrapib in reduction of cardiovascular events. In a Phase II trial called dal-PLAQUE, dalcetrapib showed only a modest decrease in atheroma plaque volume after 24 months that was even lower than what was achieved with high-dose statin treatment over the same time period.<sup>96,97</sup> The product was then licensed to the start-up Dalcour Therapeutics, to test dalcetrapib on a population with a genetic defect.<sup>98</sup>
- Anacetrapib is currently in Phase III of development. Merck announced the results of its Phase II study, DEFINE, in November 2010.<sup>99</sup> At 24 weeks, anacetrapib decreased LDL cholesterol by 40% and increased HDL cholesterol by 138% in patients already treated with a statin. The results showed no significant difference in blood pressure between the patients treated with anacetrapib versus placebo. It is important to note that Merck recently announced that anacetrapib accumulates in adipose tissues due to its strong intrinsic

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<sup>94</sup> Barter, P.J., Effects of torcetrapib in patients at high risk for coronary events. *New Engl J Med*. 2007, 357:2109-22.

<sup>95</sup> Barter, P.J., Effects of torcetrapib in patients at high risk for coronary events. *New England Journal of Medicine*. 2007, 357(21):2109-22.

<sup>96</sup> Fayed ZA, et al Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. *Lancet* 2011 378:1547-59.

<sup>97</sup> Schwartz, G.G., et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *New England Journal of Medicine*. 2012, 367(22):2089-99.

<sup>98</sup> <http://dalcourpharma.com/wp-content/uploads/2015/07/Cq%C3%A9-de-presse-ICM-et-Dalcour-VF-FR.pdf>

<sup>99</sup> Cannon CP et al. Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med* 2010, 363:2406–15.

lipophilicity. Although no specific safety findings have been noted so far, this finding may have substantial implications on its future clinical development.<sup>100</sup> Merck is currently engaged in REVEAL, a large-scale outcome clinical study and results are anticipated for 2017.<sup>101</sup>

- Evacetrapib was developed by Lilly. Lilly reported the data in 2011 from a 400-patient Phase II trial designed to assess the impact of adding different doses of the compound to standard statin doses on LDL-cholesterol and HDL-cholesterol levels, as well as on safety.<sup>102</sup> In this study, evacetrapib was tested for 12 weeks, alone or in combination with simvastatin 40 mg/day, atorvastatin 20 mg/day or rosuvastatin 10 mg/day in 400 patients with elevated LDL cholesterol or a low level of HDL cholesterol. Evacetrapib produced a dose-dependent increase in HDL cholesterol from 53.6% to 128.8% when used alone and from 78.5% to 88.5% when used in combination with a dose dependent reduction in LDL cholesterol ranging from 13.6% to 35.9%. In October 2015, Eli Lilly discontinued the development of evacetrapib for the treatment of atherosclerotic high-risk cardiovascular disease (ASCVD) after discontinuing the ACCELERATE phase III study at its inception following the recommendation of an independent committee Data analysis because of insufficient efficiency.
- TA-8995 is a less lipophilic compound that was licensed from Mitsubishi Tanabe Pharma by Dezima, a Dutch biotechnology company. It was recently announced to have been effective at raising HDL cholesterol in a small Phase IIb study.<sup>103,104</sup> In September 2015, Amgen® acquired Dezima.<sup>105</sup>

#### *Implications of this competitive landscape*

It is notable that Merck and Amgen/Dezima are no longer discussing its CETP inhibitor in the context of “increasing HDL”. Instead, they primarily point out the LDL-cholesterol lowering properties of anacetrapib and position it as a supplement to statins in high-risk patients, almost independently of their broad impact on the plasma lipid profile. It is also interesting to note that, after development of this class of drugs began, a population of CETP-deficient patients was identified by Professor Matsuzawa in Japan; despite the absence of CETP activity and high HDL-cholesterol levels, these patients experienced cardiovascular events at a rate similar to the rate in unaffected individuals thus putting into question the theory behind the expected benefit from this therapeutic strategy. Three CETP inhibitors have now failed to demonstrate improvement in large-scale, long-term clinical trials. At this point one can only wait for the results of REVEAL, the Phase III clinical trial to see if CETP inhibition can add value to the management of cardiovascular disease risk.

This large-scale, long-term study is designed to test the efficacy of a chronic use of CETP inhibitors. This is what clearly differentiates CER-001, whose primary use is acute, administered over the short-term to reduce the recurrence of a cardiovascular event in the first few months following the initial one.

In any case, even if CETP inhibitors were found to reduce cardiovascular events, because the accumulation of cholesterol in atherosclerotic disease is life-long, many patients starting such agents

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<sup>100</sup> Gotto, A.M. Jr, et al. Lipids, safety parameters, and drug concentrations after an additional 2 years of treatment with anacetrapib in the DEFINE study. *J Cardiovasc Pharmacol Ther.* 2014 19(6):543-9; Gotto, A.M. Jr., et al. Evaluation of lipids, drug concentration, and safety parameters following cessation of treatment with the cholesteryl ester transfer protein inhibitor anacetrapib in patients with or at high risk for coronary heart disease. *Am J Cardiol.* 2014, 113(1):76-83.

<sup>101</sup> <http://www.revealtrial.org/>

<sup>102</sup> Nicholls, S.J., et al. Effects of the CETP inhibitor evacetrapib administered as monotherapy or in combination with statins on HDL and LDL cholesterol: a randomized controlled trial. *JAMA.* 2011,306(19):2099-109.

<sup>103</sup> <http://www.dezimapharma.com/dezima-reports-positive-results-in-its-phase-2b-tulip-trial>.

<sup>104</sup> *Lancet.* 2015 Aug 1;386(9992):452-60. doi: 10.1016/S0140-6736(15)60158-1. Epub 2015 Jun 2.

<sup>105</sup> <http://investors.amgen.com/phoenix.zhtml?c=61656&p=irol-newsArticle&ID=2088272>

in clinical practice will already have had substantial cholesterol accumulations in the vascular system long before starting such therapies. The fact that the Phase III trials were designed to collect events over a maximum 4-year treatment period is a tacit indication that this class will likely demonstrate benefit only over long-term chronic use; in other words, the primary effect is a gradual slowing of the progressive accumulation of cholesterol. The effects of potential regression in the vascular system will become manifest only over a substantial period of time. By contrast, CER-001 improves reverse lipid transport and directly results in elimination of accumulated cholesterol from the body. In clinical trials in two different patient populations, a statistically significant reduction in vessel wall cholesterol accumulation was demonstrated after only 4-6 weeks of treatment.

### 6.8.2. LDL-cholesterol-lowering treatments

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Several compounds with new modes of action were approved (such as Repatha® or Praluent®) and the injection of Repatha® or Praluent® is indicated for use in addition to diet and maximally-tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH), homozygous familial hypercholesterolemia (HoFH), or clinical atherosclerotic cardiovascular disease (ASCVD), such as a heart attack or stroke, who require additional lowering of LDL cholesterol and are currently under development for other indications. However, the mechanisms of action are all based on a traditional paradigm, namely further lowering of LDL-cholesterol levels. These new treatments compete only with each other and with existing LDL-cholesterol lowering treatments but not with CER-001: CER-001 is intended to induce regression of atherosclerotic plaque through reverse lipid transport, and as such, CER-001 would be positioned to be administered in addition to any current or future LDL-cholesterol-lowering treatments.

As with all medications that may one day be used concomitantly with CER-001, after these experimental drugs earn market approval, Cerenis will proactively perform brief pharmacokinetic and pharmacodynamic studies of drug interaction as needed, as part of product life cycle management. In addition, Cerenis will consider conducting additional post-marketing (Phase IV) efficacy or experience studies involving newer, approved chronic LDL-cholesterol-lowering therapies should they present opportunities for exploring new possible patient-management paradigms that might complement the use of CER-001.

#### *PCSK9 inhibitors (proprotein convertase subtilisin/kexin type 9)*

PCSK9 regulates and degrades LDL receptors in the liver. The number of LDL receptors located on the hepatocyte is a key control point for circulating plasma LDL-cholesterol levels. Thus the normal action of PCSK9 reduces LDL receptor numbers and decreases the rate of LDL removal from the bloodstream, thereby increasing LDL-cholesterol concentrations. The aims of the PCSK9 inhibitor drug development programs are either to stop PCSK9 synthesis or to block binding of PCSK9 to the LDL receptor in order to prevent its degradation; a higher number of LDL receptors would thus enable further decreases in LDL cholesterol levels.

PCSK9 inhibitors, such as Repatha® (Amgen) and Praluent® (Regeneron/Sanofi) are a newer class of antibodies that have been shown to dramatically lower LDL cholesterol levels, by up to 60% when combined with a statin. PCSK9 inhibitors are monoclonal antibodies (MABs), a biologic type of drug. They bind to and inactivate a protein in the liver called proprotein convertase subtilisin/kexin 9 (PCSK9).

In GLAGOV, after an 18-month treatment, the reduction of PAV observed using the IVUS methodology was -1% compared with placebo.<sup>106</sup> The reduction of Percent Atheroma Volume (PAV)

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<sup>106</sup> Nicholls S et al. JAMA 2016 : 2373-2384

was not as important as envisaged in the publication on the conception of the study that took into consideration the line variation of the PAV versus LDL cholesterol.<sup>107</sup>

In March 2017, the FOURIER study showed that Repatha® (evolocumab, Amgen), in addition to statin therapy, resulted in a 15% statistically significant reduction in the combined primary endpoint (cardiovascular death, infarction Nonfatal myocardium (MI), nonfatal stroke, hospitalization for unstable angina pectoris or coronary revascularization). The study also showed a statistically significant reduction of 20% in the combined secondary endpoint (cardiovascular death, non-fatal first MI or non-fatal stroke). Moreover, as with recent studies aimed at a significant decrease in LDL cholesterol, no effect on cardiovascular mortality was observed. As the absolute reduction in cardiovascular risk is 1.5%, new therapies that would act through other mechanisms, different from the lowering of LDL cholesterol, would address the residual cardiovascular risk that remains important.

Such results could result in new medical guidelines after review by regulatory authorities.

Results from ODYSSEY, the outcome trial with Praluent® are expected by 2018.

In November 2016 Pfizer announced the discontinuation of the clinical development of bococizumab, their antibody against PCSK9, including their two cardiovascular outcome studies.<sup>108</sup>

A different type of PCSK9 inhibitors is inclisiran (GalNAc-conjugated RNAi). This drug-candidate is being developed by The Medicine Company and Alnylam Pharmaceuticals for the treatment of hypercholesterolemia. In contrast to anti-PCSK9 monoclonal antibodies (MAbs) that bind to PCSK9 in blood, inclisiran is a first-in-class investigational medicine that acts by turning off PCSK9 synthesis in the liver.

It should be noted that neurocognitive adverse experiences, which were also identified during clinical trials except in the FOURIER study<sup>109</sup>), have become an area of intense regulatory scrutiny, may impact the speed at which these drugs may reach the market and limit their use.

Recently, a Mendelian randomization study show that PCSK9 variants associated with lower LDL cholesterol were also associated with circulating higher fasting glucose concentration, bodyweight, and waist-to-hip ratio, and an increased risk of type 2 diabetes. Long-term safety will have to be assessed to quantify the risks and benefits of PCSK9 inhibitor treatment, as was previously done for statins.<sup>110</sup>

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<sup>107</sup> Am Heart J. 2016 Jun;176:83-92. doi: 10.1016/j.ahj.2016.01.019. Epub 2016 Feb 17.

<sup>108</sup> [http://www.pfizer.com/news/press-release/press-release-detail/pfizer\\_discontinues\\_global\\_development\\_of\\_bococizumab\\_its\\_investigational\\_pcsk9\\_inhibitor](http://www.pfizer.com/news/press-release/press-release-detail/pfizer_discontinues_global_development_of_bococizumab_its_investigational_pcsk9_inhibitor)

<sup>109</sup> <http://www.amgen.com/media/news-releases/2017/03/lowering-ldl-levels-with-repatha-evolocumab-did-not-adversely-affect-cognitive-function-in-landmark-phase-3-study/>

<sup>110</sup> Lancet Diabetes Endocrinol. 2017 Feb;5(2):97-105. doi: 10.1016/S2213-8587(16)30396-5. Epub 2016 Nov 29



## Therapies in R&D phase

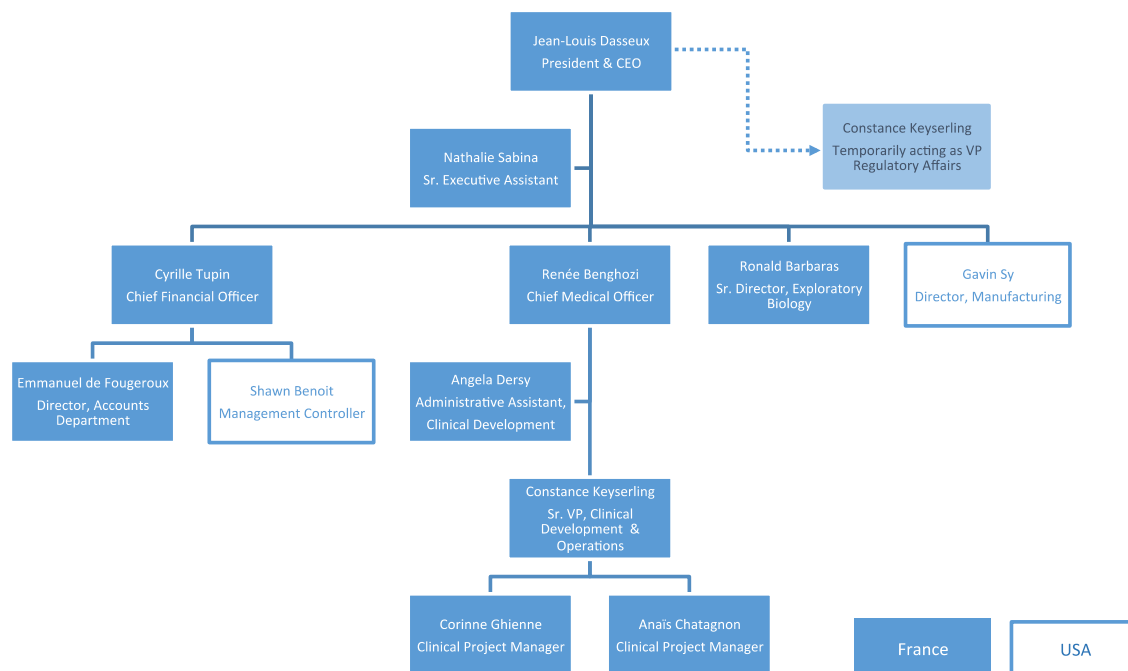
Therapy class	Product	Indication	R&D Phase	Company	Sales 2013
<b>HDL Therapies</b>					
HDL mimetics	CER-001	Post-ACS FPHA	II finalized II finalized	Cerenis Therapeutics	-
	MDCO-216	Post-ACS	II interrupted for safety reasons linked to contaminants	The Medicine Company (USA, NASDAQ)	USD 688 mn
	CSL-112	Post-ACS	IIb in progress	CSL Limited (Australia, ASE)	USD 4.95 bn
	<i>Not indicated</i>	<i>Not indicated</i>	Preclinical	Cardigant (USA) genetic sequence of the apoA-I	NA
	4WF	Atherosclerosis	Preclinical	Esperion Therapeutics (USA NASDAQ)	-
	Artpep2™ (peptide)	ACS prevention	Preclinical	Artery Therapeutics (USA)	NA
	PDS-2™ System (medical device)	Post-ACS	Preclinical	HDL Therapeutics (USA)	NA
Small molecule inducing apoA-I	RVX-208	Post-ACS	IIb in progress	Resverlogix (Canada, Toronto SE)	-
CETP Inhibitors	Torcetrapib	High risk of coronary events	III interrupted for safety reasons	Pfizer (USA, NYSE)	USD 51.6 bn
	Dalcetrapib	Post-ACS	II in progress	Roche (Switzerland, SIX)	CHF 47.8 bn
	Anacetrapib	Post-ACS	III in progress	Merck & Co (USA, NYSE)	USD 44 bn
	Evacetrapib	Post-ACS	Development terminated	Eli Lilly (USA, NYSE)	USD 23.1 bn
	TA-8995	Post-ACS	IIb in progress	Dezima Pharma (Netherlands)	NA
<b>LDL-Cholesterol-lowering treatments</b>					
PCSK9 Inhibitors	Praluent® (Alirocumab)	LDL excess	III in progress	Sanofi (France, Euronext)	EUR 33 bn
	Repatha® (Evolocumab)	LDL excess	III completed	Amgen	USD 18.7 bn
	Bococizumab	LDL excess	Development terminated	Pfizer (USA, NYSE)	USD 51.6 bn
	Inclisiran	LDL excess	II completed	The Medicines Company/Alnylam Pharmaceuticals	-

### 6.9. An experienced management team surrounded by recognized scientific experts

Cerenis brings together experts who have proven themselves globally. The combined experience and skill sets available to the Company spans the key strategic functions necessary for the successful development of its drug candidates. The majority of Cerenis' managers and employees have broad international experience and Cerenis has staff and an operational presence in both Europe and North America. The Company also leverages a network of strategic partnerships ranging from manufacturing to clinical research organizations in order to extend its reach and maximize its competitive advantage.

### 6.9.1. An experienced and complementary management team

The following chart shows the Company's management organization.



On the date of registration of this Registration Document, Cerenis had 12 employees. Of these employees, seven were engaged in research, preclinical and clinical development, and/or manufacturing activities and five were engaged in financial and general administrative activities.

- Jean-Louis Dasseux, PhD, MBA – Founder and Chief Executive Officer

Dr. Jean- Louis Dasseux is the founder of Cerenis and one of the world's leading experts in lipid metabolism, lipid-protein interaction, and cardiovascular disease. He has more than 30 years of experience in the pharmaceutical industry. Dr. Dasseux has generated more than 70 patents related to HDL, RLT, and the treatment of cardiovascular disease. He was the inventor of a high-capacity reverse lipid transport peptide HDL mimetic (ETC-642) and a series of small molecule compounds that raise HDL levels and reduce the LDL cholesterol in the blood (Bempedoic acid currently in phase III and ETC-1002). He held the positions Senior VP of Business Development and Technologies and VP of Chemistry and Technologies at Esperion Therapeutics, which developed the first generation of HDL mimetics (pro-apoA-I, apoA-I<sub>Milano</sub>, and apoA-I peptide) until its acquisition by Pfizer for USD 1.3 billion. Before joining Esperion, he was Director of Research for the French pharmaceutical company Fournier, where he established and managed its research center in Heidelberg, Germany. Jean-Louis Dasseux holds an MBA from the Ross School of Business of the University of Michigan, in the United States. He obtained his Master's in biochemistry at the University of Bordeaux II and his PhD in physical chemistry at the University of Bordeaux I. He has held postdoctoral positions at the Department of Chemistry of the University of Laval in Quebec, the Department of Physics at the University of Tennessee in Knoxville, Tennessee, and in the European Molecular Biology Laboratory at Heidelberg in Germany.

- Renée Benghozi, MD – Chief Medical Officer

Renée Benghozi has over 30 years of experience in the clinical development of molecules in the cardiovascular and diabetes fields. She is a cardiologist and graduate of the Université Paris XII. Since earning her degrees, she has been practicing cardiology at the Hospital Henri Mondor (Créteil)

and in parallel in 1982, began a career in the pharmaceutical industry (Sanofi and Novartis) as a doctor for Research and Development, project head and group leader (cardiovascular and diabetes areas). By integrating the headquarters of Novartis in Basel (Switzerland) in 1997, and then at Hoffmann-La Roche, she gained solid international experience of Phase I to Phase III clinical trials, particularly the responsibility of Phase II and III (morbidity and mortality) studies in the field of dyslipidemia for fluvastatin and a CETP modulator, dalcetrapib. At Roche, she was responsible for the development of cardiovascular strategy and evaluation of licensing deals. She was responsible as a development clinician (both preclinical and clinical) for different molecules targeting inflammation, diabetes, atherosclerotic plaque and dyslipidemia. She held various positions of responsibility and ultimately the position of *International Medical Director* of International Medical Affairs (Research and Development) for dalcetrapib, a PPAR agonist and an anti-PCSK9 until December 2014, when she left Roche.

- Cyrillic Tupin – Vice President of Finance

Mr. Tupin was previously Audit Director of Sygnatures, the largest private audit and consulting company in Toulouse, France. He spent more than seven years at PriceWaterhouseCoopers with 2 years of international experience in Canada. He has worked on a number of high-profile business transactions, including the Alcan Group takeover bid for Pechiney and the consolidation audit of Pechiney for Alcan. Mr. Tupin has been a French CPA since 2002. His CPA thesis, “Impact on Financial statements of restructuring costs, theory and practical approach for companies” was published.

- Constance Keyserling – Senior Vice President of Clinical Development and Operations

Constance Keyserling has more than 25 years of global clinical development experience, from first-in-human IND studies through post-marketing authorization studies. Prior to joining Cerenis, she was senior vice president of development operations at QuatRx, senior director of operations at Esperion, and the global head of Clinical Research Operations at Parke-Davis/Pfizer. Her areas of expertise cover a large range of activities, including: international clinical program design and management; clinical study design, management, analysis, and summarization; clinical site monitoring; clinical administration and finance; clinical outsourcing; regulatory operations; and SOP systems development. Her therapeutic areas of expertise include cardiovascular, infectious and dermatological diseases, as well as male and female health. Constance Keyserling holds a Master's degree in biostatistics from Harvard University.

- Ronald Barbaras, Ph.D. — Director of Exploratory Biology

With a PhD in biochemistry, Ronald Barbaras has over 30 years of experience in lipid metabolism, the interactions between HDL and cardiovascular disease, including the binding of lipoproteins and the synthesis of cholesterol. Ronald Barbaras was formerly research director and group leader for ATP synthase, HDL metabolism and immune modulation at the National Institute of Health and Medical Research (INSERM), the French public research organization dedicated to biological, medical and public health. He has published over 45 papers in international refereed journals.

#### 6.9.2. Scientific Advisors

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Cerenis currently retains scientific advisers who advise the Company concerning long-term scientific planning and research and development, periodically review research and development programs and advice on certain strategic aspects, including, but not limited to, the design of the clinical trials and the potential positioning of product candidates. The current scientific advisers are as follows:

Members of the Scientific Advisory Board

Name	Age	Position
Prof. John J.P. Kastelein	64	Professor of Medicine, Strategic Chair of Genetics of Cardiovascular Disease, and Chairman of the Department of Vascular Medicine at the Academic Medical Center of the University of Amsterdam

▪ Prof. John J.P. Kastelein

Prof. Kastelein is chair of the National Scientific Committee on Familial Hypercholesterolemia (EHC), a member of the Royal Dutch Society for Medicine & Physics, a member of the Council for Basic Science of the American Heart Association and the European Atherosclerosis Society, a board member of the International Task Force for CHD Prevention, a member of the Executive Board of the International Atherosclerosis Society (IAS), and a principal investigator of the Bloodomics and CardioGenics consortia.

Professor Kastelein's current research interests lie specifically in the area of hypertriglyceridemia, hypercholesterolemia and low HDL cholesterol, all conditions associated with atherosclerosis and cardiovascular disease. In 1995, Dr. Kastelein created the StOEH Foundation (Stichting Opsporing Erfelijke Hypercholesterolemie) and currently holds a position on its board of directors. Since its inception, StOEH has diagnosed over 12,000 individuals with familial hypercholesterolemia (FH).

He has published over 570 research papers in peer-reviewed journals and recently developed the use of non-invasive B-mode ultrasound studies of the carotid arteries for the diagnosis and assessment of novel treatments for atherosclerosis. The Academic Medical Centre in Amsterdam (AMC) is the global leader in the technique, now exported to many sites throughout Europe.

Prof. Kastelein received his medical degree and internal medicine training in Amsterdam in the 1980s.

New scientific advisors are consulted on issues and topics of importance to the Company. At the time of filing, the Company is in the process of recruitment.

**Rare Disease/Familial Primary Hypoalphalipoproteinemia**

- Prof. Erik Stroes, MD, PhD

Prof. Stroes is professor and president of the Department of Vascular Medicine at Amsterdam Medical Center (AMC), the University of Amsterdam, and currently presides over the Société Néerlandaise de l'Athérosclérose. [Dutch Atherosclerosis Society] He has published over 195 papers in international peer-reviewed journals. Prof. Erik Stroes research focuses on the role of the vessel walls in the development of atherogenesis. He has participated in many studies using surrogate markers such as intima media thickness and the 3 Tesla MRI technique. Recently, he has focused on lipid disorders on atherogenesis, including new genetic deficiencies in HDL and triglycerides that contribute to cardiovascular disease.

- Independent Experts on FPHA
  - Dr. Alan Remaley, National Heart, Lung, and Blood Institute, Washington, DC, United States
  - Prof. Daniel Rader, University of Pennsylvania, Philadelphia, PA, United States
  - Prof. Bryan Brewer, MedStar Institute, Washington, DC, United States
  - Dr. Samia Mora, Brigham and Women's Hospital, Boston, MA, United States

## 7. ORGANIZATIONAL CHART

### 7.1. Legal organization

The Company wholly owns a subsidiary in the United States and it has no other shareholdings.

The Company's shareholding is described in Section 21.1.7.2 of this Registration Document.

### 7.2. Group companies

Cerenis Therapeutics Inc. is located at 900 Victors Way, Suite 180, Ann Arbor, MI 48108, USA.

Telephone: +1 (734) 769-1110

Fax: +1 (734) 769-1132

### 7.3. The Group's outside funds

Cerenis Therapeutics Inc., a subsidiary wholly owned by Cerenis Therapeutics Holding S.A., conducts R&D programs for Cerenis Therapeutics Holding S.A.; Cerenis Therapeutics Inc. is involved in the management of some agreements entered into by Cerenis Therapeutics Holding S.A. Cerenis Therapeutics Holding S.A. is the sole business partner of Cerenis Therapeutics Inc. All activities of Cerenis Inc. relate to the R&D programs of Cerenis Therapeutics Holding S.A.

Cerenis Inc. reports to Cerenis Therapeutics Holding S.A. Cerenis Therapeutics Holding S.A. provides Cerenis Therapeutics Inc. material and financial support.

Cerenis Therapeutics Holding S.A. is the sole holder of all property rights related to the research conducted by Cerenis Therapeutics Inc., whatever its form. These rights automatically apply as soon as research results are produced.

All expenditure and costs incurred by Cerenis Inc. fall under the service agreement entered into between Cerenis Therapeutics Holding S.A. and Cerenis Therapeutics Inc. These rights automatically apply as soon as research results are produced. The expenses represent exact amounts spent by Cerenis Inc. for the rendering of services and cannot be pre-determined.

To assist Cerenis Therapeutics Inc. in managing its business activities, Cerenis Therapeutics Holding S.A. regularly pays an advance sum. This advance is based on a budget review and regarded as an advance on "Services Fees." In return for the services, Cerenis Therapeutics Holding S.A. pays Cerenis Therapeutics Inc. a fee equivalent to the amount of expenses incurred increased by a 5% margin ("Service Fees").

Cerenis Therapeutics Inc. sends Cerenis Therapeutics Holding S.A. invoices at the end of each month with all documentation that Cerenis Therapeutics Holding S.A. could reasonably request on the evaluation of expenses. Cerenis Therapeutics Inc. makes no profit from its activities. The ERP used by Cerenis Therapeutics Inc. is the same as that used by Cerenis Therapeutics S.A., which allows strict control over financial transactions conducted by the subsidiary.

A total of €372,180 was paid under this agreement in 2016.

## 8. PROPERTY, PLANT AND EQUIPMENT

### 8.1. Property and equipment

#### Leased property

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The premises occupied by the Company are located at:

- 265 rue de la Découverte, bâtiment A, 31670 Labège, France (registered office);
- Suite 180, MI 48108, Ann Arbor, United States (offices of Cerenis Therapeutics Inc.);
- 401 W. Morgan Road, MI 48408, Ann Arbor, United States (lab equipment storage facility).

In France, the premises are leased under a commercial lease signed with a third party who does not have any link with the Company or its executives. The surface area is 710 m<sup>2</sup> on the 1st floor of Building A and there are 30 uncovered parking spaces.

This lease was signed on September 1, 2011 for an initial term of nine years with the option of termination on a 3-year basis. The Company withdrew the request to terminate the lease agreement as from June 30, 2015 via an amendment signed on June 11, 2015. As a result, the lease will continue to be valid until the initially agreed-upon term, i.e. December 14, 2020.

The annual lease rent is €83,212.20 (excluding tax).

In the United States, the premises are rented under leases signed with third parties who have no links with the Company or its executives. The surface area is approximately 180 m<sup>2</sup> and 150 m<sup>2</sup> respectively.

These leases were signed on February 12, 2014 and February 14, 2014 respectively.

The annual lease rents are USD 54,014 and USD 16,520 respectively.

Due to the negative results of the CARAT trial, the Company will be scaling back its activities in the United States and renting less space. This change is expected to occur in the second quarter of 2017.

### 8.2. Environmental issues

The nature of the Company's activities does not entail any major environmental risks.

Environmental data from the Company's Corporate Social Responsibility report is presented in Section 17.

## 9. ANALYSIS OF THE FINANCIAL POSITION AND RESULTS

### 9.1. Overview

#### 9.1.1. Description of the Company

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Cerenis is a biotechnology company, the core business of which is research and development in new HDL (“good cholesterol”) therapies to treat cardiovascular and metabolic diseases.

To this date, the Company has been involved in a research and development phase and has therefore not generated any revenue.

The Company operates out of Toulouse (France) and out of Ann Arbor, Michigan (United States). The Company’s registered office is in Toulouse.

Since it was founded in 2005, the Company has been financed by:

- Capital increases
- Repayments received under the Research Tax Credit (CIR) program
- Repayable advances granted by Bpifrance (formerly Oséo)
- Income from investments in fixed deposits.

This section presents the results and financial position of Cerenis for the years ended December 31, 2015 and December 31, 2016.

This financial data derives from the consolidated financial statements of the Group, which is made up of Cerenis Therapeutics Holding SA (parent Company in France) and Cerenis Therapeutics Inc. (wholly owned subsidiary in the United States).

These consolidated financial statements cover a 12-month period for both the year ended December 31, 2015 and the year ended at December 31, 2016, and are prepared in accordance with the IFRS as approved by the EU.

Readers are encouraged to review not only this Section but the Registration Document as a whole.

In particular, readers are encouraged to consult the description of the Company’s business in Section 6.

Similarly, readers are encouraged to review the financial position and results of Cerenis for the years ended December 31, 2015 and December 31, 2016 with the financial statements of Cerenis, the Notes to the financial statements presented in Section 20 of this Registration Document, and the information included in Section 10.

#### 9.1.2. Sales and operating income

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In the last two years reported, the Company was in line with its research and development objectives and therefore generated no sales.



### 9.1.3. Research and Development – Sub-contracting

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R&D costs amounted to €17,004,000 at December 31, 2016.

R&D costs mainly include:

- Staff costs including direct and indirect costs of Group employees responsible for R&D including the charge relating to share-based payments (IFRS 2) for this category of worker;
- Sub-contracting and consultant expenses. These include trial costs, costs related to filing and maintaining patents, and fees paid to experts;
- Amortizations on fixed assets used in R&D activities;
- Research Tax Credit (CIR) included to decrease R&D costs.

### 9.1.4. Overhead and administrative expenses

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Overhead and administrative expenses totaled €7,031,000 at December 31, 2016.

Overhead and administrative expenses mainly include:

- Administrative staff costs including costs related to share-based payments (IFRS 2) for this category of worker;
- Legal, audit and consultancy fees;
- Travel costs;
- Costs of leasing the Company's registered office and the office of the US subsidiary.

### 9.1.5. Financial expenses and income

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Financial losses amounted to €841,000 at December 31, 2016.

Financial results mainly comprise:

- Financial income related to cash invested in futures accounts;
- Foreign exchange gains and losses resulting from changes in currency rates in transactions made in foreign currencies with foreign service-providers;
- Financial income and expenses related to BPI-OSEO repayable advances processed in accordance with (International Accounting Standards) IAS 20 "Accounting for Government Grants and Disclosure of Government Assistance" and IAS 39 "Financial Instruments: Recognition and Measurement."

### 9.1.6. Key factors impacting the Company's business

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The main factors which affected the 2016 fiscal year are as follows:

#### **"CARAT" clinical trial**

A Phase II CARAT clinical trial, the purpose of which is to assess the efficacy of CER-001 in reducing atherosclerotic plaque in post-Acute Coronary Syndrome (ACS) patients. The trial was conducted on 301 patients in four countries (the protocol provided for the recruitment of 292 patients): Australia, Hungary, the Netherlands and the United States. Patient recruitment was completed in August 2016

and the last patient received the tenth and final administration of CER-001 or a placebo in the fourth quarter of 2016.

On March 1, 2017, the Company announced that it had not achieved the main objective of the CARAT study. It learned of this after the financial statements and consolidated financial statements were approved on February 17, 2017, and after the Statutory Auditors' reports dated February 20, 2017, were issued. As a result, Note I.C to paragraph 20.1 and Note II to paragraph 20.3 do not refer to this event.

#### **"LOCATION" clinical trial**

On June 2, Cerenis announced in the scientific journal of the European Atherosclerosis Society (EAS) the findings of the LOCATION clinical trial, which demonstrate the functionality of CER-001. The trial was conducted during the first half of 2015.

#### **"TANGO" clinical trial**

A Phase III trial (TANGO) on the orphan disease FPHA to evaluate the efficacy of six months' chronic administration of CER-001 in 30 patients suffering an HDL deficiency. Active recruitment of patients for the TANGO Phase III trial is under way and findings on the principal criterion of the study should be available at the end of 2017. The Company is working with 18 sites around the world to find more patients with Familial Primary HypoAlphalipoproteinemia (FPHA), a rare but important disease, both from a clinical and an orphan pathology standpoint.

## **9.2. Comparison between the financial statements for the last two years**

### **9.2.1. Operating income and net income**

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#### **9.2.1.1. Sales and operating income**

In the last two years reported, the Company was in line with its research and development objectives and therefore generated no sales.

#### **9.2.1.2. Operating expenses by function**

Cerenis has chosen to present its income statement by function, which provides better financial data.

Operating expenses include R&D costs as well as overhead and administrative costs. As the Company has no sales activity, there were no commercial costs.

Total personnel expenses and expenses for depreciations and provisions, which are broken down into the different functions, totaled €8,438,000 in 2016 and €3,639,000 in 2015.

Between December 31, 2015 and December 31, 2016, R&D costs changed as follows:

<b>R&amp;D Expenses (EUR thousand)</b>	<b>12/31/2016</b>	<b>12/31/2015</b>
Personnel expenses	1,559	1,734
Payments in shares	1,678	192
Sub-contractors, consultants	16,405	11,339
Fees	1,031	1,190
OSEO-BPI grant	(296)	(117)
Travel costs	162	269
Charges for depreciation and provisions	50	50
Research Tax Credit (CIR)	(3,585)	(2,096)
<b>TOTAL</b>	<b>17,004</b>	<b>12,561</b>

R&D costs totaled €17,004,000 at December 31, 2016, compared with €12,561,000 at December 31, 2015.

This €4,443,000 increase is explained by:

- Increased R&D costs following the launch of the “CARAT,” “TANGO” and “LOCATION” trials;
- Increase in share-based payments in accordance with accounting standard IFRS 2 “Share-based Payment.” The cost was higher due to the award of stock options, the bonus share plan and stock warrants (see Note III.P, Section 20.1 of this Registration Document);

The research tax credit was up €1,489,000 as a result of increased R&D costs recorded during the year ended December 31, 2016.

Changes in overhead and administrative expenses between December 31, 2015 and December 31, 2016 were as follows:

<b>Overhead and administrative expenses (EUR thousand)</b>	<b>12/31/2016</b>	<b>12/31/2015</b>
Personnel expenses	1,474	1,444
Payments in shares	3,720	319
Fees	624	320
Rentals	198	204
Travel costs	319	253
Charges for depreciation and provisions	(43)	(100)
Others	739	473
<b>TOTAL</b>	<b>7,031</b>	<b>2,913</b>

Overheads and administrative expenses totaled €7,031,000 at December 31, 2016, compared with €2,913,000 at December 31, 2015.

This €4,118,000 increase is explained by:

- The increase in share-based payments in accordance with accounting standard IFRS 2 “Share-based Payment.” The cost was higher due to the award of stock options, the bonus share plan and stock warrants (see Note III.P, Section 20.1 of this Registration Document);
- The change in fees, which were up €304,000 because of the full year effect of new obligations related to listed companies (liquidity agreement, organization of general shareholders’ meetings, etc.).

The other items generally remained unchanged from one year to the next.

Operating losses increased from €15,474,000 at December 31, 2015 to €24,035,000 at December 31, 2016 because of an increase in all operating expenses.

### 9.2.1.3. Financial results

Financial loss was €841,000 at December 31, 2016, compared with a €1,164,000 loss at December 31, 2015.

The breakdown of financial results is as follows:

Financial results (EUR thousand)	12/31/2016	12/31/2015
Proceeds from deposits	442	408
Foreign exchange gains	845	697
Others	112	153
<b>Total Financial Income</b>	<b>1,399</b>	<b>1,258</b>
Foreign exchange loss	787	1,038
Interest expenses on advances	1,257	1,217
Others	196	167
<b>Total Financial Expenses</b>	<b>2,240</b>	<b>2,422</b>
<b>FINANCIAL INCOME</b>	<b>(841)</b>	<b>(1,164)</b>

The financial income recorded primarily includes:

- Financial income related to returns on futures accounts and income from investments. This financial income came to €408,000 at December 31, 2015 and €442,000 at December 31, 2016. This increase is due to a rise in average outstanding cash flow following the IPO on March 30, 2015.
- Foreign exchange gains corresponded to the impact of changes in currency exchange rates for payments made to service-providers in foreign currencies (mainly the US dollar, Canadian dollar, pound sterling, Japanese yen, and Australian dollar).

Financial expenses include mostly:

- Foreign exchange losses (please see Section above on “Foreign currency gains”); and
- Annual interest expenses on reimbursable advances from BPI resulting from accretion expense of the 2010 BPI advance by €1,257,000 for the year ended December 31, 2016. The absence of a charge for the BPO advance was due to a rescheduling agreement signed with BPI in September 2016.

#### 9.2.1.4. Corporate income tax

In view of the losses recorded during the years reported, the Group did not record any corporate income tax.

#### 9.2.1.5. Basic earnings per share

Net earnings totaled €(24,871,000) at December 31, 2016 and €(16,638,000) at December 31, 2015.

The loss per share issued (weighted average number of shares outstanding for the year) was €1.00 at December 31, 2015 and €1.39 at December 31, 2016.

### 9.2.2. Balance-sheet analysis

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#### 9.2.2.1. Non-current assets

Current assets totaled €343,000 at December 31, 2016 and €446,000 at December 31, 2015 respectively.

They include intangible assets; property, plant and equipment; and non-current financial assets.

Net intangible assets, which amounted to €5,000 at December 31, 2016 and €8,000 at December 31, 2015, was the software used by Cerenis. Since the R&D costs incurred by the Company did not yet meet the activation criteria under IAS 38, they were recognized, in full, under liabilities.

The reduction in tangible assets was largely due to recognition of depreciation expense for the year. These assets are broken down as follows:

Assets (EUR thousand)	12/31/2016	12/31/2015
Office equipment	5	9
IT hardware	17	29
Lab equipment	0	1
Other equipment	100	130
<b>TOTAL</b>	<b>122</b>	<b>169</b>

Other non-current assets only concern deposits related to the lease for the offices in Labège as well as a liquidity agreement (see Section 21.1.3.2.). The Group signed a liquidity agreement during the 2015 fiscal year. There was €204,000 in the current account dedicated to this agreement at December 31, 2016. At December 31, 2016, 23,291 treasury shares had been purchased under this agreement, valued at €194,000 in total. These treasury shares were offset against shareholders' equity.

#### 9.2.2.2. Current assets

Current assets totaled €28,722,000 at December 31, 2016 and €45,661,000 at December 31, 2015.

They included bank accounts and cash equivalents as well as other current assets.

Available cash includes current accounts at banks as well as short-term deposits, which are broken down as follows:

Available cash (EUR thousand)	12/31/2016	12/31/2015
Current bank account	5,959	2,505
Short-term deposits	18,716	40,446
<b>TOTAL</b>	<b>24,675</b>	<b>42,951</b>

Changes in cash and cash equivalents over the period are presented in Section 10.

Other assets are broken down as follows:

Other assets (EUR thousand)	31/12/2016	31/12/2015
Tax receivables	124	178
Social security receivables	0	0
Research Tax Credit	3,585	2,096
Pre-paid expenses	280	436
Others	58	0
<b>TOTAL</b>	<b>4,047</b>	<b>2,710</b>

Tax receivables correspond to VAT (Value Added Tax) to be recovered from the tax authorities.

The Research Tax Credit (CIR) is granted to businesses by the French government in order to encourage them to conduct scientific and technical research. CIR is calculated on the basis of a share of R&D costs incurred by Cerenis. Reimbursement of 2015 CIR was made on July 5, 2016 for a total of €2,096,000. Reimbursement of 2016 CIR totaling €3,585,000 should be made during 2017.

Pre-paid expenses mainly concern research services, which were invoiced but not yet delivered as at December 31, 2016.

#### 9.2.2.3. Shareholders' equity

At December 31, 2016 and December 31, 2015, total shareholders' equity amounted to €14,610,000 and €33,198,000 respectively.

Shareholders' equity was broken down into the following items and reconstituted following the success of the IPO:

- Share capital of €913,000 at December 31, 2016 and €890,000 at December 31, 2015;
- Issue premiums related to capital of €166,753,000 at December 31, 2016 and €166,032,000 at December 31, 2015;
- Accumulated losses for the years 2005 to 2016, i.e. a total of €(153,186,000) at December 31, 2016;
- Conversion reserves related to transactions with the US subsidiary, which prepares its financial statements in US dollars, i.e. a total of €130,000 (vs. €110,000 at December 31, 2015).

#### 9.2.2.4. Non-current liabilities

At December 31, 2016 and December 31, 2015, total non-current liabilities were €7,761,000 and €7,120,000 respectively.

These liabilities mainly corresponded to:

- Advances granted by the BPI (Banque Publique d'Investissement);
- Provisions for disputes;
- Provisions for retirement commitments.

Non-current liabilities related to reimbursable advances granted by BPI totaled €6,755,000 at December 31, 2016, compared with €6,094,000 at December 31, 2015. Cerenis received three repayable advances for its R&D activities. See Section 10.3.1 and Note III M of Section 20.1.

The BPI 2009 - OSEO Innovation advance of €2,500,000 was received in 2009 and 2010. It was finally repaid during the year ended December 31, 2013.

The BPI 2010 - ISI Project advance of €6,384,000 was received in 2010. At December 31, 2014, Cerenis had received €4,602,000. The balance of €1,782,000 has still not been received. This advance relates to the Phase IIb clinical trial development (CER-001) for acute coronary syndrome treatment and drug development (CER-001) to treat rare diseases.

The BPI 2012 - OSEO Innovation advance of €1,500,000 was received in 2012. At December 31, 2014, Cerenis had received €500,000. The balance will be advanced on notification of program finalization.

This aid from BPI is granted for pre-clinical development of a new drug candidate (CER-209) as HDL therapy as well as for the Phase I clinical trial.

The provisions are as follows:

Provisions (EUR thousand)	12/31/16	12/31/15
Retirement commitments	120	94
Others	886	931
<b>TOTAL</b>	<b>1,006</b>	<b>1,025</b>

The provision for retirement commitments was accounted for in accordance with IAS 19.

The reversals of net provisions totaled €46,000 for the year 2016. This provision reversal was used during the fiscal year.

At December 31, 2016, the Company's executive team made an estimate of the risks run concerning disputes with third parties and with a former employee and made a provision for them. Cerenis set aside a provision for the risk corresponding to a lawsuit.

#### 9.2.2.5. Current liabilities

At December 31, 2016 and December 31, 2015, total current liabilities totaled €6,694,000 and €5,790,000 respectively.

This position in the balance sheet mainly comprises liabilities such as:

- Trade payables: €5,415,000 at December 31, 2016 (€5,071,000 at December 31, 2015);
- Current financial liabilities: €300,000 at December 31, 2016 (€0 at December 31, 2015);  
This is the current portion of the financial debt due to BPI (2010 BPI advance);

- Tax and social security liabilities: €979,000 at December 31, 2016 (€719,000 at December 31, 2015).

Payment term for trade payables is 30 days after the end of the 10-day period in which they are delivered. Trade payables at December 31, 2016 correspond to payables either not due or overdue by more than 30 days related to the dispute described in Section 20.7 of this Registration Document.



## 10. LIQUIDITY AND CAPITAL RESOURCES

The reader should also refer to Notes III-G, H, L, M and O appended to the consolidated financial statements prepared in accordance with IFRS included in Section 20.1 “Consolidated financial statements prepared according to IFRS for year ended December 31, 2016.”

### 10.1. Information on capital, liquidity and sources of financing

#### 10.1.1. Capital-backed financing

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Prior to its Initial Public Offering dated March 30, 2015, the Company had carried out three rounds of financing.

In July 2005, the Company conducted a first fundraising, totaling €25 million.

This was followed by a second fundraising in November 2006 totaling €42 million. This second fundraising was divided into three installments:

- €14 million in November 2006;
- €14 million in December 2007;
- €14 million in December 2008.

Finally, a third fundraising was carried out between July 2010 and December 2011 for a total of €50 million. This third fundraising was divided into two installments:

- €25 million in July and October 2010;
- €24.5 million in December 2011.

On March 30, 2015, the Group carried out its Initial Public Offering on compartment B of the Euronext regulated market in Paris (“Euronext Paris”), raising €53.4 million through a capital increase.

In total, the number of shares issued was 4,207,316, which enabled completion of a capital increase of €53.4 million, to which an amount of €4.0 million of capital increase expenditure corresponding to costs generated by the Initial Public Offering was charged.

#### 10.1.2. Capital increase through the exercise of marketable securities giving access to capital

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In fiscal 2016, the exercise of founder's stock warrants (FSWs) and stock options (SOs) gave rise to capital increases in the total nominal amount of €745,000.

In addition, following the award of them, stock warrants (SWs) were subscribed in the amount of €93,000.

#### 10.1.3. Funding through loans and overdraft facilities

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The Company has never borrowed.

#### 10.1.4. Funding through repayable advances and grants

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The Company has received three repayable advances from Bpifrance (formerly Oséo). These advances are described in Notes II-Q and III-M to the consolidated financial statements prepared in

accordance with IFRS included in Section 20.1 “Financial statements prepared according to IFRS for the year ended December 31, 2016” and Section 9.2.2.4 “Non-current liabilities.”

Reimbursable advances and grants (EUR thousand)	Date	Reimbursable advances granted	Date	Reimbursements made	Reimbursable advances to be received
<b>BPI 2009 - OSEO Innovation</b>	<b>2008</b>	<b>2,500</b>		<b>(2,500)</b>	<b>0</b>
Signature		1,000	March 2009		
Milestone		1,000	July 2009		
Completion of works		500	June 2010		
				Amount paid in 2011 : 750	
				Amount paid in 2012 : 1,600	
				Amount paid in 2013 : 750	
<b>BPI 2010 - Projet ISI</b>	<b>2010</b>	<b>6,384</b>			<b>1,781</b>
Signature		553	August 2010		
Milestone 1		4,050	May 2012		
Milestone 2		823			823
Milestone 3		958			958
<b>BPI 2012 - OSEO Innovation</b>	<b>2012</b>	<b>1,500</b>			<b>1,000</b>
Signature		500	March 2012		
Milestone		750			750
Completion of works		250			250
<b>TOTAL</b>		<b>10,384</b>		<b>(2,500)</b>	<b>2,781</b>

#### 10.1.5. Funding through Research Tax Credits (CIR)

Since the Company has not entered the cost of its research in the balance sheet, Research Tax Credits are fully accounted for in the income statement, as deductions for research and development costs.

The 2015 Research Credit Tax was repaid in July 2016 in an amount of €2,096,000.

The 2016 Research Tax Credit is due to be repaid in 2017 in an amount of €3,585,000.

#### 10.1.6. Off-balance sheet items

Off-balance sheet items are outlined in Note IV-C to the consolidated financial statements included in Section 20.1 of this Registration Document.

The Company has signed a lease for its registered office in Labège. The amount of future rents stood at €181,000 at December 31, 2016.

## 10.2. Cash flow

Cash flow (EUR thousand)	12/31/16	12/31/15
<b>Net consolidated income for the period</b>	<b>(24,871)</b>	<b>(16,638)</b>
Net charges for depreciations	53	56
Net charges for provisions	(5)	(106)
Return to the results of the BPI grant	(296)	(117)
Payments in shares (IFRS 2)	5,398	511
Adjustment to fair value	1,257	1,217
Changes in WCR	(733)	1,230
Other changes	0	135
<b>Cash flow from operations</b>	<b>(19,197)</b>	<b>(13,711)</b>
Transfer of property, plant and equipment	0	0
Transfer of intangible assets	0	0
Purchase of property, plant and equipment	(5)	(161)
Purchase of intangible assets	0	(10)
<b>Cash flow from investment activities</b>	<b>(5)</b>	<b>(171)</b>
Capital increase	745	49,478
Cash received from new loans	0	0
Stock subscription warrants	93	0
Share buyback (liquidity agreement)	87	(485)
Refund of loans	0	0
Cash from BPI advances	0	0
Refund of BPI advances	0	0
<b>Cash flow for financing activities</b>	<b>925</b>	<b>48,993</b>
<b>Changes in net cash flow</b>	<b>(18,277)</b>	<b>(35,111)</b>
Exchange effect	1	(2)
Initial cash flow	42,951	7,843
<b>CLOSING CASH FLOW</b>	<b>24,675</b>	<b>42,951</b>

The cash flow statement lists three categories of cash flow:

- Cash flow from operational activities;
- Cash flow from investments;
- Cash flow from financial activities.

### 10.2.1. Cash flow from operational activities

The use of cash associated with operational activities for the years ended December 31, 2016 and December 31, 2015 totaled €119,197,000 and €13,711,000 respectively.

This upsurge is mainly accounted for by increased activity in 2016 following the launch of the “CARAT” and “TANGO” trials in 2015. During 2016, the CARAT clinical trial expenses totaled €10,786,000, while the TANGO trial expenses totaled €2,217,000. By comparison, in 2015, CARAT expenses were €4,362,000 and TANGO expenses were €647,000. Since these clinical trials were launched, CARAT expenses total €15,148,000, while TANGO expenses total €2,864,000.

#### 10.2.2. Cash flow from investments

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The use of cash associated with investment activities for the years ended December 31, 2016 and December 31, 2015 totaled €5,000 and €171,000 respectively.

Purchases during the year ended December 31, 2016 relate to transport material totaling €5,000.

#### 10.2.3. Cash flow from financing activities

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During the year ended December 31, 2015, the increase in cash from financing activities was €48,993,000 as a result of funds obtained through the Company's listing on Euronext dated March 30, 2015.

During the year ended December 31, 2016, the contribution in cash from financing activities totaled €925,000. This amount is broken down as follows:

- Capital increase: €745,000;
- Subscription of stock warrants amounting to €93,000;
- Liquidity agreement and treasury share buyback: €87,000.

#### 10.3. Borrowing terms and financing structure

Since it was founded, the Group's growth strategy has consisted mainly in successive capital increases and, to a lesser extent, of Research Tax Credit rebates and repayable advances.

Consequently, the Group has no financing through bank borrowings.

#### 10.4. Potential restrictions on the use of capital

None.

#### 10.5. Sources of expected financing for future investments

At December 31, 2016, the net amount of the Group's cash was €24,675,000 based on use of cash from operations of €19,197,000 in 2016.

All the Company's cash is readily available (fixed term deposits and current accounts) to be used for possible investments.

## 11. RESEARCH AND DEVELOPMENT, PATENTS, LICENSES AND OTHER INTELLECTUAL PROPERTY RIGHTS

### 11.1. Innovation policy

The Company develops innovative products, processes or methods, and provides technical solutions that offer unique results to enable it to gain a competitive market edge. In leveraging its own intellectual property rights and those granted under license by Nippon Chemiphar and by the Ottawa Cardiology Institute (following the transfer of assets held by ImaSight), the Company has, over many years, implemented a strategy that seeks to discover, develop and distribute a high-density lipoprotein (HDL) aimed at promoting therapies for the treatment of cardiovascular and metabolic diseases, in particular diseases aggravated by the existence of atherosclerotic plaque.

Since cardiovascular diseases (CVD) are the main cause of mortality in the world, technologies enabling HDL increase could provide solutions in the field of preventive medicine, therapeutic medicine and research. The aim is to improve health care by developing new and more effective drugs to increase HDL and by furthering our understanding of the pathogenesis and treatment of CVD and metabolic diseases. These new approaches could contribute to the introduction of medical practices that may significantly increase the quality of life and life expectancy of people with cardiovascular conditions.

Section 22 of this Registration Document deals with partnership agreements entered into with third parties for R&D projects.

### 11.2. Intellectual property protection

The table below summarizes the patent families over which the company holds property rights, as detailed in Section 11.2.1 et seq.

Patent families	Name	Product	Patent owners
Family 1	Charged lipoprotein complexes and their uses	CER-001	Cerenis Therapeutics
Family 2	Lipoprotein complexes and manufacturing and uses thereof	CER-001	Cerenis Therapeutics
Family 3	HDL therapy markers	CER-001	Cerenis Therapeutics
Family 4	Charged phospholipid compositions and methods for their use	CER-001	Exclusive sublicense granted to Cerenis Therapeutics by ImaSight on a patent licensed by the Ottawa Cardiology Institute
Family 5	Methods for the synthesis of sphingomyelins and dihydrosphingomyelins.	CER-001	Cerenis Therapeutics Holding S.A.
Family 6	Apolipoprotein A-I mimics	CER-522	Cerenis Therapeutics Holding S.A.
Family 7	Compounds, compositions and methods useful for cholesterol mobilization	CER-209	Cerenis Therapeutics Holding S.A.
Family 8	Activating agent for peroxisome proliferator activated receptor delta	CER-002	Exclusive license granted to Cerenis Therapeutics by Nippon Chemiphar Co., Ltd. for Europe and North America
Family 9	Carrier particles for drug delivery and preparation process	None to date	Exclusive sublicense granted to Cerenis Therapeutics by ImaSight on a patent licensed by the Ottawa Cardiology Institute

Patent families	Name	Product	Patent owners
Family 10	CER-001 therapy for treating Familial Primary Hypoalphalipoproteinemia	CER-001	Cerenis Therapeutics Holding S.A.

### 11.2.1. Summary of patent families by product

#### CER-001

The Company holds ownership or licensee rights on six patent families related to CER-001, a preß high-density lipoprotein (HDL) particle based on human recombinant apolipoprotein A-I and a negative charge which emulates the biological properties of natural preß HDL particles by mobilizing cholesterol and by safely facilitating reverse lipid transport, the natural pathway for the body to metabolize and eliminate cholesterol. CER-001 is under clinical investigation for the treatment of Acute Coronary Syndrome (ACS) and for two rare diseases: Familial Primary Hypoalphalipoproteinemia (FPHA) and Familial Hypercholesterolemia (FH). The Company is developing intellectual property in this area and in 2016 filed a patent application to protect a new Familial Primary Hypoalphalipoproteinemia treatment protocol (Family 10).

CER-001 is a blend of phospholipids:

- Sphingomyelin (Sph), a neutral phospholipid;
- Dipalmitoyl phosphatidylcholine (DPPC), a neutral phospholipid; and
- Dipalmitoyl phosphatidylglycerol (DPPG), a negatively charged phospholipid.
- The above are all complexed with human recombinant apolipoprotein A-I (apoA-I).

These lipoprotein complexes and their use for the treatment of dyslipidemias form part of Family 1 patents, which are fully owned by the Company.

The Company also holds full ownership of: Family 2, patents which focus on several inventions regarding CER-001, in particular the manufacturing methods of CER-001; Family 3 patents, which focus on companion diagnostic tests and the selection of doses which optimize the therapeutic effects; and Family 5 patents, which focus on synthetic Sph molecules which may be integrated into CER-001 complexes and their methods of manufacture.

The Company holds the rights for Family 4 patents concerning the use of negatively charged phospholipids to treat dyslipidemias through a license granted by the Ottawa Cardiology Institute.

#### CER-209 P2Y13 agonists

Family 7 refers to agonists, which activate the P2Y13 receptor and facilitate Reverse Cholesterol Transport (RCT), causing the metabolism and elimination of cholesterol. These P2Y13 receptor agonists and their use are covered by Family 7. This family is fully owned by the Company.

#### CER-522

CER-522 is an HDL mimetic drug based on an apoA-I peptide analog. HDL mimetic drugs are currently being assessed for the treatment and prevention of dyslipidemias, cardiovascular diseases, endothelial malfunctions and for macrovascular or microvascular conditions. CER-522 is ready to enter Phase I of clinical development for the treatment of Aortic Valve Stenosis (AVS). HDL mimetics are covered by Family 6, which is fully owned by the Company.

## **CER-002 (PPAR agonists)**

In 2005, the Company was granted patents and patent application rights under an exclusive license, aimed at the technology for agonists of peroxisome proliferator-activated receptor (PPAR) for which Nippon Chemiphar Co., Ltd. owns the patents and patent application rights. The main agent protected by these patents and patent application rights is CER-002, whose Phase I clinical trials have been completed. This family is classified as Family 8.

### **Other points**

Family 9 is another patent family granted under license by the Ottawa Cardiology Institute. It refers to a process whereby hydrophobic drugs are incorporated into synthetic HDL particles and resulting products. The Company plans to use this technology as a platform from which to develop products in the future.

### **11.2.2. Patents and patent applications**

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The commercial success of the Company will depend largely on its ability to protect its technology, in particular by obtaining and maintaining patents in France and around the world. Since it was founded in 2005, the Company has implemented a strategy to produce, protect and purchase new inventions and to protect its products and processes by filing and processing patent applications, by acquiring technologies under exclusive licenses from third parties and by maintaining the patents issued.

Since 2005, the Company has introduced research programs to promote the use of HDL mimetic drugs and P2Y<sub>13</sub> receptor agonists, technologies invented and developed by the Company for the treatment of atherosclerosis and dyslipidemias.

These programs aim to develop innovative and enhanced therapies that will enable major progress in the treatment and prevention of cardiovascular and metabolic diseases.

In addition, the Company has developed a strategy to protect its innovations in the United States and Europe as well as in other major markets such as India and China.

### **Family 1: Formulation and use of CER-001**

Family 1 is based on the discovery that a small quantity of charged phospholipids in a lipoprotein complex (3% of total phospholipid mass in the case of CER-001) suffices to increase, or is optimal in increasing, the efficacy of the complex in mobilizing cholesterol. This family includes claims related to lipoprotein complexes including Sph, the primary phospholipid in CER-001, and a small amount of negatively charged phospholipids such as DPPG, the negatively charged phospholipid in CER-001, pharmaceutical formulas containing these complexes and their use to treat acute coronary syndrome and dyslipidemias such as hypercholesterolemia.

Family 1 is fully owned by the Company.

<b>FAMILY 1</b>
<b>Title: Charged lipoprotein complexes and their uses</b>
<b>Priority application: 60/665,180</b>
<b>PCT Application No.: PCT/IB2006/000635</b>
<b>PCT registration date: March 23, 2006</b>
<b>Scheduled patent expiry date: Monday, March 23, 2026</b>
<b>Owner: Cerenis Therapeutics Holding S.A.</b>
<b>Licensee: Not applicable</b>

Country	Application No./Patent No.	Status
Australia	2006226045	Issued
Australia	2012202223	Issued
Brazil	PI 0607728-5	Under review
Canada	2,602,024	Issued
China	101170994	Issued
China	103182069	Issued
European Patent Convention	1871341	Issued Approved in Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Monaco, Netherlands, Poland, Portugal, Romania, Spain, Sweden, Slovakia, Slovenia, Switzerland, Turkey, United Kingdom
European Patent Convention	2289490	Issued Approved in Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Monaco, Netherlands, Poland, Portugal, Romania, Spain, Sweden, Slovakia, Slovenia, Switzerland, Turkey, United Kingdom
Hong Kong	1115823	Issued
Hong Kong	1156840	Issued
Israel	186169	Issued
Israel	219721	Issued
India	252844	Issued
Japan	5317691	Issued
Japan	5542166	Issued
Korea	10-14754	Issued
Korea	10-2016-7016313	Under review
Korea	10-2014-7015584	Under review
Mexico	297933	Issued
Mexico	330188	Issued
New Zealand	562346	Issued
New Zealand	582888	Issued
United States	8,206,750	Issued
United States	8,617,615	Issued
United States	9,567,388	Issued
United States	15/398,219	Under review

**Family 2: Methods to manufacture reconstituted HDL particles and the resulting highly homogeneous population of reconstituted HDL particles.**

Family 2 concerns several technologies arising from development of a commercial manufacture procedure for CER-001. The first technology involves the thermal cycling of lipid and protein agents of a lipoprotein complex until a population of homogeneous complexes is produced. This process makes it possible to repeatedly obtain extremely homogeneous complexes free of impurities encountered in other manufacturing conditions where proteins and lipids are exposed to chemicals and harsh physical conditions. Moreover, Family 2 covers very homogeneous complexes which are activated by the thermal cycling process. It also includes lipoprotein complexes which have a protein/phospholipid ratio of 1:2.7 (weighted according to mass). This latter property was deemed optimal during the development of CER-001 for lipid and protein complexation purposes.

Family 2 is fully owned by the Company.



<p style="text-align: center;"><b>FAMILY 2</b>  <b>Title: Lipoprotein complexes and manufacturing and uses thereof</b>  <b>Priority application: 61/440,371; 61/452,630; and 61/487,263</b>  <b>PCT Application No.: PCT/US12/24020</b>  <b>PCT registration date: February 6, 2012</b>  <b>Scheduled patent expiry date: February 6, 2032</b>  <b>Owner: Cerenis Therapeutics Holding S.A.</b>  <b>Licensee: Not applicable</b></p>		
<b>Country</b>	<b>Application No./Patent No.</b>	<b>Status</b>
Australia	2012214672	Issued
Australia	2015271986	Under review
Brazil	BR1120130200286	Under review
Canada	2,826,158	Under review
China	201280015257.3	Under review
China	201510717344.9	Under review
China	201510711086.3	Under review
European Patent Convention	12703947.7	Under review
European Patent Convention	14150349.0	Under review
Hong Kong	14105669.3	Under review
Hong Kong	14112302.2	Under review
Indonesia	W00201304046	Under review
Israel	227634	Under review
India	7828/DELNP/2013	Under review
Japan	2013-552722	Under review
Korea	10-2013-7023430	Under review
Mexico	343907	Issued
Mexico	MX/A/2016/011834	Under review
New Zealand	613524	Issued
Philippines	1-2013-501644	Under review
Philippines	1-2016-500191	Under review
Russian Federation	2013139066	Under review
Singapore	201306051-2	Under review
South Africa	2013/05628	Issued
Taiwan	101103979	Under review
United States	9,187,551	Issued
United States	14/334,519	Under review
United States	14/884,115	Under review

### **Family 3: Companion diagnostic tests and dosage of CER-001**

Family 3 outlines and claims companion diagnostic and dosage optimization tests for the CER-001 treatment. The first US provisional application for Family 3 was filed in 2014 and served as a priority document for US and Patent Cooperation Treaty (PCT) applications in 2015. The applications are based on the discovery of a U-shaped dose-effect ratio-curve for the CER-001 treatment and associated action mechanism. In particular, it was established that CER-001 inhibited the expression of efflux cholesterol transporters (such as ABCA1 and ABCG1) and also modulated the expression of other markers. Based on this finding, the patent applications for Family 3 outline and claim companion diagnostic tests and dosage tests for CER-001 and other HDL therapeutic products which function with this same action mechanism.

Family 3 is fully owned by the Company.

<b>FAMILY 3</b> <b>Title: HDL therapy markers</b> <b>Priority application: 61/988,095</b> <b>PCT Application No.: PCT/IB15/000854</b> <b>PCT registration date: April 30, 2015</b> <b>Scheduled patent expiry date: April 30, 2035</b> <b>Owner: Cerenis Therapeutics Holding S.A.</b> <b>Licensee: Not applicable</b>		
<b>Country</b>	<b>Application No./Patent No.</b>	<b>Status</b>
United States	14/700,351	Under review
Australia	2015260929	Under review
Brazil	1120160254708	Under review
Canada	2,947,127	Under review
China	TBD	Under review
Europe	15766230.5	Under review
Israel	248601	Under review
Japan	TBD	Under review
Korea	10-2016-7033725	Under review
Mexico	MX/A/2016/014306	Under review
New Zealand	726794	Under review
Philippines	1-2016-502167	Under review
Russia	2016144908	Under review
Singapore	11201609084Q	Under review
South Africa	2016/08301	Under review

#### **Family 4: Treatment of dyslipidemias**

Family 4 generally outlines the use of negatively charged phospholipids to treat a wide range of conditions. The claims of US patent No. 7,390,783, which is the most relevant in this family for CER-001, concern the use of negatively charged phospholipids (such as the DPPG in CER-001) to treat dyslipidemias such as hypercholesterolemia.

Family 4 was licensed to Cerenis by the Ottawa Cardiology Institute. The contract signed between this institute and Liponex, and transferred to Cerenis, is described in Sections 22.3 and 22.4 of this Registration Document.

<b>FAMILY 4</b> <b>Title: Charged phospholipid compositions and methods for their use</b>  <b>Priority application: 60/221,916</b> <b>PCT Application No.: PCT/CA2001/001102</b> <b>PCT registration date: July 31, 2001</b> <b>Scheduled patent expiry date: July 31, 2021 and June 7, 2022</b> <b>Owner: Ottawa Heart Institute</b> <b>Licensee: Cerenis Therapeutics Holding S.A.</b>		
<b>Country</b>	<b>Application No./Patent No.</b>	<b>Status</b>
United States	6,828,306	Issued
United States	7,390,783	Issued

#### **Family 5: Synthetic sphingomyelin synthesis/production methods**

Family 5 refers to synthetic sphingomyelins, which form complexes with apoA-I and analogs of this peptide to produce HDL mimetic drugs as well as synthesis and intermediate methods.

Family 5 is fully owned by the Company.

<p><b>FAMILY 5</b></p> <p><b>Title: Methods for the synthesis of sphingomyelins and dihydrosphingomyelins</b></p> <p><b>Priority application: 61/801,641</b></p> <p><b>PCT Application No.: PCT/IB2014/000494</b></p> <p><b>PCT registration date: Friday, March 14, 2014</b></p> <p><b>Scheduled patent expiry date: March 15, 2033 or March 14, 2034</b></p> <p><b>Owner: Cerenis Therapeutics Holding SA</b></p> <p><b>Licensee: None</b></p>		
<b>Country</b>	<b>Application No./Patent No.</b>	<b>Status</b>
Australia	2014229638	Under review
Brazil	1120150235581	Under review
Canada	2900902	Under review
China	201480015700.6	Under review
European Patent Convention	14729036.5	Under review
Hong Kong	16100549.8	Under review
Hong Kong	16102047.1	Under review
India	7059/DELNP/2015	Under review
Indonesia	P-00201505039	Under review
Israel	225785	Under review
Japan	2015-562366	Under review
Mexico	MX/a/2015/012877	Under review
New Zealand	710696	Under review
Philippines	1-2015-501835	Under review
South Korea	10-2015-7025911	Under review
Singapore	11201506456V	Under review
South Africa	2015/05860	Under review
United States	13/844,379	Allowed
United States	14/693,520	Under review

**Family 6: HDL peptide mimetic drug, including CER-522**

Family 6 refers to HDL mimetic drugs based on peptide analogs of apoA-I, including CER-522, and the use of these HDL mimetic drugs to treat and prevent dyslipidemia, cardiovascular disease, endothelial dysfunction, or macrovascular and microvascular conditions.

Family 6 includes patents already issued and patent applications under review in 52 jurisdictions (including Europe).

Family 6 is fully owned by the Company.

<b>FAMILY 6</b> <b>Title: Apolipoprotein A-I mimics</b> <b>Priority application: 61/152,960</b> <b>PCT Application No.: PCT/US2010/024096</b> <b>PCT registration date: February 12, 2010</b> <b>Scheduled patent expiry date: February 12, 2030 or November 29, 2030</b> <b>Owner: Cerenis Therapeutics Holding S.A.</b> <b>Licensee: None</b>		
<b>Country</b>	<b>Application No./Patent No.</b>	<b>Status</b>
Australia	2010213568	Issued
Australia	2014268255	Issued
Brazil	PI1008251-4	Under review
Canada	2,752,182	Under review
China	ZL201080016764.X	Issued
China	201410745103.0	Under review
European Patent Convention	2396017	Issued Approved in Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Former Yugoslav Republic of Macedonia, Malta, Monaco, Netherlands, Norway, Poland, Portugal, Romania, San Marino, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom
European Patent Convention	2939683	Issued Approved in Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Former Yugoslav Republic of Macedonia, Malta, Monaco, Netherlands, Norway, Poland, Portugal, Romania, San Marino, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom
Hong Kong	HK11165987	Issued
Hong Kong	15110156.2	Under review
India	6109/DELNP/2011	Under review
Indonesia	W00201102881	Under review
Indonesia	P00201404162	Under review
Israel	214576	Under review
Israel	240357	Under review
Japan	5719783	Issued
Mexico	323244	Issued
Mexico	MX/a/2014/006888	Allowed
Mexico	MX/a/2016/014789	Under review

<b>FAMILY 6</b> <b>Title: Apolipoprotein A-I mimics</b> <b>Priority application: 61/152,960</b> <b>PCT Application No.: PCT/US2010/024096</b> <b>PCT registration date: February 12, 2010</b> <b>Scheduled patent expiry date: February 12, 2030 or November 29, 2030</b> <b>Owner: Cerenis Therapeutics Holding S.A.</b> <b>Licensee: None</b>		
Country	Application No./Patent No.	Status
New Zealand	594516	Issued
Philippines	1-2011-501638	Allowed
Philippines	1-2016-501912	Under review
South Korea	10-1688547	Issued
Russia	2532222	Issued
Russia	2014134333	Under review
Singapore	173624	Issued
South Africa	2011/05997	Issued
United States	8,378,068	Issued
United States	8,993,597	Issued
United States	9,388,232	Issued
United States	15/207,158	Under review

#### **Family 7: P2Y13 receptor agonists (CER-209)**

Family 7 refers to agonists of receptor P2Y13 and their use to treat or prevent lipoprotein metabolic disorders, glucose metabolic disorders, cardiovascular conditions or an associated vascular condition, involving abnormal modulation of C-reactive protein or associated disorder, aging, Alzheimer's disease, Parkinson's disease, pancreatitis or abnormal bile production.

Family 7 is fully owned by the Company.

<b>FAMILY 7</b> <b>Title: Compounds, compositions and methods useful for cholesterol mobilization</b> <b>Priority application: 61/394,136</b> <b>PCT Application No.: PCT/US2011/056780</b> <b>PCT registration date: October 18, 2011</b> <b>Scheduled patent expiry date: October 18, 2031</b> <b>Owner: Cerenis Therapeutics Holding S.A.</b> <b>Licensee: None</b>		
Country	Application No./Patent No.	Status
Australia	2011317152	Issued
Australia	2015227476	Under review
Australia	2016203507	Under review
Brazil	1120130094850	Under review
Brazil	1220160258211	Under review
Canada	2,813,994	Under review
China	201180061000.7	Allowed
China	201610534210.8	Under review
European Patent Convention	11835025.5	Under review
Hong Kong	13111188.4	Under review
India	2523/DELNP/2013	Under review
Indonesia	W00201301081	Under review
Israel	225785	Allowed
Israel	250367	Under review
Japan	5856177	Issued
Japan	2015-241010	Under review
Japan	2016-114435	Under review
Mexico	337179	Issued
Mexico	MX/a/2015/004879	Under review
Mexico	MX/a/2016/001827	Under review

<b>FAMILY 7</b> <b>Title: Compounds, compositions and methods useful for cholesterol mobilization</b> <b>Priority application: 61/394,136</b> <b>PCT Application No.: PCT/US2011/056780</b> <b>PCT registration date: October 18, 2011</b> <b>Scheduled patent expiry date: October 18, 2031</b> <b>Owner: Cerenis Therapeutics Holding S.A.</b> <b>Licensee: None</b>		
Country	Application No./Patent No.	Status
Mexico	MX/a/2016/009150	Under review
New Zealand	607928	Issued
New Zealand	621551	Issued
New Zealand	705731	Under review
New Zealand	718514	Under review
New Zealand	728819	Under review
Philippines	1-2013-500480	Under review
Philippines	1-2016-502175	Under review
South Korea	10-2013-7011634	Under review
Russia	2576402	Issued
Russia	2015156469	Under review
Russia	2016128750	Under review
Singapore	189019	Issued
Singapore	2014012850	Under review
Singapore	102016047315	Under review
South Africa	2013/01827	Issued
South Africa	2014/02287	Under review
South Africa	2016/05798	Under review
United States	8,349,833	Issued
United States	9,085,585	Issued
United States	14/729.908	Under review
United States	15/191.820	Under review

#### **Family 8: PPAR agonists (CER-002)**

Family 8 refers to agonists of the Peroxisome Proliferator-Activated Receptor (PPAR), including PPAR $\delta$  selective agonists. This patent family is owned by Nippon Chemiphar Co., Ltd. and is covered by an exclusive license granted to the Company for Europe and North America. The Phase I clinical trials of the main compound, which is CER-002, have been completed. The Company is currently exploring various development options for CER-002 for an orphan drug indication.

<b>FAMILY 8a</b> <b>Title: Activating agent for peroxisome proliferator activated receptor delta</b> <b>Priority application: JP2001-243734</b> <b>PCT Application No.: PCT/JP02/07897</b> <b>PCT registration date: August 2, 2002</b> <b>Scheduled patent expiry date: August 2, 2022</b> <b>Owner: Nippon Chemiphar Co., Ltd.</b> <b>Licensee: Cerenis Therapeutics Holding S.A.</b>		
Country	Application No./Patent No.	Status
Australia	2002323776	Issued
Brazil	PI 0211844-0	Under review
Canada	2,457,054	Issued
European Patent Convention	1424330	Issued Approved in Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Monaco, Netherlands, Portugal, Spain, Sweden, Slovakia, Switzerland, Turkey, United Kingdom

<b>FAMILY 8a</b> <b>Title: Activating agent for peroxisome proliferator activated receptor delta</b> <b>Priority application: JP2001-243734</b> <b>PCT Application No.: PCT/JP02/07897</b> <b>PCT registration date: August 2, 2002</b> <b>Scheduled patent expiry date: August 2, 2022</b> <b>Owner: Nippon Chemiphar Co., Ltd.</b> <b>Licensee: Cerenis Therapeutics Holding S.A.</b>		
Country	Application No./Patent No.	Status
Israel	160304	Issued
Mexico	253644	Issued
United States	7,265,137	Issued
United States	7,648,999	Issued
United States	7,652,045	Issued

<b>FAMILY 8b</b> <b>Title: Activating agent for peroxisome proliferator activated receptor delta</b> <b>Priority application: JP2001-315694</b> <b>PCT Application No.: PCT/JP02/10472</b> <b>PCT registration date: October 9, 2002</b> <b>Scheduled patent expiry date: October 9, 2022</b> <b>Owner: Nippon Chemiphar Co., Ltd.</b> <b>Licensee: Cerenis Therapeutics Holding S.A.</b>		
Country	Application No./Patent No.	Status
Australia	2002335231	Issued
Brazil	PI 0213243-5	Under review
Canada	2,463,569	Issued
European Patent Convention	1445258	Issued Approved in Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Monaco, Netherlands, Portugal, Spain, Sweden, Slovakia, Switzerland, Turkey, United Kingdom
Israel	161351	Issued
Mexico	258439	Issued
United States	7,119,104	Issued
United States	7,402,597	Issued

<b>FAMILY 8c</b> <b>Title: Activating agent for peroxisome proliferator activated receptor delta</b> <b>Priority application: JP2006-114561</b> <b>PCT Application No.: PCT/JP2007/058899</b> <b>PCT registration date: April 18, 2007</b> <b>Scheduled patent expiry date: April 18, 2027</b> <b>Owner: Nippon Chemiphar Co., Ltd.</b> <b>Licensee: Cerenis Therapeutics Holding S.A.</b>		
Country	Application No./Patent No.	Status
Australia	2007239283	Issued
Australia	2013202514	Issued
Brazil	PI 0710266-6	Under review
Canada	2,649,735	Issued
European Patent Convention	2014652	Issued Approved in Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Monaco, Netherlands, Poland, Portugal, Romania, Spain, Sweden, Slovakia, Slovenia, Switzerland, Turkey, United Kingdom

<b>FAMILY 8c</b> <b>Title: Activating agent for peroxisome proliferator activated receptor delta</b> <b>Priority application: JP2006-114561</b> <b>PCT Application No.: PCT/JP2007/058899</b> <b>PCT registration date: April 18, 2007</b> <b>Scheduled patent expiry date: April 18, 2027</b> <b>Owner: Nippon Chemiphar Co., Ltd.</b> <b>Licensee: Cerenis Therapeutics Holding S.A.</b>		
Country	Application No./Patent No.	Status
Israel	194847	Issued
Mexico	310033	Issued
New Zealand	572268	Issued
Russian Federation	2435764	Issued
South Africa	2008/09148	Issued
United States	8,404,726	Issued
Norway	20084856	Under review

<b>FAMILY 8d</b> <b>Title: Activating agent for peroxisome proliferator activated receptor delta</b> <b>Priority application: JP2008-105899</b> <b>PCT Application No.: PCT/JP2009/57946</b> <b>PCT registration date: April 15, 2009</b> <b>Scheduled patent expiry date: April 15, 2029</b> <b>Owner: Nippon Chemiphar Co., Ltd.</b> <b>Licensee: Cerenis Therapeutics Holding S.A.</b>		
Country	Application No./Patent No.	Status
Australia	2009236877	Issued
Brazil	PI 0911197-2	Under review
Canada	2,721,339	Issued
European Patent Convention	09731677.2	Under review
Israel	208754	Issued
Mexico	309281	Issued
New Zealand	588612	Issued
Russian Federation	2501794	Issued
South Africa	2010/07392	Issued
United States	8,648,208	Issued



<b>FAMILY 8e</b> <b>Title: Activating agent for peroxisome proliferator activated receptor delta</b> <b>Priority application: JP2000-243596</b> <b>PCT Application No.: PCT/JP01/6836</b> <b>PCT registration date: August 9, 2001</b> <b>Scheduled patent expiry date: August 9, 2021</b> <b>Owner: Nippon Chemiphar Co., Ltd.</b> <b>Licensee: Cerenis Therapeutics Holding S.A.</b>		
Country	Application No./Patent No.	Status
United States	6,787,552	Issued

<b>FAMILY 8f</b> <b>Title: Activating agent for peroxisome proliferator activated receptor delta</b> <b>Priority application: JP2001-86145</b> <b>PCT Application No.: PCT/JP02/1422</b> <b>PCT registration date: February 19, 2002</b> <b>Scheduled patent expiry date: February 19, 2022</b> <b>Owner: Nippon Chemiphar Co., Ltd.</b> <b>Licensee: Cerenis Therapeutics Holding S.A.</b>		
Country	Application No./Patent No.	Status
United States	7,078,422	Issued

### **Family 9: Carrier particles for drug administration**

Family 9 refers to processes to prepare HDL synthetic particles that contain hydrophobic drugs and the formulated particles.

Family 9 was licensed to Cerenis by the Ottawa Cardiology Institute. The contract, signed between this institute and Liponex and awarded to Cerenis, is described in Sections 22.3 and 22.4 of this Registration Document.

<b>FAMILY 9</b> <b>Title: Carrier particles for drug delivery and preparation process</b> <b>Priority application: N/A</b> <b>Registration date in United States: February 14, 2000</b> <b>Scheduled patent expiry date: February 14, 2020</b> <b>Owner: Ottawa Heart Institute</b> <b>Licensee: Cerenis Therapeutics Holding S.A.</b>		
Country	Application No./Patent No.	Status
United States	6,514,523	Issued

### **Family 10: CER-001 therapy for treating Familial Primary Hypoalphalipoproteinemia**

<b>FAMILY 10</b> <b>Title: CER-001 therapy for treating Familial Primary Hypoalphalipoproteinemia</b> <b>Priority application: 62/373,508</b> <b>PCT Application No.: PCT/FR2016/052073</b> <b>PCT registration date: August 11, 2016</b> <b>Scheduled patent expiry date: August 11, 2036 (based on a PCT application filed on August 11, 2016)</b> <b>Owner: Cerenis Therapeutics Holding S.A.</b> <b>Licensee: Not applicable</b>		
Country	Application No./Patent No.	Status
United States	62/373,508	Under review

### **11.2.3. Partnership, research, service supply and license contracts granted by or to the Company**

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Please refer to Section 22 of this present Registration Document.

### **11.2.4. Type and scope of patents**

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All the patents and patent applications above, whether under an exclusive license to or fully owned by the Company, constitute the entire portfolio of the Company, i.e. a total of 78 patent applications under review and 190 patents issued.

All these rights encompass families of patents whose periods of validity range from 2020 (for Family 9) to 2032 (for Family 2), and up until 2035 if the patents for Family 3 are issued, which guarantees some flexibility in process management and in the strategic use of rights by the Company's executive officers, in keeping with the Company's objectives.

A technology that may be protected by filing and processing patent applications and by maintaining patent rights issued is being produced. The required duration for a scientific project to progress sufficiently and for its findings to be regarded as reliable before any decision on patents can be taken varies according to the type of invention.

Patent applications currently under review cover compounds, their use in human therapy and chemical synthesis methods.

### **11.2.5. Protected territories**

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The Company's patent applications are generally registered in the form of international applications and are reviewed in the jurisdictions of major markets, in particular in the United States, Europe and Japan. In addition, the Company's patent applications are often reviewed in Canada, Australia, China, India, Mexico and Israel.

## **11.3. Other information on intellectual property**

The Company owns the following trademarks:

- Trademark No. 3435966 registered in the United States
- Community wordmark No. 4596805
- Trademark No. 16 4 296 399 registered in France
- Trademark No. 16 4 296 403 registered in France

Cerenis owns the URL of its website: [www.cerenis.com](http://www.cerenis.com)

## **11.4. Disputes over intellectual property rights**

None.

## 12. INFORMATION ON COMPANY DEVELOPMENTS

### 12.1. Main Company developments since the end of the last financial year

In March 2017, the Company announced that the main criterion of CARAT, a Phase II clinical trial, had not been achieved. As a result, the indication of secondary prevention in patients with acute coronary syndrome (ACS) was suspended.

The Company is pursuing its clinical development program, the most recent of which is detailed in Chapter 6 of this Registration Document. This development is mainly focused on two distinct programs:

(a): CER-001, a mimetic of HDL. A Phase III study (TANGO) for the indication of FHFA orphan disease to evaluate the effect of six months of chronic CER 001 treatment in 30 patients with HDL deficiency. Active patient recruitment in the TANGO Phase III study is ongoing and results are expected to be available by the end of fiscal year 2017. The Company is committed to 18 sites worldwide to support patient availability with primary familial HypoAlphalipoproteinemia (FPHA), a rare but clinically important disease as an orphan pathology.

(b): CER-209, an innovative and selective P2Y<sub>13</sub> receptor agonist, reduces both atherosclerosis and steatohepatitis in preclinical models. The company has been granted US Food and Drug Administration (FDA) authorization to initiate clinical studies including the start of the Phase I study. The company is continuing the clinical development of this Phase I clinical program.

### 12.2. Identified trends, uncertainties, expenditure undertakings or events that may have an impact on the Company's prospects

As a result of the announcement of CARAT's results, the company is reorganizing to reflect the failure to meet the primary endpoint of the study for its future development.

This will result in a reduction in staff numbers, notably at the level of research and development but also at the administrative level in order to refocus the company on the phase III activity for the orphan indication and the development of the Phase I Clinic for the CER-209.

In addition to the workforce reduction, reductions in overhead will be implemented to reduce the Company's cash flow.

All these decisions will be implemented during the second quarter of 2017 and should produce savings of around €0.5 million in the second half.

### **13. FORECASTS AND PROJECTIONS ON COMPANY PROFITS**

The Company does not publish forecasts or projections on its profits.

## **14. ADMINISTRATIVE, EXECUTIVE, SUPERVISORY AND GENERAL MANAGEMENT BODIES**

### **14.1. Overview of the founders, executives and directors**

Up until July 12, 2005, the Company operated as a simplified joint-stock company.

The General Shareholders' Meeting of July 12, 2005 approved the transformation of the Company into a joint-stock company (*société anonyme*) with a board of directors and adopted new governance rules.

A summary description of the main provisions in the Company's bylaws and internal rules regarding the Board of Directors and the Specialized Committees is included in Section 21.2 "Articles of Incorporation and Bylaws" and Section 16.3 "Specialized Committees" of this Registration Document.

#### **14.1.1. Members of the Board of Directors**

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As at the date of this Registration Document, the following persons were members of the Board of Directors:

Name	Mandate	Other missions in the Company	Date of election and renewal	Term of office
<b>Richard Pasternak</b>	Chairman of the Board	Compensation Committee (Chairman) Audit Committee Search Committee	Date of appointment: Board meeting of 10/26/2011 Ratification: General Shareholders' Meeting of 5/9/2012 Renewal: General Shareholders' Meeting of 5/9/2012 Renewal: General Shareholders' Meeting of 2/6/2015 Elected Chairman of the Board: Board meeting of 5/28/2014	General Shareholders' Meeting for 2018
<b>Jean-Louis Dasseux</b>	Chief Executive Officer Director		Date elected: General Shareholders' Meeting of 7/12/2005 Renewal: General Shareholders' Meeting of 5/9/2008 Renewal: General Shareholders' Meeting of 5/9/2012 Renewal: General Shareholders' Meeting of 2/6/2015 Appointed Chief Executive Officer: Board meeting of 7/12/2005	General Shareholders' Meeting for 2018
<b>Michael Davidson</b>	Independent Director	Research Committee (Chairman)	Date of appointment: 1/16/2015 Ratification: General Shareholders' Meeting of 2/6/2015 Renewal: General Shareholders' Meeting of 2/6/2015	General Shareholders' Meeting for 2018
<b>Marc Rivière</b>	Director	Compensation Committee	Date of appointment: 1/16/2015 Ratification: General Shareholders' Meeting of 2/6/2015 Renewal: General Shareholders' Meeting of 2/6/2015	General Shareholders' Meeting for 2018
<b>Christian Chavy</b>	Independent Director	Audit Committee (Chairman)	Date elected: General Shareholders' Meeting of 2/6/2015	General Shareholders' Meeting for 2018
<b>Catherine Moukheibir</b>	Independent Director	Audit Committee	Date of appointment: Board meeting of 5/27/2015 Ratification: General Shareholders' Meeting of 9/29/2015	General Shareholders' Meeting for 2018
<b>Laura A. Coruzzi</b>	Independent Director	Compensation Committee Research Committee	Date of appointment: Board meeting of 5/27/2015 Ratification: General Shareholders' Meeting of 9/29/2015	General Shareholders' Meeting for 2018
<b>Bpifrance Participations represented by Olivier Martinez</b>	Observer		Date elected: General Shareholders' Meeting of 7/20/2010 Renewal: General Shareholders' Meeting of 2/6/2015 Change in permanent representative: Board meeting of 5/27/2015	General Shareholders' Meeting for 2018

The Directors are appointed for a renewable period of 3 years. The Chairman is appointed for the term of his mandate.

The business address of the Chairman of the Board of Directors and the Chief Executive Officer is the registered office of the Company.

The business addresses of the other Directors and the observer are as follows:

Marc Rivière: 2 Place Alexis Nihon, Suite 902, 3500 Blvd De Maisonneuve West, Westmount, Quebec H3Z 3C1, Canada

Michael Davidson: University of Chicago, Pritzker School of Medicine, 924 East 57th Street #104, Chicago, IL 60637, United States

Christian Chavy: Ixaltis, Immeuble Alliance, Bâtiment A, 178 rue des Frères Lumières, 74160 Archamps Technopole, France

Catherine Moukheibir: Immeuble la Perle Bleue, rue Furn El Hayek Achrafieh – Beirut (Lebanon)

Laura A. Coruzzi: ReGenXBIO Inc, 400 Madison Ave, Suite 8F, New York, NY 10017, USA

Bpifrance Participations: 27/31, avenue du général Leclerc, 94710 Maisons Alfort Cedex

The management expertise and experience of the persons listed above have been gained in their current and previous employment and management positions (see Section 14.1.5 of this Registration Document).

No family ties or affiliations exist between the persons listed above.

To the best of the Company's knowledge, as of the date of this document and during the last five years, no member of the Board of Directors or Management has:

- been convicted of fraud;
- been linked with a bankruptcy procedure, seizure of assets or liquidation;
- been disqualified by a court from serving as a member of an administrative, management or supervisory body or from acting in the management or administration of the business of an issuer;
- been ordered to pay penalties or been the subject of official public sanctions by statutory or regulatory authorities (including designated professional bodies).

#### 14.1.2. Other current corporate officer positions

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On the date of this Registration Document, the other corporate officer positions currently held by the members of the Board of Directors are as follows:

Name	Company	Type of office	Legal framework
Richard Pasternak	Essentialis Therapeutics	Director	American company
	Magenta Medical Ltd	Director	Israeli company
	Bridge Medicines	Scientific advisor	American company
Jean-Louis Dasseux	Cerenis Therapeutics Inc.	CEO	American company
Christian Chavy	<i>Personally</i> Ixaltis	Chairman of the Board	Simplified joint-stock company
Michael Davidson	<i>personally</i> Corvidia Therapeutics	CEO	Société de droit américain
Marc Rivière	<i>Personally</i> GLWL Inc	Director	Canadian company
	Esperas Inc	Director	Canadian company
	Aurka Inc	Observer	Canadian company
	AL-S Pharma AG	Director	Swiss company
	Optina Diagnostics	Director	Canadian company
	MRCL Inc	Founder & President	Canadian company
	Festival Classica OBNL	Director	Canadian association
Catherine Moukheibir	<i>Personally</i> Ablynx nv	Director	Listed Belgium company
	MedDay Pharmaceuticals	Chairman of the Board	French company
	Zealand Pharma	Director	Danish company
	GenKyoTex	Director	Swiss company
Laura A. Coruzzi	<i>Personally</i> Taaneh	Director	American company

All positions are held outside the Group with the exception of that of Chief Executive Officer of Cerenis Therapeutics Inc., which is held by Jean-Louis Dasseux.

#### 14.1.3. Directors whose terms expired in 2016

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None.



#### 14.1.4. Other corporate officer positions held the last five years which have ended

As at the date of this Registration Document, the other corporate officer positions held by the members of the Board of Directors in the last five years, which have now ended, are as follows:

Offices held in the last five years, having ended as of today		
Name	Company	Office
Richard Pasternak	Association of Black Cardiologists Founder of the American Heart Association	Director General manager
Jean-Louis Dasseux	-	
Christian Chavy	Personally Gedeon Richter Preglem Greer Laboratoires Inc Stallergenes	Director Director Director and Chief Executive Officer
Michael Davidson	-	-
Marc Rivière	Aptalis (formerly Axcan) Canada Colucid	Director Observer
Catherine Moukheibir	Personally OctoPlus,NL (company sold) Creabilis (company sold) Innate Pharma	Director Chairman of the Board Membre of the Executive Board
Laura A. Coruzzi	-	

#### 14.1.5. Biographies of the Directors



##### **Richard PASTERNAK**

*Chairman of the Board of Directors and Director*

Dr. Richard C. Pasternak has spent the last 35 years as a clinician-researcher in both academia and the pharmaceutical industry. He is currently a professor in the Department of Medicine and Pharmacology at Weill Cornell Medical College, a senior advisor to Bay City Capital and Bridge Medicines, and a strategic consultant. He has served on several boards of directors and is currently Chairman of the Board of the Directors of Cerenis Therapeutics (as well as Chairman of the Compensation Committee), Director of Essentialis Therapeutics (and acting CEO since March 2012) and Director of Magenta Medical Ltd.

Dr. Pasternak retired from Merck and Co. in 2010, where he served as Vice President of Clinical Research and Head of the Cardiovascular Therapeutic Area (2004-2008), and Vice President, Head of Global Scientific Affairs and Scientific Leadership (2008-2010). His various positions led him to play a key communications role on crucial global issues regarding regulatory affairs. He also worked on strategic development, advised on regulatory and medical affairs, and addressed health policy issues. As an executive officer, he liaised with senior management regarding medical and scientific affairs.

Before joining Merck, Dr. Pasternak was Director of Preventive Cardiology and Cardiac Rehabilitation at Massachusetts General Hospital, Boston, and Professor of Medicine at Harvard Medical School after being a member of the Harvard faculty since 1983. He obtained his B.A. and M.D. from Yale University and completed his medical training and cardiology studies at Massachusetts General Hospital.

Dr. Pasternak has a long-standing interest in vascular diseases, lipid disorders and atherosclerosis, in addition to epidemiology, disease prevention, patterns of practice and disease management. He was a member of the NIH Coordinating Committee of the National Cholesterol Education Program (NCEP) and third adult treatment panel (ATP III), has served on numerous national and international committees, and has published and presented his work at many conferences.



**Jean-Louis DASSEUX**

*CEO, Director*

Dr. Jean-Louis Dasseux is the founder of Cerenis and one of the world's leading experts in lipid metabolism, lipid-protein interaction, and cardiovascular disease. He has more than 25 years of experience in the pharmaceutical industry. Dr. Dasseux has generated more than 69 patents related to HDL, RLT, and the treatment of cardiovascular disease. He was the inventor of a high-capacity reverse lipid transport peptide HDL mimetic drug (ETC-642) and a series of small molecule compounds that raise blood HDL levels (ETC-1001 and ETC-1002). He held management positions at Esperion Therapeutics (Sr. Vice President of Business Development & Technologies, and Vice President of Chemistry & Technologies), a company that developed the first generation of HDL mimetic drugs (pro-apoA-I, apoA-I Milano, peptide apoA-I) until the company was bought by Pfizer for USD 1.3 billion. Before joining Esperion, he was Research Director at Fournier, the French pharmaceutical group, where he set up and headed the research center in Heidelberg, Germany. Jean-Louis Dasseux holds an MBA from the Ross School of Business of the University of Michigan, in the United States. He earned his Master's Degree in Biochemistry from Bordeaux II University and his Ph.D. in Physical Chemistry from Bordeaux I University. He has held postdoctoral research positions at the Department of Chemistry of the University of Laval in Quebec, the Department of Physics at the University of Tennessee in Knoxville, Tennessee, and at the European Molecular Biology Laboratory in Heidelberg, Germany.



**Marc RIVIÈRE**

*Director*

Marc Rivière joined the TVM Capital Life Science team based in Montreal, Canada, in 2013 after spending 20 years in international drug development and the previous 10 years in medical practice and public health in Europe and the Middle East. Marc Rivière's expertise covers all aspects of drug development in different clinical indications, from pre-clinical development to post-market monitoring. At TVM Capital Life Science, he focused on assessing potential transactions and the management of investments in therapeutics. Before joining TVM Capital Life Science, Marc Rivière served as Vice President at Axcan Pharma Inc. in charge of clinical development, medical affairs and pharmacovigilance and was a member of the Axcan Licensing Committee. He has also held the positions of Senior Vice President, Clinical Development, at Caprion Pharmaceuticals; Chief Medical Officer of Bioniche Life Sciences Inc.;

CEO of Xenon Genetics Inc.; Vice President of Clinical Affairs at Aeterna Labs and Executive Vice President and Regional Director at Quintiles Inc. Marc Rivière earned his M.D. from Paul Sabatier University, Toulouse, and his Specialist Degree in Tropical Diseases from Bordeaux II University.



**Christian CHAVY**

*Director*

Christian Chavy served as Chief Executive Officer of the Stallergenes Group from March 2014 to March 2016.

Prior to that date, beginning in 2010, he held strategic positions within the ARES Life Science investment fund, dedicated to health. He also held the position of President of World Operations for Actelion Pharmaceuticals (United States, Europe, Japan and rest of the world). Before joining Actelion, he was Vice President of the medicine and reproduction Strategic Unit at Serono in Geneva and President of the French subsidiary of Serono. He also spent five years in the Rhône Poulenc Rorer Group as President of Rorer Canada after having been President and CEO of Rorer France. Christian Chavy is a graduate of ESSEC and a former student of the Institut de Contrôle de Gestion de Paris (ICG).



**Michael DAVIDSON**

*Director*

Michael H. Davidson is Professor of Medicine and Director of the Lipid Clinic at the University of Chicago. He is also Chief Physician and Executive Vice President of Omthera Pharmaceuticals, a subsidiary of Astra Zeneca Pharmaceuticals.

Dr. Davidson is a leading expert in lipidology. He has conducted over 1,000 clinical trials, published over 300 articles in medical journals and has written three books on lipidology. His research experience includes pharmaceutical and nutritional clinical trials, including advanced research on statins, new drugs designed to reduce lipid levels, and Omega-3 fatty acids. He was a founding member of the National Lipid Association and introduced self-training modules which lead to a Certificate in Lipidology. He was also the founding CEO of the Chicago Center for Clinical Research, the largest clinical research site in the United States, which was purchased by Pharmaceutical Product Development in 1996. Dr. Davidson was also Chief Physician and co-founder of Omthera Pharmaceuticals in 2008, which was acquired by Astra Zeneca in 2013 for USD 440 million.

Dr. Davidson specialized in internal medicine, cardiology and clinical lipidology. He is a member of the American College of Cardiology and American College of Chest Physicians. He also served as President (2010-2011) of the National Lipid Association. Experts rank Dr. Davidson fourth among the world's experts on lipids. He has been listed in the magazine "The Best Doctors in America" over the last ten years and was named Father of the Year by the American Diabetes Association in 2010.



**Catherine MOUKHEIBIR**

*Director*

Catherine Moukheibir has more than 20 years of experience in finance, including 15 years in the biotech industry, and has held a number of positions in management and as company director. At Innate Pharma, where she is a member of the Management Board, she was responsible for a major financial restructuring. Before joining Innate, Ms. Moukheibir served as Chief Finance Officer at Movetis, a Belgian biotech company (2008 to 2010), where she worked on the IPO on Euronext Brussels, and then on the acquisition by Shire. She currently serves on the boards of MedDay Pharla, Ablynx and Zealand. Prior to that, she was Director of Capital Markets for the Zeltia Group (2001-2007), a Spanish biopharmaceutical and chemical company, where she spearheaded the financial strategy. Before joining Zeltia, she was Management Consultant and then Executive Director for two leading investment banks: Salomon Smith Barney and Morgan Stanley.



**Laura A. CORUZZI**

*Director*

Laura A. Coruzzi is the Senior Vice President of Intellectual Property at RegenXBio. Prior to joining RegenXBio, Ms. Coruzzi was a partner at Jones Day, an international legal practice. She counsels clients on patent strategies for biotech and pharmaceutical therapeutics and diagnostics. Her practice encompasses all aspects of patent law, including prosecution, litigation and appeals, in a variety of disciplines in the life sciences, including genetic engineering, molecular biology, virology, vaccines, immunology, therapeutic antibodies, other biologic and small molecule therapeutics, diagnostics, drug discovery, and drug delivery. Before joining Jones Day, Ms. Coruzzi was one of the first members of Pennie & Edmonds' biotechnology group founded by S. Leslie Misrock, affectionately known as the "father of biotechnology patent law." Most recently, she was a member of the team representing Myriad in Association for Molecular Pathology v. Myriad Genetics (U.S. Supreme Court 2013). Ms. Coruzzi her Ph.D. in Biology from Fordham University and completed a post-doctoral fellowship at the Mount Sinai School of Medicine, New York, before entering the practice of law.



**Olivier MARTINEZ**

*Representative of Bpifrance Participations, Observer*

Olivier Martinez is Investments Director within the Innovation Department of Bpifrance Investissement.

From 1992 to 1997, Olivier Martinez was a student researcher at the Pasteur Institute and later at the Curie Institute in the field of cellular biology. Following completion of a management training program, Olivier joined the Life Sciences Group of Gemini Consulting, where he spent two years working on projects in the pharmaceuticals and health sectors. In 2000, he joined Bioam Gestion as project manager and was appointed

Investment Director and member of the Executive Board in 2004. Following the takeover of Bioam Gestion by CDC Entreprises in July 2010, Olivier Martinez joined the Life Sciences team of CDC Entreprises, which manages InnoBio and Bioam funds and advises the Fonds Stratégique d'Investissement (FSI) on its investments in biotechnology companies. CDC Entreprises, the FSI, FSI Régions and Oséo are today grouped within Bpifrance, the public investment bank.

Olivier Martinez is a graduate of the École Normale Supérieure (Ulm). He holds a Doctorate in Cellular Biology from Paris XI University and a diploma from the School of Engineers, which he earned in 1998.

#### **14.1.6. Executive securities transactions**

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No securities transactions were disclosed by executives in 2016.

#### **14.2. Conflicts of interest within administrative bodies and within senior management**

To the Company's knowledge on the date of this document, no conflicts of interest have been identified between the duties of each member of the Board and Management with respect to the Company in their capacity as corporate officers and their private interests or other duties.

To the Company's knowledge on the date of this document, there is no arrangement or agreement signed with the principal shareholders, clients or suppliers under the terms of which one of the members of the Board of Directors or Management has been selected in this capacity

To the Company's knowledge on the date of this document, there is no restriction approved by the members of the Board of Directors and Management concerning the sale of their stake in the capital of the Company.

## 15. COMPENSATIONS AND BENEFITS

### 15.1. Compensation of Directors and officers

The tables below are consistent with AMF recommendation no. 2014-14.

**Table 1: Summary table of compensation, stock options (SO) and bonus shares (BS) granted to each corporate executive officer**

Summary table of compensation, stock options (SO) and bonus shares (BS) granted to each corporate executive officer			
	2014	2015	2016
<b>Richard Pasternak, Chairman of the Board*</b>			
Compensation for the year	EUR 23,333	EUR 80,000	EUR 0
Valuation of multi-year variable compensation allocated during the year			
Valuation of the stock options (SO) allocated during the year (detailed in table 4)			EUR 150,547
Valuation of the bonus shares (detailed in table 4)			
<b>Total</b>	<b>EUR 23,333</b>	<b>EUR 80,000</b>	<b>EUR 193,547</b>
<b>Jean-Louis Dasseux, Chief Executive Officer</b>			
Compensation of the year (detailed in table 2)	EUR 409,812	EUR 618,070	EUR 462,376
Valuation of multi-year variable compensation allocated during the year			
Valuation of the stock options (SO) allocated during the year (detailed in table 4)			
Valuation of the bonus shares (detailed in table 6)		EUR 185,137	EUR 2,651,873
<b>Total</b>	<b>EUR 409,812</b>	<b>EUR 803,207</b>	<b>EUR 3,114,249</b>

*\*Ongoing mandate as of June 1st 2014 and Director before this date*

**Table 2: Summary table of the compensation of each corporate executive officer**

The following table shows the compensation due to executive corporate officers for the years ended December 31, 2014, 2015 and 2016 and the gross compensation paid to said persons during the same years.

	2014		2015		2016	
	Amounts due <sup>(1)</sup>	Amounts paid <sup>(2)</sup>	Amounts due <sup>(1)</sup>	Amounts paid <sup>(2)</sup>	Amounts due <sup>(1)</sup>	Amounts paid <sup>(2)</sup>
<b>Richard Pasternak, Chairman of the Board*</b>						
Fixed compensation <sup>(2)</sup>	EUR 23,333	EUR 18,636	EUR 40,000	EUR 40,000	EUR 40,000	EUR 40,000
Annual variable compensation						
Multi-year variable compensation						
Exceptional compensation			EUR 40,000	EUR 30,000 <sup>(5)</sup>	EUR 0	EUR 10,000 <sup>(8)</sup>
Directors' fees	EUR 10,417	EUR 16,667			EUR 3,000	EUR 3,000 <sup>(9)</sup>
Benefits in kind						
<b>TOTAL</b>	<b>EUR 33,750</b>	<b>EUR 35,303</b>	<b>EUR 80,000</b>	<b>EUR 70,000</b>	<b>EUR 43,000</b>	<b>EUR 53,000</b>
<b>Jean-Louis Dasseux</b>						
Fixed compensation <sup>(2)</sup>	EUR 378,400	EUR 378,400	EUR 361,446	EUR 361,446	EUR 365,600	EUR 365,600
Annual variable compensation	EUR 31,412		EUR 166,262	EUR 66,412	EUR 58,496	EUR 166,262
Multi-year variable compensation						
Exceptional compensation			EUR 52,082 <sup>(6)</sup>	EUR 52,082 <sup>(6)</sup>		
Directors' fees						
Benefits in kind			EUR 38,280 <sup>(6)(7)</sup>	EUR 11,697 <sup>(6)(7)</sup>	EUR 38,280 <sup>(6)(7)</sup>	EUR 25,520 <sup>(6)(7)</sup>
<b>TOTAL</b>	<b>EUR 409,812</b>	<b>EUR 378,400</b>	<b>EUR 618,070</b>	<b>EUR 483,900</b>	<b>EUR 462,376</b>	<b>EUR 557,382</b>

\* Ongoing mandate as of June 1st 2014 and Director before this date

(1) For the year.

(2) For the year.

(3) Mr. Dasseux's compensation consists of a fixed compensation for his corporate office, which amounted to €275,346.45 for 2014, and fees under his service contract which amounted to €103,053.48 (excl. taxes) for 2014 (see Section 16.2.1 "Service contract with Jean-Louis Dasseux, Director and Chief Executive Officer" of this Registration Document). This agreement ended in 2015 following the IPO.

For 2015, the Board of Directors, meeting on January 16, 2015, set Mr. Dasseux's gross annual compensation at €361,446.

For 2016, the Board of Directors, meeting on January 21, 2016, set Mr. Dasseux's gross annual compensation at €365,600.

(4) The 2014 bonus was based on five criteria: (i) identification of CER-001 development opportunities (30%), (ii) organization of CER-001 evaluation meetings with international experts (25%), (iii) establishment of a Company financing strategy (15%), (iv) Company restructuring prior to May 2014 (25%), and (v) closure of the two laboratories (5%). This bonus carried a discretionary portion equivalent to €35,000, which was correlated with the launch of the IPO process. This portion was paid to him in March 2015. The assessment about objectives attainment was done by the Board of Directors upon recommendation of the Compensation Committee.

The Board of Directors meeting on January 16, 2015 set the 2015 bonus target for Mr. Dasseux at 40% of his gross annual compensation for 2015, and set the following criteria: (i) success of the IPO (40%), (ii) production of clinical batches of CER-001 (20%), (iii) inclusion of the first patient in the Phase II CARAT-HDL study (20%) and (iv) inclusion of the first patient in the Phase II/III TANGO study (20%). This portion was paid to him in January 2016. The assessment about objectives attainment was done by the Board of Directors upon recommendation of the Compensation Committee.

The Board of Directors' meeting on January 21, 2016 set the 2016 bonus target for Mr. Dasseux at 40% of his gross annual compensation for 2016, and set the following criteria: (i) progress and results of the CARAT clinical trial (40%), (ii) progress and recruitment of patients for the TANGO clinical trial (20%), (iii) production of clinical batches of CER-001 (20%), (iv) award of FDA approval (IND, Investigational New Drug application) for CER-209 (10%), (v) success of additional refinancing following the award of the IND for CER-209 (10%).

(5) At its meeting of May 27, 2015, the Board of Directors decided to give Richard Pasternak, in his position as Chairman of the Board, a bonus of €10,000 gross for his past assistance and a bonus of €20,000 gross for the work performed during the IPO.

(6) At its meeting of May 27, 2015, the Board of Directors decided to award €90,362 gross to Jean-Louis Dasseux, as Chief Executive Officer, which will take the form of a company car (calculation of the costs over 18 months: in-kind benefit and amortization of the vehicle purchased by the Company) and a cash payment for the balance.

This exceptional compensation was paid because of the success of the IPO.

(7) The amount indicated as benefit in kind represents the amount paid by the Company for providing a company car, the cost applied for 5.5 months in 2015 and 12 months in 2016 to the total valuation calculated over 18 months.

(8) At its meeting of January 21, 2016, the Board of Directors decided to give Richard Pasternak, in his position as Chairman of the Board, a bonus of €10,000 gross.

(9) For chairing the Compensation Committee.



**Table 3: Summary table of Directors' fees and other compensation received by non-executive corporate officers**

Non executive corporate officers	Compensation	Net amounts paid in 2014	Net amounts paid in 2015	Net amounts paid in 2016
Guy Paul Nohra <sup>(1)</sup>	Director's fees	EUR 0	EUR 0	EUR 0
	Other compensation	EUR 0	EUR 0	EUR 0
Sofinnova Partners represented by Denis Lucquin <sup>(3)</sup>	Director's fees	EUR 0	EUR 0	EUR 0
	Other compensation	EUR 0	EUR 0	EUR 0
HealthCap IV Bis represented by Johan Christenson <sup>(2)</sup>	Director's fees	EUR 0	EUR 0	EUR 0
	Other compensation	EUR 0	EUR 0	EUR 0
Alexandra Goll <sup>(1)</sup>	Director's fees	EUR 0	EUR 0	EUR 0
	Other compensation	EUR 0	EUR 0	EUR 0
Marc Rivière <sup>(4)</sup>	Director's fees	EUR 0	EUR 0	EUR 0
	Other compensation	EUR 0	EUR 0	EUR 0
Michael Davidson <sup>(4)</sup>	Director's fees	EUR 0	EUR 17,378	EUR 16,100
	Other compensation	EUR 0	EUR 0	EUR 0
Christian Chavy <sup>(5)</sup>	Director's fees	EUR 0	EUR 15,875	EUR 14,605
	Other compensation	EUR 0	EUR 0	EUR 0
Catherine Moukheibir <sup>(6)</sup>	Director's fees	EUR 0	EUR 15,000	EUR 20,000
	Other compensation	EUR 0	EUR 0	EUR 0
Laura A. Coruzzi <sup>(6)</sup>	Director's fees	EUR 0	EUR 0	EUR 26,600 <sup>(7)</sup>
	Other compensation	EUR 0	EUR 0	EUR 0
<b>TOTAL</b>		<b>EUR 0</b>	<b>EUR 48,253</b>	<b>EUR 77,305</b>

<sup>1</sup> Director until January 16, 2015

<sup>2</sup> Director until, May 27, 2015

<sup>3</sup> Director until December 26, 2015

<sup>4</sup> Director since January 16, 2015 (appointment by the Board on January 16, 2015, ratified by the General Shareholders' Meeting of February 6, 2015)

<sup>5</sup> Director since February 6, 2015 (election by the General Shareholders' Meeting of February 6, 2015)

<sup>6</sup> Director since May 27, 2015 (appointment by the Board on May 27, 2015, ratified by the General Shareholders' Meeting of September 29, 2015)

<sup>7</sup> Amount paid in 2016, including Directors' fees due in respect of 2015 and 2016

At its meeting of August 25, 2015, the Board decided to set the compensation for the independent directors at €25,000 gross per year on the basis of actual participation, in person or via telecommunication, at all meetings of the Board; this amount is reduced in proportion to the total number of meetings in the case of absences.

The observer does not receive attendance fees.

At its meeting of April 25, 2016, and on the recommendation of the Compensation Committee, the Board set the following new rules for allocating Directors' fees, applicable as from 2016:

- Amount of Directors' fees to be set at €5,000 per in-person meeting, based on four meetings per year, with the possibility to participate by telephone no more than once per year with the Chairman's agreement;
- An additional amount of €5,000 to be granted in the event of attendance at the majority of the meetings by telephone, actual attendance being assessed by the Chairman;
- The annual amount to be capped at €25,000;
- For those members who chair one of the Board's committees, an additional payment of €3,000 shall be granted;



- Possibility for those members who have provided special support to the Company at the behest of the Board to receive a one-off payment of €3,000;
- Total Directors' fees to be set at €115,000 (it being specified that this budget was approved by the General Shareholders' Meeting of June 10, 2016).

**Table 4: Stock warrant (SWs) and/or founder's stock warrants (FSWs) and/or stock options (SOs) awarded to each executive corporate officer by the Company or any company of its Group during the year ended December 31, 2016.**

Executive Officer	Date of grant	Nature	Valuation according Black & Sholes	Allocation	Subscription price per share	Vesting period
Richard Pasternak	01/22/2016	Warrants	EUR 150,547	134,417	EUR 9.36	01/22/2016 to 01/22/2026

The Chairman of the Board must keep 10% of the shares resulting from the exercise of stock options in registered form until the end of his duties.

No SWs or FSWs were awarded to corporate officers in 2016.

**Table 5: Stock warrants (SWs) and/or founder's share warrants (FSWs) and/or stock options (SOs) exercised by each executive corporate officer during the year ended December 31, 2016**

None.

**Table 6: Bonus shares allotted to each corporate officer during the years ended December 31, 2015 and 2016**

Bonus shares granted to each corporate officer						
Performance shares granted by the General Shareholders' meeting throughout the year to each corporate officer by the issuer and by any company of the Group	N° and date of plan	Number of shares allocated during the year	Valuation of the shares with the method used for the consolidated financial statements	Vesting date	Availability date	Conditions of performance
Jean-Louis Dasseux Managing Director	3 December 2015	200	2,420,000	3 December 2016	3 December 2017	Condition of presence
Jean-Louis Dasseux Managing director	21 January 2016	18,683	173,237	21 January 2017	21 January 2017	Condition of presence
Jean-Louis Dasseux Managing Director	21 January 2016	52,580	243,773	The furthest of these two dates: - 21 January 2017 - establishment of the performance condition	21 January 2018	The Board of 13 March 2017 established that the performance condition was not reached
<b>TOTAL for Jean-Louis Dasseux</b>		<b>271,263</b>	<b>2,837,010</b>			

The Chief Executive Officer will retain 10% of the shares awarded in registered from until the end of his duties.

**Table 7: Bonus shares allotted which became available for each corporate officer during the year ended December 31, 2016**

None.

**Table 8: History of the awards of stock warrants (SWs), founder's share warrants (FSWs) and stock options (SO) to corporate officers**

Refer to the tables in Sections 21.1.4.1 "Stock warrants plan," 21.1.4.2 "FSW plan," and 21.1.4.3 "Option plan" of this Registration Document.

**Table 9: Stock warrants (BSA) or founder's stock warrants (BSPCE) and stock options (SO) made to the top 10 non-officer employees and warrants they have exercised**

	2016		
	BSPCE	BSA	Options
Average weighted price	EUR 5,45		EUR 4,22
Number of BSPCE, SO or BSA allotted during each of these years to the ten Group employees awarded the largest number of BSPCE, SO or BSA thus awarded on the date of the Registration Document	0	0	0
Number of BSPCE, SO or BSA allotted during each of these years to the ten Group employees awarded the largest number of BSPCE, SO or BSA thus exercised on the Date of the Registration Document	43,250	0	10,000

**Table 10: History of bonus shares allotments**

HISTORY OF BONUS SHARES ALLOCATION				
INFORMATION ON BONUS SHARES				
General Meeting date	09/28/2015	09/28/2015	09/28/2015	09/28/2015
Board meeting date	12/03/2015	01/21/2016	01/21/2016	06/10/2016
Total number of free shares including the number allocated to:	365,000	40,000	160,000	5,000
<i>Jean-Louis Dasseux, Chief Executive Officer (4)</i>	<i>200,000</i>	<i>18.683</i>	<i>52,580</i>	<i>-</i>
Shares vesting date	12/03/2016 (1)	01/21/2017 (2)	(3)	10/06/2017 (2)
End of retention period	12/03/2017	01/21/2018	(5)	06/10/2018
Number of shares vested at 03/15/2017	365,000	40,000	0	0
Number of shares cancelled or void at 03/15/2017	0	0	160,000 (6)	0
Free shares allocated in vesting period at 03/15/2017	-	-	-	5,000

<sup>(1)</sup> Vesting is not subject to any performance condition; this allotment was made following the success of the IPO. However, the party must be present, as required.

<sup>(2)</sup> Vesting is not subject to any performance condition. However, the party must be present, as required.

<sup>(3)</sup> Full vesting will occur at the later of the following two dates: (i) one year from the allotment date (i.e. January 21, 2017) or (ii) at the time satisfaction of the principal criterion of the CARAT trial is verified, subject to the party being present, as required.

<sup>(4)</sup> The Chief Executive Officer must keep 10% of the shares thus allotted in registered form until the end of his duties.

<sup>(5)</sup> Shares must be retained for a minimum of one year as from when they vest.

<sup>(6)</sup> The Board meeting of March 13, 2017, recorded the failure to achieve the performance objective for this allocation of bonus shares (see paragraph 16.5.3.2.4).

**Table 11**

The following table provides clarifications as to the compensation conditions and other benefits granted to executive corporate officers:

Table setting the compensation conditions and other benefits granted to executive corporate officers								
	Employment contract		Additional retirement plan		Severance payments or benefits due, or which could be owed because of termination or change of position		Indemnities due under a non-competition clause	
	Yes	No	Yes	No	Yes	No	Yes	No
<b>Richard Pasternak</b> Chairman of the Board and Director		x		x		x		x
Date term begins: Cooptation at Board of 10/26/2011, approval by General Meeting of 05/09/2012 Date term ends: General Shareholders' Meeting called to approve the financial statements for the year								
<b>Jean-Louis Dasseux</b> Chief Executive Officer and Director		x	x		x			x
Date term begins: General Shareholders' Meeting of 07/12/2005 Date term ends: General Shareholders' Meeting called to approve the financial statements for the year								

Note: cf. section below for the detail of the compensation for termination of service

The Company has introduced an "Article 83" defined contribution supplemental retirement plan, with retroactive effect from January 1, 2016.

The main features of this agreement, which applies to Mr. Dasseux as well as to all company employees, are as follows:

- A group life insurance contract with compulsory membership and defined contributions (provided for under Article 83 of the French Tax Code, Sections 20 and 22 of Article R. 321-1 of the French Insurance Code, and Article 242.1 of the French Social Security Code);
- Contract offered to all staff in accordance with Article L. 242.-1 of the French Social Security Code and implementing decrees;
- Contract offered to all staff without length-of-service conditions; corporate officers (*assimilés salariés* – statutory employees) must obtain approval from their relevant body to be eligible;
- The reference salary is the gross salary paid to plan beneficiaries;
- The benefits are accrued after each payment, in the form of financial savings that are converted into an annuity on retirement;
- Benefits are funded by an employer contribution of 1.20% of salary; employees may make voluntary contributions as appropriate;
- An annuity estimate is given in the individual annual statements sent out every April; the amounts depend on the elected benefits, retirement age and voluntary contributions;
- No tax; contributions made to the plan are exempt from social security up to a limit of 5% of salary not to exceed five times the annual social security ceiling; only an employer contribution (*forfait social*) of 20% of contributions payable by Cerenis is collected by the URSSAF.

The expense recognized by Cerenis for Mr. Dasseux in 2016 was €6,477, to which should be added the 20% employer contribution.

#### **15.2. Sums provisioned or recognized by the Company for the purpose of paying pensions, retirement or other benefits to Directors and executives**

The Company has not set aside any monies for the purposes of payment of pensions, retirements and other benefits to executive officers.

The Company has not paid any arrival or departure bonuses to executive officers.

#### **15.3. Elements of compensation and benefits due or which could be owed because of or after the termination of duties as executives of the Company**

On February 27, 2015, the Board modified the conditions for payment of the severance package to Mr. Dasseux, following the recommendations of the Compensation Committee, in relation to the essential character of the presence of the CEO to the pursuit of clinical studies made by the Company and the development of its activities.

The new severance conditions are as follows:

In the event of (i) dismissal of Mr. Dasseux from his position as Chief Executive Officer for reasons other than a violation of the laws or of the Company's bylaws, or gross negligence or misconduct, or (ii) non-renewal not agreed to by Mr. Dasseux for reasons other than a violation of the laws or of the Company's bylaws, or gross negligence or misconduct, the Board of Directors may pay him an indemnity, the gross amount of which shall be equal to the sum of the gross compensation he has received from the Company, for any reason, during the twenty-four (24) months prior to his departure, if the following two criteria are met on the date of departure:

- A management structure is in place to run at least one of the two clinical trials (TANGO or CARAT trials); it is specified that this criterion will be considered to have been met if, on the date of termination, a Chief Medical Officer in charge of both trials has been hired, the Company has the necessary funding to run at least one of the two, and the first patient has been enrolled in at least one trial; and
- An average stock market capitalization of the Company is at least equal to €80 million over a three-month period after the Company's IPO.

#### **15.4. Loans and guarantees granted to Directors**

None.

## 15.5. Report on the 2017 compensation policy

The Say On Pay report approved previously by the Board of Directors meeting of April 27, 2017, appears below:

### **CERENIS THERAPEUTICS HOLDING**

A limited liability company with capital of €915,163.15  
Registered office: 265, rue de la Découverte, 31670 Labège  
TOULOUSE TRADE AND COMPANIES REGISTER NO. 481 637 718

### **Approval of the principles and criteria for determining, distributing and allocating total compensation and in kind benefits that may be awarded to the Chairman of the Board of Directors and the CEO (*ninth and tenth resolutions*)**

This part constitutes the report issued in accordance with Articles L. 225-37-2 and R. 225-29-1 of the French Commercial Code.

In determining the total compensation of the executive corporate officers, the Board of Directors, on a proposal by the Compensation Committee, has taken into account the following principles, pursuant to the recommendations of R13 of the September 2016 edition of the MiddleNext corporate governance code:

- ♦ **Thoroughness:** the determination of the compensation of executive officers must be thorough: fixed portion, variable portion (bonuses), stock options, bonus shares, attendance fees, pension conditions and specific benefits must be incorporated in the holistic assessment of the compensation.
- ♦ **Balance** among the elements of compensation: each element of compensation must exist for a reason and must correspond to the common good of the company.
- ♦ **Benchmarking:** to the extent possible, this compensation must be assessed within the context of a reference profession and market and adjusted to the company's circumstances, while also paying attention to its inflationary effect.
- ♦ **Consistency:** the executive corporate officer's compensation must be aligned with that of the other company executives and employees.
- ♦ **Understandability** of the rules: the rules must be simple and transparent; the performance criteria used to establish the variable portion of the compensation or, where applicable, for the allocation of stock options or bonus shares, must be connected to the company's performance, correspond to its goals, and be challenging, explicable, and, to the extent possible, sustainable. They must be detailed without calling into question the confidentiality that may be justified in the case of some elements.
- ♦ **Measurement:** the determination of the compensation and allocation of stock options or bonus shares must strike the right balance and simultaneously factor in the common good of the company, market practices and the executives' performances.
- ♦ **Transparency:** "shareholders" are informed annually in accordance with applicable regulations of the entire compensation and benefits received by executives.

To determine the compensation policy, the Board reviewed all current projects and future prospects. The Board also examined the recent events that have affected the Company, particularly the CARAT results, which were published on March 1, 2017; the TANGO trial, which is continuing; and the start of the clinical development of CER-209.

### **1/ Principles and criteria for determining, distributing and allocating total compensation and in kind benefits that may be awarded to the Chairman of the Board of Directors and the CEO**

The principles and criteria set by the Board, on the recommendation of the Compensation Committee, are as follows:

- Fixed compensation
  - The fixed compensation of the Chairman of the Board of Directors is set by taking into consideration the level and difficulty of the responsibilities, experience in the position, seniority in the Company and the practices of comparable companies.
- Allocation of stock options and stock warrants (SWs)

Stock options may be allocated to the Chairman of the Board of Directors.

The Chairman of the Board must retain 10% of the shares that come from the exercise of stock options until the end of his duties.

Stock warrants may also be allocated to him in order to give him a stake in the fluctuation of the market price, by guaranteeing a personal financial investment as part of the subscription of the warrant.

- Exceptional compensation
  1. The Board of Directors may decide, on a proposal by the Compensation Committee, to grant exceptional compensation to the Chairman of the Board of Directors under very specific circumstances. The payment of this type of compensation must be able to be justified by an event such as the completion of a major transaction for the Company, etc.

The exceptional compensation is capped at 40% of annual fixed compensation.

- Attendance fees

The Chairman of the Board receives a fixed amount in attendance fees for his duties as Chairman of the Compensation Committee.

Where applicable, the payment of exceptional compensation awarded in 2017 is contingent on the approval by the General Shareholders' Meeting of the compensation of the Chairman of the Board of Directors that is paid or allocated for said financial year. (ex post vote).

### **2/ Principles and criteria for determining, distributing and allocating the total compensation and in kind benefits package that may be awarded to the CEO**

The principles and criteria set by the Board, on the recommendation of the Compensation Committee, are as follows:

- Fixed compensation

- The fixed compensation of the CEO is set by taking into consideration the level and difficulty of the responsibilities, experience in the position, seniority in the Company and the practices of comparable companies.

The Board of Directors reexamines the amount of the fixed compensation on an annual basis after reviewing the work of the Compensation Committee.

- Annual variable compensation

The target variable compensation corresponds to 40% of the annual fixed compensation, with the stipulation that in all cases, annual variable compensation is capped at 50% of annual fixed compensation.

The CEO is eligible for annual variable compensation. The Board of Directors, on the recommendation of the Compensation Committee, determines each year the diversified, challenging, precise and pre-established performance criteria that allow for a complete analysis of the performance, in alignment with the Company's medium-term strategy and shareholders' interests. These criteria relate mainly to the progress of the R&D programs, but also to the search for funding, the establishment of partnerships and the implementation of restructuring measures.

The performance criteria chosen for financial year 2017, in two stages, are:

Criteria determined before the announcement of the results of the CARAT trial, representing 45% of the 2017 criteria:

- Results of the CARAT trial
- Progress of the TANGO trial
- Completion of the CER-209 Phase I (single dose) trial

Criteria determined after the announcement of the results of the CARAT trial, for the balance, i.e., 55% of the 2017 criteria:

- Interim analysis of the TANGO trial
- Funding of Cerenis's growth
- Search for new opportunities

For confidentiality reasons, the specific features of the performance conditions connected to the progress of the R&D programs are not made public.

The portion of the variable compensation that was contingent on the results of the CARAT trial, set through a decision prior to March 1 (the day of the announcement of the failure to achieve the main objective of the CARAT trial), will not be paid and the corresponding amount will not be reallocated to other targets.

Every year, the Board of Directors conducts a detailed analysis of the level of achievement of the performance conditions, on the basis of the work of the Compensation Committee.

At the same time, the Board sets new relevant performance conditions with regard to the progress of the different R&D programs and the key stages in the Company's growth and funding.

- Allocation of bonus shares

The CEO may be eligible for allocations of bonus shares, which are fully subject to a service condition and fully or partially subject to the achievement of a performance condition or conditions.

The CEO must retain at least 10% of the bonus shares that are granted to him until the end of his duties.

An employee profit-sharing mechanism in accordance with Article L. 225-197-6 of the French Commercial Code, such as the allocation of bonus shares to all Company employees, is provided for as part of the allocations to the CEO.

- Exceptional compensation

2. The Board of Directors may decide, on a proposal from the Compensation Committee, to grant exceptional compensation to the CEO under specific circumstances. The payment of this type of compensation must be justified by an event such as the completion of a major transaction for the Company, etc.

The exceptional compensation is capped at 40% of annual fixed compensation.

- Attendance fees

The CEO does not receive attendance fees as part of his director's duties.

- In kind benefits

The CEO has a company vehicle.

The payment of variable compensation and, where applicable, exceptional compensation, awarded in 2017 is contingent on the approval by the General Shareholders' Meeting of the compensation of the CEO that is paid or allocated for said financial year. (ex post vote).

### **3/ Commitments to the CEO on the basis of paragraphs 1 and 6 of Article L. 225-42-1 of the French Commercial Code**

- Severance pay

In the event of (i) dismissal of the CEO from his position as Chief Executive Officer for reasons other than a violation of the laws or of the Company's bylaws, or gross negligence or misconduct, or (ii) non-renewal not agreed to by Mr. Dasseux for reasons other than a violation of the laws or of the Company's bylaws, or gross negligence or misconduct, the Board of Directors may pay him an indemnity, the gross amount of which shall be equal to the fixed compensation, excluding the variable portion, that he will have received from the Company, during the twenty-four (24) months prior to his departure, if the following two criteria are met on the date of departure:

- a management structure is in place to run at least one of the two clinical trials (TANGO or CARAT trials); it is specified that this criterion will be considered to have been met if, on the date of termination, a Chief Medical Officer in charge of both trials has been hired, the



Company has the necessary funding to run at least one of the two, and the first patient has been enrolled in at least one trial; and

- an average stock market capitalization of the company at least equal to €80 million over a three-month period after the Company's IPO.
- Pension

The CEO is eligible for a defined contribution supplemental retirement plan.

We are requesting that you vote to approve the ninth and tenth resolutions on the principles and criteria presented above.

The Board of Directors

## 16. FUNCTIONING OF THE ADMINISTRATIVE AND MANAGEMENT BODIES

### 16.1. Management of the Company

The Company is a limited-liability company with a Board of Directors.

On July 12, 2005, the Board of Directors passed a decision to separate the functions of Chairman and CEO. Since that date, the Board of Directors is presided over by a Chairman of the Board, a position currently held by Richard Pasternak. Jean-Louis Dasseux represents the Company with regard to third parties in his capacity as CEO.

A detailed description of the Board of Directors' composition, including the expiration date of board members' terms of office, appears in Section 14.1.1, "Composition of the Board of Directors", of this Registration Document.

### 16.2. Service Contracts between the Directors and the Company

To the Company's knowledge and as of the date this document was created, there are no service contracts tying Directors and the CEO to the Company or to one of its subsidiaries.

### 16.3. Specialized committees

At its meeting of March 9, 2007, the Board of Directors decided to set up two committees to assist the former with its duties. The role and operational procedures of the Audit Committee and Compensation Committee are specified in the Board's Internal Rules and Regulations according to the terms and conditions listed below.

#### 16.3.1. Audit Committee

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##### 16.3.1.1. Tasks – Remit

The Audit Committee ensures the monitoring of issues related to the processing and control of accounting and financial information. Namely, the Audit Committee is responsible, without prejudice to the powers of the Board of Directors, for:

- Overseeing the financial reporting process and, where necessary, making recommendations to ensure it is complete;
- Overseeing the effectiveness of internal control and risk management systems and, where necessary, internal audit systems regarding procedures for preparing and processing accounting and financial information, without this undermining the Committee's independence;
- Overseeing the Statutory Auditors' assignment by reporting the observations and conclusions of the French High Council for Statutory Audit (H3C) following the audits performed in application of Articles L.821-9 *et seq.* of the French Commercial Code; and
- Issuing a recommendation relative to the Statutory Auditors proposed for appointment by the General Shareholders' Meeting. This recommendation to the Board of Directors is prepared in accordance with the provisions of Article 16 of Regulation (EU) 537/2014 mentioned above. The Committee also issues a recommendation to the Board when it is time to reappoint the Statutory Auditors, in accordance with Article L. 823-3-1 of the French Commercial Code;

- Ensuring that the Statutory Auditors comply with their independence conditions; where necessary, the Committee will take the measures required to apply Section 3 of Article 4 of Regulation (EU) 537/2014 and ensure compliance the conditions stated in the Regulation's Article 6;
- Approving the provision of services other than the certification of accounts referred to Article L. 822-11-2 of the French Commercial Code.

It reports regularly to the Board of Directors on its activities, on the results of its role in certifying the accounts, on how this role has contributed to the completeness of financial reporting, and the role it has played in the process. It notifies the Board promptly of any problems encountered.

The Board of Directors or the Chairman of said Board may also submit other matters to the Committee for such to issue an opinion or recommendation. Similarly, the Audit Committee may address any matter and issue opinions on such.

Within this context, the members of the Audit Committee may invite any guest, subject to ensuring the confidentiality of the discussions by the latter.

The Audit Committee may decide to hear the Company's CEO and perform any internal or external audits on any matter it considers as falling within its realm, provided it notifies the Board of Directors first. It also has the authority to interview persons who participate in the preparation of the financial statements or their audit (Administrative and Financial Manager, and main persons responsible for financial management).

The Audit Committee may also interview the Auditors, whom it is authorized to interview without the presence of any Company representative.

In any case, the Audit Committee's powers are merely advisory.

#### **16.3.1.2. Composition – Status - Compensation**

The Audit Committee is composed of at least three (3) members appointed by the Company's Board of Directors, following consultation with the Compensation Committee. All of the members of the Audit Committee must be chosen from among the members of the Company's Board of Directors, excluding those exercising management functions and including at least one who must have specific skills in financial or accounting matters and be independent within the meaning given to that term in accordance with the provisions of the MiddleNext Code of Corporate Governance, bearing in mind that all members must, nonetheless, possess the required minimum skills in financial and accounting matters.

The Chairman of the Audit Committee is appointed by the members of the Audit Committee for the duration of his or her term as a member of the Committee.

The duration of the terms of office of the Audit Committee members coincides with that of the terms of office as members of the Board of Directors, and ends at the first meeting of the Board of Directors held after the Annual General Shareholders' Meeting called to approve the accounts for the year over the course of which the term of office as Board member has expired.

The term of office of the members of the Audit Committee is renewable.

In addition, the Board of Directors may, at any time, terminate the duties of a member of the Committee, without prior notice and without having to justify its decision; the member is not entitled

to claim any compensation. Similarly, any member may, at any time, step down from his or her post, without having to justify his or her decision.

The members of the Audit Committee will not be compensated for the performance of their tasks, with the exception of Directors' fees. Their post within the Audit Committee may, however, entitle them to receive attendance fees in their capacity as Directors.

In the event of death or of resignation, for any reason whatsoever, of a member during their term of office, the Board of Directors may appoint a replacement for this member for the duration of the Director term of office of the new designated member.

The provisions laid down in the Internal Rules and Regulations of the Board of Directors regarding the obligations of discretion, reserve, and professional secrecy as well as those relative to conflicts of interest are applicable to the members of the Audit Committee.

The Committee may invite any person, internal or external to the Company, to participate in its meetings and in its work.

The Audit Committee's makeup is outlined in paragraph 16.5.1.2

### **16.3.1.3. Functioning and procedures**

#### *16.3.1.3.1. Convening – Meetings*

The Audit Committee meets as often as deemed necessary, and at least twice (2) a year before the Board of Directors' meeting called to approve the Company's financial statements, consolidated financial statements and interim financial statements (half-yearly and quarterly), where applicable, at the request of its Chairman.

Meeting notices are sent in writing (particularly via email) by the Audit Committee's Chairman five (5) days in advance, except for urgent meetings. The Audit Committee may also be convened verbally. If all members of the Audit Committee are present or represented, meetings may be held without prior notice. The Audit Committee may also meet at the request of two of its members or of the Chairman of the Company's Board of Directors.

Audit Committee meetings will be held at the registered office or at any other venue indicated in the call to meeting notice. They may also be held by videoconference or by any telecommunications means as specified in the Board of Directors' Internal Rules and Regulations.

#### *16.3.1.3.2. Quorum and majority*

The Audit Committee may only validly deliberate if at least half of its members are present in person, participating via videoconference or other telecommunications means or represented.

Decisions are adopted by a majority of the participating or represented members; the Chairman does not have the casting vote in the event of deadlock.

Members may be represented by any other member of the Audit Committee within the limits of a member's representation powers.

#### *16.3.1.3.3. Report*

The Chairman of the Audit Committee is tasked with ensuring that the Audit Committee's activity reports to the Board of Directors keep the Board fully informed, thereby facilitating its deliberations.

The annual report includes a presentation on the work of the Committee during the past year.

If, while carrying out its duties, the Audit Committee detects a material risk that does not appear to be adequately handled, the Chairman of the Audit Committee must immediately alert the Chairman of the Board of Directors.

### **16.3.2. Compensation Committee**

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#### **16.3.2.1. Tasks – Remit**

The Compensation Committee is specifically responsible for:

- Reviewing the main objectives proposed by senior management with regard to compensation for Company senior managers who are not executive corporate officers, including bonus share and stock option plans;
- Reviewing the compensation of senior managers who are not executive corporate officers, including bonus share and stock option plans, retirement and pension plans and benefits in kind;
- Making recommendations and proposals to the Board of Directors regarding:
  - Compensation, retirement and pension plans, benefits in kind, and other financial entitlements, including in the event that corporate officers are removed from their positions. The Committee proposes compensation amounts and structures, and notably rules for setting the variable portion, which takes into account the Company's strategy, objectives and results as well as market practices; and
  - Bonus share and stock option plans, and any other similar incentive plan, and, in particular, allocations in registered form to corporate officers eligible for this type of plan;
- Reviewing the total amount of attendance fees and how they are divided up between the Directors, as well as terms and conditions for reimbursing potential expenses incurred by members of the Board of Directors;
- Preparing and presenting, where necessary, the reports stipulated in the Board of Directors' Internal Rules and Regulations;
- Preparing any other recommendation that may be requested of the Committee by the Board of Directors regarding compensation; and
- Generally speaking, the Compensation Committee will provide any advice and make any appropriate recommendation in the above areas.

Pending the implementation of a potential Appointments Committee, the Compensation Committee may assist the Board of Directors in identifying, assessing and proposing appointments of independent Directors.

The Board of Directors or the Chairman of said Board may also submit other matters to the committee for such to issue an opinion or recommendation. Similarly, the Compensation Committee may address any matter and issue opinions on such.

As part of this process, members of the Compensation Committee may invite any senior manager of the Company whose expertise could help address an item on the agenda, provided that they observe confidentiality regarding any board discussions in which they participate.

#### **16.3.2.2. Composition – Compensation**

The Compensation Committee is composed of at least three (3) members appointed by the Company's Board of Directors. All of the members of the Compensation Committee must be chosen from among the members of the Company's Board of Directors, excluding those exercising management functions and including at least one who must be independent within the meaning given to that term in accordance with the provisions of the MiddleNext Code of Corporate Governance.

The Chairman of the Compensation Committee is appointed by the members of the Audit Committee for the duration of his or her term as a member of the Committee.

The duration of Compensation Committee members' terms of office coincides with their Board of Directors' term of office and ends at the first Board of Directors' meeting held after the Annual General Shareholders' Meeting called to approve the financial statements for the year in which the Director's term of office has expired.

The term of office of the Compensation Committee's members is renewable.

In addition, the Board of Directors may, at any time, terminate the duties of a member of the Committee, without prior notice and without having to justify its decision; the member is not entitled to claim any compensation. Similarly, any member may, at any time, step down from his or her post, without having to justify his or her decision.

The members of the Compensation Committee will not be compensated for the performance of their tasks, with the exception of directors' fees. Their post within the Compensation Committee may, however, entitle them to receive attendance fees in their capacity as Directors.

In the event of death or of resignation, for any reason whatsoever, of a member during their term of office, the Board of Directors may appoint a replacement for this member for the duration of the Director term of office of the new designated member.

The provisions set forth in the Board of Directors' Internal Rules and Regulations regarding the obligations of discretion, reserve, professional secrecy as well as those relating to conflicts of interest are applicable to the members of the Compensation Committee.

The Compensation Committee's makeup is outlined in paragraph 16.5.1.2

#### **16.3.2.3. Functioning and procedures**

##### ***16.3.2.3.1. Convening – Meetings***

The Compensation Committee meets as often as it deems necessary, and at least twice (2) a year, as convened by its Chairman.

Meeting notices are sent in writing (particularly via email) by the Compensation Committee's Chairman five (5) days in advance, except for urgent meetings. The Compensation Committee may also be convened verbally. If all members of the Compensation Committee are present or represented, the meetings may be held without prior notice.

The Compensation Committee may also meet at the request of two of its members or of the Chairman of the Company's Board of Directors.

The meetings of the Compensation Committee will be held at the registered office or any other venue indicated in the meeting notice. They may also be held by videoconference or by any telecommunications means as specified in the Board of Directors' Internal Rules and Regulations.

The Chairman of the Company's Board of Directors may be invited to each meeting of the Compensation Committee if he or she is not a member, but with no casting vote. The Chairman does not attend the deliberations regarding himself or herself.

Non-executive Directors, who are not members of the Compensation Committee, can freely participate in its meetings.

#### *16.3.2.3.2. Quorum and majority*

The Compensation Committee may only validly deliberate if at least half of its members are present in person, participating via videoconference or other telecommunications means or represented.

Decisions are adopted by a majority of the participating or represented members; the Chairman does not have the casting vote in the event of deadlock.

Members may be represented by any other member of the Compensation Committee within the limits of a member's representation powers.

#### *16.3.2.3.3. Report*

The Chairman of the Compensation Committee is tasked with ensuring that the Compensation Committee's activity reports to the Board of Directors keep the Board fully informed, thereby facilitating its deliberations.

The annual report includes a presentation on the work of the Committee during the past year.

The Compensation Committee reviews the Company's draft report in terms of executive compensations.

### **16.4. Observers**

The Company has an observer, Bpifrance Participations (formerly Fonds Stratégique d'Investissement), represented by Olivier Martinez, appointed on July 20, 2010 for a three-year term, renewed during the General Shareholders' Meeting held on February 6, 2015.

Under the terms of Article 20 of the Company's bylaws, the General Shareholders' Meeting may appoint up to two observers for three (3) year terms, which will expire at the end of the Annual General Shareholders' Meeting called to approve the accounts for the year ended and held in the year during which their term of office expired.

They are removed by decision of the Shareholders gathered at their General Meeting.

The observers are invited to all the meetings of the Company's Board of Directors under the same terms of attendance as the Directors. They have the same right to information as the Directors.

They participate in the meetings of the Company's Board of Directors with an advisory, non-deliberative vote.

## 16.5. Chairman's Report on Corporate Governance and Internal Control

Dear shareholders,

Board of Directors' Chairmen of limited-liability companies whose securities are admitted for trading on a regulated market (Euronext Paris) are required to issue a report along with this document, which includes:

- the code of corporate governance to which the Company refers, specifying any provisions excluded and the reasons for this;
- the Board of Directors' composition and application of the principle of balanced representation of women and men within its Board of Directors;
- the conditions for preparing and organizing the board's work;
- the specific terms and conditions relating to shareholder participation in General Shareholders' Meetings;
- any limitations on the CEO's powers;
- the principles and rules approved to determine compensation and benefits of any kind granted to executive officers;
- the items likely to have an impact in the event of a public tender offer;
- the internal control and risk management procedures put in place by the Company;
- the financial risks associated with the effects of climate change and measures taken by the company to reduce them.

This report was reviewed in depth by the Audit Committee on Friday, February 17, 2017, was submitted for approval by the Board of Directors on February 17, 2017, and was then forwarded to the Statutory Auditors.

### **I - CORPORATE GOVERNANCE**

In terms of corporate governance, our Company refers to the MiddleNext Code of Corporate Governance, dated September 2016, available on MiddleNext's website ([www.middlenext.com](http://www.middlenext.com)), hereafter referred to as the Reference Code.

The Board declares that it has read the items presented in the "key points" section of this Code and reviews them regularly.

However, the following provisions of this Code have not been followed at times:

- At its meeting of December 3, 2015, the Board of Directors decided to grant bonus shares to the CEO. During this meeting, the Board specifically decided that this grant would not be subject to performance conditions, as the decision was taken following the success of the IPO.

As a result, the Company did not strictly comply with recommendation R.18 of the MiddleNext Code, which states that any partial or full vesting must be subject to performance conditions.



However, in this particular case, the grant was decided on after a prior performance condition was achieved, which led to a successful IPO. Moreover, it is specified that recommendation R.18 of the MiddleNext Code has been complied with for previous bonus share grants, the vesting of which was partially subject to performance conditions.

- In addition, on January 22, 2016, the CEO, acting on the Board's delegation, decided to grant stock warrants to the Chairman of the Board of Directors. Performance conditions are not required to be met to exercise these warrants.

As a result, the Company did not strictly comply with recommendation R.18 of the MiddleNext Code, which states that all or part of a stock warrant exercise must be subject to performance conditions.

However, in this particular case, the grant was decided on after a prior performance condition was achieved, which led to a successful IPO.

- Furthermore, the term of office for Board members is set at 3 years. No provision has been made for the staggering of terms of office (Recommendation R.9 of the MiddleNext Code). Given the short length of the terms of office (3 years), staggering is difficult in practice, unless the terms of office of certain Directors are reduced to 1 or 2 years for this purpose, which is not advisable as it would affect the stability of the Board.

## **The Board of Directors and the Committees**

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### **The Board of Directors**

#### *Composition of the Board*

The term of office for Directors is 3 years; in the event of replacement of a Director who has resigned, his/her successor is co-opted for the remaining term.

At December 31, 2016, the Board was composed of eight members: including seven Directors and one non-voting observer.

Name	Duties in the Company	Independen t	Age	Gender	Nationality	Number of Company shares held	1 <sup>st</sup> Appointment General Shareholders' Meeting Renewal General Shareholders' Meeting	Year term of office expired *
Richard Pasternak	Chairman of the Board Comp. C. (Chmn.) Audit C. Research C.	No	69	M	American	1,617	Chairman: Board meeting of 5/28/2014  Board meeting of 10/26/2011 General Shareholders' Meeting of 5/09/2012 General Shareholders' Meeting of 2/06/2015	2018
Jean-Louis Dasseux	CEO Director	No	60	M	French	1,211,919	CEO: Board meeting of 7/12/2005 General Shareholders' Meeting of 7/12/2005 Board meeting of 5/29/2005 General Shareholders' Meeting of 5/09/2012 General Shareholders' Meeting of 2/06/2015	2018
Michael Davidson	Director Research C. (Chmn.)	Yes	61	M	American	1,102	Board meeting of 1/16/2015 General Shareholders' Meeting of 2/06/2015	2018
Marc Rivière	Director Compensation C.	No	59	M	French	0	Board meeting of 1/16/2015 General Shareholders' Meeting of 2/06/2015	2018
Christian Chavy	Director Audit C. (Chmn.)	Yes	68	M	French	2,756	General Shareholders' Meeting of 2/6/2015	2018
Catherine Moukheibir	Director Audit C.	Yes	58	F	British	0	Board meeting of 5/27/2015 General Shareholders' Meeting of 9/29/2015	2018
Laura A. Coruzzi	Director Compensation C. Research C.	Yes	65	F	American	0	Board meeting of 5/27/2015 General Shareholders' Meeting of 9/29/2015	2018
Bpifrance Participations represented by Olivier Martinez	Observer	No	47	M	French	0	General Shareholders' Meeting of 7/20/2010 General Shareholders' Meeting of 2/06/2015 Permanent Change of Representative: Board meeting of 5/27/2015	2018
<b>TOTAL</b>	<b>8</b>	<b>4</b>				<b>1,217,394</b>		

\* At the end of the General Shareholders' Meeting held during the year indicated in the table, convened to approve the financial statements for the year ended

There were no changes in Board membership during 2016.

The posts held by corporate officers in other companies are presented in Section 14 of the annual Registration Document.

#### • **Independence of Board Members**

Among the members of the Board, four of them are considered as independent in accordance with the criteria set forth in the MiddleNext Code of Corporate Governance in its third recommendation (repeated in Article 3 of the Board's Internal Rules and Regulations), namely: Laura A. Coruzzi, Catherine Moukheibir, Michael Davidson and Christian Chavy.

The table below presents a summary of the situation of Independent Directors with regard to the independence criteria used:

Independence Criterion	Laura A. Coruzzi	Catherine Moukheibir	Michael Davidson	Christian Chavy
Has not been an employee or corporate executive officer of the Company or of a Group company during the past five years	X	X	X	X
Has not had a significant business relationship with the Company or its Group (customer, supplier, competitor, service provider, creditor, banker, etc.) during the past two years	X	X	X	X
Has not been a core shareholder of the Company or has not held a significant percentage of the voting rights	X	X	X	X
Has not had a close relationship or close family ties with a corporate officer or a core shareholder	X	X	X	X
Has not been a statutory auditor of the Company during the past six years	X	X	X	X
<b>Finding concerning Independence</b>	<b>Independent</b>	<b>Independent</b>	<b>Independent</b>	<b>Independent</b>

It is specified that no Independent Director may maintain a business relationship with the Company or its Group.

- ***Representation of Women and Men Within the Board***

As a reminder, the Board has two women and five men among its members, i.e. a difference of three between the members of each sex.

The Company's goals in terms of board membership diversification are as follows: following the General Shareholders' Meeting held in 2017 to approve the financial statements for the year ended, the difference between the number of members of each sex may not be more than 2.

To comply with the legal provisions in this regard, a proposal is planned to be submitted to the next General Shareholders' Meeting in 2017 to appoint one woman as a member of the Board of Directors, in addition to the existing members.

Following the said meeting, and subject to the adopting of this resolution, the Board of Directors will be composed of three women and five men, i.e. a difference of two between the members of each sex. It will therefore comply with the legal provisions in relation to gender parity within the Board.

***Conditions for preparing the Board's work***

In order to enable Board members to properly prepare for meetings, the Chairman must strive to communicate all necessary information and documentation in advance.

As a result of the above, the draft financial statements were submitted to the Directors 15 days prior to the Board meeting convened to approve them.

***Holding board meetings***

Meeting notices are made in writing at least five days in advance, in accordance with the provisions of Article 16 of the bylaws.

The Board met eight times during 2016.

Throughout 2016, the Directors' average attendance rate at meetings was 95%.

The details of the attendance of directors at each Board meeting of 2016 are shown below:

Name \ Date	Jan. 21, 2016	March 1, 2016	April 25, 2016	June 10, 2016	Sep. 2, 2016	Sep. 28, 2016	Dec. 1, 2016	Dec. 16, 2016	Total
Richard Pasternak	X	X	X	X	X	X	X	X	100%
Jean-Louis Dasseux	X	X	X	X	X	X	X	X	100%
Michael Davidson	X	X	X	X	X	X	X	X	100%
Marc Rivière	X	X	X	X	X	X	X	X	100%
Christian Chavy	X	X	X	X	X	X	X	X	100%
Catherine Moukheibir	X	X	X	X	X	X	Abs.	Abs.	75%
Laura A. Coruzzi	Abs.	x	X	X	X	X	X	X	88%
TOTAL	86%	100%	100%	100%	100%	100%	86%	86%	

The Statutory Auditors were regularly invited to the Board of Directors' meeting to approve the half-year or year-end financial statements.

Moreover, an "executive" session of the Board of Directors was held on March 1, 2016 in the absence of Mr. Dasseux.

#### *The Board's Internal Rules and Regulations*

On January 16, 2015, the Board of Directors adopted Internal Rules and Regulations, applicable since the IPO. It was amended by the Board of Directors of February 17, 2017, to take into account the new provisions from the Market Abuse Reform, the Audit Reform and the new MiddleNext Code.

The Board's Internal Rules and Regulations are available on the Company's website: <http://www.cerenis.com/fr/a-propos-de-cerenis/conseil-d-administration>

#### *Managing conflicts of interest within the Board*

With regard to preventing and managing conflicts of interest, Article 2.5 of the Board's Internal Rules and Regulations state that:

*"Each Director has the right as well as the obligation to inform the Board of Directors immediately of any conflict of interest, even potential or future conflicts of interest with the Company, or one of its subsidiaries, in which they may find themselves or may be likely to find themselves. He or she must abstain from participating in discussions and votes on issues that relate to said conflicts of interest.*

*The Chairman of the Board of Directors or half of the Directors present may also decide that a Director should abstain from discussions and from votes on issues that relate to said conflicts of interest. In this situation, the Director undertakes to leave the Board of Directors meeting during discussions and votes on issues relating to said conflicts of interest. [...]*

*A Director, or a permanent representative if the Director is a legal entity, may not become involved in companies or businesses that compete with the Company in a personal capacity without informing the Board of Directors of this in advance and receiving the Board's prior approval.*

*A Director who is no longer able to fulfill his or her duties on the Board or on the Committees on which he or she sits must resign."*

The Board conducts a review of known conflicts of interest once a year.

#### *Topics discussed during Board Meetings and activity report*

The following topics have been discussed during Board Meetings:

- approvals of capital following the exercise of founders' warrants (BSPCE) and stock options;
- approving half-year and year-end financial statements;
- assessing the Board's work;
- summarizing the Committees' work;
- preparing and sending notices for the Annual General Shareholders' Meeting also called to deliberate on financial delegations;
- authorizing the implementation of the share buyback program;
- recording the resignation of a Director;
- reviewing the independence of Directors;
- looking at balanced gender representation on the Board;
- looking at committee membership;
- reviewing 2015 performance – setting of compensation for corporate officers;
- grants of bonus shares;
- looking at the R&D activities and the trials in progress;

Moreover, it is specified, in accordance with recommendation R.14 of the MiddleNext Code, that the question of the succession of senior executives will be regularly included in the agenda of the Board, or the committees, starting in 2017.

#### *Assessing the Board's work*

During its meeting of February 17, 2017, the Board conducted an assessment of its functioning in order to improve working conditions.

This assessment was performed internally using self-assessment surveys sent to Directors, which addressed the topics below, as well as individual interviews between the Chairman of the Board and each Board Member. The surveys covered: the main challenges the Company faces, opportunities to be assessed, matters that were either not discussed enough or not at all during Board Meetings, management performance, reviewing the Code of Ethics and improving the Board's work.

The results of this assessment showed that the Board's functioning was deemed highly satisfactory.

The results of the assessment were presented and discussed during a Board Meeting.

During this meeting, the Board discussed several areas for improvement: more preparation by Board members for Board meetings and setting up a Research Committee meeting open to all board members the night before Board meetings.

### **Organization and functioning of specialized committees**

The Board has formed three committees:

#### *The Audit Committee*

For the Audit Committee, the Company refers to the report of the AMF Task Force chaired by Mr. Poupart Lafarge on the Audit Committee, dated July 22, 2010.

This Committee comprises three members: Mr. Chavy, Independent Director, Mr. Pasternak, Chairman of the Board, and Ms. Moukheibir, Independent Director.

The criteria used to assess the independence of members of the committees, and of the Audit Committee in particular, are the same as the criteria used to assess the independence of regular Board members.

Mr. Chavy (Committee Chairman) and Ms. Moukheibir are considered to be independent with finance and accounting expertise.

Their subject-matter expertise has been used by the Board given their current and past positions outlined in Section 14.1.5 of this annual Registration Document.

In addition, the third member of the committee also has some of the minimum required finance and accounting experience.

Mr. Chavy chairs the Committee.

The Audit Committee's missions, operating procedures and composition are presented in Section 16.3.1 of this document

During 2016, the committee met four times and carried out the following work: Looked at the use of funds raised during the IPO, reviewed the 2016 budget and prepared the budget for 2017 and 2018, discussed the budget and strategy for new opportunities, reviewed the financial statements for the year ended December 31, 2015, reviewed the management report, the draft annual Registration Document and various documents relating to approving the financial statements, reviewed internal control procedures.

The rate of attendance at this committee was 100%.

The members of the Committee had sufficient time to review the financial and accounting documents, and had the opportunity to listen to the Statutory Auditors, the CFO, the Head of Accounting and the Head of Treasury.

The Committee reported its work to the Board, which acknowledged it, and followed all of the Board's recommendations.

During its annual assessment, the Board evaluated the Audit Committee's work in relation to the objectives it had set for the Committee. The Board deemed the Committee's work highly satisfactory and formulated the following areas of improvement: work to anticipate different success or failure scenarios for clinical trials in progress.

### *The Compensation Committee*

The Compensation Committee comprises three members: Mr. Pasternak, Chairman of the Board, Mr. Rivière and Ms. Coruzzi, Independent Director.

Mr. Pasternak chairs the committee.

The Compensation Committee's duties, operating procedures and composition are presented in Section 16.3.2 of this document.

During 2016, the committee met four times.

It carried out the following work in particular: Discussions regarding salary increases, performance bonus for 2015, stock option and bonus share plans, proposals for stock warrant and bonus share grants, assessment of new candidates, presentation of the level of achievement of 2016 objectives, review of individual performance and salary increases for the year, recommendations on individual bonuses, discussions on 2017 objectives.

The rate of attendance at this committee was 100%

The Committee reported on its work to the Board, which acknowledged it, and followed all of the Board's recommendations

### *The Research Committee*

The Research Committee comprises three members: Mr. Davidson, Independent Director, Ms. Coruzzi, Independent Director, and Mr. Pasternak.

Mr. Davidson chairs the Committee.

The Research Committee is notably responsible for:

- helping the Board monitor current trials and keeping the Board informed of progress on the trials, and in particular, reviewing the audit schedule, working with management to define how to report to the Board, reviewing results, looking at publication strategy again;
- helping the Board identify and analyze new development opportunities;
- facilitating the Board's communications with the *Scientific Advisory Board*.

Their subject-matter expertise has been used by the Board given their current and past positions outlined in Section 14.1.5 of this annual Registration Document.

During 2016, the Committee met seven times and carried out the following work: follow-up on the conduct of clinical studies and programs, follow-up on audit carried out on studies in progress, research centers and systems, and the monitoring and analysis of changes in competitors.

The rate of attendance at this committee was 100%.

## **Senior Management and Board Chairman**

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### **Senior Management Methods**

The positions of CEO and Chairman of the Board have been separate since July 12, 2005.

During its meeting of February 6, 2015, the Board confirmed the separation of positions and renewed the Chairman and the CEO in their position.

Richard Pasternak chairs the Board and Jean-Louis Dasseux is in charge of the Company's general management.

### **Limitation of the CEO's powers**

In accordance with Article 1 of the Internal Rules and Regulations, the Board of Directors approves the Company's significant transactions before senior management implements them. These transactions include:

- any decision to transfer any substantial asset or any substantial intellectual/industrial property belonging to the Company;
- any decision to purchase strategic assets, and particularly industrial property, for the Company;
- any decision to create a subsidiary or carry out any transaction on securities from any of the Company's subsidiaries;
- any material transaction likely to impact the Company's strategy or change its financial structure or scope of business;
- any significant decision to set up a new location abroad.

Furthermore, the CEO must submit the Company's annual budget to the Board of Directors for approval as well as any revision of the budget, and must act within the limits set forth by the budget approved by the Board of Directors.

### **Specific assignments entrusted to the Chairman of the Board**

In 2015, the Chairman had the one specific assignment of supporting the company in its IPO. No specific assignment was given to him in 2016.

## **Compensation of Corporate Officers**

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### **Compensation of Board Members**

#### **Directors' fees**

The budget for attendance fees amounts to EUR 115,000. It was voted on by the General Shareholders' Meeting held on Friday, June 10, 2016.

At their meeting on August 25, 2015, the Board decided to set the compensation for the independent directors at EUR 25,000 gross per year on the basis of attendance, in person or via telecommunication, at all meetings of the Board; this amount is reduced in proportion to the total number of meetings in the case of absences. As an exception to the above, for 2015, only Board meetings after shares were first listed on the Euronext exchange will be taken into account for the calculation.

The amount of attendance fees paid during 2016 is shown in Section 15 of the annual Registration Document.



During its meeting on April 25, 2016, the Board, at the recommendation of the Compensation Committee, set the new rules for distribution of attendance fees applicable from 2016, as follows:

- To set the amount for attendance fees at EUR 5,000 per meeting attended in person, based on four meetings a year, with the possibility - no more than once a year and with the approval of the Chairman - of attending by telephone;
- To grant an additional amount of EUR 5,000 in the case of attendance at the majority of exceptional meetings by telephone, as physical attendance is appreciated by the Chairman;
- To cap the annual amount at EUR 25,000;
- For members who chair one of the Board's committees, an additional amount of EUR 3,000 will be granted;
- The possibility, for members who have made a special contribution to supporting the Company at the request of the Board, to receive an exceptional amount of EUR 3,000;
- To set the total amount of attendance fees at EUR 115,000.

It is specified that only Independent Directors are entitled to receive attendance fees.

#### **Stock warrants (BSAs)**

At its meeting on August 25, 2015, the Board also decided to grant up to 33,250 BSAs on the arrival of an Independent Director and 10,000 BSA for each year, with the exercise of said BSAs being subject to the same performance criteria as those that will be set for grants made to Company executives and employees.

As part of this decision, the CEO, upon a sub-delegation by the Board of Directors dated January 22, 2016, decided to grant Independent Directors on the Board, namely Laura Coruzzi, Catherine Moukheibir, Christian Chavy and Michael Davidson, a total of 133,000 warrants, 33,250 each.

Ms. Moukheibir did not subscribe her BSAs, so as a result, they are no longer valid.

Their issue price will equal EUR 9.36. They will be exercisable based on a rate of 1/24<sup>th</sup> at the end of each calendar month starting on December 3, 2015.

In addition, concerning the policy for granting BSAs to Independent Directors, at its meeting on April 25, 2016 the Board decided to:

- Reduce the number of BSAs granted at the time of appointment;
- Limit grants to exceptional circumstances;
- Retain the same methods for price setting as those currently in force.

#### **Compensation of executive officers**

The Board approved the executive officer compensation policy and the compensation of each executive officer upon the Compensation Committee's proposal.

This policy thoroughly addresses fixed, variable and special compensation in addition to benefits of any kind granted by the Company (pension, severance pay, etc.).

It is determined not only depending on the work performed, results obtained, and responsibility assumed, but also according to the practices of similar companies and the compensation of other company executives.

### **Chairman of the Board of Directors**

The Chairman of the Board receives EUR 40,000 in fixed compensation for his duties as Chairman of the Board.

He also received EUR 10,000 in special compensation in 2016.

### **CEO**

The CEO's compensation is broken down as follows:

#### *Determining the fixed portion*

The Board approves the fixed portion of the CEO's compensation during the first board meeting following year-end for each financial year.

The Board takes inflation and overall Company performance into consideration when determining this compensation.

#### *Determining the Variable Portion of Compensation*

At the beginning of every year, the Board sets variable compensation criteria for the year in progress.

It also assesses if the objectives set for the previous year were achieved and the amount of variable compensation due as a result at the beginning of every year.

The criteria set by the Board for the CEO's variable compensation for 2014, 2015 and 2016 are detailed in Section 15.1 under table 2 (which specifies the compensation amounts due and paid to the CEO).

Regarding the variable portion versus the fixed portion, the target amount of variable compensation for 2016 was set at 40% of his annual fixed compensation.

#### *Special compensation*

In 2016, no special compensation was granted to the CEO

#### *Stock warrants (BSA), stock options and bonus share grants*

- Allocation policy
- **BSA**

As a reminder, the policy on granting warrants to Independent Directors is detailed above.

- **Stock options**

Acting on a sub-delegation by the Board, on January 22, 2016, the CEO decided to grant 134,417 stock options to the Chairman of the Board.

The subscription price was set at EUR 9.36 and corresponds to 80% of the average listing price over the 20 days prior to the grant date.

- **Bonus shares**

On December 3, 2015, following the success of the IPO, the Board of Directors decided to grant bonus shares, not subject to performance conditions, to employees of the Company as well as to the CEO.

In addition, on January 21, 2016, the Board of Directors decided to grant bonus shares to Company employees as well as to the CEO. For each recipient, 20% of shares granted are not subject to performance conditions, with the remaining 80% being subject to one performance condition related to achieving the primary criterion of a clinical trial (CARAT). The Board of Directors meeting of March 13, 2017, noted that the performance condition for this allocation of bonus shares had not been met. See paragraph 15.1, Table 10.

When an employee is recruited on a permanent contract, the Board may allocate ordinary shares free of charge. For 2016, the Board allocated bonus shares, not subject to performance conditions, on one occasion following a recruitment.

Under these two plans, the vesting period was set to one year (with the understanding that for shares subject to the performance condition, the vesting period would take place on the later of the two following dates: one year after the decision to grant the shares, or when the performance condition is achieved).

Under these two plans, the lock-up period was set to one year starting from the definitive vesting date.

- Stock option and bonus share retention policy

In terms of stock options, the Board decided to require that 10% of the shares from exercising stock options must be held by the Chairman of the Board in registered form until his duties end.

In terms of bonus share grants, the Board, in its meetings held on December 3, 2015, and January 21, 2016, decided to require that 10% of bonus shares granted must be held in registered form by the CEO until the termination of his duties.

#### *Benefits in kind*

The CEO has a company vehicle made available to him as a benefit.

The Chairman of the Board does not receive benefits in kind.

*Allowances, benefits and compensation granted to officers due to termination or change in their duties - Retirement - Employment contract.*

These items are shown in table 11 inserted into Section 15.1 of this document.

## Shareholder participation in General Shareholders' Meetings

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Shareholder participation methods for General Shareholders' Meetings are listed in Article 26 of the bylaws.

The meeting comprises all shareholders, regardless of the number of shares they hold.

The right to participate in Shareholders' Meetings is subject to registering shares in the shareholder's name or in the name of the broker registered on the shareholder's behalf at least two business days prior to the meeting at midnight Paris time (CET) (i) either in the registered share accounts held by the Company, (ii) or in the bearer security accounts held by an authorized broker.

Registration in bearer security accounts is recorded via a participation certificate issued by the authorized broker.

In the event that a shareholder is unable to attend the meeting in person, shareholders may choose between one of the three following options:

- Give a proxy to an individual or legal entity of their choice under the terms and conditions of Article 225-106 of the French Commercial Code;
- Send a proxy to the Company without indicating a representative;
- Vote by mail.

Shareholder requests to file draft resolutions or agenda items must be sent to the registered office via registered mail with acknowledgement of receipt or via an electronic telecommunications method no later than twenty-five days before the Shareholders' Meeting is held, and cannot be sent more than twenty days after the date that the notice is published in the French bulletin of mandatory legal notices (BALO).

## Items likely to have an impact in the event of a Public Tender Offer

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See the management report cross-reference table shown in Section 28 of this document.

## Financial risks related to the effects of climate change and measures taken by the Company to mitigate them

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The Company does not anticipate a significant impact on its organization and activities related to climate change.

## **II INTERNAL CONTROL AND RISK MANAGEMENT PROCEDURES**

Upon the Chairman of the Board of Directors' request, the Finance Department compiled the information contained in this Report based on various work carried out in the area of the Group's internal control.

The internal control system covers the Group, which includes the parent company and subsidiary.

### 1. Internal Control Definition and Purpose

The Group implemented an internal control policy and a certain number of procedures as part of its IPO on the regulated NYSE Euronext market in Paris.

Cerenis created this report in accordance with the AMF's reference framework, which pertains to risk management and internal control systems for small- and mid-caps.

This process aims to provide reasonable assurance that the following objectives have been achieved:

- compliance with laws and regulations currently in effect;
- creating and rolling out guidelines defined by the Board of Directors;
- proper functioning of the Group's internal processes, notably those related to safeguarding assets and safety of persons;
- reliability of financial information;
- preventing and controlling risks inherent to the Group's business, be they operational, industrial or financial in nature;
- preventing and controlling risks from errors or fraud.

The Board of Directors designed the internal control system and keeps it updated. This requires regular and adequate communication so that company managers and employees can implement it. It is founded on rules of conduct and integrity upheld by the governance bodies and communicated to everyone. It is based on the following principles:

- an organization with a clear definition of responsibilities that has sufficient resources and skills and that relies on appropriate information systems and procedures;
- a risk management system that aims to list out, analyze and manage the main risks identified in relation to the objectives;
- control activities that are proportionate to the challenges arising in each process and designed to reduce risks that are liable to impact the Group's ability to meet objectives;
- continual monitoring of the internal control system as well as regular reviews of its functioning.

This system helps control the business and ensure that operations are efficient and that resources are used efficiently without providing an absolute guarantee that the Group's objectives will be met.

## 2. Internal Control Elements

Currently, the internal control system depends on considerable autonomy and collaboration within the Group, encouraging the Group to align objectives, resources and methods implemented.

It is based on a clear and precise definition of objectives and delegations, a human resources policy that ensures the Group has adequate staff and skills, information systems and customized tools.

### 2.1. Organization of Internal Control and Operating Procedures

- Board of Directors, Audit Committee, Research Committee and Compensation Committee

The Board of Directors is responsible for defining, managing and monitoring internal control. It is assisted by the Audit and Compensation Committees, whose responsibilities are listed above.

If necessary, the Board of Directors and its committees can conduct the audits and verifications that it considers relevant, consult with any person or take any initiatives it deems necessary on the subject.

During 2016, the “clinical” audit of the CARAT research, which was launched in 2015, was continued.

The company asked a specialist company to conduct a similar audit program on the TANGO research in 2016.

This company is dedicated to managing quality, processes and risks in the areas of clinical research, epidemiology and drug safety. The purpose of the audit program, which involves all stakeholders in the clinical trial (sponsor, research centers, research companies under contract, service providers, etc.) is to verify:

- the safety of the patients and respect for their rights;
  - compliance of the trial with applicable regulations and recommendations;
  - the quality of the data collected.
- Managers and employees

Broad guidelines and objectives are determined by the Board of Directors to then be introduced and implemented by company employees.

Team Meetings are regularly held to provide updates and discuss difficulties and progress made on projects. This results in corrective action.

Since the Group’s staff is limited, everyone is made aware of issues daily and the Group organizes a meeting once or twice per year to remind everyone of these objectives.

- Procedures

Despite having limited staff, the Group strives to comply with the principle of separation of duties. The Group has set up an ERP with a separation of duties system and a very strict approval process. These systems have been integrated into the ERP and take into account materiality thresholds to define different levels of approval and authorization.

Managerial structures, based on internal and external delegations of power, have been defined to manage the Group’s operations. As a result, all Group employees are involved in the internal control system.

Procedures implemented by the Group as part of its internal control are reviewed and assessed by the Statutory Auditors. Conclusions drawn from this work are communicated to the Finance Department to enable the department to come up with corrective action and improve the Group’s internal control.

Protecting sensitive data is a concern for everyone involved in the Group (employees, senior managers, etc.). When the Group organizes a meeting, generally, everyone is reminded that it is vital that they be aware of the confidential nature of information disclosed, and that dissemination of this information must be controlled, both internally and externally.

## 2.2. Internal dissemination of information

The main managers in the company have been present from the beginning; they are the primary advisors responsible for ensuring that procedures are applied.

The Group relies on written procedures, which were all reviewed and transmitted to employees in the first quarter of 2016. To ensure that these procedures had been followed, they were asked to confirm that they had read them.

All these procedures are also available on a shared space on the network.

## 2.3. Identifying and managing risks

A risk mapping of the Group's inherent risks is presented in Section 4 of the annual Registration Document. This section details the risk factors that could have a significant adverse effect on its business, financial position and results.

Faced with a certain number of these risks, the Group has adopted a cautious policy with regard to insurance and risk coverage and believes the insurance coverage it currently has is appropriate for all operations.

The conclusions drawn from the Statutory Auditors' work on internal control enable the finance department to expand the risk identification system.

## 2.4. Control activities

In order to meet its objectives, the Group has implemented several organizational and technical systems. The main measures implemented are described below:

- Management Controls:
  - The Company closes the books on a monthly basis with almost the same level of quality as a half-year or year-end closing.
  - The Company also audits the budget by comparing the monthly budget reports validated by the Board of Directors.
  - Lastly, the Company has cash monitoring tools to better manage its cash and to optimize revenue related to its cash surpluses.
- Reporting: the Company uses these items in its presentations to the various committees:
  - Budget tracking, presentation of variations and analysis.
  - Clinical trial monitoring and comparison with budgets.
- IT security: the Group owns the data servers, email management is outsourced; the Group has signed an outsourcing contract with a local company. Aware of the risks and challenges related to IT security, the Group developed a private Cloud solution, which has been in operation since February 2016.
- Intellectual property: the Group has protected all of its research with patents. The Group relies on a network of law firms that specialize in intellectual property, and more specifically in pharmaceuticals.
- The main contracts by which the Group is bound are reviewed by specialized lawyers according to their specialization (corporate law, tax law, labor law).

- Communications with investors: the Group communicates its financial calendar, indicating dates that its financial and accounting information will be available, and publishes this information on the Group's website in compliance with regulations currently in effect.
- Security of persons and premises:

Access to premises is secured by keypads, and surveillance is carried out on nights and weekends by a remote surveillance company that sends a security guard when an intrusion has been detected.

## 2.5. Internal control relating to financial and accounting reporting

Accounting and financial processes correspond to the entire set of activities which transform the business transactions undertaken by the Group into accounting and financial data. These procedures are primarily implemented by the Accounting and Finance Department.

The accounting and finance function is managed internally by two people, one of whom is the CFO, assisted by an independent accounting firm for both the parent company based in France and also for the subsidiary based in the USA (French accounting, tax and labor regulations).

The preparation of pay slips and social security and tax declarations for employees is outsourced to an accounting firm in France and a specialized company in the United States.

Month-end, described above, is completed within a maximum 15 days, depending on how critical it is.

### 2.5.1. The Financial statement production and consolidation process

As part of preparing the consolidated financial statements, the internal control and accounting scope was established on Saturday, December 31, 2016 by:

- The parent company: Cerenis Therapeutics Holding SA, based in Labège - France
- Cerenis Therapeutics Inc., based in Ann Arbor, Michigan - USA

The consolidated, corporate financial statements for the year are commented on and accompanied by an annual financial report, and interim financial statements are accompanied by an interim business report.

In compliance with the standards applicable in each country, the financial statements of the two entities making up the Group are prepared by:

- Cerenis Therapeutics Holding SA: daily accounting management is performed internally, and payroll processing and tax reviews are entrusted to a professional accountant.
- Cerenis Therapeutics Inc.: daily management is also performed internally; reviews of tax-related matters are handled by a specialized firm.

The consolidated financial statements, prepared in accordance with IFRS, are produced internally with the help of an independent accounting firm, separate from the one that works on the French corporate financial statements.



### 2.5.2. Information system organization and security

The accounting information system is organized using the following tools:

- An ERP (Enterprise Resource Planning) system SAP Business One; integrated software manages accounting processes in a structured and interconnected way. During the year, the Group updated the version of its software, migrating to the latest version 9.1. This tool manages orders and purchases with the existence of workflow to secure data processes and flows as well as accounting and finance management; all of these documents are digitized and related to different items. Using SAP B1 helps the Group meet tax administration obligations on electronic accounting controls (exporting a file with accounting entries).

Hosting, maintenance and backups are outsourced; use is made possible via a private fiber optic link for desk-bound employees at headquarters and via a secured link (<https://>) for traveling employees and the US subsidiary's employees.

- Consolidation software acquired in its single-user version; database backups are regularly carried out and saved on different sites
- Since the Group uses third-party service providers to perform certain tasks – pay, fixed asset management and tax reviews – it lets the accounting firm handle the backing up of data. However, the Group requires that a backup of the file be saved on its servers every year after the accounts are closed
- Tools developed on Excel

The Group carried out a full overhaul of its information systems with the deployment of a private Cloud in the first quarter of 2016. This new architecture will strengthen data security and will help improve the company's performance.

### 2.5.3. Procedures for Managing External Financial Information

The employees have all been informed of the risks connected with the disclosure of inside information and insider dealing; they have all received the code of conduct applied within the company. The Company has registered all its staff on the list of permanent insiders.

The Company has outsourced the management of the various employee shareholding incentive plans to a specialized banking institution. The beneficiaries of these instruments must go through their private interface to perform all purchase/sale operations. The Company has forwarded its financial calendar to its services provider and keeps it informed of any changes. The opening and closing periods of the windows are therefore managed by this services provider.

In addition, in accordance with the regulations, the Group has implemented a list of parties known as "permanent insiders," which is submitted to the Board of Directors once a year. The company will open a list of temporary insiders as and when it considers this necessary.

All financial, clinical or strategic communications are reviewed and validated by members of the Senior Management and the Board of Directors.

Financial information is disclosed in strict compliance with market operating rules and the principle of equal shareholder treatment.

## 2.6. Outlook

The internal control system cannot fully guarantee that the Group's objectives in the area will be met. There are inherent limits to any internal control system, particularly with regard to uncertainties in the outside world, the use of good judgment or disruptions that could happen due to a failure or simple error, a breach of control rules by management and collusion.

However, in 2017, the Group will continue its ongoing process to customize its internal control procedures and will focus its efforts particularly on:

- continuing to institute and apply internal procedures;
- continuing to raise employees and managements' awareness on regularly reviewing risks and developing efficient tools customized to the company and its staff's needs.

Chairman of the Board

## **CERENIS THERAPEUTICS HOLDING**

Société Anonyme

265, rue de la Découverte

31670 Labège

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### **Statutory Auditors' report, prepared in accordance with Article L.225-235 of French company law on the report prepared by the Chairman of the Board of Directors of the company**

For the year ended December 31st, 2016

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This is a free translation into English of the statutory auditors' report issued in French prepared in accordance with Article L.225-235 of French company law on the report prepared by the Chairman of the Board of Directors on the internal control and risk management procedures relating to the preparation and processing of accounting and financial information issued in French and is provided solely for the convenience of English speaking users. This report should be read in conjunction and construed in accordance with French law and the relevant professional standards applicable in France.

To the Shareholders,

In our capacity as Statutory Auditors of Cerenis Therapeutics Holding and in accordance with Article L.225-235 of French company law, we hereby report on the report prepared by the Chairman of your company in accordance with Article L.225-37 of French company law for the year ended December 31, 2016.

It is the Chairman's responsibility to prepare, and submit to the Board of Directors for approval, a report on the internal control and risk management procedures implemented by the company and containing the other disclosures required by Article L.225-37 of French company law, particularly in terms of corporate governance.

It is our responsibility:

- to report to you on the information contained in the Chairman's report in respect of the internal control and risk management procedures relating to the preparation and processing of the accounting and financial information, and
- to attest that this report contains the other disclosures required by Article L.225-37 of French company law, it being specified that we are not responsible for verifying the fairness of these disclosures.

We conducted our work in accordance with professional standards applicable in France.

### **Information on the internal control and risk management procedures relating to the preparation and processing of accounting and financial information**

The professional standards require that we perform the necessary procedures to assess the fairness of the information provided in the Chairman's report in respect of the internal control and risk management procedures relating to the preparation and processing of the accounting and financial information. These procedures consisted mainly in:

- obtaining an understanding of the internal control and risk management procedures relating to the preparation and processing of the accounting and financial information on which the information presented in the Chairman's report is based and the existing documentation;
- obtaining an understanding of the work involved in the preparation of this information and the existing documentation;
- determining if any significant weaknesses in the internal control procedures relating to the preparation and processing of the accounting and financial information that we would have noted in the course of our engagement are properly disclosed in the Chairman's report.

On the basis of our work, we have nothing to report on the information in respect of the company's internal control and risk management procedures relating to the preparation and processing of accounting and financial information contained in the report prepared by the Chairman of the Board in accordance with Article L.225-37 of French company law.

### **Other disclosures**

We hereby attest that the Chairman's report includes the other disclosures required by Article L.225-37 of French company law.

Nantes and Balma, on 20 February 2017

The statutory auditors French original signed by

**HLP Audit**

**Deloitte & Associés**

Freddy GARCIN

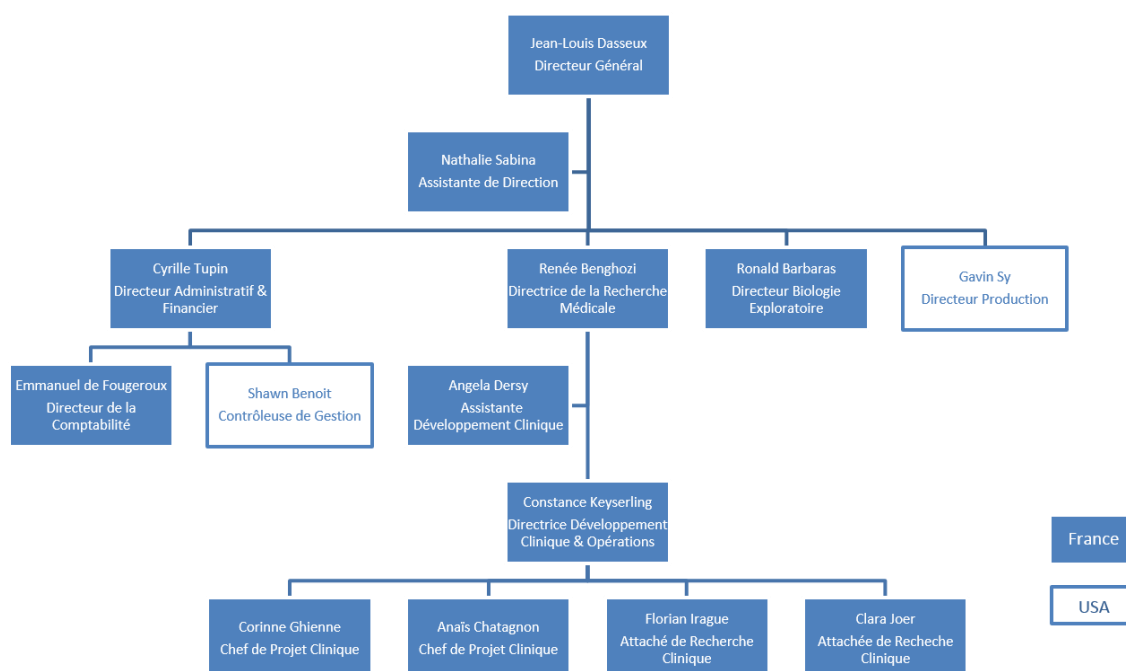
Etienne ALIBERT

Partner

Partner

## 17. EMPLOYEES

### 17.1. Number of employees and distribution by function



The Company's senior managers have extensive experience in their respective fields. This experience is summarized in Section 6.6 "Company Structure" of this Registration Document.

The average workforce, for the Company and its subsidiary, consisted of 14 employees in 2016, versus 12 employees in 2015.

### 17.2. Equity interests and stock options held by the corporate officers

The number of Company shares held by the corporate officers is provided in Section 1.1.1 of the Chairman's Report, which is included in Section 16.5 of this document.

In addition, the SWs, Stock Options, and FSWs held by the corporate officers appear in Section 21.1.4.

Finally, the Bonus Shares held by the corporate officers are indicated in Section 15.1 of this document.

### 17.3. Collective Bargaining Agreement relating to Employee Share Plans

The Company has not established any Collective Bargaining Agreement regarding an Employee Share Scheme.

### 17.4. Incentive and Profit-Sharing Plan Agreement

None.

## 17.5. Corporate, Social and Environmental Responsibility Report

The purpose of this report is to describe the commitment and plans of Cerenis in respect to its corporate, social and environmental responsibilities. This report was prepared in accordance with the requirements set forth in Article 225-102-1(5) of the French Commercial Code. It has been audited by an independent external organization whose report is attached to this document.

The corporate scope covers Cerenis Therapeutics Holding SA, based in France and Cerenis Therapeutics Inc., its wholly owned subsidiary based in the United States, hereinafter referred to together as the “Group”.

The scope regarding the environmental indicators covers only Cerenis Therapeutics Holding SA. The other entity, Cerenis Therapeutics Inc., is therefore excluded; we consider that its environmental impact is not significant for the Group.

### Corporate Responsibility

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#### Employment

Cerenis Therapeutics is an international biopharmaceutical Company dedicated to the discovery and development of new HDL therapies for the treatment of cardiovascular and metabolic diseases. Cerenis develops HDL mimetics and molecules that raise the concentration of HDL in order to induce rapid regression of atheromatous plaque in at-risk patients and patients with HDL deficiency.

The Company considers that its employees are its key resource for achieving its objectives. Consequently, its ability to attract, retain and motivate its employees is vital.

The employment contracts signed between the Company and its employees specify duties of loyalty and trustworthiness, service exclusivity, and professional secrecy and confidentiality. The contracts also include a non-solicitation clause.

- Employees

The Company had 14 full-time employees at December 31, 2016, compared to 12 at December 31, 2015.

The workplace for employees in France is at Labège (31670), and for employees of the US subsidiary it is at Ann Arbor (Michigan).

The employees are sub-divided by status, by type of contract, by department and by age, as follows:

	France	USA	2016	France	USA	2015
Total employees at 12/31	12	2	14	10	2	12
Managers	11	2	13	9	2	11
Non-Managers	1		1	1		1
Permanent Employees (CDI)	10	2	12	10	2	12
Female	6	1	7	5	1	6
Male	4	1	5	5	1	6
Temporary Employees (CDD)	2	0	2	0	0	0
Female	1		1			0
Male	1		1			0
Administrative	3	1	4	3	1	4
Business Development	0.5		0.5	0.5		0.5
R&D	8.5	1	9.5	6.5	1	7.5
Biology	1		1	1		1
Production		1	1		1	1
Clinical	7.5		7.5	5.5		5.5
Average age	46.08	45	45.9	49.7	44	48.75
30 to 39	4	1	5	2	1	3
40 to 49	3		3	3		3
50 to 59	3	1	4	4	1	5
60+	2		2	1		1

Employees are distinguished by their high skill levels: 93% of the workforce are executives. These include five employees (36% of the total headcount) with doctorates in science, medicine or pharmacy.

- Hires and dismissals

Details of changes during 2016 (hires and departures) are as follows:

	France	USA	Total
Total number of employees at 12/31/2015	10	2	12
Recruitment	3		3
Resignation	1		1
Total number of employees at 12/31/2016	12	2	14

There were no dismissals during the period.

In order to thrive, the Company prioritizes stable, long-term jobs. However, to handle increased activity related to the monitoring of two clinical trials, the Company recruited two temporary clinical research associates who have one-year contracts.

Recruitment: the recruitment process implemented by the Company is based on:

- widespread circulation of job offers, by increasing the number of circulation channels;
- respect for equal opportunities and gender parity;

- a relevant and rigorous assessment of applicants, so that neither applicants nor managers waste any time;
- the applicant's skills, but also on his/her personal skills and character.

Hiring interviews are conducted as follows:

- an interview with the future line manager, to discuss details of tasks and assignments, in complete confidentiality;
- a meeting with the team and other employees of the Company so that the candidate can introduce himself/herself and also assess the corporate environment and culture: the company recruits an employee, but the applicant joins a company by adopting its plans;
- every applicant receives a response, even if this is negative.

Development of the workforce: the Company applies forward-looking management for employees and skills.

- the Company regularly plans in advance for the skills it needs, depending on the results obtained or on its strategic direction. It presents its options during budget meetings, and this information is regularly updated
- career development: since the company's staff is small, each employee's roles and duties are currently clearly defined and prioritized. The Company is studying the introduction of career appraisals in order to map out employees' professional development and the means of achieving this (training, change of job, etc.)
- compensation and development

The payroll is one of the main operating expenses. The company's personnel expenses fell by 5.1% during 2016. Conducting research operations, particularly monitoring clinical studies, requires significant, qualified human resources.

Changes in personnel expenses are as follows:

	2016	2015	Var.	%
Total payroll (in € 000s)	3,016	3,178	-162	-5.1%

An employee's level of compensation is defined solely on the basis of the position held and in line with salaries in the market.

The Company has decided to supplement the compensation of its permanent employees with bonuses based on the achievement of individual objectives (50%) and related to the company's overall performance (50%).

Senior management employees receive individual bonuses based entirely on the company's overall performance.

The bonuses, approved by the Compensation Committee on the proposal of the management, are paid in the first quarter of the following year.

On recruitment, during annual assessments or when major objectives are achieved, the Company may also grant all permanent employees various equity sharing schemes, such as



*bons de souscription de parts de créateur d'entreprise* ('BSPCE' or French stock options for company start-ups), stock options, equity warrants or bonus shares. All these schemes are approved by the Compensation Committee and adopted by the Board of Directors within the powers authorized by the General Shareholders' Meeting.

Starting from January 1, 2016, the Company has introduced for all employees a defined contributions supplementary pension contract (Art. 83).

All components of compensation are presented by management to the Compensation Committee, which approves overall and individual proposals.

Moreover, during individual year-end appraisals, the compensation of the employees is reviewed, taking into consideration one or more of the following factors:

- changes in their skills and the responsibilities assigned to them;
- a comparison with market salaries for equivalent posts;
- the impact of inflation.

### **Organization of the work**

The employment contracts of employees are governed under the Collective Bargaining Agreement for the Pharmaceutical Industries (CCN 3104)

- Working hours

Several methods for adjusting working hours are provided for the following categories:

- Non-executive employees: the employee is required to comply with the working hours in force within the Company which is fixed at 35 hours.
- Independent executive employees: given the autonomy accorded to independent executives in the performance of his/her duties and the organization of his/her working hours, the employee is not subject to the collective working hours in force within the Company. Thus, the employee is free to organize his/her activity within the limit of 169 hours of work per month. This results in them working an additional 17 hours and 33 minutes (17h33m) which are paid at the applicable higher rate.
- Senior executives: are not subject to the laws and regulations governing working hours, night work, daily breaks and days off during weekends and holidays. They therefore have complete freedom and independence to organize and manage their work schedule in order to perform the duties and tasks assigned to them.

- Absence from work

The rate of absence from work is insignificant. It relates exclusively to days absent because of illness. There have not been any absences relating to an accident in the workplace or to an occupational illness.

### **Employee relations**

- Labor relations

No formal labor relations system is currently in place because the Company has not exceeded the mandatory thresholds.

The Company believes it has good relations with its staff. Direct dialogue between Senior Management and Employees is encouraged. The working environment is centered around active internal communication and a hands-on management which encourages employees to help set goals and to participate in decisions concerning projects and life in the company.

Since the workforce has not, for 12 months (consecutive or not) during the past 36 months, reached the size required to have employee representatives, the Company has not organized employee elections. As soon as the criteria are met, the Company will fulfill this obligation.

- Statement on Collective Bargaining Agreements

Not applicable because of the absence of a body representing the employees.

## **Health and Safety**

- Health and Safety conditions

The Company's only premises, located in Labège, comprise 700 m<sup>2</sup> of street-level offices, accessible to people with reduced mobility and enclosed by a green area. The building has a large, fully equipped kitchen enabling employees to eat on the premises.

A private parking area is available to all employees.

The Company maintains its fire extinguishers and fire evacuation signs and all its electrical installations are certified annually.

- Report of agreements signed

The Company filed the required declarations regarding its facilities and has the authorizations necessary for conducting its business activities. Technical controls and checks of the facilities are conducted in accordance with the laws in force.

- Workplace accidents and occupational illnesses

In 2015 and 2016 the Company recorded no incident that resulted from, and may therefore be classified as, a workplace or work-travel accident.

No occupational or work-related illness was declared in 2015 or in 2016.

No permanent disability was notified to the Company for this year or for previous years.

## **Training**

- Policy implemented

The level of training of employees is high, and the Company attaches particular importance to the high level of expertise of each member of staff. Every year, employees are invited to submit a training request during their individual reviews.

The courses taken are in:

- theoretical and practical training in order to acquire or maintain skills;
- written or oral communication in English or in French for foreign employees.

The Company requires certain high-level executives, particularly researchers, to attend the main conferences and meetings in their area of expertise. In addition, researchers are encouraged to make and submit publications and posters at scientific conferences in order to present their results.

- Number of hours of training

In the last two financial years, the total number of hours of training given was as follows:

	2016	2015
Total number of hours of training	49 hours	61 hours

Four people received training in 2015, and only one in 2016.

The hours spent by employees at the major professional conferences (AHA, ACC, ESC, etc.) are not quantified.

The information and approach to be followed for the Professional Training Contract (CPF) has been distributed to all employees.

## Equal treatment

- Equal treatment of Women and Men

The Company pays special attention to the diversity of its teams; the percentage of female employees is as follows:

	France	USA	2016	France	USA	2015
Total employees at 12/31	12	2	14	10	2	12
Female	7	1	8	5	1	6
Male	5	1	6	5	1	6
Feminization rate	58.3%	50.0%	57.1%	50.0%	50.0%	50.0%

The proportion of female managers was identical in 2015 and 2016 and is 50%.

The Board of Directors has two female members out of a total of seven members (nearly 29%). At December 31, 2015, the Company was in compliance with the legal requirements on this matter applicable on that date: the Board of Directors was required to have at least 20% female members.

The Company has until the General Shareholders' Meeting in 2017, convened to approve the financial statements closed as at December 31, 2016, to comply with the regulations on diversifying the composition of the board:

- if the board has up to eight directors, the difference between the number of men and women may not be greater than two;

- if the board has more than eight directors, it must be at least 40% male or female.
- Employment and inclusion of workers with disabilities

Although all recruiting is open to workers with disabilities, few candidates apply.

The Company has no legal hiring obligation because it has fewer than 20 employees; it pays no financial contribution to Agefiph, the French Association for Employment of Workers with Disabilities. During the past year, the Company placed more than EUR 1,200 in orders with the various *Centres d'Aide par le Travail* (employment centers for the disabled).

- Anti-discrimination policy

Since it was founded, the rich diversity in educational and cultural backgrounds, and the mix of generations, have all been key factors in the success of Cerenis' projects.

### **Promotion and compliance with the requirements of the basic conventions of the International Labor Organization (ILO)**

All employees of the Company are based either in France or in the United States. The Company has always complied with the regulations in force in each country.

Some of the information requested is not relevant given the activity of the Group.

### **Environmental information**

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Because its business is research (research and development of drugs), the Company believes that its environmental impact is low. Most of its research activity has been conducted in its laboratories, while development activities are entrusted to service providers.

To date, its business activity does not include either industrial production or distribution, which means that there is no significant consumption of raw materials for production intended for sale, nor any significant discharges into the environment, nor any greenhouse gas emissions. The Company's business activities do not require the use of town gas or any special gases. They do not generate any noise that may be a nuisance to the employees or residents in the surrounding areas.

Moreover, the Company conducts its research activities within an extremely strict regulatory framework with which it complies.

The Company has all the authorizations necessary to conduct its business activities.

## General environmental policy

- Organization of the Company to take environmental matters into consideration and, if applicable, procedures for environmental assessment or certification

In order to limit travel and its impact on the environment, the Company tries to use video/audio conferencing systems as much as possible.

The Company has transferred all its servers to a data center, which has the appropriate environmental measures in place. This enables the Company to reduce its greenhouse gas emissions by reducing or eliminating the need for air conditioning in the rooms where the servers are located. In addition, the “cloud” system allows employees to access the data from any location. This reduces their carbon footprint in the event of remote work.

When the Company sends letters via express delivery, it offsets its carbon footprint by accepting a price increase on these deliveries. This increase is used by the service provider to fund sustainable development initiatives ranging from methane destruction to alternative energies and forest conservation. These initiatives not only reduce the impact of the mail deliveries on the planet but also support research on new clean energy.

The Company also uses electronic services to send registered letters with acknowledgement of receipt.

The Company leases the premises it occupies; it is not responsible for the facilities installed that could have a negative impact on the environment and in terms of sustainable development. However, it has asked the owner to shut down the obsolete heating plant in the building and to install new air conditioning units. The Company now has thermal regulating equipment in compliance with current environmental requirements.

- Training and information for employees on protecting the environment

No specific procedures have been introduced; the Company relies only on the willingness and common sense of each employee. These topics are frequently discussed informally in the common parts, such as around the coffee machine and in the kitchen.

- The resources allocated to the prevention of environmental risks and pollution

No specific procedures have been introduced; the Company relies only on the willingness and common sense of each employee.

- The amount of the provisions and coverage for environmental risks, unless this information could seriously harm the Company in a current dispute

No provision for environmental risks needs to be declared.

## Pollution and waste management

- The measures to prevent, reduce or clean up discharges into the air, water and soil that seriously impact the environment

As the Company conducts office-based business activities, as a tenant, it assumes that the property owner has ensured that the premises it uses are compliant.

Its business activity does not generate discharges into the air, water or soil.

Concerning air emissions, the Company has a fleet of cars and a significant amount of business travel (by plane and train) takes place throughout the year. An estimate of GHG emissions has been provided in Section 2.4-1.

- Waste prevention, recycling and elimination measures

- Management of IT resources

The Company has opted to virtualize its servers and this task has been entrusted to local IT services providers.

The Company's IT resources consist exclusively of laptop computers and these machines are replaced only when the equipment becomes obsolete. Extending the life cycle of computer equipment, without giving in to the dictates of the data builders, limits the Company's environmental impact but we are not able to quantify this.

- Electronic data

The implementation of concrete measures to replace paper with electronic documents has multiple positive impacts on the environment. It reduces not only the use of paper and printing-related consumables (ink cartridges and energy), but also the physical transport of documents and, eventually, the waste to be recycled. The Company encourages its partners to print only the pages on which signatures must be placed and encourages suppliers to issue electronic invoices.

Paper consumption more than doubled compared to 2015 (+125%); this was related to the growth in the workforce and in the Company's business activities (the launch of two clinical trials in the second half of 2015).

	2016	2015
Paper consumption (in Kg)	296	133

- Optimization of resources

Supply of LED screens

Recycling of ink cartridges by the supplier

- Optimization of travel

Decrease in air travel whenever possible through the use of audio/video conferencing. Optimization of travel (meetings at locations that are easy to access for participants, for example). Arrangement of multiple meetings so as to combine them during a single trip.

- Waste management

The building occupied by the Company offers several waste sorting and recycling bins. The Company generates very little non-recyclable waste; paper documents are shredded for confidentiality reasons.

Precise measurements of the impact of these daily actions have not been taken.

- Consideration of noise-related nuisances and, if applicable, any form of pollution specific to an activity

This indicator is not relevant for the Company, primarily because its activities are conducted in a building located within a business park in a semi-urban area, in the immediate proximity of a highway toll plaza.

## **Circular economy**

### *Waste prevention and management*

- Prevention, recycling, reuse, other forms of waste recovery and elimination: this indicator is not relevant for the Company in light of its activities.
- Efforts to fight food waste: this indicator does not apply to the Company because of the nature its business activities and because it does not offer catering services.

### *Sustainable use of resources*

- Water consumption and supply according to local requirements

Most of the water used is for sanitary purposes; given its non-consuming activities, the Company is barely concerned by these matters of consumption and supply.

Since its offices are leased, an accurate assessment of water consumption data is hard to make because it depends on the charge management systems provided by the lessors.

- Consumption of raw materials and the measures taken to improve the efficiency of use

See the point discussed above.

- Energy consumption, the measures taken to improve energy efficiency and the use of renewable energy sources

Energy consumption for heat and lighting, without the portion relating to the common parts, is presented below:

	2016	2015
Energy consumption (in kWh)	69,214	52,847

The increase in consumption can be explained in the growth of the workforce and especially by the fact that as of September 2015, the heat/air conditioning is no longer centralized. Following construction done in summer 2015, the building owner had these devices individualized, and they are now connected to the companies' meters.

The Company currently does not use any form of renewable energy to meet its energy needs.

- Use of soils

The Company's activity takes place exclusively in a building in Labège; it leases an area of 700 m<sup>2</sup>, which has remained unchanged since 2012.

## Climate change

- Significant greenhouse gas (GHG) emission items generated by the Company's activities
  - EDF consumption: electricity consumption has generated greenhouse gas emissions in the following proportions:

	2016	2015
Electricity consumption (T. CO2 eq.)	5.68	4.33

- Automobile fleet: the Company has three vehicles for senior management with CO<sub>2</sub> emissions of 149, 156 and 159 g/km, running on diesel fuel. The first vehicle was acquired in 2011, and the other two in 2015.

In addition, the Company periodically uses rental vehicles.

	2016	2015
Diesel for vehicle (T. CO2 eq.)	7.71	3.51

The increase is due mainly to the fact that the last two vehicles were purchased in the second half of 2015.

- Air travel: the Company's IPO required a lot of travel, mainly in France and Europe. Since then, the senior management team continues to travel to meet investors and financial analysts. Numerous trips are also required in order to monitor the clinical trials that have begun in a range of countries: Australia, the United States, Canada, Israel and Europe (France, Belgium, the Netherlands, Italy and Hungary).

The calculation of GHG emissions for 2016 was provided by the Air France Business Travel Center for flights operated by the group's airlines (Air France, KLM, Hop and Delta Airlines). The Company tries to use this airline and its partner airlines for most of its travel.



The result is that, as of the end of December, Cerenis' employees had taken 258 flights on the different airlines of the Air France Group, representing emissions of 51.547 tons of CO<sub>2</sub>, compared to 311 flights representing 49.42 tons of CO<sub>2</sub> in 2015.

	No. flights	2016	No. flights	2015
Air travel (T. CO <sub>2</sub> eq.)	258	51.55	311	49.42

In addition, for destinations not served by the airline companies within the Air France Group, such as Adelaide in Australia, Cerenis uses another air carrier. In 2016, as in 2015, there were six trips to Adelaide; we are unable to calculate the emissions for these journeys.

The Company has occasionally used other European airlines: in 2016, it reserved eight flights on Lufthansa, Brussels Airlines and British Airways.

- Adaptation to the consequences of climate change

The Company does not anticipate any significant impact from climate change on its organization and business activities.

It considers that the financial risks associated with the effects of climate change, and the measures it would need to take to reduce them by implementing a low-carbon strategy in all areas of its business, need not be assessed because they are believed to be insignificant at this stage of the Company's development.

### Protection of biodiversity

- Measures taken to preserve biodiversity

The Company's activities have no significant impact on biodiversity and no specific protection measure has been taken.

Despite considering its environmental impact to be low, the Company and its employees are committed to sustainable development on a daily basis: reduction of paper consumption, recycling of office consumables, selective sorting and reduction of household waste. The employees also advocate changing our partners' practices by recommending that they use electronic formats and audio/video conferencing, and that they reduce travel and optimize agenda management.

### Societal information

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#### Territorial, economic and social impact of the activity

- Employment and regional development

The Company was founded in 2005 and currently employs 12 people locally.

The Company welcomes into its workforce, without discrimination, all persons who have the skills necessary for its growth. Whenever possible, it gives priority to local networks and helps to attract high-level executives to Toulouse.

It has always allocated its Apprenticeship Tax contribution to schools and universities in Toulouse.

The senior management team always responds favorably to requests to share its experience.

It is also a member of the France Biotech Association.

- Resident or local populations

The richness of the pool of businesses with skills in Life Sciences enables Cerenis to enter into partnerships with local companies and thus participate in the growth of the local economy.

**Relations maintained with the persons or organizations interested in the Company's activity, particularly employment associations, educational institutions, environmental protection associations, consumer groups and local residents**

- Conditions for dialogue with these persons or organizations

The Company responds to all inquiries about the biotechnology sector.

- Partnership or sponsorship programs

The Company is currently studying the steps it can take locally, at the environmental level, and in terms of preserving biodiversity. Employees are requested to submit their ideas or the causes that are important to them.

**Subcontractors and suppliers**

- Considerations regarding social and environmental challenges in procurement

The Company does not plan to establish specific "CSR" criteria in the selection of its suppliers.

Selection of suppliers has always been based on an analysis of their ability to meet the company's requirements. The Company has always sought to work with the most competent companies in their field in terms of their technological capacity and expertise, but also on the basis of their compliance with Good Clinical Practices, Good Laboratory Practices and Good Manufacturing Practices, as described in European and US regulations. Finally, the Company has always given priority to local or domestic companies, provided that they have comparable expertise.

- Magnitude of subcontracting and considerations regarding their social and environmental responsibility in relations with suppliers and subcontractors

Each activity of the Company is partially subcontracted; in particular, this includes the manufacture of products and preclinical and clinical trials. An administrative portion is also subcontracted: legal, a portion of the financial services, and management of intellectual property.

The Company has always considered its suppliers and health professionals as partners in its corporate responsibility process.

This philosophy, which is not covered by contracts, applies to all suppliers:

- o the Clinical Research Organizations (CRO), which provide clinical trial services
- o the Clinical Manufacturing Organizations (CMO), which provide the materials necessary to conduct the clinical trials

For the TANGO trial, the Company asked that a consultant conduct an audit program.

This company is dedicated to managing quality, processes and risks in the areas of clinical research, epidemiology and drug safety.

The audit program, which covers all stakeholders in the clinical trial (developer, investigation sites, research company under contract, service providers, etc.), seeks to verify:

- the safety of the patients and respect for their rights;
- the trial's compliance with the applicable regulations and recommendations;
- the quality of the data collected.

This audit program is currently running as planned.

A similar program was put in place for the CARAT trial.

#### **Fair trading practices**

- Actions initiated to prevent corruption

The Company has established internal control procedures to prevent corruption (strict separation of tasks).

Its employment contracts specify obligations of loyalty and faithfulness, exclusivity of service, and professional secrecy and confidentiality.

For staff with access to privileged information which could impact the price of shares, employees are required to sign and comply with the written Code of Ethics in force in the Company and intended to prevent violations and insider trading. In addition, temporary lists of insiders may be drawn up, if necessary.

- Measures taken for consumers' health and safety

To date, none of the Company's candidate drugs have been authorized for commercialization. The most advanced are tested on humans as part of clinical trials governed by very strict regulations. Compliance with these regulations at all stages of the drug development process guarantees the protection of the health and safety of consumers.

#### **Other actions taken to support Human Rights**

Given its size, the nature of its pharmaceutical activity, which is by definition highly regulated, and the geographic scope of its activity, the Company does not face problems relating to the violation of human rights.

**17.6. Report by one of the Statutory Auditors, appointed as independent third party, on the consolidated human resources, environmental and social information included in the management report**

This is a free English translation of the Statutory Auditors' report issued in French and is provided solely for the convenience of English-speaking readers. This report should be read in conjunction with, and construed in accordance with, French law and professional standards applicable in France.

For the year ended December 31<sup>st</sup>, 2016

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To the Shareholders,

In our capacity as Statutory Auditors of Cerenis Therapeutics Holding, (the “Company”), appointed as independent third party and certified by COFRAC under numbers 3-1048<sup>111</sup>, we hereby report to you on the consolidated human resources, environmental and social information for the year ended December 31<sup>st</sup>, 2016 included in the management report (hereinafter named “CSR Information”), pursuant to article L.225-102-1 of the French Commercial Code (*Code de commerce*).

**Company’s responsibility**

The *Management Board* is responsible for preparing a company's management report including the CSR Information required by article R.225-105-1 of the French Commercial Code in accordance with the procedures used by the Company (hereinafter the “Guidelines”), summarized in the management report.

**Independence and quality control**

Our independence is defined by regulatory texts, the French Code of ethics (*Code de déontologie*) of our profession and the requirements of article L.822-11 of the French Commercial Code. In addition, we have implemented a system of quality control including documented policies and procedures regarding compliance with the ethical requirements, French professional standards and applicable legal and regulatory requirements.

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<sup>111</sup> whose scope is available at [www.cofrac.fr](http://www.cofrac.fr)

## **Statutory Auditor's responsibility**

On the basis of our work, our responsibility is to:

- attest that the required CSR Information is included in the management report or, in the event of non-disclosure of a part or all of the CSR Information, that an explanation is provided in accordance with the third paragraph of article R.225-105 of the French Commercial Code (Attestation regarding the completeness of CSR Information);
- express a limited assurance conclusion that the CSR Information taken as a whole is, in all material respects, fairly presented in accordance with the Guidelines (Conclusion on the fairness of CSR Information).

Our work involved three persons and was conducted between in February during one week period. We were assisted in our work by our sustainability experts.

We performed our work in accordance with the order dated 13 May 2013 defining the conditions under which the independent third party performs its engagement and the professional guidance issued by the French Institute of statutory auditors (Compagnie nationale des commissaires aux comptes) relating to this engagement and with ISAE 3000<sup>112</sup> concerning our conclusion on the fairness of CSR Information.

### **Attestation regarding the completeness of CSR Information**

#### ***Nature and scope of our work***

On the basis of interviews with the individuals in charge of the relevant departments, we obtained an understanding of the Company's sustainability strategy regarding human resources and environmental impacts of its activities and its social commitments and, where applicable, any actions or programmes arising from them.

We compared the CSR Information presented in the management report with the list provided in article R.225-105-1 of the French Commercial Code.

For any consolidated information that is not disclosed, we verified that explanations were provided in accordance with article R.225-105, paragraph 3 of the French Commercial Code.

We verified that the CSR Information covers the scope of consolidation, i.e., the Company, its subsidiaries as defined by article L.233-1 and the controlled entities as defined by article L.233-3 of the French Commercial Code within the limitations set out in the methodological note, presented as an introduction of the CSR section of the management report.

#### ***Conclusion***

Based on the work performed and given the limitations mentioned above, we attest that the required CSR Information has been disclosed in the management report.

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<sup>112</sup> ISAE 3000 – Assurance engagements other than audits or reviews of historical financial information

### *Nature and scope of our work*

We conducted one interview with the person responsible for preparing the CSR Information in the departments in charge of collecting the information and, where appropriate, responsible for internal control and risk management procedures, in order to:

- assess the suitability of the Guidelines in terms of their relevance, completeness, reliability, neutrality and understandability, and taking into account industry best practices where appropriate;
- verify the implementation of data-collection, compilation, processing and control process to reach completeness and consistency of the CSR Information and obtain an understanding of the internal control and risk management procedures used to prepare the CSR Information.

We determined the nature and scope of our tests and procedures based on the nature and importance of the CSR Information with respect to the characteristics of the Company, the human resources and environmental challenges of its activities, its sustainability strategy and industry best practices.

Regarding the CSR Information that we considered to be the most important<sup>113</sup>:

- at parent entity level, we referred to documentary sources and conducted interviews to corroborate the qualitative information (organisation, policies, actions), performed analytical procedures on the quantitative information and verified, using sampling techniques, the calculations and the consolidation of the data. We also verified that the information was consistent and in agreement with the other information in the management report;
- at the level of a representative sample of entities selected by us<sup>114</sup> on the basis of their activity, their contribution to the consolidated indicators, their location and a risk analysis, we conducted interviews to verify that procedures are properly applied, and we performed tests of details, using sampling techniques, in order to verify the calculations and reconcile the data with the supporting documents. The selected sample represents on average 86% of headcount and 100% of quantitative environmental data disclosed.

For the remaining consolidated CSR Information, we assessed its consistency based on our understanding of the company.

We also assessed the relevance of explanations provided for any information that was not disclosed, either in whole or in part.

We believe that the sampling methods and sample sizes we have used, based on our professional judgement, are sufficient to provide a basis for our limited assurance conclusion; a higher level of assurance would have required us to carry out more extensive procedures. Due to the use of sampling techniques and other limitations inherent to information and internal control systems, the risk of not detecting a material misstatement in the CSR information cannot be totally eliminated.

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<sup>113</sup> Total employees at 31/12 and sub-division; total number of hours of training; paper consumption; electricity consumption; greenhouse gas emissions; clinical trials audit program documentation

<sup>114</sup> Cerenis Therapeutics Holding SA

### ***Conclusion***

Based on the work performed, no material misstatement has come to our attention that causes us to believe that the CSR Information, taken as a whole, is not presented fairly in accordance with the Guidelines.

Neuilly-sur-Seine, February the 20th, 2017

One of the Statutory Auditors

Deloitte & Associés

Etienne Alibert

Partner

## **18. PRINCIPAL SHAREHOLDERS**

### **18.1. Distribution of capital and voting rights**

Refer to Section 21.1.7 of this Registration Document.

### **18.2. Voting rights**

As of today, each shareholder's voting rights are equal to the number of shares that they hold.

### **18.3. Control of the Company**

On the date of this Registration Document, no shareholder individually holds control of the Company or a significant percentage that could suggest control of the Company as defined by Article L. 233-3 of the French Commercial Code.

To the Company's knowledge, there is no Shareholders' Agreement as of this date.

To the Company's knowledge, there is no action in concert among shareholders on the date of this Registration Document.

### **18.4. Agreements that may result in a change of control**

No particular element of the bylaws, charter or issuer regulation could have the effect of delaying, deferring, or preventing a change of control.

### **18.5. Statement of pledges of Company shares**

To the Company's knowledge, there is no pledge of the Company shares.



## **19. TRANSACTIONS WITH RELATED PARTIES**

### **19.1. Intra-group transactions**

The Company has one subsidiary on the date of this Registration Document.

Please refer to Section 7.3 of this Registration Document.

### **19.2. Significant agreements entered into with related parties during the year ended December 31, 2016**

Please refer to the Statutory Auditors' special report in Section 19.3.

## CERENIS THERAPEUTICS HOLDING

Société anonyme

265, rue de la Découverte

31670 Labège

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### Statutory Auditors' special report on regulated agreements and commitments

Shareholders' General Meeting held to approve the financial statements for the financial year ended  
31 December 2016

*This is a free translation into English of the statutory auditors' special report on regulated agreements and commitments with third parties that is issued in the French language and is provided solely for the convenience of English speaking readers. This report on regulated agreements and commitments should be read in conjunction with, and construed in accordance with, French law and professional auditing standards applicable in France. It should be understood that the agreements reported on are only those provided by the French Commercial Code and that the report does not apply to those related party transactions described in IAS 24 or other equivalent accounting standards.*

To the Shareholders,

In our capacity as Statutory Auditors of your Company, we hereby report to you on regulated agreements and commitments.

The terms of our engagement require us to communicate to you, based on the information provided to us, the principal terms and conditions of those agreements and commitments, and the reasons put forward for their benefit to the company, which have been brought to our attention or which we may have discovered in the course of our audit, without having to express an opinion on their usefulness and appropriateness or identify such other agreements and commitments, if any. It is your responsibility, pursuant to Article R.225-31 of the French Commercial Code (Code de commerce), to assess the interest involved in respect of the conclusion of these agreements and commitments for the purpose of approving them.

Our role is also to provide you with the information stipulated in Article R.225-31 of the French Commercial Code relating to the implementation during the past financial year of agreements and commitments previously approved by the Shareholders' General Meeting, if any.

We conducted the procedures we deemed necessary in accordance with the professional guidelines of the French National Institute of Statutory Auditors (Compagnie Nationale des Commissaires aux Comptes) relating to this engagement. These procedures consisted in agreeing the information provided to us with the relevant source documents.

**AGREEMENTS AND COMMITMENTS SUBMITTED FOR THE APPROVAL OF THE SHAREHOLDERS’  
GENERAL MEETING**

Pursuant to Article L.225-40 of the French Commercial Code, the following agreements and commitments, which were previously authorized by the Board of directors, have been brought to our attention.

**Implementation of a new defined contribution supplemental retirement plan (“Article 83”) benefiting all Company personnel, including Mr. Dasseux**

Person concerned: Mr. Jean-Louis Dasseux, CEO of CERENIS THERAPEUTICS HOLDING

Nature and purpose: At its meeting of June 10, 2016, the Board of Directors implemented a new defined contribution supplemental retirement plan (“Article 83”) benefiting all Company personnel, including Mr. Dasseux.

The main features of this agreement, which applies to Mr. Dasseux as well as to all company employees, are as follows:

- a group life insurance contract with compulsory membership and defined contributions (provided for under Article 83 of the French Tax Code (code général des impôts), sections 20 and 22 of Article R.321-1 of the French Insurance Code (code des assurances), and Article 242-1 of the French Social Security Code (code de la sécurité sociale);
- a contract offered to all staff in accordance with Article L.242-1 of the French Social Security Code and implementing decrees;
- a contract offered to all staff without length-of-service conditions. Corporate officers (equivalent to employees) must obtain approval from their relevant body to be eligible;
- the reference salary is the gross salary paid to the beneficiaries of the plan;
- the benefits vest after each payment in the form of savings, to be converted into an annuity at the time of retirement;
- benefits are funded by an employer’s contribution of 1.20% of salaries. Employees may, if applicable, make voluntary contributions;
- an estimate of the annuity income is outlined in the individual annual statements delivered every April. The amounts depend on the elected benefits, on the age at retirement, and on the individual optional contributions;
- the contributions paid are exempt from social security up to a maximum of 5% of the salaries limited to five times the annual social security ceiling. Only an employer contribution of 20% of the contributions payable by the Company is due to the URSSAF.

Reasons: The Board of Directors considered that it was in the Company's interest to allow its Chief Executive Officer to benefit from the same supplemental retirement plan as that granted to all members of the Company's staff so as not to exclude him from the group plan that has been implemented.

Terms and conditions: The expense recognized by the Company for Mr. Dasseux in fiscal 2016 was €6,477, to which should be added the 20% employer contribution.

**AGREEMENTS AND COMMITMENTS ALREADY APPROVED BY THE SHAREHOLDERS' GENERAL MEETING**

In accordance with Article L.225-30 of the French Commercial Code, we have been advised that the following agreements and commitments approved in previous years by the Shareholders' General Meeting have had continuing effect during the past fiscal year.

**Compensation for the revocation or non-renewal of Mr. Dasseux, CEO**

Person concerned: Mr. Jean-Louis Dasseux, CEO of CERENIS THERAPEUTICS HOLDING

Nature and purpose: On February 27, 2016, the Board modified the conditions for payment of the severance package to Mr. Dasseux, in accordance with Article L.225-42-1 of the French Commercial Code (code de commerce):

In the event of (i) dismissal of Mr. Dasseux from his position as Chief Executive Officer for reasons other than a violation of the laws or of the Company's bylaws, or gross negligence or misconduct, or (ii) non-renewal not agreed to by Mr. Dasseux for reasons other than a violation of the laws or of the Company's bylaws, or gross negligence or misconduct, the Board of Directors may pay him an indemnity, the gross amount of which shall be equal to the sum of the gross compensation he has received from the Company, for any reason, during the twenty-four (24) months prior to his departure, if the following two criteria are met on the date of departure:

- A management structure is in place to run at least one of the two clinical trials (TANGO or CARAT trials); it is specified that this criterion will be considered to have been met if, on the date of termination, a Chief Medical Officer in charge of both trials has been hired, the Company has the necessary funding to run at least one of the two, and the first patient has been enrolled in at least one trial;
- An average stock market capitalization of the company at least equal to EUR 80 million over a three-month period after the Company's IPO.

Motivation:

The Board decided the conclusion of this agreement in relation to the essential character of the presence of the CEO to the pursuit of clinical studies made by the Company and the development of its activities.

Terms:

This agreement had no impact during the year.

Nantes and Balma, on 20 February 2017

The statutory auditors

**HLP Audit**

**Deloitte et Associés**

Freddy GARCIN

Partner

Etienne ALIBERT

Partner

## 20. FINANCIAL INFORMATION RELATING TO THE COMPANY'S ASSETS, FINANCIAL POSITION AND INCOME

On March 1, 2017, the Company announced that it had not achieved the main objective of the CARAT study. It learned of this after the financial statements and consolidated financial statements were approved on February 17, 2017, and after the Statutory Auditors' reports dated February 20, 2017, were issued. As a result, Note I.C to paragraph 20.1 and Note II to paragraph 20.3 do not refer to this event.

### 20.1. Consolidated financial statements as at December 31, 2016 under IFRS

#### CONSOLIDATED STATEMENT OF FINANCIAL POSITION

##### ASSETS

*(in thousands of euros)*

	Note	Dec. 31 2016	Dec. 31 2015
Intangible assets	III.A	5	8
Tangible assets	III.B	122	169
Other non-current assets	III.C	216	269
Deferred tax assets	III.U	0	0
<b>Total non-current assets</b>		<b>343</b>	<b>446</b>
Inventories and work in progress	III.D	0	0
Accounts receivable	III.E	0	0
Other current assets	III.F	4,047	2,710
Cash and cash equivalents	III.G	24,675	42,951
<b>Total Current Assets</b>		<b>28,722</b>	<b>45,661</b>
<b>TOTAL ASSETS</b>		<b>29,065</b>	<b>46,107</b>

LIABILITIES

(in thousands of euros)

	Note	Dec. 31 2016	Dec. 31 2015
Share capital	III.H	913	890
Additional paid-in capital	III.H	166,753	166,032
Reserves and retained earnings		(128,315)	(117,195)
Loss for the period		(24,871)	(16,638)
Foreign currency translation reserves		130	110
Non-controlling interests		0	0
<b>Total shareholders' equity</b>		<b>14,610</b>	<b>33,198</b>
Long-term liabilities	III.M	6,755	6,094
Non-current provisions	III.I	1,006	1,025
Deferred tax liabilities	III.U	0	0
Other non-current liabilities		0	0
<b>Total non-current liabilities</b>		<b>7,761</b>	<b>7,120</b>
Current provisions	III.I	0	0
Trade payables	III.J	5,415	5,071
Other current liabilities	III.K	979	719
Current financial liabilities	III.L	300	0
<b>Total current liabilities</b>		<b>6,694</b>	<b>5,790</b>
<b>TOTAL LIABILITIES</b>		<b>29,065</b>	<b>46,107</b>

## CONSOLIDATED STATEMENT OF COMPREHENSIVE INCOME

*(in thousands of euros)*

	Note	Dec. 31 2016	Dec. 31 2015
Revenue	III.Q	0	0
Production costs		0	0
General and administrative expenses	III.R	(7,031)	(2,913)
R&D costs	III.S	(17,004)	(12,561)
<b>Operating Income</b>		<b>(24,035)</b>	<b>(15,474)</b>
Financial revenue	III.T	1,399	1,258
Financial expenses	III.T	(2,240)	(2,422)
<b>Financial income</b>		<b>(841)</b>	<b>(1,164)</b>
Tax on profits	III.U	5	0
<b>NET INCOME</b>		<b>(24,871)</b>	<b>(16,638)</b>
Average number of shares (basic)	III.V	17,907 860	16,632,272
Loss per share (€)	III.V	(1.39)	(1.00)
Number of shares (diluted)	III.V	19,391,287	206,544,108 (*)

On the date that the Company's shares were admitted and first listed on the regulated market, all preferred shares were converted into common shares, with one common share being equivalent to one preferred share. The ratchets associated with category C preferred shares consequently became null and void as of March 30, 2015.

## OTHER COMPREHENSIVE INCOME

*(in thousands of euros)*

	Note	Dec. 31 2016	Dec. 31 2015
<b>Net income / (loss)</b>		<b>(24,871)</b>	<b>(16,638)</b>
<i>Items that will not be recyclable subsequently to profit and loss</i>			
- Actuarial gains and losses on defined benefit plans	III.N	(9)	0
<i>Items that may be recyclable subsequently to profit and loss</i>			
- Currency exchange translation		0	0
<b>Comprehensive income</b>		<b>(24,880)</b>	<b>(16,638)</b>



# **CONSOLIDATED STATEMENTS OF CHANGES IN EQUITY**

<i>(in thousands of euros)</i>	Number of shares	Share capital	Additional paid-in capital	Retained earnings	Foreign currency translation reserves	Actuarial gains and losses	Other Reserves	Total
<b>Shareholders' Equity at 1/1/2015</b>	<b>13,161,787</b>	<b>658</b>	<b>116,785</b>	<b>(123,852)</b>	<b>47</b>	<b>(16)</b>	<b>6,391</b>	<b>12</b>
Loss of the period				(16,638)				(16,638)
Proceeds from issuance of shares	4,633,091	232	49,247					49,479
Payment in shares							511	511
Foreign currency translation reserves								
Treasury shares				(229)				(229)
<b>Shareholders' Equity at 12/31/2015</b>	<b>17,794,878</b>	<b>890</b>	<b>166,032</b>	<b>(140,719)</b>	<b>110</b>	<b>(16)</b>	<b>6,902</b>	<b>33,198</b>
Loss of the period				(24,871)				(24,871)
Proceeds from issuance of shares	468,385	23	722					745
Payment in shares							5,398	5,398
Foreign currency translation reserves					20			20
Share subscription warrants				93				93
Actuarial gain/(loss)						(9)		(9)
Own shares				35				35
<b>Shareholders' Equity at 12/31/2016</b>	<b>18,263,263</b>	<b>913</b>	<b>166,754</b>	<b>(165,462)</b>	<b>130</b>	<b>(25)</b>	<b>12,300</b>	<b>14,610</b>

## CONSOLIDATED STATEMENT OF CASH-FLOWS

*(in thousands of euros)*

	Note	Dec. 31 2016	Dec. 31 2015
<b>Consolidated net income (loss)</b>		<b>(24,871)</b>	<b>(16,638)</b>
Amortization (net) of assets		53	56
Depreciation	III.I	(5)	(106)
Payment in shares (IFRS 2)	III.P	5,398	511
Reversal of income of the BPI subsidy	III.M	(296)	(117)
Change in BPI redeemable advance	III.M	1,257	1,217
Others non-cash operations		0	135
<b>Net cash before changes in working capital</b>		<b>(18,464)</b>	<b>(14,941)</b>
Income taxes	III.U	0	0
Cash effects from financial revenue and expenses		0	0
<b>Net cash before changes in working capital</b>		<b>(18,464)</b>	<b>(14,941)</b>
Change in working capital	III.W	(733)	1,230
Taxes paid	III.U	0	0
<b>Net cash used in operating activities</b>		<b>(19,197)</b>	<b>(13,711)</b>
Proceeds from disposals of property, plant and equipment		0	0
Proceeds from intangible assets		0	0
Capital expenditure: property, plant and equipment		(5)	(161)
Capital expenditure: intangible assets		0	(10)
<b>Net cash from (used in) investing activities</b>		<b>(5)</b>	<b>(171)</b>
Proceeds from issuance of shares	III.H	745	49,478
Share subscription warrants		93	0
Proceeds from issuance of long-term debt		0	0
Repurchase of own shares (liquidity agreement)		87	(485)
Repayment of long-term debt		0	0
Proceeds from BPI redeemable advance		0	0
Repayment from BPI redeemable advance	III.L and M	0	0
<b>Net cash from (used in) financing activities</b>		<b>925</b>	<b>48,993</b>
<b>Changes in net cash flows</b>		<b>(18,277)</b>	<b>35,111</b>
Effect of exchange rate fluctuations		1	(2)
Opening balance sheet cash position	III.G	42,951	7,843
<b>Year-end cash position</b>	III.G	<b>24,675</b>	<b>42,951</b>

## CERENIS THERAPEUTICS -

### NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

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# I PRESENTATION OF THE GROUP

## I.A PRESENTATION OF THE GROUP

These consolidated financial statements include Cerenis Therapeutics S.A. (hereinafter “Cerenis S.A.”) and its American subsidiary Cerenis Therapeutics Inc. (hereinafter “Cerenis Inc.”). The terms the “Group” or “Cerenis” refer to Cerenis Therapeutics S.A. together with its consolidated subsidiary. Cerenis Inc. is wholly owned by Cerenis S.A.

Cerenis Therapeutics is a French limited liability company (“société anonyme”) governed by French law. Registered office is located at 265 rue de la Découverte, 31670 Labège, France. The Company is registered under the number “481 637 718 RCS Toulouse”, with the register of the Toulouse Commercial Court (“Tribunal de Commerce de Toulouse”). The Company is incorporated under the legal regime of a limited liability company with a Board of Directors.

Cerenis is an international biopharmaceutical company focused on discovery and development of new HDL therapies (“good cholesterol”) for treating cardiovascular and metabolic diseases.

The therapies that are designed to increase HDL represent the next revolution in the treatment of cardiovascular diseases. It has been clinically demonstrated that the HDL therapy may lead to a reduction in atherosclerotic plaque and that an increase in HDL may reduce mortality and morbidity.

Cerenis is developing a product which has the potential to become the first and the best HDL recombinant (CER-001) on the market.

CER-001 has successfully completed the Phase I clinical trial. This product has been designed to rapidly reduce atherosclerotic plaque in patients with a high risk of a cardiovascular event. It is based on Cerenis’ multiple innovations in HDL therapy, which has enabled the identification and development of HDL particles, with high purity and efficiency.

Cerenis Therapeutics has operations in Toulouse, France and Ann Arbor (Michigan), United States. The Company’s registered office is in Toulouse.

Since its founding in 2005, Cerenis has attracted numerous investors. In July 2005, the Company completed a financing round (Series A) of €25 million.

This was followed in November 2006 by a second financing round (Series B) of €42 million.

A third increase in capital raising €50 million (Series C) was made between July 2010 and December 2011.

On March 30, 2015, the Group carried out its Initial Public Offering on compartment B of the Euronext regulated market in Paris (“Euronext Paris”), raising €53.4 million through a capital increase (4,207,316 shares issued).

A liquidity agreement was also signed and came into effect when trading began on March 30, 2015.

## I.B SIGNIFICANT EVENTS

The main factors affecting the period from January 1, 2016 to December 31, 2016 were as follows:

- “CARAT” clinical trial

A Phase II CARAT clinical trial, the purpose of which is to assess the efficacy of CER-001 in reducing atherosclerotic plaque in post-Acute Coronary Syndrome (ACS) patients. This trial will involve 301 patients in four countries: Australia, Hungary, the Netherlands and the United States. Patient recruitment was completed in August 2016 and the last patient received the tenth and final administration of CER-001 or a placebo in the fourth quarter of 2016. The findings of this trial are expected at the end of the first quarter of 2017.

- “TANGO” clinical trial

A Phase III trial (TANGO) on the orphan disease FHFA to evaluate the efficacy of six months’ chronic administration of CER-001 in 30 patients suffering an HDL deficiency. Active recruitment of patients for the TANGO Phase III trial is under way and findings should be available in the third quarter of 2017. The Company is working with 18 sites around the world to find more patients with Familial Primary HypoAlphalipoproteinemia (FHFA), a rare but important disease, both from a clinical and an orphan pathology standpoint.

- “LOCATION” clinical trial

On June 2, Cerenis announced in the European Atherosclerosis Society (EAS) scientific journal the findings of the LOCATION clinical trial, which demonstrate the functionality of CER-001. The trial was carried out during the first half of 2015.

- FDA authorization to begin clinical trials with CER-209

The US Food and Drug Administration (FDA) informed Cerenis Therapeutics that CER-209 could enter into clinical development. This authorization from the FDA (IND, Investigational New Drug application) is for a Phase I clinical trial for the CER-209 candidate drug, a P2Y<sub>13</sub> receptor agonist, in healthy volunteers, into non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD).

## I.C EVENTS OCCURRING AFTER THE CLOSING DATE

No significant events occurred after December 31, 2016.

## II SUMMARY OF SIGNIFICANT ACCOUNTING PRINCIPLES

### II.A BASIS OF PREPARATION

#### *i. General information*

The IFRS financial statements for the fiscal year ended December 31, 2016 have been approved by the Board of Directors' meeting of February 17, 2017.

The financial statements are rounded to the nearest thousand (€000). The consolidated financial statements cover the twelve-month periods ended December 31, 2016 and December 31, 2015.

The Board of Directors adopted the going concern principle.

The Company's historical loss-making situation is down to the innovative character of the products developed, which involves a research phase spanning several years.

#### *ii. Statement of compliance with IFRS*

Pursuant to European Regulation (EC) No. 1606/2002 on the application of international accounting standards, the consolidated financial statements of December 31, 2016 were prepared according to IFRS as approved by the European Union at December 31, 2016.

International Financial Reporting Standards include:

- IFRS;
- IAS (International Accounting Standard) and SIC interpretations (Standing Interpretations Committee);
- IFRIC (International Financial Reporting Interpretations Committee).

#### *iii. Application of standards and interpretations effective as of December 31, 2016*

The accounting principles and methods for the consolidated financial statements as at December 31, 2016 are identical to those used in the preparation of the annual consolidated financial statements for the year ended December 31, 2015, except for the new standards applicable with effect from January 1, 2016, which are presented in Note iv below. These financial statements were prepared in accordance with the International Financial Reporting Standards ("IFRS") as adopted by the European Union and available on the site: [http://ec.europa.eu/internal\\_market/ias\\_fr.html-adoptedcommission](http://ec.europa.eu/internal_market/ias_fr.html-adoptedcommission).

They were prepared using the historical cost convention, except for the financial assets and liabilities recognized at fair value through profit and loss.

Assets and liabilities under twelve months are presented as current.

All other assets and liabilities are classified as non-current.

Expenses in profit and loss are presented by destination.

**iv. New standards, amendments and interpretations applicable in 2016**

The application of the following new and updated standards and major interpretations became mandatory for the first time for the fiscal year beginning January 1, 2016:

- IFRS 11: “Joint arrangements”;
- Amendments to IFRS 10 – IFRS 12 – IAS 28: “Clarification of the consolidation exemption”;
- IAS 1: “Disclosure initiative”;
- IAS 16 and IAS 38: “Clarification of acceptable methods of depreciation and amortization”;
- IAS 16 and IAS 41: “Bearer plants”;
- IAS 19: “Defined benefit plans: employee contributions”;
- IAS 27: “Equity method in separate financial statements”;
- IFRS 2: “Definition of vesting conditions and non-vesting conditions”;
- IFRS 3: “Regrouping and consistency of provisions related to variable payments”;
- IFRS 8: “Aggregation of operating segments” and “reconciliation of segment assets”;
- IFRS 13: “Short-term receivables and payables”;
- IAS 16 and IAS 38: “Revaluation model and proportional adjustment”;
- IAS 24: “Definition of senior managers and disclosures to be provided”;
- IFRS 5: “Change in the terms for the release of assets”;
- IFRS 7: “Asset management agreements” and “Application of amendments to IFRS 7 regarding compensation-related disclosures in the condensed interim financial statements”;
- IAS 19: “Discount rate – regional market issue”;
- IAS 34: “Information provided elsewhere in the interim financial report”;
- Annual improvements – 2010-2012 cycle;
- Annual improvements – 2012-2014 cycle.

These standards do not affect the Group’s financial statements.

**v. Standards and interpretations applicable subsequent to December 31, 2016**

- IFRS 15: “Revenue from contracts with customers”;
- IFRS 9: “Financial Instruments (classification and measurement of financial assets and liabilities, hedge accounting)”;
- IFRS 16: “Leases”;
- Amendments to IAS 7: “Disclosures related to financing activities”;
- Amendments to IAS 32: “Recognition of deferred tax assets for unrealized losses”;
- Amendments to IFRS 2: “Classification and measurement of share-based payment transactions.”

The Group does not anticipate these future standards to have a material impact on its financial statements.



## **II.B PRINCIPLES OF CONSOLIDATION**

### ***i. Basis of consolidation***

Companies over which the Group exercises control direct or indirect control are fully consolidated. Control exists when the Group has the power, directly or indirectly, to govern the financial and operating policies of an enterprise so as to obtain benefits from its activities.

The full consolidation method consists in consolidating all assets, liabilities, income and expenses. The share of the assets and income attributable to minority shareholders is recorded as “minority interests” in the balance sheet and the consolidated income statement and in the statement of financial position. The financial statements of subsidiaries are included in the consolidated financial statements from the date that control starts.

The companies are consolidated on the basis of their restated corporate accounts in order to comply with the Group’s guidelines and accounting practices and with GAAP.

The Group has a subsidiary in the United States (Ann Arbor). This subsidiary is wholly owned and fully consolidated.

### ***ii. Annual closing date***

The annual closing date of the individual financial statements is December 31 for all the consolidated companies.

### ***iii. Intercompany transactions***

All intercompany balances and transactions have been eliminated in consolidation. The same applies to Group internal earnings (dividends, proceeds from disposals), which are removed from consolidated income. Unrealized losses are eliminated in the same way as unrealized gains, but only to the extent that there is no evidence of impairment.

## **II.C USE OF ESTIMATES AND JUDGMENTS**

In order to prepare financial statements, the board of directors may carry out estimations and assumptions that affect the reported amounts of assets and liabilities and of revenues and expenses as well as information disclosed in the notes to financial statements.

These estimates and underlying assumptions are based on past experience and other factors deemed relevant in view of the economic circumstances.

These assumptions are used in connection with professional judgment to determine book value of assets and liabilities when other methods cannot be used.

The measurement of some assets and liabilities in the preparation of these financial statements include assumptions made by management particularly on the following items:

- Recoverable value of tangible and intangible assets and their useful life (Notes III.A and III.B);
- Valuation of provisions and employee benefits (Notes III.I and III.N);
- Research tax credit (Note III.M);

- The estimate of future payments relating to the schedule for the repayment of the advances, to the technical progress of the studies conducted by the Group and to the Group's ability to finance these projects to completion (Note III-M);
- Income tax and recording of deferred taxes (Note III.U);
- Fair value of equity granted (Note III.P).

## **II.D FOREIGN CURRENCY TRANSLATION OF THE FINANCIAL STATEMENTS OF FOREIGN SUBSIDIARIES**

The functional currency is the euro (€).

As at reporting date, the assets and liabilities of a foreign operation whose functional currency is not the euro are translated by using the closing rate. Income and expenses of a foreign entity operation whose functional currency is not the euro are translated by using the average currency rate for the period for the statement of change in cash flow.

The exchange differences arising on the translation are taken directly to a separate component of equity (currency translation adjustment).

The schedule below presents foreign exchange rates for the main currency used within the group:

US dollar	Dec. 31, 2016	Dec. 31, 2015
Average rate	1.1066	1.1096
Closing rate	1.0541	1.0887

## **II.E FOREIGN CURRENCY TRANSACTIONS**

Transactions in foreign currencies are initially recorded in the functional currency by applying the exchange rate between the functional currency and the foreign currency at the date of the transaction.

At each balance sheet date, assets, liabilities and cash denominated in foreign currencies recorded at historical cost are retranslated at their euro equivalent.

All differences arising from foreign currency payables and receivables are taken to profit and loss (financial income - loss).

## **II.F BUSINESS COMBINATIONS AND GOODWILL**

Business combinations are recorded in accordance with the revised IFRS 3.

Cerenis has not performed any business combination since its incorporation, and therefore as at December 31, 2016 its balance sheet does not record any goodwill.

## II.G RESEARCH AND DEVELOPMENT COSTS

### *i. R&D costs*

Les frais de recherche sont comptabilisés comme des dépenses à mesure qu'ils sont engagés.

In accordance with IAS 38 (Intangible Assets), research expenditures are recorded as incurred under the caption "Research and development costs."

### *ii. Development costs*

Development costs relate to costs incurred to develop new products in order to sell them to a third party or to market them.

In accordance with IAS 38, internally generated development costs are recognized as an intangible asset when they fulfil certain criteria.

The Group must ensure that the following six criteria can be demonstrated simultaneously:

- The technical feasibility of completing the intangible asset development in order to use it or sell it;
- The Group's intention to complete the intangible asset development in order to use it or sell it;
- The Group's ability to use or sell the intangible asset;
- The probability that the project will generate probable future economic benefits for the Group, either by marketing or by its use internally;
- The availability of adequate technical, financial and other resources to complete the development and use or sell the intangible asset;
- The ability to measure the development expenditure reliably.

Development costs are discounted starting only on the date on which the conditions have been met. The asset is recorded at its production cost.

The start date for amortization begins at the end of the development phase, when the asset is ready for use.

The amortization period extends over the period of expected future economic benefits. An impairment test is performed during the development period.

Due to the risks and uncertainties relating to the innovative nature and character of the Group's projects, Cerenis considers that the six criteria are considered not to have been met until marketing approval has been obtained from the regulatory authorities.

Taking into account the risks inherent in the development programs and the progress of current projects headed by the Group, Cerenis considered that the criteria defined by IAS 38 are not met. Developments costs are therefore recorded as incurred in the income statement of December 31, 2016.

### **iii. Accounting for research and development costs and patents acquired**

Research and development costs and patents acquired are recognized as intangible assets provided they meet the accounting criteria under IAS 38, namely that they are:

- a resource controlled by the Group;
- a resource expected to provide future economic benefit;
- an identifiable resource that is either separable or arises from contractual or legal rights.

Cerenis uses third parties to perform certain parts of its research and development activities. The contracts relating to these research and development activities may be structured in different ways. In most cases these contracts specify upfront payments or milestone payments made on completion of various stages or payments for one-off orders.

As part of its activities, Cerenis signed a partnership agreement with Novasep in 2010. On signature of this agreement, Cerenis made an upfront payment of €2,000,000 to finance the research and development of a manufacturing process for CER-001 by Novasep. If Cerenis were to decide in the future to terminate this agreement and continue the production of CER-001 with another supplier, the Group would have the option either to buy the purification equipment or to pay damages for breach of contract.

For this reason, the upfront sum paid by Cerenis on signature of the contract does not meet the criteria for an intangible asset. The payment was therefore entered as an expense when it was made in 2010.

## **II.H OTHER INTANGIBLE ASSETS**

Trademarks, software and other intangible assets are initially recognized at the acquisition or production cost, subsequently reduced by depreciation charges and impairment losses.

They are amortized on a straight-line basis over their useful lives.

These depreciation rates are reviewed on a regular basis.

Cerenis used the following depreciation rate:

Type	Rate
Software	3 years

Changes in IAS 38 Intangible Assets do not impact the depreciation methods applied.

## **II.I PROPERTY, PLANT AND EQUIPMENT**

Property, plant and equipment are valued at their cost of acquisition or production, including related expenses or the cost of preparing the asset for its intended use.

When an asset is acquired, its cost is spread between the main asset and its different component parts, which are recognized separately. In order to simplify matters, incidental expenses are attributed to the main asset.

Given that the assets acquired by the Group are not intended to be sold before the end of their economic life, no residual value has been applied to the various non-current fixed assets.

The depreciation method reflects the pace of consumption of the future economic benefits associated with the asset.

The depreciation amount for each item of property, plant and equipment is calculated on a straight-line basis over the estimated useful life of the assets. The useful life of, and depreciation methods for, these assets are reviewed and modified, if necessary, at the end of each financial year.

The useful lives of property, plant and equipment are as follows:

Type	Rate
Office equipment	3 years
IT equipment	3 years
Research and development equipment	3 – 5 years
Other equipment	3 – 5 years

Depreciation of property, plant and equipment is recognized as an expense in the income statement, in the relevant classification of expense, by function (research and development costs or general administrative expenses).

Day-to-day maintenance costs of property, plant and equipment are expensed as incurred (research and development costs or general administrative expenses).

Changes to IAS 16 Tangible Assets do not impact the depreciation methods applied.

## **II.J FINANCE LEASES AND OPERATING LEASES**

### ***i. Finance leases***

As at December 31, 2016, the Group did not have any finance leasing commitments.

### ***ii. Operating leases***

Leases that do not have the characteristics of finance leases under IAS 17 are recognized as operating leases.

The payments made under these leases are recognized as an expense on a straight-line basis over the term of the lease.

## **II.K IMPAIRMENT OF PROPERTY, PLANT AND EQUIPMENT, INTANGIBLE ASSETS AND GOODWILL**

For tangible and intangible assets with finite useful lives, the carrying value of the Group's assets are reviewed at each closing date to determine whether there is any evidence that an asset has suffered a loss in value. If such evidence is identified (loss of value in the market or accelerated obsolescence, for example), an impairment test is conducted.

The purpose of this test is to compare the carrying value of the asset with its recoverable value.

The recoverable value of an asset is the higher of its net sales price and its value in use. Value in use is the discounted value of the estimated future cash flows expected from the use of an asset and from its disposal at the end of its useful life.

Where the carrying amount of an asset exceeds its recoverable amount, an impairment loss is recognized in the income statement.

As at December 31, 2016, there was no record of any loss in value.

## **II.L FINANCIAL ASSETS**

Financial assets include:

- Assets available for sale;
- Assets held to maturity;
- Loans and debt;
- Assets assessed at fair value through profit or loss.

The valuation and recording of financial assets and liabilities are defined by IAS 39 "Financial Instruments: Recognition and Measurement."

### ***i. Assets held to maturity***

These securities are exclusively securities with fixed or predetermined interest and established maturity dates, other than loans and receivables which the Company intends and is able to maintain until maturity. After initial recognition at their fair value, they are valued and recorded at the amortized cost using the Effective Interest Rate method.

Assets held to maturity are monitored for objective evidence of impairment. A financial asset is depreciated if its carrying value is higher than its recoverable value estimated during depreciation tests. The loss of value is recorded in the income statement.

### ***ii. Assets at fair value through profit or loss***

Assets treated as held for trading include assets that the Group intends to resell in the near future at a profit, which are part of a portfolio of financial instruments managed as a whole and for which short-term sales are the usual practice.

Tradable assets may also include assets that are voluntarily classified in this category, independently of the criteria listed above.

**iii. Receivables**

Receivables are valued at their nominal value less impairment losses for unrecoverable amounts.

## **II.M CASH AND CASH EQUIVALENTS**

Cash and cash equivalents comprise:

- Petty cash and cash at bank;
- Short-term investments (less than three months): term deposits with progressive interest rates, fixed-term deposit and interest -bearing accounts.

Outstanding bank overdrafts are an integral part of the Group's cash management and a component of cash and cash equivalents for the purposes of the cash flow statement.

Liquid short-term investments that are readily convertible into cash and subject to an insignificant risk of changes in value are considered as cash equivalents.

These investments are recognized at their fair value, offset by entries in financial income.

## **II.N COSTS OF CAPITAL INCREASES**

Incremental costs directly attributable to the issue of ordinary shares and stock options are recognized as a deduction from equity, net of any tax effects.

This expense covers the external costs directly attributable to the transaction, particularly the fees of legal advisors and the legal formalities.

## **II.O FINANCIAL LIABILITIES**

**i. Financial liabilities at amortized costs**

Loans and other financial liabilities are valued initially at their fair value, then at the amortized cost, calculated using the Effective Interest Rate Method.

**ii. Liabilities at fair value through profit or loss**

The liabilities at fair value through profit or loss are valued at fair value.

**iii. Fair value**

The fair value of financial instruments traded on an active market is based on the market price on the reporting date.

## II.P PROVISIONS

In accordance with IAS 37 (Provisions, Contingent Liabilities and Contingent Assets), Cerenis records a provision for each event which fulfills the following conditions:

- A contractual or implicit obligation resulting from an event prior to the reporting date;
- Probability or certainty that an outflow of resources to a third party will be required to extinguish the obligation, without an offsetting entry, after the reporting date;
- A reliable estimate of the increase in value.

The estimate of the valuation of the provisions is reviewed at each balance sheet date. The provisions are maintained unless the Company can decide clearly and with certainty on unwinding them.

Except in duly justified cases, the provisions are recorded in the balance sheet under non-current liabilities.

Provisions are discounted if necessary. This issue only concerns provision for retirement indemnity in the Group (Note III.N).

## II.Q GOVERNMENT GRANTS

### *i. Repayable advances*

The Group benefits from a certain amount of public funding in the form of repayable advances.

They have been recognized in accordance with IAS 20 (Accounting for Government Grants) as advances made at below-market interest rates and are assessed in accordance with IAS 39 (Financial Instruments: Recognition and Measurement), first at fair value, then at the amortized cost.

The sum resulting from the benefit obtained from a repayable advance bearing no interest is treated as a subsidy recognized as a reduction to the cost of research, under "R&D costs." This amount is calculated with a discount rate corresponding to a market rate at the date of the advance.

Accordingly, when estimating the liability, the Company must:

- Make its best estimate of the period during which it will benefit from the advance;
- Calculate the amount of the subsidy as the difference between the nominal amount of the advance and its discounted value using the market rate for a debt with similar risk profile for the Company. The interest expense thus calculated is recorded in the financial net income.

The fair value of these advances was calculated, when contracts were signed, on the basis of an interest rate of 17%.

This rate was chosen because of the volatility and the risks inherent in the projects to which such repayable advances were made.

These subsidies and advances are set out in detail in Note III.M.



## **ii. Research Tax Credit**

The Research Tax Credit (CIR) is granted to businesses by the French government in order to encourage them to conduct scientific and technical research.

CIR is a share of R&D costs incurred by Cerenis.

It is recorded as a reduction in R&D costs.

## **II.R TRADE PAYABLES**

Trade payables are recognized initially at fair value and subsequently measured at amortized cost.

## **II.S EMPLOYEE BENEFITS**

Employee benefits are accounted for in accordance with IAS 19 (Employee Benefits).

Following a review of French and American regulations, these provisions only concern the French company regarding retirement indemnities and rewards for long service.

### **i. Defined contribution plans**

The Group accounts for pension costs related to defined contribution plans as they are incurred.

### **ii. Defined benefit plans**

The Group's commitments relate to indemnities payable upon retirement.

In accordance with IAS 19 regarding defined benefit plans, obligations arising from these plans are funded and measured on an actuarial basis using the Projected Unit Credit Method.

The estimate of Group commitments in relation to the staff of the French companies is calculated by an independent service provider.

Based on actuarial assumptions, this method takes into account:

- The probability of the future length of service of the employee,
- The level of future compensation,
- Life expectancy,
- Staff turnover.

The amount is discounted to their present value based on a discount rate determined with reference to the yields on high-quality long-dated bonds (IBOXX Corporates AA). The valuation includes social charges.

Actuarial gains and losses are recognized in "Other comprehensive income."

The cost of current services (i.e. for the period) is presented as charges for the period, either under "General and administrative expenses" or under "R&D costs" depending on the function of each member of staff concerned.

### **iii. Rewards for long-services**

The Group does not account for commitments relating to awards for long service, since these are not significant.

## **II.T SHARE-BASED PAYMENT**

Certain employees, managers, members of the Board of Directors and members of the Scientific Advisory Board of the Group receive compensation in the form of share-based payments according to five types of plan:

- BSPCE – Bons de Souscription de Parts de Créateurs d’Entreprises (founder's stock warrants, “FSWs”);
- BSA – Bons de Souscriptions d’Actions (stock warrants, “SWs”);
- Stock options (“SOs”);
- Bonus shares;
- Performance-based bonus shares.

### Bonus shares

In accordance with IFRS 2, the fair value used for bonus shares is the share price on the award date.

### Performance-based bonus shares

In accordance with IFRS 2, the fair value used for performance-based bonus shares is the share price on the award date, adjusted for the number of equity instruments depending on the performance conditions.

### Stock options

The fair value of the options awarded is determined using the Black-Scholes-Merton option pricing model.

In accordance with IFRS 2, the cost of transactions settled using equity instruments is recognized as an expense in the period during which the equity instruments vest, balanced by an increase in equity.

If an employee leaves during the vesting period of these rights, the charges previously recorded under IFRS 2 for this employee are reversed in the fiscal year.

### SWs

Under IFRS, these are treated as equity instruments recognized in equity up to the consideration received and do not give rise to the recognition of an expense.

These plans have been set forth in detail in Note III.P.

## **II.U SALES – REVENUE RECOGNITION**

Revenue is recognized when all of the following conditions have been met:

- the risks and rewards of ownership have been transferred to the customer;
- the Group no longer has effective control over the goods sold;
- the amount of revenue and costs associated with the transaction can be measured reliably.

Cerenis is a biotechnology company working in the research and development phase and therefore the Group does not make any sales.

Given this situation, the Group has not carried out an analysis of the application of IFRS 15 “Revenue from Contracts with Customers.”

## **II.V EARNINGS PER SHARE**

The earnings/loss per share is calculated using the weighted average number of shares outstanding during the reporting period.

The earnings/loss per share after dilution is calculated using the weighted average number of shares outstanding, including the dilutive effect of potentially dilutive ordinary shares, such as warrants and convertible debt.

Shares should be treated as dilutive when, and only when, their conversion to ordinary shares would reduce the net income per share.

## **II.W TAX**

Income tax expense comprises current and deferred tax.

Income tax includes the expense (or income) both from tax due and from deferred tax.

The Group recognizes deferred tax in the event of:

- Deductible temporary differences between the fiscal and accounting values of the assets and liabilities in the consolidated balance sheet;
- Impacts on net income from consolidation adjustments.

Assets relating to loss carry-forwards of Group companies are not recognized as deferred tax if a reasonable recovery horizon has not been established.

Deferred taxes are calculated using the Liability Method, by applying the latest rate of tax in effect for each company based on the number of years over which the Group expects the assets to be realized and liabilities settled.

In accordance with IAS 12, deferred tax assets and liabilities cannot be discounted.

## **II.X STATEMENT OF CASH FLOWS**

The statement of cash flows is prepared in accordance with IAS 7.

It includes:

- Operating activities;
- Investment activities;
- Funding activities.

Operational cash flow is calculated using the Indirect Method: income and expenses with no impact on cash flow are added to, or subtracted from, net income.

Opening and closing cash positions comprise cash, cash equivalents and bank overdrafts.

## **II.Y OPERATING SEGMENTS**

In accordance with IFRS 8, the Group is currently focused on, and only recognizes, one operating segment: the research and development of innovative medicines.

## **II.Z MANAGEMENT AND MEASUREMENT OF FINANCIAL RISK**

Cerenis may be exposed to different types of financial risk.

The Group uses simple methods, suited to its size, to limit the potential adverse effects of such risks on its financial position.

The Group does not use financial instruments for speculative purposes.

### ***i. Interest rate risk***

The Group has no material exposure to interest rate risk, since it has not taken on any floating-rate or fixed-rate debt.

For the most part, the Group's exposure mainly concerns cash equivalents, which are fixed-term deposits. Changes in interest rates have a direct impact on the rate of return of these investments and the cash flows they generate.

### ***ii. Foreign exchange risk***

The main risks related to the impact of foreign exchange are not considered to be material. The Group pays only a few suppliers in foreign currency (US dollars, Canadian dollars, Australian dollars, British pounds or Japanese yen).

The Group, at this stage in its development, has not entered into any currency hedging arrangements.

Foreign exchange risk mainly concerns the general and administrative expenses of the American subsidiary. The latter's purpose is to conduct part of the Group's research work. It, is fully financed by the parent company with which it has a recharging agreement.

**iii.      *Liquidity risk***

Since its incorporation, the Group has funded its growth by successive increases in capital, by obtaining state aid for innovation (repayable advances from the BPI, the state investment bank) and by the reimbursement of Research Tax Credits. It has never had recourse to bank loans.

As a result, the Group is not exposed to any liquidity risk caused by the possible enforcement of clauses for the early repayment of bank loans.

The Company regularly monitors its risk of liquidity shortages by means of a cash-flow budget, updated monthly.

As at December 31, 2016, the Group's cash and cash equivalents amounted to €24,675,000.

**iv.      *Credit risk***

Credit risk relates to deposits with banks and financial institutions.

The Group invests its cash with leading financial institutions and is therefore not exposed to any material risk from its cash and cash equivalents.

### III DETAILED NOTES

#### III.A INTANGIBLE ASSETS

Intangible assets are broken down as follows:

	Software	TOTAL
<b>Net amount at Jan. 1, 2015</b>	<b>0</b>	<b>0</b>
Additions	10	10
Disposals	0	0
Depreciation for the year	2	2
Impairment	0	0
Effect of exchange rate fluctuations	0	0
<b>Net amount at Dec. 31, 2015</b>	<b>8</b>	<b>8</b>
Additions	0	0
Disposals	0	0
Depreciation for the year	(3)	(3)
Impairment	0	0
Effect of exchange rate fluctuations	0	0
<b>Net amount at Dec. 31, 2016</b>	<b>5</b>	<b>5</b>

As at December 31, 2016, intangible assets comprised only the software acquired by the Group.

Depreciation for fiscal year ended December 31, 2016 amounted to €3,000.

#### III.B PROPERTY, PLANT AND EQUIPMENT

The Group owns laboratory equipment, office equipment and computer equipment.

Cerenis does not own any buildings.

Net plant and equipment are set forth in detail below.

	Land and buildings	Office equipment	IT equipment	Laboratory equipment	Other equipment	TOTAL
<b>Net amount at Jan. 1, 2015</b>	<b>0</b>	<b>15</b>	<b>33</b>	<b>3</b>	<b>10</b>	<b>61</b>
Additions	0	0	20	0	142	162
Disposals	0	0	0	(1)	0	(1)
Depreciation for	0	(6)	(24)	(1)	(22)	(53)
Impairment	0	0	0	0	0	0
<b>Net amount at Dec. 31, 2015</b>	<b>0</b>	<b>9</b>	<b>29</b>	<b>1</b>	<b>130</b>	<b>169</b>
Additions	0	0	2	0	3	5
Disposals	0	(3)	0	0	0	(3)
Depreciation for	0	(1)	(14)	(1)	(33)	(49)
Impairment	0	0	0	0	0	0
<b>Net amount at Dec. 31, 2016</b>	<b>0</b>	<b>5</b>	<b>17</b>	<b>0</b>	<b>100</b>	<b>122</b>

As at December 31 2016, property, plant and equipment was mostly composed of transport equipment, IT equipment and office furniture and equipment for its head office premises.

Depreciation for fiscal year ended December 31, 2016 amounted to €49,000.

### III.C OTHER NON-CURRENT ASSETS

	Dec. 31, 2016	Dec. 31, 2015
Deposits	12	12
Liquidity agreement	204	257
<b>TOTAL</b>	<b>216</b>	<b>269</b>

The item “Other non-current assets” concerns deposits relating to the lease for the offices at Labège and a liquidity agreement.

For this reason, 23,291 treasury shares were allocated to reduce the equity at December 31, 2016 and the remaining cash was kept in other non-current assets.

### III.D INVENTORY

Cerenis does not hold any inventories.

### III.E TRADE RECEIVABLES

Since it does not have any sales, the Group does not have trade receivables.

### III.F OTHER CURRENT ASSETS

	Dec. 31, 2016	Dec. 31, 2015
Tax receivables	124	178
Social security receivables	0	0
R&D tax credit	3,585	2,096
Prepaid expenses	280	436
Other receivables	58	0
<b>TOTAL</b>	<b>4,047</b>	<b>2,710</b>

Dec. 31, 2015	Due date < 1 year	Due date > 1 year
Tax receivables	178	0
Social security receivables	0	0
R&D tax credit	2,096	0
Prepaid expenses	436	0
Other receivables	0	0
<b>TOTAL</b>	<b>2,710</b>	<b>0</b>

Dec. 31, 2016	Due date < 1 year	Due date > 1 year
Tax receivables	124	0
Social security receivables	0	0
R&D tax credit	3,585	0
Prepaid expenses	280	0
Other receivables	58	0
<b>TOTAL</b>	<b>4,047</b>	<b>0</b>

The Group benefits from the provisions of the French General Tax Code relating to Research Tax Credits (CIRs). In accordance with the principles outlined in Note II.Q, the CIR is recorded as a reduction in the “R&D costs” during the year in which the eligible expenses are incurred.

The 2015 Research Tax Credit was repaid on July 5, 2016 for the amount of €2,096,000.

Repayment of the 2016 Research Tax Credit is expected to be made during the 2017 fiscal year.

The tax receivables relate primarily to a VAT credit and to a deductible VAT balance.

The prepaid expenses relate to costs incurred for clinical trials.

### III.G CASH AND CASH EQUIVALENTS

Cash and cash equivalents included in the statement of cash flow and in the consolidated statement of financial position relate to:

- Cash at bank;
- Short-term deposits (term deposits with progressive interest rates, fixed-term deposits, interest-bearing accounts).

	Dec. 31, 2016	Dec. 31, 2015
Cash	5,959	2,505
Short-term investments	18,716	40,446
<b>TOTAL</b>	<b>24,675</b>	<b>42,951</b>

At December 31, 2016, the amount of cash in US dollars was equivalent to €2,496,000 compared to €1,828,000 at December 31, 2015.

At December 31, 2016, the amount of cash in Australian dollars was equivalent to €910,000 compared to €3,139,000 at December 31, 2015.

### III.H SHARE CAPITAL

The share capital of the Company changed as follows between January 1, 2015 and December 31, 2016:



Date	Number of shares	Par value	Capital increase in €	Share premium in €	Cumulative nominal	
					In €	Number of shares
January 1, 2015	13,161,788	0.05		116,784,435	658,089	13,161,788
Capital increase of January 13, 2015	419,774	0.05	20,989	0	679,078	13,581,562
Capital increase of March 30, 2015	4,207,316	0.05	210,366	49,191,969	889,444	17,788,878
Exercise of SFWs on December 18 and 22, 2015	6,000	0.05	300	55,560	889,744	17,794,878
Close December 31, 2015	17,794,878	0.05	231,655	166,031,964	889,744	17,794,878
Exercise of SFWs in fiscal 2016	103,385	0.05	5,169	739,500	894,913	17,898,263
Exercise of bonus shares in fiscal 2016	365,000	0.05	18,250	(18,250)	913,163	18,263,263
Close December 31, 2016	18,263,263	0.05	23,419	166,753,214	913,163	18,263,263

#### **Capital increases in fiscal 2016**

- Exercise of FSWs  
Exercise of 103,385 FSWs by current and former employees
- Exercise of bonus shares  
Exercise of 365,000 bonus shares

#### **Situation at December 31, 2016**

Share capital is made up of 18,263,263 common stock with a par value of €0.05, namely €913,000.

### III.I PROVISIONS

The provisions include:

	Dec. 31, 2016	Dec. 31, 2015
Retirement benefits	120	94
Risks and disputes	886	931
<b>TOTAL</b>	<b>1,006</b>	<b>1,025</b>

Transfers to provisions for risks amounted to €50,000 and reversals of provisions to €95,000 for fiscal 2016. This reversal of provision was used during the fiscal year.

On December 31, 2016, the Company's executive team calculated an estimate of the risks incurred concerning disputes with third parties and a former employee and set aside a provision for them. Cerenis set aside a provision for the risk relating to a lawsuit.

Defined benefit plans provision is detailed in Note III.N.

### III.J TRADE PAYABLES

	Dec. 31, 2016	Dec. 31, 2015
Trade payables	5,415	5,071
<b>TOTAL</b>	<b>5,415</b>	<b>5,071</b>

Trade payables relate to service providers.

Trade payments are not discounted as they are payable within one year.

### III.K OTHER CURRENT LIABILITIES

	Dec. 31, 2016	Dec. 31, 2015
Employee-related liabilities	961	707
Tax liabilities	18	12
Other liabilities	0	0
<b>TOTAL</b>	<b>979</b>	<b>719</b>

Dec. 31, 2015	Due date < 1 year	Due date > 1 year
Employee-related liabilities	707	0
Tax liabilities	12	0
Other liabilities	0	0
<b>TOTAL</b>	<b>719</b>	<b>0</b>

Dec. 31, 2016	Due date < 1 year	Due date > 1 year
Employee-related liabilities	961	0
Tax liabilities	18	0
Other liabilities	0	0
<b>TOTAL</b>	<b>979</b>	<b>0</b>

The social taxes are essentially composed of liabilities to employees and payroll liabilities to the social agencies.

Tax liabilities are composed of the taxes levied on wages.

### III.L CURRENT FINANCIAL LIABILITIES

Current financial liabilities relate to redeemable advance (Note III.M).

	Dec. 31, 2016	Dec. 31, 2015
Repayable advances	300	0
Other financial liabilities	0	0
<b>TOTAL</b>	<b>300</b>	<b>0</b>

### III.M GOVERNMENT GRANTS

#### i. Research Tax Credit

The Research Tax Credit (CIR) is reimbursed by the French tax authority in the course of the following fiscal year. It is recorded in the balance sheet under other current assets (refer to Note III.F) It appears as:

	Dec. 31, 2016	Dec. 31, 2015
Research Tax credit	3,585	2,096

#### ii. Repayable advances BPI

As explained above (Note II.Q), the Group received repayable advances from the BPI.

##### a) Statement of financial position

At December 31, 2016 and December 31, 2015, the situation was as follows:

	Dec. 31, 2015	Financial results	R&D costs	Dec. 31, 2016
Fair value advance	(7,393)	(1,257)	0	(8,650)
Cash to be received	1,781	0	0	1,781
<b>BPI 2010 advance</b>	<b>(5,612)</b>	<b>(1,257)</b>	<b>0</b>	<b>(6,869)</b>
Fair value advance	(983)	0	0	(983)
Deferred revenue	(499)	0	296	(203)
Cash to be received	1,000	0	0	1,000
<b>BPI 2012 advance</b>	<b>(482)</b>	<b>0</b>	<b>296</b>	<b>(186)</b>
<b>Total</b>	<b>(6,094)</b>	<b>(1,257)</b>	<b>296</b>	<b>(7,055)</b>
<i>of which long-term financial liabilities</i>	<i>(6,094)</i>	<i>(1,257)</i>	<i>296</i>	<i>6,755</i>
<i>of which current liabilities</i>	<i>0</i>			<i>300</i>

The deferred income of €203,000 is the amount of the subsidy calculated in accordance with IAS 20 which has not yet been allocated to the R&D costs funded by this advance.

For the fiscal year ending December 31, 2016, a total of €296,000 was offset against the costs of research (see Note III.S) due to the progress of the trial.

*b) Consolidated comprehensive income – Net financial income*

	Financial expenses	Financial revenue	Impact on financial income
Dec. 31, 2016	(1,257)	0	(1,257)
Dec. 31, 2015	(1,217)	0	(1,217)

The financial expenses recognized within the framework of OSEO repayable advances result from the effects of the passage of time. The financial profits are linked to the re-estimation of the repayment schedule.

*iii. “BPI 2010” advance: Project ISI*

Amount €6,384,000 (of which €4,602,000 received at December 31, 2016)

Interest rate 0%

Reimbursement: From May 2017 to May 2025

In 2010, the Group obtained a €6,384,000 repayable advance. At December 31, 2016, Cerenis received €4,602,000. The remaining amount (€1,782,000) has not yet been cashed and its payment remains dependent upon the progress of the project. At December 31, 2016, Cerenis had the option to call this amount.

This advance concerns:

- A Phase IIb clinical development (CER-001) for the treatment of the acute coronary syndrome;
- The development (CER-001) of an orphan drug.

The fair value of the BPI liability corresponds to the current value of the advance, less the outstanding amounts receivable.

The fair value, in effect on the date of contract, has been calculated with a 17% discount rate. This rate has been used due to the high level of risk linked to Group projects subject to this repayable advance.

At the time the advance was arranged, the Company reported a subsidy corresponding to the difference between the amount of the advance and the fair value of that advance at the time of lending to benefit from the advantage afforded by this. This subsidy was offset against R&D costs for a cumulative amount of € 1,322,000 over the financial years 2010 and 2011.

This advance bears interest and a redemption premium is applied in the event that the project proves successful. In this instance, Cerenis would have to pay the BPI up to €20,000,000, covering the repayment of the advance, all interest accrued and the redemption premium. This assumption has been used to estimate the fair value of the repayable advance.

This procedure for reimbursement of this repayable advance will occur at two levels:

- The Group will reimburse the advance for a total amount of €7,400,000 over a five-year period, with effect from the fiscal year when the Company achieves CER-001 cumulated sales greater than €20,000,000 according to the schedule below;
- The Group will have to pay a premium for a total amount of €12,600,000, which represents 4% of CER-001 sales with effect from the fiscal year when the Company achieves cumulated sales exceed €300,000,000.

	Repayment activation	Amount	Total
CER-001 sales	Cumulative sales > €20,000,000	Year 1: €300,000	Total: €7,400,000
		Year 2: €500,000	
		Year 3: €1,000,000	
		Year 4: €2,000,000	
		Year 5: €3,600,000	
	Cumulative sales > €300,000,000	4% of sales over 4 years	Cap amount: €12,600,000

In case of failure, the company will have to reimburse an amount of €600,000.

Initially, Cerenis estimated that its first sales would start in 2014.

Nevertheless, following CHI-SQUARE results and the launch of the “CARAT” and “TANGO” studies (refer to Note I.B above), the Group does not anticipate sales before 2017 regarding orphan drug disease study. As a consequence, the reimbursement should be realized between June 2017 and March 2025.

As a consequence, the repayment schedule of BPI repayable advance has been re-estimated, based on management best estimate to start to reimburse in 2017. On August 27, 2014, Cerenis has received the update of the reimbursement schedule from OSEO.

As at December 31, 2016, this advance has been recorded in the amount of €6,868,000. This amount has been recorded in long-term liability; the Group does not anticipate any reimbursement before the year ended December 31, 2017.

The interest payment amounts to €1,257,000.

**iv. “BPI 2012” advance: OSEO Innovation**

Amount €1,500,000 (of which €500,000 received at December 31, 2014)

Interest rate 0%

Reimbursement: From June 2014 to March 2017

The Group obtained support from BPI for the pre-clinical development of its portfolio of HDL-related products (CER-209), for the treatment of cardiovascular and metabolic diseases as well as the Phase I clinical trial.

As at December 31, 2016, Cerenis received €500,000. The balance will be paid when the program finalization is notified.

This advance should initially be reimbursed between June 2014 and March 2017 according to the following schedule:

Year ended December 31, 2014:	€300,000
Year ended December 31, 2015:	€475,000
Year ended December 31, 2016:	€575,000
Year ended December 31, 2017:	€150,000

In case of project failure, Cerenis will have to reimburse an amount of €600,000 in according with the following schedule;

Year ended December 31, 2014:	€300,000
Year ended December 31, 2015:	€300,000

In accordance with IAS 20 and IAS 39, these interest-free advances have been recorded at fair value.

The fair value in effect on the date of contract has been calculated with a 17% discount rate. This rate has been used due to the high level of risk linked to Group projects subject to this repayable advance.

During fiscal year 2014, the repayment schedule of the repayable advance was re-estimated and renegotiated, based on management's best estimate in order to take into account the expected reimbursements with effect from 2017.

Following this negotiation, the repayment schedule was reviewed and extended. It was set out as follows:

Year ended December 31, 2017:	€400,000
Year ended December 31, 2018:	€500,000
Year ended December 31, 2019:	€600,000

The repayment schedule in case of failure was also renegotiated and set out as follows:

Year ended December 31, 2017:	€300,000
Year ended December 31, 2018:	€300,000

At December 31, 2016, following the rescheduling agreement signed with BPI on September 9, 2016, the reimbursement schedule for the BPI 2012 advance was reviewed to take into account a one-year time lag in the program's implementation. In view of the reimbursement plan, the Group did not record any financial income for the year ended December 31, 2016 due to the fact that the discounting of future cash flow had shifted by one year.

### **III.N PENSION PLANS, END OF SERVICE BENEFITS AND OTHER POST-RETIREMENT BENEFITS**

#### ***i. Retirement benefits***

The Group records retirement benefit commitments in accordance with IAS 19 (Note II.R). This commitment only concerns French employees.

The main actuarial assumptions used are:

Hypothesis	Dec. 31, 2016	Dec. 31, 2015
Discount rate	1.31%	1.89%
Life expectancy	INSEE 2013	INSEE 2013
Retirement age	65 years	62 years
Social charges rate	43%	43%
Average rate of salary increase	3%	3%
Personnel turnover rate	5%	5%

The discount rate is calculated with reference to the market rate at December 31, 2016, based on the average rate for companies in the top category, namely the IBOXX Corporates AA index.

The commitment is recorded in the balance sheet in non-current liabilities: non-current provisions, for the total amount of the commitment.

As at December 31, 2016, a provision of €120,000 was recorded.

A provision was recorded in the amount of €17,000 for the fiscal year ended December 31, 2016. One part of this provision reversal was recognized as a deduction from R&D costs and the other as a deduction from general and administrative expenses.

The actuarial gain was €9,000, recognized in Group equity.

There were no indemnities paid in the fiscal year ended December 31, 2016.

## **ii. Rewards for long-services**

These were not recorded as the commitment was not significant at December 31, 2016.

## **III.O LONG-TERM DEBT**

Long-term debts relate to repayable advances (Note III.M).

	Dec. 31, 2016	Dec. 31, 2015
Repayable advances	6,755	6,094
<b>TOTAL</b>	<b>6,755</b>	<b>6,094</b>

## **III.P SHARE-BASED PAYMENTS**

Since its creation, the Company has granted several stock options, stock warrant (SW) and founder's stock warrant (FSW) plans, as well as bonus shares.

### **i. Main features of the plans**

#### **a) SWs – FSWs – Stock options**

The principal information relating to these plans is as follows:

Beneficiaries: Company employees and Directors, members of the Board of Directors, and members of the Scientific Advisory Committee;

Period of exercise of the warrants: 10 years maximum;

The exercise price is at least equal to the fair value at the date of being granted;

The right to exercise the warrants is acquired on a progressive basis over a period of four years, with an acquisition limit of one year.

**b) Bonus shares**

Beneficiaries: Company employees and directors;

The acquisition period, at the end of which shares will be permanently awarded on the express condition that the beneficiary is still an employee or Director at the date of acquisition, is set at one year.

From the date of permanent acquisition, the holding period, at the end of which shares may be freely sold, is set at one year.

Shares issued at the end of the acquisition period will be new common shares, to be issued by means of a capital increase through the capitalization of reserves. Holders will be entitled to the associated rights and benefits as of the date of issue.

The CEO must hold 10% of such shares as registered shares until such time as he leaves office.

**ii. Stock options, FSWs, SWs and bonus shares granted in 2015 and 2016**

	Number of options Dec. 31, 2016	Average exercise price Dec. 31, 2016	Number of options Dec. 31, 2015	Average exercise price Dec. 31, 2015
Balance at start of period	1,263,044	9.49	1,470,430	8.27
Options granted	472,417	9.54	365,000	12.16
Options exercised	468,385	11.07	6,000	9.31
Options expired	207,915	0	566,386	0
Balance at end of period	1,059,161	9.02	1,263,044	9.49

**a) Details of the agreed plans**

The following schedule details the unit evaluations of the attributed options and notes the hypotheses:

Type of plan	Grant date	Number of options awarded	Number of options cancelled	Number of options exercised	Number of options vested	Exercise price (€)
FSW Options	2006	76,500	33,250	43,250	0	5.45
	2006	222,500	142,412	80,088	0	4.22/7.32
SWs	2006	15,000	15,000	0	0	7.32
FSWs	2007	64,376	10,313	0	54,063	7.32
Options	2007	250,626	238,126	0	12,500	7.32
SWs	2007	48,250	48,250	0	0	7.32



Type of plan	Grant date	Number of options awarded	Number of options cancelled	Number of options exercised	Number of options vested	Exercise price (€)
FSWs	2008	236,475	211,325	0	25,150	7.69
Options	2008	68,950	60,300	0	8,650	7.69
SWs	2008	10,000	10,000	0	0	7.69
FSWs	2009	163,800	141,675	1,025	21,100	7.66
Options	2009	131,300	115,900	1,000	14,400	7.66
SWs	2009	10,000	10,000	0	0	7.66
Options	2010	85,500	70,600	0	14,900	7.77/8.74
SWs	2010	43,250	43,250	0	0	7.77/8.74
FSWs	2010	83,000	37,600	0	45,400	7.77
FSWs	2011	303,000	105,865	56,135	141,000	8.74/9.31
Options	2011	112,500	85,700	0	26,800	8.74/9.31
SWs	2011	0	0	0	0	8.74
FSWs	2012	191,381	31,900	0	159,481	9.31
SWs	2012	77,667	44,417	0	33,250	9.31
Options	2012	41,100	33,700	0	7,400	9.31
FSWs	2013	443,714	403,414	0	37,782	9.49
Options	2013	166,286	162,686	0	3,375	9.49
SWs	2013	74,000	62,000	0	11,250	9.49
Bonus shares	2015	365,000	0	365,000	0	12.16
Bonus shares	2016	200,000	0	0	0	9.81
Bonus shares	2016	5,000	0	0	0	8.40
SWs	2016	133,000	33,250	0	0	9.36
Options	2016	134,417	0	0	134,417	9.36
<b>TOTAL</b>		<b>3,756,592</b>	<b>2,150,933</b>	<b>546,498</b>	<b>750,918</b>	

b) *Position at December 31, 2016*

Options exercised

The following options were exercised during the financial year ending December 31, 2016:

Date	Number of options	Unit price
Jan 5, 2016	5,000	9.31
Jan 12, 2016	6,500	9.31
Feb. 10, 2016	10,000	5.45
Feb. 11, 2016	18,635	9.31
Mar. 3, 2016	10,000	4.22
Mar. 4, 2016	10,000	9.31
Mar. 9, 2016	10,000	9.31
Apr. 15, 2016	33,250	5.45
Dec. 3, 2016	365,000	12.16
<b>TOTAL</b>	<b>468,385</b>	<b>11.07</b>

### Options granted

The Group has granted the following options:

Date	Type	Number	Unit price
Jan. 21, 2016	Bonus shares	200,000	9.81
Jan. 22, 2016	SWs	133,000 (*)	9.36
Jan. 22, 2016	Options	134,417	9.36
Jun. 10, 2016	Bonus shares	5,000	8.40

(\*) Of which 33,250 were cancelled.

The bonus shares granted in respect of the fiscal year include 160,000 performance-based shares broken down as follows:

Plan date	Persons concerned	Number of shares awarded	Valuation under IFRS 2
Jan. 21, 2016	Jean-Louis Dasseux, CEO	52,580	244
Jan. 22, 2016	Other staff members	107,420	509
	Total	160,000	753

Vesting is subject to a performance condition, namely the achievement of the main criterion of the CARAT trial.

This performance condition, which is not a market condition, is taken as consideration by adjusting the number of equity instruments included in the valuation of the transaction amount.

The following amounts have been recorded in the consolidated financial statements:

	Dec. 31, 2016	Dec. 31, 2015
Share-based payments - Cost during the period	5,398	511

### III.Q SALES

As at December 31, 2016 and December 31, 2015, the Group has not recorded any sales.

### III.R GENERAL AND ADMINISTRATIVE EXPENSES

The table below shows a breakdown of general and administrative expenses:

Type	Dec. 31, 2016	Dec. 31, 2015
Salaries and social security contributions	1,474	1,444
Share-based payments	3,720	319
Travel expenses	319	253
Lawyers	378	297
Consultants	246	23
Depreciation expenses and Provision	(43)	(100)
Miscellaneous expenses	937	677
<b>TOTAL</b>	<b>7,031</b>	<b>2,913</b>

### III.S RESEARCH AND DEVELOPMENT COSTS

The research costs are broken down as follows:

Type	Dec. 31, 2016	Dec. 31, 2015
Salaries and social security contributions	1,559	1,734
Share-based payments	1,678	192
R&D costs (trials)	16,405	11,339
Other R&D costs	1,243	1,509
BPI-OSEO subsidy	(296)	(117)
Research tax credit	(3,585)	(2,096)
<b>TOTAL</b>	<b>17,004</b>	<b>12,561</b>

The increase in research and development costs is explained primarily by the launch of the “CARAT” and “TANGO” trials, as described in Note I.B.

### III.T FINANCIAL REVENUE AND EXPENSE

Financial revenue and expense is broken down are as follows:

Type	Dec. 31, 2016	Dec. 31, 2015
<i>Financial revenue</i>		
Income from deposits	442	408
Foreign exchange gains	845	697
Other financial income	112	153
<b>TOTAL</b>	<b>1,399</b>	<b>1,258</b>
<i>Financial expenses</i>		
Foreign exchange losses	787	1,038
BPI financial expenses	1,257	1,217
Other financial expenses	196	167
<b>TOTAL</b>	<b>2,240</b>	<b>2,422</b>
<b>FINANCIAL REVENUE</b>	<b>(841)</b>	<b>(1,164)</b>

### III.U CURRENT AND DEFERRED TAXES

The Group recognizes current and deferred tax as described in Note II.W.

#### i. *Effective tax rate*

The difference between the effective tax rate and the standard corporate rate of income tax applicable in France is described below:

	Dec. 31, 2016	Dec. 31, 2015
Net income	(24,871)	(16,638)

Tax expense	0	0
Pre-tax income	(24,871)	(16,638)
Tax rate	34%	34%
Notional tax	(8,456)	5,657
Tax expense	0	0
Effective tax rate	0%	0%

The permanent fiscal-accounting variances at December 31, 2015 and at December 31, 2016 are not material. The net tax loss carry forwards which have not been applied are presented in Note III-U-iii.

**ii. Current taxes**

The tax expense at December 31, 2016 is zero.

**iii. Deferred tax**

	Dec. 31, 2016	Dec. 31, 2015
Deferred tax asset	0	0
Deferred tax liability	0	0

Tax losses are recognized as deferred tax assets provided that it is probable that future taxable profits will be available against which they can be booked.

As at December 31, 2016 it was not possible to determine with sufficient certainty when Cerenis will make a profit. Therefore, the Company has not recognized the deferred tax assets under "Tax loss carry-forward and temporary variances."

The tax loss carried forwards can be broken down as follows:

Financial year	Tax loss carry forward (€000s)
Before Jan. 1, 2014	124,745
2014	6,302
2015	17,232
2016	22,119
<b>TOTAL</b>	<b>170,398</b>

The losses thus described may be carried forward indefinitely.

### III.V EARNINGS PER SHARE

Basic net income/loss per share is computed using the weighted average number of shares outstanding:

Earnings per share	Dec. 31, 2016	Dec. 31, 2015
Net income	(24,871)	(16,638)
Weighted average number of shares	17,907,860	16,632,272
Earnings per share	(1.39)	(1.00)

As the net result is a loss, the FSWs, SWs, bonus shares and stock options granting access to the capital in a deferred manner are considered to be anti-dilutive. Diluted earnings per share are therefore identical to the basic earnings per share.

### III.W CASH FLOW STATEMENT

The working capital requirement is as follows:

	Dec. 31, 2016	Dec. 31, 2015
Variance in inventories	0	0
Variance in trade receivables	0	0
Variance in current assets	(1,337)	(211)
Variance in trade payables	604	(1,019)
<b>TOTAL</b>	<b>(733)</b>	<b>(1,230)</b>

The variance in the working capital requirement of €733,000 is affected by the following fluctuations:

Increase in fiscal and social liabilities	(4)
Increase in Research Tax Credit liability	(1,489)
Decrease in prepaid expenses	156
Increase in suppliers' item	344
Increase in other current liabilities	<u>260</u>
<i>Total</i>	<i>(733)</i>

## IV OTHER INFORMATION

### IV.A FINANCIAL INSTRUMENTS

Cerenis does not use any derivative financial instruments.

	Category	Dec. 31, 2016 Carrying value	Dec. 31, 2016 Fair value	Dec. 31, 2015 Carrying value	Dec. 31, 2015 Fair value
Cash and cash equivalents	Financial asset at fair value	24,675	24,675	42,951	42,951
Non-current assets	Loans and receivables	12	12	12	12
Other current assets	Loans and receivables	4,047	4,047	2,710	2,710
Financial liabilities	Financial liabilities measured at amortized cost*	7,055	7,254	6,094	6,298
Trade payables	Financial liabilities measured at amortized cost	5,415	5,415	5,071	5,071
Other liabilities	Financial liabilities measured at amortized cost	974	974	719	719

\*As at December 31, 2016 the fair value of the BPI repayable advances has been calculated applying a discount rate of 16.5%, compared to 17% used for the carrying value.

### IV.B RELATED PARTIES

The Board has provided for a termination fee to be paid to the CEO in the event of dismissal or non-renewal of his term of office provided the termination is not the consequence of a violation of the law or the bylaws or serious misconduct.

The amount of compensation granted to the three members of the Executive Committee is set out below:

	Dec. 31, 2016	Dec. 31, 2015
Fixed part of salaries	721	897
Variable part of salaries	222	199
Benefits in kind	13	8
Social security contributions	395	465
Employment contract	0	0
<b>TOTAL</b>	<b>1,351</b>	<b>1,569</b>

For the fiscal year ended December 31, 2016, a total of 75,944 free performance-based shares were awarded to members of the Executive Committee.

## IV.C CONTRACTUAL COMMITMENTS AND OTHER COMMITMENTS GIVEN AND RECEIVED

### i. Leasing commitments

	€000s
Fiscal year ending Dec. 31, 2017	123
Fiscal year ending Dec. 31, 2018 and beyond	58
<b>TOTAL</b>	<b>181</b>

The leasing expense for the fiscal year to December 31, 2016 amounted to €198,000 (€201,000 at December 31, 2015).

### ii. Commitments received

As at December 31, 2016 Cerenis had not received any commitments.

## IV.D RISK MANAGEMENT

Risk management within the Group is described in detail in Note II.Z.

## IV.E EMPLOYEES AND COMPENSATION

### i. Employees

The employees of the Group may be presented as follows:

	Dec. 31, 2016	Dec. 31, 2015
Chemistry/Biology	1	1
Production	1	1
Clinical	7.5	5.5
Business Development	0.5	0.5
Administrative	4	4
<b>TOTAL</b>	<b>14</b>	<b>12</b>

	Dec. 31, 2016	Dec. 31, 2015
France	12	10
USA	2	2
<b>TOTAL</b>	<b>14</b>	<b>12</b>

### ii. Compensation

	Dec. 31, 2016	Dec. 31, 2015
Salaries and social security contributions	3,033	3,178
<b>TOTAL</b>	<b>3,033</b>	<b>3,178</b>

## IV.F STATUTORY AUDITORS' FEES

The fees of the statutory auditors break down as follows:

Type and Organization	Dec. 31, 2016 Deloitte & Associés	Dec. 31, 2016 HLP	Dec. 31, 2016 %	Dec. 31, 2015 Deloitte & Associés	Dec. 31, 2015 HLP	Dec. 31, 2015 %
CERTIFICATION AND LIMITED HALF-YEARLY REVIEW OF THE INDIVIDUAL AND CONSOLIDATED FINANCIAL STATEMENTS						
Cerenis S.A.	47	31	100%	45	30	100%
Cerenis Inc.	0	0	0%	0	0	0%
Sub-total	47	31	100%	45	30	100%
SERVICES OTHER THAN CERTIFICATION OF THE ACCOUNTS						
Cerenis S.A.	16.5	8	100%	15	7	81%
Cerenis Inc.	0	0	0%	5	0	19%
Sub-total	16.5	8	100%	20	7	100%
<b>TOTAL</b>	<b>63.5</b>	<b>39</b>	<b>100%</b>	<b>65</b>	<b>37</b>	<b>100%</b>

## IV.G LIST OF CONSOLIDATED COMPANIES

The list of consolidated companies is set out below:

Name of the Company	Registered office	Consolidation method		% Share capital		% Equity interest	
		2016	2015	2016	2015	2016	2015
Cerenis Therapeutics S.A.	265 rue de la Découverte Bâtiment A 31670 LABEGE France	Parent company	Parent company	Parent company	Parent company	Parent company	Parent company
Cerenis Therapeutics Inc.	900 Victors Way Suite 180 Ann Arbor MI 48108 USA	Global consolidation	Global consolidation	100%	100%	100%	100%

## V OPERATING SEGMENTS

The Group is focused on a single business activity: the research and development of new HDL (“good cholesterol”) therapies for the treatment of cardiovascular and metabolic diseases.

The Group operates in two geographic zones, France and the United States.



	Dec. 31, 2016		Dec. 31, 2015	
	France	USA	France	USA
<b>INCOME STATEMENT</b>				
Sales	0	0	0	0
Inter-segment	0	0	0	0
Total revenues	0	0	0	0
Operating income	(24,061)	26	(15,495)	21
Financial income	(841)	0	(1,164)	0
Income tax	0	5	0	0
Net Income	(24,902)	31	(16,659)	21
<b>OTHER INFORMATION</b>				
Depreciation and amortization	52	1	49	8
Investments	5	0	171	0
<b>BALANCE SHEET</b>				
Assets	28,367	698	45,453	654
Liabilities	(14,434)	(21)	(12,878)	(32)
Shareholders' equity	(13,934)	(676)	(32,577)	(622)

## CERENIS THERAPEUTICS HOLDING

Société Anonyme

265, rue de la Découverte, Bât. A

31 670 Labège

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### Statutory auditor's report on the consolidated financial statements

(Period from January 1<sup>st</sup> to December 31, 2016)

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This is a free translation into English of the statutory auditors' report on the consolidated financial statements issued in the French language and is provided solely for the convenience of English speaking users.

The statutory auditors' report includes information specifically required by French law in such reports, whether modified or not. This information is presented below the opinion on the consolidated financial statements and includes explanatory paragraphs discussing the auditors' assessments of certain significant accounting and auditing matters. These assessments were made for the purpose of issuing an audit opinion on the consolidated financial statements taken as a whole and not to provide separate assurance on individual account captions or on information taken outside of the consolidated financial statements.

This report also includes information relating to the specific verification of information given in the management report.

This report should be read in conjunction with, 0061nd is construed in accordance with, French law and professional auditing standards applicable in France.

To the Shareholders,

In compliance with the assignment entrusted to us by your annual general meeting, we hereby report to you, for the year ended December 31, 2016, on:

- the audit of the accompanying consolidated financial statements of Cerenis Therapeutics Holding;
- the justification of our assessments;
- the specific verification required by law.

These consolidated financial statements have been approved by Board of Directors. Our role is to express an opinion on these consolidated financial statements based on our audit.

## **I. Opinion on the consolidated financial statements**

We conducted our audit in accordance with professional standards applicable in France; those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement. An audit involves performing procedures, using sampling techniques or other methods of selection, to obtain audit evidence about the amounts and disclosures in the consolidated financial statements. An audit also includes evaluating the appropriateness of accounting policies used and the reasonableness of accounting estimates made, as well as the overall presentation of the consolidated financial statements. We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our audit opinion.

In our opinion, the consolidated financial statements give a true and fair view of the assets and liabilities and of the financial position of the Group as at December 31, 2016 and of the results of its operations for the year then ended in accordance with International Financial Reporting Standards as adopted by the European Union.

## **II. Opinion on the consolidated financial statements**

In accordance with the requirements of article L. 823-9 of the French Commercial Code relating to the justification of our assessments, we bring to your attention the following matters:

### **Shares based payment**

Disclosure II.T of the notes to consolidated financial statements discloses shares based payment's valuation method and related accounting policies. Our works has been to review underlying data and hypothesis used to value current year charges and to check that disclosure III.P of the notes to consolidated financial statements discloses an appropriate information.

### **Redeemable advance**

Disclosure II.Q.i of the notes to consolidated financial statements discloses redeemable advance valuation method and accounting related policies. Our works has been to review underlying hypothesis, discounted net debt valuation and to check that disclosure III.M.ii of the notes to consolidated financial statements discloses an appropriate information.

These assessments were made as part of our audit of the consolidated financial statements taken as a whole, and therefore contributed to the opinion we formed which is expressed in the first part of this report.

## **III. Opinion on the consolidated financial statements**

As required by law, we have also verified in accordance with professional standards applicable in France the information presented in the Group's management report.

We have no matters to report as to its fair presentation and its consistency with the consolidated financial statements.

Nantes and Balma, on 20 February 2017

The statutory auditors

*French original signed by*

**HLP Audit**

**Deloitte & Associés**

Freddy GARCIN

Partner

Etienne ALIBERT

Partner

**20.3. Financial statements for the year ended December 31, 2016 prepared in accordance with French GAAP**

ASSETS		12/31/2016			12/31/2015	Variation	
		Gross	Depreciations and Provisions	Net	Net	Euros	%
	Uncalled share capital (I)						
F I X E D  A S S E T S	<b>Intangible fixed assets</b>						
	Formation expenses						
	Research and development expenses						
	Concessions, patents, licences, trade marks	119,863	115,151	4,712	8,045	-3,333	-41.42%
	Goodwill (1)						
	Other intangible assets						
	Advances and deposits on intangible assets						
	<b>Tangible fixed assets</b>						
	Lands building						
	Machinery and equipment						
	Other tangible fixed assets	923,560	801,414	122,146	167,765	-45,619	-27.19%
	Fixed assets in progress						
	Advances and deposit payment						
	<b>Financial assets (2)</b>						
	Shares in group companies						
	Other investments						
	Amounts owed by group and related companies						
	Other financial investments						
	Loans						
	Other financial assets	411,076	69	411,006	498,609	-87,603	-17.57%
	<b>TOTAL II</b>	<b>1,454,499</b>	<b>916,634</b>	<b>537,865</b>	<b>674,419</b>	<b>-136,554</b>	<b>-20.25%</b>
C U R R E N T  A S S E T S	<b>Inventories</b>						
	Raw materials, supplies	4,344	4,344				
	Goods in progress						
	Services in progress						
	Intermediate products and finished products						
	Goods for sale						
	Advances and deposits on orders	49		49	98	-49	-50.00%
	<b>Debtors</b>						
	Trade debtors and related accounts						
	Other debtors	3,789,146		3,789,146	2,290,465	1,498,681	65.43%
	Called up share capital unpaid						
	Stocks and shares	18,716,105		18,716,105	40,446,536	-21,730,431	-53.73%
	Banks and financial accounts	5,950,134		5,950,134	2,460,523	3,489,611	141.82%
	Prepayments (3)	265,669		265,669	421,774	-156,105	-37.01%
	<b>TOTAL III</b>	<b>28,725,447</b>	<b>4,344</b>	<b>28,721,103</b>	<b>45,619,397</b>	<b>-16,898,293</b>	<b>-37.04%</b>
E X P E N S E S	Costs to be spread over several years (IV)						
	Redeemed debentures premium (V)						
	Unrealized loss on exchange adjustments (VI)	292,593		292,593	251,730	40,863	16.23%
	<b>TOTAL ASSETS (I+II+III+IV+V+VI)</b>	<b>30,472,540</b>	<b>920,978</b>	<b>29,551,562</b>	<b>46,545,547</b>	<b>-16,993,985</b>	<b>-36.51%</b>

(1) Including lease right

(2) Including less than one year

(3) Including more than one year

LIABILITIES		12/31/16	12/31/15	Variation	
				Euros	%
S H A R E H O L D E R  E Q U I T Y	Share capital (including paid: 889,744)	913,163	889,744	23,419	2.63%
	Share premium account	166,846,981	166,031,966	815,016	0.49%
	Reevaluation surplus				
	<b>Reserves</b>				
	Legal reserves				
	Statutory reserves				
	Regulation reserves				
	Other reserves				
	Profit or loss brought forward	-133,036,405	-117,986,020	-15,050,385	12.76%
	<b>Net result of the exercise</b>	<b>-18,528,014</b>	<b>-15,050,384</b>	<b>-3,477,630</b>	<b>23.11%</b>
E Q U I T Y	Government grants				
	Statutory provisions				
	<b>TOTAL I</b>	<b>16,195,726</b>	<b>33,885,306</b>	<b>-17,689,580</b>	<b>-52.20%</b>
O T H E R E Q U I T Y	Income from financial investments				
	Conditional state advances	5,102,943	5,102,943		
	<b>TOTAL II</b>	<b>5,102,943</b>	<b>5,102,943</b>		
P R O V I S I O N S	Provisions for risks	1,178,066	1,182,899	-4,833	-0.41%
	Provisions for charges				
	<b>TOTAL III</b>	<b>1,178,066</b>	<b>1,182,899</b>	<b>-4,833</b>	<b>-0.41%</b>
C R E D I T O R S  ( 1 )	<b>Financial liabilities</b>				
	Convertible debentures loans				
	Other debentures loans				
	Bank borrowings				
	Bank overdraft and credit balance				
	Other loans and similar debts	675,058	596,802	78,256	13.11%
	Advances and deposits paid for orders in progress				
	<b>Operating liabilities</b>				
	Trade creditors and related accounts	5,423,338	5,077,965	345,373	6.80%
	Tax and social security creditors	971,779	696,171	275,608	39.59%
P R E P A I D S	Amounts owed for fixed assets and related accounts				
	Other liabilities				
	<b>TOTAL IV</b>	<b>7,070,175</b>	<b>6,370,938</b>	<b>699,237</b>	<b>10.98%</b>
P R E P A I D S	Deferred income (1)				
	Unrealized profit on exchange adjustment (V)	4,652	3,462	1,190	0.34
<b>TOTAL GENERAL (I+II+III+IV+V)</b>		<b>29,551,562</b>	<b>46,545,547</b>	<b>-16,993,985</b>	<b>-36.51%</b>

(†) Including less than one year

	12/31/16			12/31/15	Variation	
	France	Exportation	Total		Euros	%
<b>Operating income</b>						
Sales of good						
Sales of finished products						
Sales of finished services						
<b>Net turnover</b>						
Manufactured products inventory variance						
Production capitalised						
Operating grants						
Depreciation and provisions adjustments			19,655	12,788	6,868	53.71%
Other income			601	17	585	3522.89%
<b>Total Operating Income (I)</b>			<b>20,257</b>	<b>12,804</b>	<b>7,453</b>	<b>58.20%</b>
<b>Operating expenses (2)</b>						
Purchase of goods						
Stock variation of goods						
Purchase of raw material						
Stock variation of raw material						
Other purchases and expenses *			19,551,921	14,218,362	5,333,559	37.51%
Miscellaneous taxes			87,805	78,517	9,288	11.83%
Wages and salaries			1,551,558	2,030,475	-478,917	-23.59%
Social security charges			1,239,484	858,573	380,911	44.37%
Operating depreciation or provision						
Depreciation on assets			51,103	48,501	2,602	5.36%
Provisions on assets						
Provisions on current assets						
Provision for contingency						
Other expenses			109,516	80,728	28,788	35.66%
<b>Total Operating Expenses (II)</b>			<b>22,591,389</b>	<b>17,315,156</b>	<b>5,276,233</b>	<b>30.47%</b>
<b>1 - Operating Profit (I - II)</b>			<b>-22,571,132</b>	<b>-17,302,352</b>	<b>-5,268,780</b>	<b>30.45%</b>
<b>Net result from joint ventures</b>						
Attributable profit or loss transferred						
Profit or loss transferred (IV)						

(1) Including income related to previous financial years

(2) Including expenses related to previous financial years

	12/31/16	12/31/15	Variation	
			Euros	%
<b>Net financial income</b>				
Income from investments (3)				
Income from other financial assets (3)				
Other interests and similar income (3)	442,770	407,800	34,970	8.58%
Provisions written back and deferred financial expenses	251,730	117,320	134,410	114.57%
Profit on exchange	592,876	577,697	15,179	2.63%
Net income on disposal for stock and shares				
<b>Total V</b>	<b>1,287,376</b>	<b>1,102,817</b>	<b>184,559</b>	<b>16.74%</b>
<b>Financial expenses</b>				
Financial depreciations and provisions	292,662	251,730	40,932	16.26%
Inteests payable (4)				
Loss on exchange	494,223	787,199	-292,976	-37.22%
Net book value of fixed assets disposed				
<b>Total VI</b>	<b>786,885</b>	<b>1,038,929</b>	<b>-252,044</b>	<b>-24.26%</b>
<b>2 - Financial Income (V - VI)</b>	<b>500,491</b>	<b>63,887</b>	<b>436,604</b>	<b>683.40%</b>
<b>3 - Current income before taxes (I-II+III-IV+V-VI)</b>	<b>-22,070,641</b>	<b>-17,238,465</b>	<b>-4,832,176</b>	<b>28.03%</b>
<b>Extraordinary income</b>				
Extraordinary income				
Extraordinary income on capital transactions	109,432	152,331	-42,899	-28.16%
Provisions written back: extraordinary income	95,696	154,638	-58,942	-38.12%
<b>Total VII</b>	<b>205,128</b>	<b>306,969</b>	<b>-101,841</b>	<b>-33.18%</b>
<b>Extraordinary expenses</b>				
Extraordinary costs on trading activities	90		90	100%
Extraordinary costs on capital transactions	197,000	166,271	30,729	18.48%
Extraordinary costs for depreciations and provisions	50,000	48,601	1,399	2.88%
<b>Total VIII</b>	<b>247,090</b>	<b>214,872</b>	<b>32,218</b>	<b>14.99%</b>
<b>4 - Net extraordinary income (VII-VIII)</b>	<b>-41,962</b>	<b>92,097</b>	<b>-134,059</b>	<b>-145.56%</b>
Employees' shares (IX)				
Corporate income tax (X)	-3,584,589	-2,095,984	-1,488,605	71.02%
<b>Total Income (I+III+V+VII)</b>	<b>1,512,761</b>	<b>1,422,590</b>	<b>90,171</b>	<b>6.34%</b>
<b>Total Expenses (II+IV+VI+VIII+IX+X)</b>	<b>20,040,775</b>	<b>16,472,973</b>	<b>3,567,801</b>	<b>21.66%</b>
<b>5 - Net profit or loss</b>	<b>-18,528,014</b>	<b>-15,050,384</b>	<b>-3,477,630</b>	<b>23.11%</b>

\* Including: Equipment leasing  
Real estate leasing

(3) Including income concerning related companies

(4) Including interest concerning related companies



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## **Fiscal year from January 1 to December 31, 2016**

Notes to the balance sheet prior to the breakdown, in which the total balance sheet amounts to €29,551,561.69, and to the year's income statement presented in list form, in which revenue stands at €0, resulting in a deficit of €18,528,014.15.

The fiscal year lasts 12 months, covering the period from January 1 to December 31, 2016.

The notes and tables presented below form an integral part of the annual accounts.

### **I      SIGNIFICANT EVENTS DURING THE FISCAL YEAR**

The main factors affecting the period from January 1 to December 31, 2016 were as follows:

- *“CARAT” clinical trial*

A Phase II CARAT clinical trial, the purpose of which is to assess the efficacy of CER-001 in reducing atherosclerotic plaque in post-Acute Coronary Syndrome (ACS) patients. This trial will involve 301 patients in four countries: Australia, Hungary, the Netherlands and the United States. Patient recruitment was completed in August 2016 and the last patient received the tenth and final administration of CER-001 or a placebo in the fourth quarter of 2016. The findings of this trial are expected at the end of the first quarter of 2017.

- *“TANGO” clinical trial*

A Phase III trial (TANGO) on the orphan disease FHFA to evaluate the efficacy of six months' chronic administration of CER-001 in 30 patients suffering an HDL deficiency. Active recruitment of patients for the TANGO Phase III trial is under way and findings should be available in the third quarter of 2017. The Company is working with 18 sites around the world to find more patients with Familial Primary HypoAlphalipoproteinemia (FPHA), a rare but important disease, both from a clinical and an orphan pathology standpoint.

- *“LOCATION” clinical trial*

On June 2, Cerenis announced in the scientific journal of the European Atherosclerosis Society (EAS) the findings of the LOCATION clinical trial, which demonstrate the functionality of CER-001. The trial was conducted during the first half of 2015.

- *FDA authorization to begin clinical trials with CER-209*

The US Food and Drug Administration (FDA) informed Cerenis Therapeutics that CER-209 could enter into clinical development. This authorization from the FDA (IND, Investigational New Drug application) is for a Phase I clinical trial for the CER-209 candidate drug, a P2Y13 receptor agonist, in healthy volunteers, into non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD).

### **II      EVENTS OCCURRING AFTER THE CLOSING DATE**

No material event occurred after December 31, 2016.

### III ACCOUNTING POLICIES

(Commercial Code – Article L.123-196, paragraphs 1 and 2)

(PCG [French GAAP] – Article 831-1/1)

#### General principles and conventions

Financial statements for the year ended have been prepared and presented in accordance with the principles set forth in Articles 121-1 and 121-5 *et seq.* of the 2014 Plan Comptable Général (French GAAP).

The historical cost method was adopted as the basic method of accounting.

Accounting conventions have been applied in line with the provisions of the Commercial Code, of the Accounting Decree of November 29, 1983 and of the 2015-06 rules of the ANC (the French accounting standards body) concerning the rewriting of the general chart of accounts applicable at the closing of the fiscal year.

Income and expenses in foreign currency are recorded at their equivalent value as at the transaction date. Foreign currency debts, receivables and cash and cash equivalents are recorded in the balance sheet as the equivalent in euros converted at the rate applicable at the financial year end.

Any difference arising from converting the foreign-currency liabilities and receivables at this latter rate appears in the balance sheet under “Translation adjustment.” A provision for exchange risks is established on any unrealized foreign exchange losses that are not offset.

The Crédit d’Impôt Compétitivité Emploi (CICE, the French tax credit for employment and competitiveness), corresponding to eligible compensation for the calendar year, was recognized, pursuant to the recommendations of the French accounting standards body, under line item 649 – Payroll expenses.

The objective of the CICE is to improve the competitiveness of businesses.

The Board adopted the going concern principle.

The Company's historical loss-making situation is explained by the innovative character of the products developed that involves a research phase spanning several years.

#### Consistency:

The accounting methods adopted for this financial year are similar to those of the previous year.

#### IV ADDITIONAL INFORMATION CONCERNING THE BALANCE SHEET

The following statements are presented in euros.

##### IV.A Statement of assets

Fixed assets (in euros)	Gross value at the beginning of the year	Increases	
		Writing up	Additions
Software	119,863		
<b>Total intangible assets</b>	<b>119,863</b>		
General facilities, sundry fixtures and fittings	42,217		
Transportation equipment	198,975		3,305
Furniture, office and computer equipment	217,304		2,175
Laboratory equipment	464,192		
<b>Total property, plant et equipment</b>	<b>922,688</b>		<b>5,480</b>
Loans and other financial assets	12,549		
Liquidity contracts: Treasury shares & cash and cash equivalents	486,060		399,326
<b>Total financial assets</b>	<b>498,609</b>		<b>399,326</b>
<b>TOTAL FIXED ASSETS</b>	<b>1,541,161</b>		<b>404,806</b>

Fixed assets (in euros)	Diminutions		Gross value at the end of the year	Writting up initial value at the end of the year
	Item to item transfer	Disposals retirement		
Software			119,863	119,863
<b>Total intangible assets</b>			<b>119,863</b>	<b>119,863</b>
General facilities, sundry fixtures and fittings			42,217	42,217
Transportation equipment			202,280	202,280
Furniture, office and computer equipment		4,608	214,871	214,871
Laboratory equipment			464,192	464,192
<b>Total property, plant et equipment</b>		<b>4,608</b>	<b>923,560</b>	<b>923,560</b>
Loans and other financial assets		799	11,750	11,750
Liquidity contracts: Treasury shares & cash and cash equivalents		486,060	399,326	399,326
<b>Total financial assets</b>		<b>486,859</b>	<b>411,076</b>	<b>411,076</b>
<b>TOTAL FIXED ASSETS</b>		<b>491,467</b>	<b>1,454,499</b>	<b>1,454,499</b>

## IV.B Statement of depreciation

Situations and transactions (in euros)	Amount at start of the year	Provision for the fiscal year	Reductions in reversals	Amount at end of year
Software	111,818	3,333		115,151
<b>Total depreciation of intangible assets</b>	<b>111,818</b>	<b>3,333</b>		<b>115,151</b>
General facilities, sundry fixtures and fittings	32,761	4,707		37,468
Transportation equipment	69,015	28,339		97,353
Furniture, office and computer equipment	188,955	14,725	1,279	202,401
Laboratory equipment	464,192			464,192
<b>Total depreciation of tangible assets</b>	<b>754,923</b>	<b>47,771</b>	<b>1,279</b>	<b>801,414</b>
<b>TOTAL DEPRECIATION</b>	<b>866,741</b>	<b>51,103</b>	<b>1,279</b>	<b>916,565</b>

Breakdown of provisions	Depreciation on a straight line	Declining-balance depreciation	Exceptional depreciation	Accelerated depreciation	
				Provisions	Reversals
Software	3,333				
<b>Total depreciation of intangible assets</b>	<b>3,333</b>				
General facilities, sundry fixtures and fittings	4,707				
Transportation equipment	28,339				
Furniture, office and computer equipment	14,725				
Laboratory equipment					
<b>Total depreciation of tangible assets</b>	<b>47,771</b>				
<b>TOTAL DEPRECIATION</b>	<b>51,103</b>				

## IV.C Statement of provisions

Provisions (in euros)	Amount at start of the year	Provision for the fiscal year	Reductions in reversals	Amount at end of year
Provision for exchange losses	251,730	292,593	251,730	292,593
Provisions for risks and contingencies	931,169	50,000	95,696	885,473
<b>Total provisions for risks and contingencies</b>	<b>1,182,899</b>	<b>342,593</b>	<b>347,426</b>	<b>1,178,066</b>
Treasury shares		69		69
Inventories and work in progress	4,344			4,344
<b>Total provisions for depreciation</b>	<b>4,344</b>	<b>69</b>		<b>4,413</b>
<b>TOTAL PROVISIONS</b>	<b>1,187,243</b>	<b>342,662</b>	<b>347,426</b>	<b>1,182,479</b>
<b>Of which provisions and reversals</b>				
operational				
financial		292,662	251,730	
exceptional		50,000	95,696	

The net reversals of provisions for fiscal 2016 totaled €5,000. This provision reversal was used during the fiscal year.

On December 31, 2016, the Company's executive team calculated an estimate of the risks incurred concerning disputes with third parties and a former employee and set aside a provision for them.

#### IV.D Schedule of receivables and liabilities

Statements of receivables (in euros)	Gross amount	≤ 1 year	> 1 year
Other financial assets	11,750		11,750
Liquidity contract: Treasury shares & cash and cash equivalents	399,256	399,256	
Trade receivables and related accounts	17,689	17,689	
Social security and other welfare agencies			
R&D tax credit	3,584,589	3,584,589	
Tax credit for competitiveness and employment	4,140	4,140	
Value-added tax	124,835	124,835	
Group and associated companies			
Other receivables	57,942	57,942	
Prepaid expenses	265,669	265,669	
<b>TOTAL RECEIVABLES</b>	<b>4,465,871</b>	<b>4,454,121</b>	<b>11,750</b>

Statements of liabilities (in euros)	Gross amount	≤ 1 year	From 1 to 5 years	> 5 years
Trade payables and related accounts	5,423,337	5,423,337		
Personnel costs and similar	118,546	118,546		
Social security and other welfare agencies	829,888	829,888		
Statement of payable expenses	23,346	23,346		
Group and associated companies	675,058	675,058		
<b>TOTAL DETTES</b>	<b>7,070,175</b>	<b>7,070,175</b>		

The €3,584,589 corporate income tax receivable corresponds to the 2016 Research Tax Credit, restitution of which has been claimed by the Company. The 2015 Research Tax Credit recognized in the amount of €2,095,984 was received by the Company in July 2016.

The amount of the tax credit for employment and competitiveness (CICE) for fiscal 2016 amounting to €4,140,000, for which the Company has requested repayment, has been recognized as a payroll deduction.

The use of this CICE conforms with the objectives of the French General Tax Code (CGI) Article 244(4) C, in particular regarding investments and the reconstitution of shareholders' equity. The tax credit generated over the last calendar year was applied as follows:

Description of efforts	Amount
- investment	
- research	4,140
- innovation	
- training	
- hiring	
- exploration of new markets	
- ecological and energy transition	
- replenishment of the working capital	
<b>TOTAL</b>	<b>4,140</b>

It did not, therefore, make it possible to fund an increase in the distribution of profits or an increase in executive compensation.

#### IV.E Conditional financial liabilities

In March 2010, the ISI Apotheose project, presented in partnership with NOVASEP, received €10.7 million in support from OSEO Innovation. CERENIS THERAPEUTICS' share was €6.7 million. These sums are being disbursed on the basis of the expenses incurred at each pre-defined key stage. Since the conditions for key stage 1 had been fulfilled, the repayable advance (€4,049,838) and government subsidy (€107,146) were paid in May 2012. By letter dated August 27, 2014, BPI France allowed Cerenis to extend the end of the program. The R&D phase of the project was therefore extended to December 31, 2016.

In early 2012, OSEO Innovation granted CERENIS THERAPEUTICS a repayable advance of €1.5 million. This repayable advance is conditional on the progress of the CER-209 program. Full payment of this state aid is conditional on completion of the stages defined in the contract. If successful, repayment will be made by installments starting on March 31, 2018 until December 31, 2020. On December 31, 2012, Cerenis received the first payment of €500,000.

Financial liabilities (in euros)	Gross amount	≤ 1 year	From 1 to 5 years	> 5 years
OSEO/ISI repayable advance	4,602,943		4,602,943	
OSEO/CER-2009 repayable advance	500,000		500,000	
<b>TOTAL LIABILITIES</b>	<b>5,102,943</b>		<b>5,102,943</b>	

#### IV.F Structure of the authorized capital

##### Authorized capital

The authorized capital at December 31, 2016 was €913,163.15. It is divided into 18,263,263 fully subscribed and paid-up shares, each with a par value of €0.05.

This does not include the stock warrants (SWs), founder's stock warrants (FSWs), stock options (SOs) and bonus shares (BSs) awarded to certain individuals, whether or not company employees.

	Dec. 31, 2015	Capital increase	Dec. 31, 2016	
Ordinary shares	17,794,878	468,385	18,263,263	913,163.15
	<b>17,794,878</b>	<b>468,385</b>	<b>18,263,263</b>	

The capital increase results from:

- The exercise of 103,385 FSWs and stock options by current and former employees;
- The award of 365,000 bonus shares at the end of the one-year vesting period.

### Stock warrants, founder's stock warrants, stock options and bonus shares

Since its founding in 2005, the Company has issued stock warrants (SWs), founder's stock warrants (FSWs), stock options (SOs) and bonus shares (BSs); the various plans are outlined below:

Plan	Grant date	Number of instruments granted	Number of instruments forfeited	Number of instruments exercised	Number of instruments vested	Exercise price (€)
BSCPE	2006	76,500	33,250	43,250	0	5.45
SO	2006	222,500	142,412	80,088	0	4,22 / 7,32
BSA	2006	15,000	15,000	0	0	7.32
BSCPE	2007	64,376	10,313	0	54,063	7.32
SO	2007	250,626	238,126	0	12,500	7.32
BSA	2007	48,250	48,250	0	0	7.32
BSCPE	2008	236,475	211,325	0	25,150	7.69
SO	2008	68,950	60,300	0	8,650	7.69
BSA	2008	10,000	10,000	0	0	7.69
BSCPE	2009	163,800	141,675	1,025	21,100	7.66
SO	2009	131,300	115,900	1,000	14,400	7.66
BSA	2009	10,000	10,000	0	0	7.66
SO	2010	85,500	70,600	0	14,900	7,77 / 8,74
BSA	2010	43,250	43,250	0	0	7,77 / 8,74
BSCPE	2010	83,000	37,600	0	45,400	7.77
BSCPE	2011	303,000	105,865	56,135	141,000	8,74 / 9,31
SO	2011	112,500	85,700	0	26,800	8,74 / 9,31
BSA	2011	0	0	0	0	8.74
BSCPE	2012	191,381	31,900	0	159,481	9.31
BSA	2012	77,667	44,417	0	33,250	9.31
SO	2012	41,100	33,700	0	7,400	9.31
BSCPE	2013	443,714	403,414	0	37,782	9.49
SO	2013	166,286	162,686	0	3,375	9.49
BSA	2013	74,000	62,000	0	11,250	9.49
AGA	2015	365,000	0	365,000	0	12.16
AGA	2016	200,000	0	0	0	9.81
AGA	2016	5,000	0	0	0	8.40
BSA	2016	133,000	33,250	0	0	9.36
SO	2016	134,417	0	0	134,417	9.36
<b>TOTAL</b>		<b>3,756,592</b>	<b>2,150,933</b>	<b>546,498</b>	<b>750,918</b>	

The main features of these profit-sharing instruments with access to the equity capital are:

- Beneficiaries of the SWs, FSWs
  - and SOs: the Company's employees and directors, members of the Board of Directors and members of the Scientific Advisory Committee;
  - Exercise period: 10 years maximum;
  - Exercise price: equal to at least the fair value on the grant date;
  - Exercise right: acquired progressively over a period of four years, with an acquisition limit of one year.
- For the bonus shares:
  - Beneficiaries: company employees and directors;



- Vesting period: set a one year at the end of which the shares will vest on the express condition that the beneficiary is still an employee or corporate officer on that date;
- Lock-up period: set at one year from the vesting date. At the end of this lock-up period, the shares may be freely transferred by holders.

The shares issued at the end of the vesting period will be new common stock, issued by means of a capital increase through the capitalization of reserves. Holders will be entitled to the associated rights and benefits as of their date of issue.

The CEO must hold 10% of such shares as registered shares, until such time as he or she leaves office.

### **Changes in shareholders' equity**

The table of changes in shareholders' equity is presented below:

	CHANGES IN EQUITY					
	Nb of shares	Share capital	Issue premium	Retained earnings	Result	TOTAL
Balance at 12/31/2015	17,794,878	889,744	166,031,966	-117,986,020	-15,050,384	33,885,306
Exercise of BSCPE	103,385	5,169	739,500			744,669
Exercise of BSA				93,765		93,765
Issue of bonus shares	365,000	18,250	-18,250			0
Appropriation of earnings				-15,050,384	15,050,384	0
2016 results					-18,528,014	-18,528,014
<b>Balance at 12/31/2016</b>	<b>18,263,263</b>	<b>913,163</b>	<b>166,753,216</b>	<b>-132,942,639</b>	<b>-18,528,014</b>	<b>16,195,726</b>

### **IV.G Applied research and development costs**

The Company enters research and development costs on the asset side when they met the criteria set forth under Article 311-3 of the Plan Comptable Général (French GAAP).

Since these criteria were not met on the reporting date, the expenses incurred during the financial year have not been capitalized.

### **IV.H Other intangible assets**

Patents, licenses and other intangible fixed assets are shown at their acquisition costs, excluding the costs incurred in their acquisition.

These items are depreciated over the period of their use by the Company, namely:

Class	Assets	Depreciation period
Software	119,863	18 to 36 months

#### IV.I Valuation of property, plant and equipment

The gross value of property, plant and equipment corresponds to the value at which they were initially recorded in the Company's balance sheet considering the costs required to make them operational, but excluding the costs incurred in their acquisition.

#### IV.J Valuation of financial assets

The financial assets comprise deposits associated with the renting of the offices in Labège and with the liquidity agreement.

The Company is continuing to operate the liquidity agreement that it entered into following the IPO. The agreement's checking account totaled €204,687.68 at December 31, 2016. A total of 23,291 treasury shares were purchased pursuant to this agreement, valued at €194,637.85 at December 31, 2016.

#### IV.K Valuation of depreciation

The following depreciation periods and methods were adopted:

Class	Method	Depreciation period
Sundry fixtures and fittings	Straight-line	10 years
Laboratory equipment	Straight-line	3 years
Office equipment	Straight-line	3 to 7 years
Computers	Straight-line	3 years
Furniture	Straight-line	10 years

#### IV.L Valuation of receivables and payables

Receivables and payables have been valued at their nominal value.

Foreign currency payables were recorded using the closing rate at December 31, 2016.

#### IV.M Valuation of securities

Securities have been valued at their acquisition costs, excluding the costs incurred in their acquisition.

In the event of the sale of securities of the same type conferring the same rights, the value of the securities was estimated at the weighted average purchase price.

#### IV.N Depreciation of securities

Securities, where applicable, were depreciated by means of a provision to take into account:

- For listed securities, the average price in the last month of the financial year,
- For unlisted securities, the probable market value at the close of the financial year.

#### IV.O Cash and cash equivalents in euros

Cash on hand or at bank was valued at its nominal value.

#### IV.P Cash and cash equivalents in foreign currency

Foreign cash and cash equivalents were converted into euros based on the closing rate at December 31, 2016.

Currency translation adjustments were directly recorded in income for the financial year under exchange gains and losses.

#### IV.Q Accrued income

Accrued income corresponds to interest on term accounts.

Accrued income amount included in the following items of the balance sheet (in euros)	Amount
Interests from securities	716,105
<b>TOTAL ACCRUED INCOME</b>	<b>716,105</b>

#### IV.R Accrued expenses

Accrued expenses amount included in the following items of the balance sheet (in euros)	Amount
Unbilled payables on Overheads	217,153
Unbilled payables on research and development	1,484,134
Unbilled payables, SAB	25,000
Liabilities to staff	118,546
Amounts due to social security expenses	239,140
Statement of accrued expenses	18,601
<b>TOTAL ACCRUED EXPENSES</b>	<b>2,102,573</b>

Accrued research and development costs mainly correspond to the costs incurred for clinical trials.

#### IV.S Prepaid income and expenses

Prepaid expenses (in euros)	Amount
Overhead operating costs	41,523
R&D operating costs	224,146
<b>TOTAL</b>	<b>265,669</b>

The amounts recorded as prepaid expenses correspond to costs and expenses covering the 2016 financial year.

#### IV.T Related-party disclosures

The Board has provided for a termination fee to be paid to the CEO in the event of dismissal or non-renewal of his term of office provided the termination is not the consequence of a violation of the law or the bylaws, or of serious misconduct.

The amount of compensation granted to the three members of the Executive Committee is set out below:

	12/31/16	12/31/15
Fixed remuneration	721	897
Variable remuneration	222	199
Benefits in kind	13	8
Social contributions	395	465
<b>TOTAL</b>	<b>1,351</b>	<b>1,569</b>

## V ADDITIONAL INFORMATION ON THE INCOME STATEMENT

### V.A Compensation of senior executives

Given the small number of employees in the Company, providing information on their compensation would amount to a disclosure of their individual compensation.

### V.B Lease contracts

The Company has no lease contracts.

## VI FINANCIAL COMMITMENTS AND OTHER DISCLOSURES

### VI.A Repayable advances from OSEO

#### Schedule for payment of the repayable advances:

The contracts signed provide that the repayable advances should be advanced when each key stage is completed. Based on the current schedule, the expected payments are as follows:

Amounts in euros	Initial payment	EC1	EC2	EC3	TOTAL
ISI repayable advance	553,105	4,049,838	823,078	957,533	6,383,554
CER-209 repayable advance	500,000	750,000	250,000		1,500,000

#### Financial repayment mechanisms:

##### ISI repayable advance

The procedure for repayment of this repayable advance will be applied at two levels, based on the following timetable:

- The repayment of the advance in a total amount of €7,400,000 over a five-year period, with effect from the fiscal year when the Company has achieved cumulative CER-001 sales of more than €20,000,000;
- The payment of a repayment premium in a total amount of €12,600,000 representing 4% of sales from the year when the Company has achieved cumulative CER-001 sales of more than €300,000,000.

	Application threshold	Amount	Total
CER-001 sales	Cumulative sales > €20,000K	Year 1: €300K Year 2: €500K Year 3: €1,000K Year 4: €2,000K Year 5: €3,600K	Total: 7 400 K€
	Cumulative sales > €300,000K	4% of sales over 4 years	Maximum amount: €12,600K

In the event of failure of the project, the Company will have to repay an amount of €600,000.

Initially, Cerenis estimated that its first sales would start in 2014.

Given the results from the CHI-SQUARE trials and from the launch of the “CARAT” and “TANGO” trials (refer to Note I.B above), the Group does not anticipate sales in respect of the orphan drug disease trial. As a consequence, the reimbursement should be realized between June 2017 and March 2025.

As a consequence, the repayment schedule of BPI repayable advance has been re-estimated, based on management best estimate to start to reimburse in 2017. On August 27, 2014, Cerenis has received the update of the reimbursement schedule from OSEO.

#### CER-209 repayable advance

The contract with OSEO stipulates that in the event of technical success, Cerenis will repay this amount according to a pre-established schedule staggered over the period from June 30, 2014 to March 31, 2017.

During fiscal 2014, the repayment schedule of the repayable advance was re-estimated and renegotiated, based on management’s best estimate, in order to take into account the expected reimbursements with effect from 2017.

Following this negotiation, the repayment schedule was reviewed and extended. It was set out as follows:

Year ended December 31, 2017: €400,000

Year ended December 31, 2018: €500,000

Year ended December 31, 2019: €600,000

The repayment schedule in case of failure was also renegotiated and set out as follows:

Year ended December 31, 2017: €300,000

Year ended December 31, 2018: €300,000

In the event that the project is unsuccessful, Cerenis Therapeutics will repay €600,000.

At December 31, 2016, following the rescheduling agreement signed with BPI on September 9, 2016, the reimbursement schedule for the BPI 2012 advance was reviewed to take into account a one-year time lag in the program's implementation.

#### **VI.B Pension and retirement commitments**

Under the collective bargaining agreement applicable to Pharmacy: Industry, the Company's retirement commitments amounted to €120,000 at December 31, 2016.

## VI.C Personal Training Account (CPF)

Since January 1, 2015, a new pathway to training was put in place through a personal training account (PTA). This personal account is populated with training hours that can be used by any worker throughout their active life to obtain an educational qualification. The PTA replaced the individual right to training (Dif) on January 1, 2015; however, workers will not lose their hours, which they can use until December 31, 2020.

At December 31, 2016, the volume of cumulative training hour entitlements that have not yet been exercised by current workers was 878.

## VI.D Increase and reduction of future tax debt

Nature of timing differences (in € thousands)	Amount
Loss carried forward before 01/01/14	124,745
Loss carried forward for 2014	6,302
Loss carried forward for 2015	17,232
Loss carried forward for 2016	22,119
<b>TOTAL</b>	<b>170,398</b>

## VI.E List of subsidiaries and shareholdings

LIST OF SUBSIDIARIES AND SHAREHOLDING									
	Capital (in \$)	Shareholders' equity other than share capital	Shareholding in %	Book value of securities held	Loans and advances granted by the company but not yet prepaid (in euros)	Guarantees and securities	TO excl. tax (in euros)	Profit (in euros)	Dividends
<b>Subsidiaries Shareholding &gt; 50%)</b>									
1 - CERENIS INC	\$5	\$644,361	\$1	\$0	\$675,058	\$0	\$372,180	\$30,501	\$0

## **VII ADDITIONAL INFORMATION**

### **VII.A Workforce**

The Company had 12 employees at December 31, 2016 compared with 10 at December 31, 2015.

### **VII.B Consolidated financial statements**

Following its IPO and entry into a regulated market, the Company implemented mandatory consolidated financial statements.

### **VII.C Statutory Auditors' fees**

The Statutory Auditors' fees for auditing the statutory accounts and services other than the certification of the accounts amounted to €102,500, of which €63,500 was for Deloitte & Associés (of which €16,500 for services other than the certification of the accounts) and €39,000 for HLP (of which €8,000 for services other than the certification of the accounts).



## CERENIS THERAPEUTICS HOLDING

Société anonyme  
265, rue de la Découverte  
31670 Labège

### Statutory auditors' report on the financial statements

for the year ended 31 December 2016

*This is a free translation into English of the statutory auditors' report issued in French and is provided solely for the convenience of English speaking readers. The statutory auditors' report includes information specifically required by French law in such reports, whether modified or not. This information is presented below the opinion on the financial statements and includes an explanatory paragraph discussing the auditors' assessments of certain significant accounting and auditing matters. These assessments were considered for the purpose of issuing an audit opinion on the financial statements taken as a whole and not to provide separate assurance on individual account captions or on information taken outside of the financial statements.*

*This report also includes information relating to the specific verification of information given in the management report and in the documents addressed to shareholders.*

*This report should be read in conjunction with, and construed in accordance with, French law and professional auditing standards applicable in France.*

To the Shareholders,

In compliance with the assignment entrusted to us by your annual general meeting, we hereby report to you, for the year ended 31 December 2016, on:

- the audit of the accompanying financial statements of CERENIS THERAPEUTICS HOLDING;
- the justification of our assessments;
- the specific verification and information required by law.

These financial statements have been approved by the Board of Directors. Our role is to express an opinion on these financial statements based on our audit.

#### **I. Opinion on the financial statement**

We conducted our audit in accordance with professional standards applicable in France; those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit involves performing procedures, using sampling techniques or other methods of selection, to obtain audit evidence about the amounts and disclosures in the financial statements. An audit also includes evaluating

the appropriateness of accounting policies used and the reasonableness of accounting estimates made, as well as the overall presentation of the financial statements. We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our audit opinion.

In our opinion, the financial statements give a true and fair view of the assets and liabilities and of the financial position of the Company as at 31 December 2016 and of the results of its operations for the year then ended in accordance with French accounting principles.

## **II. Justification of our assessments**

In accordance with the requirements of article L. 823-9 of the French Commercial Code (code de commerce) relating to the justification of our assessments, we hereby inform you that our assessments covered the appropriateness of accounting policies used and the reasonableness of the significant estimates and the overall presentation of the financial statements.

These assessments were made as part of our audit of the financial statements taken as a whole, and therefore contributed to the opinion we formed which is expressed in the first part of this report.

## **III. Specific verifications and information**

We have also performed, in accordance with professional standards applicable in France, the specific verifications required by French law.

We have no matters to report as to the fair presentation and the consistency with the financial statements of the information given in the management report of the Board of Directors and in the documents addressed to shareholders with respect to the financial position and the financial statements.

Concerning the information given in accordance with the requirements of article L. 225-102-1 of the French Commercial Code (code de commerce) relating to remunerations and benefits received by the directors and any other commitments made in their favor, we have verified its consistency with the financial statements, or with the underlying information used to prepare these financial statements and, where applicable, with the information obtained by your company from companies controlling your company or controlled by it. Based on this work, we attest the accuracy and fair presentation of this information.

In accordance with French law, we have verified that the required information concerning the identity of the shareholders and holders of the voting rights has been properly disclosed in the management report.

Nantes and Balma, on 20 February 2017

The statutory auditors

French original signed by

**HLP Audit**

**Deloitte & Associés**

Freddy GARCIN

Partner

Etienne ALIBERT

Partner

## 20.5. Date of the last financial information

The latest financial reporting date is December 31, 2016.

## 20.6. Dividend distribution policy

### 20.6.1. Dividends and reserves distributed by the Company in the last three years

None.

### 20.6.2. Distribution policy

There is no plan to initiate a dividend payment policy in the short term given the Company's stage of development.

## 20.7. Legal and arbitration proceedings

### *Employee disputes*

Ms. Daniela Oniciu, a former employee of the Company, filed a claim before the Labor Tribunal (Conseil de Prud'hommes) of Toulouse on March 4, 2014 in order to challenge her layoff due to economic reasons, requesting that €250,582 be paid to her by the Company. After an initial hearing with the Office of Judgment with the Toulouse Labor Tribunal on July 29, 2015, the members of the Tribunal announced a tie vote and the case was referred to the Chief Adjudicator. The hearing to break the tie vote was held on January 7, 2016; under advisement, all of the former employee's claims were dismissed. The appeal period has not expired at the date of this Registration Document.

This dispute gave rise to a provision in the accounts (see Note III.I to the financial statements provided in Section 20.1 of this Registration Document).

### *Claim against the Montreal Heart Institute*

Cerenis has filed in June 2014 a claim for damages against the Montreal Heart Institute (Institut de Cardiologie de Montréal (ICM)) before the Superior Court of Quebec to seek compensation for the damages suffered by Cerenis due to the ICM's negligence in the performance of the service agreement between the Company and the ICM in connection with the CHI SQUARE trial conducted.

There are no other government, legal or arbitration proceedings, or any proceedings of which the Company is aware, that are pending or threatened and that are likely to have or have had a material impact on the financial position and/or profitability of the Company and/or Group during the last 12 months, other than those referred to above.

## 20.8. Material changes in the financial or commercial position

In March 2017, the Company announced that the main criterion of CARAT, a Phase II clinical trial, had not been achieved. As a result, the indication of secondary prevention in acute coronary syndrome (ACS) patients was suspended.

The Company is continuing its clinical development program, the most recent data for which are outlined in Section 6 of this Registration Document. This development focuses primarily on two separate programs: the TANGO Phase III trial and the clinical development of CER-209.

At March 31, 2017, the Group's net cash balance was €19.0 million. All the company's cash flow is realizable (term deposits and current accounts) in order to fund current R&D programs.

## 20.9. Table of results for the last five fiscal years

The following table presents the results of the last five fiscal years:

In Euros	12/31/2012	12/31/2013	12/31/2014	12/31/2015	12/31/2016
<b>FINANCIAL POSITION AT THE END OF YEAR</b>					
Share capital	658.089	658.089	658.089	889,743	913,163
Number of shares issued	13,161,788	13,161,788	13,161,788	17,794,878	18,263,263
<b>OVERALL RESULT OF EFFECTIVE OPERATIONS</b>					
Turnover excluding taxes					
Earnings before income taxes, depreciation and amortization	-21,246,892	-10,531,263	-6,089,620	-17,069,494	-22,066,264
Income taxes	-625,824	-1,933,434	-1,176,779	-2,095,984	-3,584,589
Profit after tax, amortization and provisions	-21,585,886	-8,726,028	-5,643,890	-15,050,384	-18,528,014
Amount of profits distributed					
<b>RESULT OF OPERATIONS REDUCED ON A SINGLE ACTION</b>					
Profits after tax, but before amortization and provisions	-1.59	-0.65	-0.37	-0.84	-1.01
Profit after tax, amortization and provisions	-1.64	-0.66	-0.43	-0.85	-1.01
Dividends paid to each share	0	0	0	0	0
<b>STAFF</b>					
Number of employees	18	16	7	10	12
Amount of payroll	2,264,782	1,916,845	1,683,485	2,030,475	1,551,558
"Amount of benefits paid	907,179	796,793	700,900	858,573	1,239,484

## 21. SUPPLEMENTAL INFORMATION

### 21.1. Share capital

#### 21.1.1. Amount of the share capital

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At February 28, 2017, the share capital totaled €915,163.15, divided into 18,303,263 common shares with a par value of €0.05 each, fully paid up.

On the same date, those 18,303,263 common shares represented 18,303,263 theoretical voting rights and 18,278,275 actual voting rights, the difference between the theoretical number of voting rights and the actual number of voting rights representing the number of treasury shares.

It should be noted that the class A, B and C preferred shares, which existed prior to the IPO, were automatically converted into common shares with an exchange ratio of one common share for one preferred share in the context of the listing of the shares for trading on Euronext Paris.

#### 21.1.2. Securities not representing capital

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None.

#### 21.1.3. Number, book value and nominal value of the shares held by the Company or on its behalf

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##### 21.1.3.1. Current authorizations

The Company's shareholders, gathered at their General Meeting of June 10, 2016, authorized the Board of Directors, for a period of eighteen months from the meeting, to implement a buyback program for the Company's shares pursuant to the provisions stipulated in Article L. 225-209 of the French Commercial Code under the conditions described below:

**Maximum number of shares that may be purchased:** 10% of the share capital on the date of the share buyback. When the shares are acquired for the purpose of promoting the coordination and the liquidity of the securities, the number of shares taken into account for the calculation of the limit of 10% provided for above is the number of shares purchased, minus the number of shares sold during the authorization period.

##### **Objectives of the buybacks:**

- Stimulating the secondary market or the liquidity of the CERENIS THERAPEUTICS HOLDING share through an investment service provider under a liquidity contract that complies with the AMAFI Charter of Ethics accepted by the regulations;
- Retaining purchased shares and using them at a later date as consideration or payment for potential acquisitions;
- Covering stock option plans and/or bonus share plans (or similar plans) for the benefit of the employees and/or corporate officers of the Group, as well as all allocations of shares for a company or group savings plan (or similar plan), for profit-sharing and/or all other forms of stock allocation to the employees and/or corporate officers of the Group;
- Covering transferable securities entitling to allotment of Company shares in accordance with the regulations in force;

- Potentially cancelling vested shares, pursuant to the authorization granted or conferred by the Extraordinary General Shareholders' Meeting.

**Maximum purchase price:** €40 per share.

**Maximum amount of funds that may be allocated to share buyback:** €10,000,000

#### **21.1.3.2. Number of treasury shares purchased and sold by the Company in 2016**

In the context of the aforementioned stock buyback program, the Company purchased and sold treasury shares in 2016 as follows:

- Number of shares purchased: 417,592  
Average purchase price: €8.43
- Number of shares sold: 412,964  
Average selling price: €8.39
- Total trading costs: €25,000

Number of shares recorded at year-end: 23,291

Value at purchase price: €194,638

Value at par value: €1,164.55

Reason for acquisition	% of capital
Liquidity contract	0.13%
Employee share ownership	0
Security giving entitlement to allocation of shares	0
External growth operations	0
Cancellation	0

The shares held by the Company have not been used since the last authority granted by the shareholders at their General Meeting.

The shares held by the Company have not been reallocated for other purposes since the last authority granted by the shareholders at their General Meeting.

#### **21.1.3.3. Description of the share buyback program**

Pursuant to Articles 241-2 of the AMF General Regulation, this description is intended to outline the purposes and conditions of the Company's program to buy back its own shares. This program will be submitted for authorization at the General Shareholders' Meeting to be held on June 9, 2017.

##### **1) Distribution of the equity securities held by objective established on Feb. 28, 2017:**

Number of securities held directly and indirectly: 24,988 shares representing 0.14% of the Company's share capital.

Number of shares held divided by objective:

- Stimulation of the price through an AMAFI liquidity contract: 0.14 %
- External growth transactions: 0
- Hedging of stock options or other employee shareholding schemes: 0
- Hedging of securities entitling to share allotment: 0
- Cancellation: 0

## 2) New share buyback program

- **Authorization for the program:** General Shareholders' Meeting of June 9, 2017
- **Securities in question:** common shares
- **Maximum percentage of share capital for which the buyback is authorized:** 10% of the share capital (1,830,326 shares at February 28, 2017); it is specified that this limit is assessed at the date of the buybacks in order to take into consideration any capital increases or reductions that may occur throughout the duration of the program. The number of shares used to calculate this limit represents the number of shares purchased, minus the number of shares resold throughout the duration of the program within the framework of the liquidity objective.

As the Company may not hold more than 10% of its share capital, based on the number of shares already held, which is 24,988 shares (i.e. 0.14% of the share capital), the maximum number of shares that may be purchased will be 1,805,338 (which is 9.86% of the share capital), unless the shares already held are sold or cancelled.

- **Maximum purchase price:** €50
- **Maximum amount of the program:** €5 million
- **Buyback conditions:** the purchases, sales and transfers may be executed by any means on the market or privately, including through block transactions on securities; it is specified that the resolution proposed for shareholder authorization does not limit the proportion of the program that may be achieved through the purchases of blocks of securities.

However, without prior authorization from the General Shareholders' Meeting, the Board will be unable to use this authority from the date a public tender offer for the Company's shares is filed until the end of the offer period.

### Objectives:

- Stimulating the secondary market or the liquidity of the CERENIS THERAPEUTICS HOLDING share through an investment service provider under a liquidity contract that complies with the AMAFI Charter of Ethics accepted by the regulations;
- Retaining the shares purchased and subsequently offering them in exchange or as payment in the context of potential external growth transactions; it is specified that the shares acquired for this purpose may not exceed 5% of the capital of the Company;
- Covering stock option plans and/or bonus share plans (or similar plans) for the benefit of the employees and/or corporate officers of the group, as well as all allocations of shares for a company or group savings plan (or similar plan), for profit-sharing and/or all other forms of stock allocation to the employees and/or corporate officers of the group;

- Covering transferable securities entitling to allotment of Company shares in accordance with the regulations in force;
- Potentially cancelling vested shares, pursuant to the authorization granted by the General Shareholders' Meeting of June 10, 2016 under its extraordinary eighth resolution.
- **Period of the program:** 18 months from the General Shareholders' Meeting of June 9, 2017, i.e. until December 8, 2018.

#### 21.1.4. Convertible or exchangeable securities with warrants<sup>i</sup>

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On March 15, 2017, the following securities give rights to capital:

	SW (1)	FSW (2)	Options (3)	Bonus Shares (4)	TOTAL
<b>Total number of shares that may be subscribed or purchased</b>	<b>145,000</b>	<b>486,494</b>	<b>222,667</b>	<b>165,000</b>	<b>1,019,161</b>

*Note 1, 2 and 3: the exercise price of the various categories of SWs, stock options and FSWs is indicated in the notes listed above, under the tables in Sections 21.1.4.1, 21.1.4.2 and 21.1.4.3.*

*Note 4: bonus shares are currently being acquired.*

##### 21.1.4.1. Stock warrants (SW) plan

With the exception of the corporate officers, the beneficiaries of stock warrants are the members of the Scientific Advisory Board and the independent Directors on the Board of Directors.

As at the date of this document, there are no longer any SWs granted before 2012 that are likely to be exercised.



2012/2014

	BSA 03-2012	BSA 02-2013	BSA 04-2013	TOTAL
Date of meeting	28 June 2011	9 May 2012	9 May 2012	
Date of grant by the Board of Directors	20 March 2012	12 February 2013	15 April 2013	
Total number of warrants authorized *	755,750	713,528		
Total number of warrants allocated	77,667	24,000	50,000	151,667
<b>Total number of shares that may be subscribed or purchased</b>	<b>77,667</b>	<b>24,000</b>	<b>50,000</b>	<b>151,667</b>
<i>Of which many may be subscribed or purchased by the corporate officers:</i>				
<i>Jean-Pierre Garnier</i>	44,417	12,000	20,000	76,417
<i>Richard Pasternak</i>	33,250	12,000	10,000	55,250
Number of non corporate beneficiaries	0	0	2	
Starting point of exercise of the warrants	<i>Note 1a</i>	<i>Note 1b</i>	<i>Note 1c</i>	
Expiry date of the warrants	20 March 2022	12 February 2023	15 April 2023	
BSA exercise price	9.31	9.49	9.49	
Terms and conditions	<i>Note 2a</i>	<i>Note 2b</i>	<i>Note 2c</i>	
Number of shares subscribed	0	0	0	0
Total number of warrants cancelled or void	44,417	12,000	50,000	106,417
Number of remaining warrants	33,250	12,000	0	45,250
Total number of shares that can be subscribed	33,250	12,000	0	45,250

\* The authorized amounts of 755,750 and 713,528 are global maximum amounts that include the FSWs, SWs, and stock options that may be granted by the Board of Directors with the authorization of the General Shareholders' Meeting.

*Note 1a: 33,250 SWs may be exercised by their holders as follows:*

- 25% of the SWs become exercisable on October 26, 2012 (anniversary date of the appointment of the holder as a Director) and the remaining 75% will be exercised in the same manner each quarter over the following three years (6.25% of the SWs may be exercised every quarter for 12 quarters after the anniversary date).

*Note 1b: The SWs may be exercised by their holder as follows:*

- 25% of the SWs become exercisable on February 12, 2014 and the remaining 75% will be exercised in the same manner each quarter over the following three years (6.25% of the SWs may be exercised every quarter for 12 quarters after the anniversary date).

*Note 1c: All of the 50,000 SWs granted on April 15, 2013 have expired.*

*Note 2a, b and c: Each SW entitles the holder to purchase one (1) of the Company's common stock. The number of common stock subscribed must be fully paid up at the time of their subscription by payment in cash, including where appropriate by set off against liquid and payable claims on the Company.*

*No SW may be transferred for a period of six years.*

2015/2016

	<b>BSA 01-2016</b>
Date of meeting	06 February 2015
Date of grant by the Board of Directors	Decision of the CEO on 22 January 2016 pursuant to the subdelegation of the BoD of 3 December 2015
Total number of warrants authorized *	133,000
<b>Total number of shares that may be subscribed or purchased</b>	<b>99,750</b>
<i>Of which many may be subscribed or purchased by the corporate officers:</i>	
<i>Laura A. Coruzzi, Director (independent)</i>	33,250
<i>Christian Chavy, Director (independent)</i>	33,250
<i>Michael Davidson, Director (independent)</i>	33,250
Number of non corporate beneficiaries	0
Starting point of exercise of the warrants	<i>Note 1a</i>
Expiry date of the warrants	22 January 2026
BSA exercise price	9.36
Terms and conditions	<i>Note 2a</i>
Number of shares subscribed	0
Total number of warrants cancelled or void	33,250
Number of remaining warrants	99,750
Total number of shares that can be subscribed	99,750

*Note 1a: The SW may be exercised according to the following schedule: 1/24th at the end of each calendar month elapsed as of December 3, 2015*

*Note 2a: Each SW gives the right to purchase one (1) of the Company's common stock. The number of common stock subscribed must be fully paid up at the time of their subscription by payment in cash, including where appropriate by set off against liquid and payable claims on the Company.*

#### **21.1.4.2. FSW Plan**

With the exception of the corporate officers, the beneficiaries of FSWs are employees of the Company.

As at the date of this document, there are no longer any FSWs granted before 2007 that are likely to be exercised.

## 2007/2008

	BCE 03-2007	BCE 05-2007	BCE 01-2008	BCE 03-2008	BCE 05-2008	TOTAL
Date of meeting	9 March 2007	9 March 2007	9 March 2007	9 March 2007	9 March 2007	
Date of grant by the Board of Directors	9 March 2007	10 May 2007	28 January 2008	6 March 2008	29 May 2008	
Total number of BSPCE authorized *			986,000			
Total number of BSPCE allocated	62,376	2,000	133,000	18,475	85,000	300.851
<b>Total number of shares that may be subscribed or purchased</b>	<b>62,376</b>	<b>2,000</b>	<b>133,000</b>	<b>18,475</b>	<b>85,000</b>	<b>300.851</b>
<i>Of which many may be subscribed or purchased by the corporate officers:</i>						
<i>Jean-Louis Dasseux</i>	10,000			7,500		17,500
Number of non corporate beneficiaries	4	1	1	4	4	
Starting point of exercise of the BSPCE			Note 1			
Expiry date of the BSPCE	9 March 2017	10 May 2017	28 January 2018	6 March 2018	29 May 2018	
BSPCE exercise price	7.32	7.32	7.69	7.69	7.69	
Terms and conditions	Note 2a	Note 2b	Note 2c	Note 2d	Note 2e	
Number of shares subscribed	0	0	0			0
Total number of BSPCE cancelled or void	62,376	2,000	133,000	3,325	75,000	275.701
Number of remaining BSPCE	0	0	0	15,150	10,000	25,150
Total number of shares that can be subscribed	0	0	0	15,150	10,000	25,150

\* The authorized amount of 986,000 is a global maximum amount that includes the FSWs, SWs, and stock options that may be granted by the Board of Directors with the authorization of the General Shareholders' Meeting.

Note 1: All the FSWs granted on May 10, 2007, January 28, 2008, March 6, 2008 and May 29, 2008, which have not expired, are exercisable as of this day.

Note 2a: All the FSWs granted on March 9, 2007, have expired.

Note 2b, c, d and e: Each FSW entitles the holder to purchase one (1) of the Company's common stock. The number of common stock subscribed must be fully paid up at the time of their subscription by payment in cash, including where appropriate by set off against liquid and payable claims on the Company.

## 2009

	BCE 03-2009	BCE 01-2010	BCE 04-2010	TOTAL
Date of meeting	30 January 2009	20 May 2009	20 May 2009	
Date of grant by the Board of Directors	3 March 2009	28 January 2010	13 April 2010	
Total number of BSPCE authorized *	314,323	514,323		
Total number of BSPCE allocated	163,800	63,000	20,000	246,800
<b>Total number of shares that may be subscribed or purchased</b>	<b>163,800</b>	<b>63,000</b>	<b>20,000</b>	<b>246,800</b>
<i>Of which many may be subscribed or purchased by the corporate officers:</i>				
<i>Jean-Louis Dasseux</i>	10,000	12,800		22,800
<i>André Mueller</i>	12,000	12,000		24,000
Number of non corporate beneficiaries	13	12	1	
Starting point of exercise of the BSPCE		Note 1		
Expiry date of the BSPCE	3 March 2019	28 January 2020	13 April 2020	
BSPCE exercise price	7.66	7.77	7.77	
Terms and conditions		Note 2		
Number of shares subscribed	1,025	0	0	1.025
Total number of BSPCE cancelled or void	141,675	37,600	0	179,275
Number of remaining BSPCE	21,100	25,400	20,000	66,500
Total number of shares that can be subscribed	21,100	25,400	20,000	66,500

\* The authorized amounts of 314,323 and 514,323 are global maximum amounts that include the FSWs, the SWs, and the options that may be granted by the Board of Directors with the authorization of the General Shareholders' Meeting.

Note 1: All the FSWs granted on March 3, 2009, January 28, 2010, and April 13, 2010, which have not expired, are exercisable as of this day.

Note 2: Each FSW entitles the holder to purchase one (1) of the Company's common stock. The common stock purchased must be fully paid up in cash at the time of their purchase, including when paid by set off against liquid and claims payable by the Company.

	<b>BCE 02-2011</b>	<b>BCE 05-2011</b>	<b>TOTAL</b>
Date of meeting	20 July 2010	20 July 2010	
Date of grant by the Board of Directors	15 February 2011	5 May 2011	
Total number of BSPCE authorized *	735,000		
Total number of BSPCE allocated	80,000	68,000	148,000
<b>Total number of shares that may be subscribed or purchased</b>	<b>80,000</b>	<b>68,000</b>	<b>148,000</b>
<i>Of which many may be subscribed or purchased by the corporate officers:</i>			
Jean-Louis Dasseux	80,000		80,000
André Mueller		12,000	12,000
Number of non corporate beneficiaries		10	
Starting point of exercise of the BSPCE	<i>Note 1a</i>	<i>Note 1b</i>	
Expiry date of the BSPCE	15 February 2021	5 May 2021	
BSPCE exercise price	8.74	8.74	
Terms and conditions	<i>Note 2a</i>	<i>Note 2b</i>	
Number of shares subscribed	0	0	0
Total number of BSPCE cancelled or void	0	37,000	37,000
Number of remaining BSPCE	80,000	31,000	111,000
Total number of shares that can be subscribed	80,000	31,000	111,000

\* The authorized amount of 735,000 is a global maximum amount that includes the FSWs, the SWs, and the options that may be granted by the Board of Directors with the authorization of the General Shareholders' Meeting.

*Note 1a: The FSWs allocated on February 15, 2011 may be exercised as follows:*

- 25% of the FSWs become exercisable on February 15, 2012 (grant anniversary date) and the remaining 75% will be exercised in the same manner each quarter over the following three years (6.25% of the FSWs may be exercised every quarter for 12 quarters after the anniversary date).

*Note 1b: The FSWs allocated on May 5, 2011 may be exercised as follows:*

- 25% of the FSWs become exercisable on May 5, 2012 (grant anniversary date) and the remaining 75% will be exercised in the same manner each quarter over the following three years (6.25% of the FSWs may be exercised every quarter for 12 quarters after the anniversary date).

*Note 2a and b: Each FSW entitles the holder to purchase one (1) of the Company's common stock. The common stock purchased must be fully paid up in cash at the time of their purchase, including when paid by set off against liquid and claims payable by the Company.*

	BCE 04-2010	BCE 12-2011	BCE 03-2012	TOTAL
Date of meeting	28 June 2011	28 June 2011	28 June 2011	
Date of grant by the Board of Directors	26 October 2011	7 December 2011	20 March 2012	
Total number of BSPCE authorized *		755,750		
Total number of BSPCE allocated	145,000	10,000	185,381	340.381
<b>Total number of shares that may be subscribed or purchased</b>	<b>145,000</b>	<b>10,000</b>	<b>185,381</b>	<b>340.381</b>
<i>Of which many may be subscribed or purchased by the corporate officers:</i>				
Jean-Louis Dasseux			126,481	126.481
Number of non corporate beneficiaries	3	3	14	
Starting point of exercise of the BSPCE	<i>Note 1a</i>	<i>Note 1b</i>	<i>Note 1c</i>	
Expiry date of the BSPCE	26 October 2021	7 December 2021	20 March 2022	
BSPCE exercise price	9.31	9.31	9.31	
Terms and conditions	<i>Note 2a</i>	<i>Note 2b</i>	<i>Note 2c</i>	
Number of shares subscribed	56,135	0	0	56.135
Total number of BSPCE cancelled or void	58,865	10,000	25,900	94.765
Number of remaining BSPCE	30,000	0	159.481	189.481
Total number of shares that can be subscribed	30,000	0	159.481	189.481

\* The authorized amount of 755,750 is a global maximum amount that includes the FSWs, the SWs, and the options that may be granted by the Board of Directors with the authorization of the General Shareholders' Meeting.

*Note 1a: 30,000 FSWs granted on October 26, 2011 may be exercised as follows:*

- 25% of the FSWs become exercisable on October 26, 2012 (hiring anniversary date) and the remaining FSWs exercisable every quarter for three years beyond this date.

*Note 1b: All of the FSWs allocated on December 7, 2011 have expired.*

*Note 1c: 58,900 FSWs granted on March 20, 2012 may be exercised as follows:*

- 25% of the FSWs become exercisable on March 20, 2013 (grant anniversary date) and the remaining 75% will be exercised in the same manner each quarter over the following three years (6.25% of the FSWs may be exercised every quarter for 12 quarters after the anniversary date).  
The 126,481 FSWs awarded to Jean-Louis Dasseux become wholly exercisable on the date on which the following occurs: (i) a transaction on the capital allowing the investors to sell at least 20% of their shares or (ii) an IPO, for a share price at least equal to €35.

*Note 2a, b and c: Each FSW entitles the holder to purchase one (1) of the Company's common stock. The common stock purchased must be fully paid up in cash at the time of their purchase, including when paid by set off against liquid and claims payable by the Company.*

2012

	BCE 07-2012	BCE 02-2013	BCE 04-2013	TOTAL
Date of meeting	9 May 2012	9 May 2012	9 May 2012	
Date of grant by the Board of Directors	27 July 2012	12 February 2013	15 April 2013	
Total number of BSPCE authorized *		713,528		
Total number of BSPCE allocated	6,000	76,600	367,114	449.714
<b>Total number of shares that may be subscribed or purchased</b>	<b>6,000</b>	<b>76,600</b>	<b>367,114</b>	<b>449.714</b>
<i>Of which many may be subscribed or purchased by the corporate officers:</i>				
<i>Jean-Louis Dasseux</i>			90,091	90.091
Number of non corporate beneficiaries	2	16	16	
Starting point of exercise of the BSPCE	<i>Note 1a</i>	<i>Note 1b</i>	<i>Note 1c</i>	
Expiry date of the BSPCE	27 July 2022	12 February 2023	20 March 2022	
BSPCE exercise price	9.31	9.49	9.49	
Terms and conditions	<i>Note 2a</i>	<i>Note 2b</i>	<i>Note 2c</i>	
Number of shares subscribed	0	0	0	0
Total number of BSPCE cancelled or void	6,000	36,300	367,114	409.414
Number of remaining BSPCE	0	40,300	0	40,300
Total number of shares that can be subscribed	0	40,300	0	40,300

\* The authorized amount of 713,528 is a global maximum amount that includes the FSWs, the SWs, and the options that may be granted by the Board of Directors with the authorization of the General Shareholders' Meeting.

*Note 1a and 1c: All of the FSWs granted on July 27, 2012 and April 15, 2013, have expired.*

*Note 1b: The FSWs allocated on Tuesday, February 12, 2013 may be exercised as follows:*

- 25% of the FSWs become exercisable on February 12, 2014 (grant anniversary date) and the remaining 75% will be exercised in the same manner each quarter over the following three years (6.25% of the FSWs may be exercised every quarter for 12 quarters after the anniversary date).

*Note 2a, b and c: Each FSW entitles the holder to purchase one (1) of the Company's common stock. The common stock purchased must be fully paid up in cash at the time of their purchase, including when paid by set off against liquid and claims payable by the Company.*

### 21.1.4.3. Options Plan

With the exception of the corporate officers, the beneficiaries of the options are the employees of the Company.

As at the date of this document, there are no longer any options granted before 2007 that are likely to be exercised.

2007/2008

	Options 03-2007	Options 05-2007	Options 01-2008	Options 03-2008	Options 05-2008	TOTAL
Date of meeting	9 March 2007	9 March 2007	9 March 2007	9 March 2007	9 March 2007	
Date of grant by the Board of Directors	9 March 2007	10 May 2007	28 January 2008	6 March 2008	29 May 2008	
Total number of Options authorized *			986,000			
Total number of Options allocated	240,626	10,000	10,000	48,950	10,000	319,576
<b>Total number of shares that may be subscribed or purchased</b>	<b>240,626</b>	<b>10,000</b>	<b>10,000</b>	<b>48,950</b>	<b>10,000</b>	<b>319,576</b>
<i>Of which many may be subscribed or purchased by the corporate officers:</i>						
<i>André Mueller</i>	12,000			12,000		24,000
Number of non corporate beneficiaries	6	1	1	8	1	
Starting point of exercise of Options			Note 1			
Expiry date of Options	9 March 2017	10 May 2017	28 January 2018	6 March 2018	29 May 2018	
Options exercise price	7.32	7.32	7.69	7.69	7.69	
Terms and conditions	Note 2a	Note 2b	Note 2c	Note 2d	Note 2e	
Number of shares subscribed	0	0	0	0	0	0
Total number of Options cancelled or void	240,626	0	10,000	40,300	10,000	300,926
Number of remaining Options	0	10,000	0	8,650	0	18,650
Total number of shares that can be subscribed	0	10,000	0	8,650	0	18,650

\* The authorized amount of 986,000 is a global maximum amount that includes the FSWs, the SWs, and the options that may be granted by the Board of Directors with the authorization of the General Shareholders' Meeting.

Note 1: All the options granted on May 10, 2007, January 28, 2008, March 6, 2008, and May 29, 2008, which have not expired, are exercisable as of this day.

Note 2a: All the stock options granted on March 9, 2007, have expired.

Note 2b, c, d and e: Each option entitles the holder to purchase one (1) of the Company's common stock.

2009/2010

	Options 03-2009	Options 07-2009	Options 01-2010	Options 09-2010	Options 10-2010	TOTAL
Date of meeting	9 March 2007	9 March 2007	9 March 2007	20 July 2010	20 July 2010	
Date of grant by the Board of Directors	3 March 2009	29 July 2009	28 January 2010	2 September 2010	26 October 2010	
Total number of Options authorized *		986,000		735,000		
Total number of Options allocated	71,300	60,000	74,000	4,000	7,500	216,800
<b>Total number of shares that may be subscribed or purchased</b>	<b>71,300</b>	<b>60,000</b>	<b>74,000</b>	<b>4,000</b>	<b>7,500</b>	<b>216,800</b>
<i>Of which many may be subscribed or purchased by the corporate officers:</i>						
Number of non corporate beneficiaries	12	1	12	1	1	
Starting point of exercise of Options			Note 1			
Expiry date of Options	3 March 2019	29 July 2019	28 January 2020	2 September 2020	26 October 2020	
Options exercise price	7.66	7.66	7.77	8.74	8.74	
Terms and conditions	Note 2a	Note 2b	Note 2c	Note 2d	Note 2e	
Number of shares subscribed	0	1,000	0	0	0	1,000
Total number of Options cancelled or void	56,900	59,000	59,100	4,000	7,500	186,500
Number of remaining Options	14,400	0	14,900	0	0	29,300
Total number of shares that can be subscribed	14,400	0	14,900	0	0	29,300

\* The authorized amounts of 986,000 and 735,000 are global maximum amounts that include the FSWs, the SWs, and the options that may be granted by the Board of Directors with the authorization of the General Shareholders' Meeting.

Note 1: All the options granted on March 3, 2009, July 29, 2009, January 28, 2010, September 2, 2010 and October 26, 2010, which have not expired, are exercisable as of this day.

Note 2a, b, c, d and e: Each option entitles the holder to purchase one (1) of the Company's common stock.

## 2011

	Options 02-2011	Options 05-2011	Options 10-2011	Options 12-2011	Options 03-2012	TOTAL
Date of meeting	20 July 2010	20 July 2010	28 June 2011	28 June 2011	28 June 2011	
Date of grant by the Board of Directors	15 February 2011	5 May 2011	26 October 2011	7 December 2011	20 March 2012	
Total number of Options authorized *	735,000			755,750		
Total number of Options allocated	32,500	54,000	10,000	16,000	21,100	133,600
<b>Total number of shares that may be subscribed or purchased</b>	<b>32,500</b>	<b>54,000</b>	<b>10,000</b>	<b>16,000</b>	<b>21,100</b>	<b>133,600</b>
<i>Of which many may be subscribed or purchased by the corporate officers:</i>						
Number of non corporate beneficiaries	1	8	1	2	9	
Starting point of exercise of Options	<i>Note 1a</i>	<i>Note 1b</i>	<i>Note 1c</i>	<i>Note 1d</i>	<i>Note 1e</i>	
Expiry date of Options	15 February 2021	5 May 2021	26 October 2021	7 December 2021	20 March 2022	
Options exercise price	8.74	8.74	9.31	9.31	9.31	
Terms and conditions	<i>Note 2a</i>	<i>Note 2b</i>	<i>Note 2c</i>	<i>Note 2d</i>	<i>Note 2e</i>	
Number of shares subscribed	0	0	0	0	0	0
Total number of Options cancelled or void	32,500	27,200	10,000	16,000	13,700	99,400
Number of remaining Options	0	26,800	0	0	7,400	34,200
Total number of shares that can be subscribed	0	26,800	0	0	7,400	34,200

\* The authorized amounts of 735,000 and 755,750 are global maximum amounts that include the FSWs, the SWs, and the options that may be granted by the Board of Directors with the authorization of the General Shareholders' Meeting.

Note 1a, 1c and 1d: all of the options granted on February 15, 2011, October 26, 2011, and December 7, 2011 have expired.

Note 1b: The options may be exercised by their holder as follows:

- 25% become exercisable on May 5, 2012 (grant anniversary date) and the remaining 75% will be exercised in the same manner each quarter over the following three years (6.25% of the options may be exercised every quarter for 12 quarters after the anniversary date).

Note 1e: The options may be exercised by their holder as follows:

- 25% become exercisable on March 20, 2013 (grant anniversary date) and the remaining 75% will be exercised in the same manner each quarter over the following three years (6.25% of the options may be exercised every quarter for 12 quarters after the anniversary date).

Note 2a, b, c, d and e: Each option entitles the holder to purchase one (1) of the Company's common stock.

## 2012

	Options 07-2012	Options 02-2013	Options 04-2013	TOTAL
Date of meeting	9 May 2012	9 May 2012	9 May 2012	
Date of grant by the Board of Directors	27 July 2012	12 February 2013	15 April 2013	
Total number of Options authorized *	713,528			
Total number of Options allocated	20,000	33,400	132,886	186,286
<b>Total number of shares that may be subscribed or purchased</b>	<b>20,000</b>	<b>33,400</b>	<b>132,886</b>	<b>186,286</b>
<i>Of which many may be subscribed or purchased by the corporate officers:</i>				
Number of non corporate beneficiaries	1	10	10	
Starting point of exercise of Options	<i>Note 1a</i>	<i>Note 1b</i>	<i>Note 1c</i>	
Expiry date of Options	27 July 2022	12 February 2023	15 April 2023	
Options exercise price	9.31	9.49	9.49	
Terms and conditions	<i>Note 2a</i>	<i>Note 2b</i>	<i>Note 2c</i>	
Number of shares subscribed	0	0	0	0
Total number of Options cancelled or void	20,000	29,800	132,886	182,686
Number of remaining Options	0	3,600	0	3,600
Total number of shares that can be subscribed	0	3,600	0	3,600

\* The authorized amount of 713,528 is a global maximum amount that includes the FSWs, the SWs, and the options that may be granted by the Board of Directors with the authorization of the General Shareholders' Meeting.

Note 1a and c: All of the options granted on July 27, 2012, and April 15, 2013 have expired.

Note 1b: The options may be exercised by their holder as follows:

- 25% become exercisable on February 12, 2014 (grant anniversary date) and the remaining 75% will be exercised in the same manner each quarter over the following three years (6.25% of the options may be exercised every quarter for 12 quarters after the anniversary date).



Note 2a, b and c: Each option entitles the holder to purchase one (1) of the Company's common stock.

2015-2016

	<b>Options 01-2016</b>
Date of meeting	6 February 2015
Date of grant by the Board of Directors	Decision of the CEO on 22 January 2016 pursuant to the subdelegation of the BoD of 3 December 2015
Total number of Options authorized *	134,417
Total number of Options allocated	134,417
<b>Total number of shares that may be subscribed or purchased</b>	<b>134,417</b>
<i>Of which many may be subscribed or purchased by the corporate officers:</i>	
<i>Monsieur Richard Pasternak, Président du Conseil *</i>	134,417
Number of non corporate beneficiaries	1
Starting point of exercise of Options	Note 1
Expiry date of Options	22 January 2026
Options exercise price	9.36
Terms and conditions	Note 2
Number of shares subscribed	0
Total number of Options cancelled or void	0
Number of remaining Options	134,417
Total number of shares that can be subscribed	134,417

Note 1: The options may be exercised by their holder starting on the date when they are issued.

Note 2: Each option entitles the holder to purchase one (1) of the Company's common stock.

\* The Chairman of the Board must keep in registered form at least 10% of the shares resulting from the exercise of the options.

#### **21.1.4.4. Bonus shares**

Please refer to Section 15.1, "Directors' and Executives' Compensation," table 10, regarding the history of bonus share awards. Note that all shares awarded as bonus shares shall be new shares.

### 21.1.5. Warrants and/or bonds attached to share capital that has been issued but not fully paid up and capital increase commitments

The financial powers and authorities bestowed upon the Board of Directors are summarized below:

Type of delegation of power or authority	Date of the Extraordinary General Shareholders' Meeting	Expiry date	Amount authorized	Used in previous years	Used in 2016	Residual amount
Delegation to increase the capital by the incorporation of reserves, earnings or premiums <sup>1</sup>	Jun. 10, 2016	Aug. 9, 2018	€100,000 <sup>2</sup>	Not applicable  (N/A)	-	€100,000 <sup>2</sup>
Delegation to issue common stock and marketable securities with pre-emptive rights maintained <sup>1</sup>	Jun. 10, 2016	Aug. 9, 2018	€350,000 <sup>2</sup>  (common stock)  €50,000,000 <sup>3</sup>  (debt securities)	N/A	-	€350,000 <sup>2</sup>  (common stock)  €50,000,000 <sup>3</sup>  (debt securities)
Delegation to issue common stock and marketable securities, with cancellation of the pre-emptive rights, by a public offering <sup>1</sup>	Jun. 10, 2016	Aug. 9, 2018	€350,000 <sup>2</sup>  (common stock)  €50,000,000 <sup>3</sup>  (debt securities)	N/A	-	€350,000 <sup>2</sup>  (common stock)  €50,000,000 <sup>3</sup>  (debt securities)
Delegation to issue common stock and marketable securities, with cancellation of the pre-emptive rights through a private placement <sup>1,5</sup>	Jun. 10, 2016	Aug. 9, 2018	€350,000 <sup>2</sup> & 20% of capital per year  (common stock)  €50,000,000 <sup>3</sup>  (debt securities)	N/A	-	€350,000 <sup>2</sup> & 20% of capital per year  (common stock)  €50,000,000 <sup>3</sup>  (debt securities)
Delegation to issue common stock and marketable securities, with cancellation of the pre-emptive rights to a category of individuals <sup>1,6</sup>	Jun. 10, 2016	Dec. 9, 2017	€350,000 <sup>2</sup>  (common stock)  €50,000,000 <sup>3</sup>  (debt securities)	N/A	-	€350,000 <sup>2</sup>  (common stock)  €50,000,000 <sup>3</sup>  (debt securities)
Delegation to increase the capital in consideration for a contribution in shares or marketable securities <sup>1</sup>	Jun. 10, 2016	Aug. 9, 2018	10% of the share capital on the day of the General Shareholders' Meeting <sup>2</sup>	N/A	-	10% of the share capital on the day of the General Shareholders' Meeting <sup>2</sup>

Type of delegation of power or authority	Date of the Extraordinary General Shareholders' Meeting	Expiry date	Amount authorized	Used in previous years	Used in 2016	Residual amount
Delegation to issue SWs, SW-ANEs, SW-ARs) <sup>1</sup>	Jun. 10, 2016	Dec. 9, 2017	€15.000	N/A	-	€15.000
Authorization to issue subscription warrants or stock options <sup>1</sup>	Feb. 6, 2015	Apr. 5, 2018	€79,797.80 (capital increase) <sup>4</sup>	-	134,417 options (or a maximum potential capital increase of €6,720.85)	€37,926.95 (capital increase)
Authorization to award bonus shares <sup>1</sup>	Sept. 28, 2015	Nov. 27, 2018	6.5% of capital at the date of the Shareholders' Meeting (i.e. 1,156,277 shares, or a maximum possible capital increase of €57,813.85) <sup>4</sup>	365,000 shares	205.000 shares	586,277 shares or a maximum potential capital increase of €29,313.85

(1) The Board may not, except with the prior authorization of the General Shareholders' Meeting, use this delegation during the period of a public tender offer for the Company's stock initiated by a third party until the end of the offer period.

(2) Added to the overall limit of €350,000 (common shares).

(3) Added to the overall limit of €50,000,000 (debt instruments).

(4) Added to an overall limit of €79,797.80 (set by the General Shareholders' Meeting of February 6, 2015 and which applies (i) to delegations granted in respect of SWs and FSWs by said meeting and which are now null and void, and (ii) to authorizations in respect of stock options and bonus shares still in force).

(5) The issue price of the shares will be equal to or greater than the minimum required by legal or regulatory provisions in force on the date of the Board's decision; presently, this involves the provisions of Articles L. 225-136 and R. 225-119 of the French Commercial Code.

(6) In favor of the following categories of persons: (i) family offices and business angels, French or foreign companies or collective savings funds investing in the pharmaceutical or biotech industry; and (ii) pharmaceutical companies or laboratories.

### 21.1.6. Information relating to the share capital of Group companies that is subject to an option or a conditional or unconditional agreement to subject it to options

To the Company's knowledge, there are no call or put options or other commitments for the benefit of the Company's shareholders or granted by them relating to the Company's shares.

### 21.1.7. Changes in the share capital

#### 21.1.7.1. Table of changes in the share capital

The table below shows the changes in share capital up to March 15, 2017.

Date	Nature of operation	Capital in €	Premium in €	Number of shares created	Number of shares composing the capital	Nominal value in €	Share capital in €	Issue price in €
20 March 2012	Capital increase (exercise of options)	454.40	0.00	9,088	13,159,763	0.05	657,988.15	4.22
20 March 2012	Capital increase (exercise of options)	50.00	0.00	1,000	13,160,763	0.05	658,038.15	7.66
20 March 2012	Capital increase (exercise of BCE)	51.25	0.00	1,025	13,161,788	0.05	658,089.40	7.66
16 January 2015	Capital increase (exercise of BCE)	20,988.70	NA	419,774	13,581,562	0.05	679,078.10	0.05
25 March 2015	Capital increase (IPO)	210,365.80	53,222,547.40	4,207,316	17,788,878	0.05	889,443.90	12.7
December 2015	Capital increase (exercise of BCE)	300.00	0.00	6,000	17,794,878	0.05	889,743.90	9.31
	<b>Share capital as of 31 December 2015</b>				<b>17,794,878</b>	<b>0.05</b>	<b>889,743.90</b>	
January 2016	Capital increase (exercise of BCE)	575.00	106,490.00	11,500	17,806,378	0.05	890,318.90	9.31
1 March 2016	Capital increase (exercise of BCE)	500.00	54,000.00	10,000	17,816,378	0.05	890,818.90	5.45
1 March 2016	Capital increase (exercise of BCE)	931.75	172,560.10	18,635	17,835,013	0.05	891,750.65	9.31
1 March 2016	Capital increase (exercise of stock options)	500.00	41,700.00	10,000	17,845,013	0.05	892,250.65	4.22
4 March 2016	Capital increase (exercise of BCE)	500.00	92,600.00	10,000	17,855,013	0.05	892,750.65	9.31
9 March 2016	Capital increase (exercise of BCE)	500.00	92,600.00	10,000	17,865,013	0.05	893,250.65	9.31
15 April 2016	Capital increase (exercise of BCE)	1,662.50	179,550.00	33,250	17,898,263	0.05	894,913.15	5.45
3 December 2016	Granting of free shares	18,250.00	0.00	365,000	18,263,263	0.05	913,163.15	0.05
	<b>Share capital as of 31 December 2016</b>				<b>18,263,263</b>	<b>0.05</b>	<b>913,163.15</b>	
21 January 2017	Granting of bonus shares	2,000.00	0.00	40,000	18,303,263	0.05	915,163.15	0.05

#### 21.1.7.2. Changes in the holding structure of the equity capital over the last three years

Shareholders	12/31/2014 % Capital Vote rights	12/31/2015 *		12/31/2016 *	
		Number of shares Vote rights	% Capital Vote rights	Number of shares Vote rights	% Capital Vote rights
<b>Total top management</b>	<b>4.59%</b>	<b>1,029,646</b>	<b>5.79%</b>	<b>1,344,646</b>	<b>7.36%</b>
Jean-Louis Dasseux	4.46%	1,011,919	5.69%	1,211,919	6.64%
Cyrille Tupin	0.13%	17,727	0.10%	132,727	0.73%
<b>Total Finance shareholders</b>	<b>75.32%</b>	<b>10,809,169</b>	<b>60.74%</b>	<b>9,264,284</b>	<b>50.73%</b>
Sofinnova (FR)	21.61%	2,844,083	15.98%	2,683,602	14.69%
HealthCap (Sweden, Swiss)	21.28%	2,801,424	15.74%	1,422,983	7.79%
Alta Partners (US)	11.78%	1,550,445	8.71%	1,458,079	7.98%
BPI Participations (FR)	10.84%	1,426,534	8.02%	1,426,534	7.81%
TVM Life Science Ventures	9.81%	1,290,308	7.25%	1,213,439	6.64%
JP Morgan Asset Management		896,375	4.80%	1,059,647	5.80%
<b>Public</b>	<b>20.09%</b>	<b>5,937,400</b>	<b>33.37%</b>	<b>7,630,412</b>	<b>41.78%</b>
<b>Treasury shares</b>		<b>18,663</b>	<b>0.10%</b>	<b>23,921</b>	<b>0.13%</b>
<b>TOTAL</b>	<b>100.00%</b>	<b>17,794,878</b>	<b>100.00%</b>	<b>18,263,263</b>	<b>100.00%</b>

\* Based on information brought to the Company's attention, in particular for holders of bearer shares, via declarations of when thresholds are crossed (under the law and the bylaws) and post-IPO lock-up commitments at December 31, 2015 for investors.

The calculation of the percentage of voting rights indicated in the table above is based on theoretical voting rights, it being specified that the difference between theoretical and actual voting rights is minimal.

In 2015, the Company launched a public tender offer as part of its IPO. The Company's shares have been admitted for trading on the Euronext Paris exchange since March 30, 2015.

As of the date of registration of the Registration Document, the Company's shares are traded on the Euronext Paris exchange (Compartment C).

To the Company's knowledge, no other shareholder holds more than 5% of the capital or voting rights, either directly or indirectly, alone or in concert.

Employee share ownership at December 31, 2016 within the meaning of Article L. 225-102 of the French Commercial Code (considering the shares held under a "PEE" or "FCPE" employee savings funds, as well as registered shares granted to employees under Article L. 225-197-1 of the French Commercial Code and which have vested) amounted to 165,000.

#### **21.1.7.3. Legal threshold crossings declared in 2016**

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##### **AMF Notice 216C2890**

December 22, 2016

In a letter received on December 22, 2016, JP Morgan Asset Management (UK) Limited (60 Victoria Embankment, London, EC4Y 0JP, United Kingdom), (controlled by JP Morgan Asset Management Holdings Inc.), acting on behalf, and as representative, of its clients, declared it had crossed CERENIS THERAPEUTICS HOLDING's 5% capital and voting rights threshold on December 16, 2016 and held 1,059,647 CERENIS THERAPEUTICS HOLDING shares on behalf of said clients, which represented **5.92% of the Company's share capital and voting rights**.

This threshold crossing was due to an off-market acquisition of CERENIS THERAPEUTICS HOLDING shares.

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##### **AMF Notice 216C2848**

December 19, 2016

In a letter received on December 19, 2016, **HealthCap IV LP** (c/o HealthCap IV GP S.A., 18 avenue d'Ouchy, 1006 Lausanne, Switzerland) declared that individually it had **crossed below** CERENIS THERAPEUTICS HOLDING's **5% capital and voting rights** threshold on December 16, 2016 and individually held **780,603** CERENIS THERAPEUTICS HOLDING shares, representing **4.36% of the Company's equity capital and voting rights**.

This threshold crossing was due to a sale of CERENIS THERAPEUTICS HOLDING shares on the open market.

On this occasion, the **concert party** comprising HealthCap IV KB (LP), HealthCap IV LP (LLP), HealthCap IV Bis LP (LLP) and Ofco Club IV (LLC) **had not crossed any thresholds** and held 1,422,983

CERENIS THERAPEUTICS HOLDING shares at December 16, 2016 representing the same number of voting rights, which is 7.95% of the Company's capital and voting rights, broken down as follows:

	Shares and voting rights	% of equity capital and voting rights
HealthCap IV LP	780,603	4.36
HealthCap IV Bis LP	564,053	3.15
HealthCap IV KB	56,987	0.32
Ofco Club IV	21,340	0.12
<b>Total for concert party</b>	<b>1,422,983</b>	<b>7.95</b>

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#### AMF Notice 216C2814

December 14, 2016

In a letter received on December 14, 2016, the **concert party** comprising HealthCap IV KB (LP), HealthCap IV LP (LLP), HealthCap IV Bis LP (LLP) and Ofco Club IV (LLC) declared that it had **crossed below** CERENIS THERAPEUTICS HOLDING's **10% capital and voting rights** threshold on December 9, 2016 and held 1,714,565 CERENIS THERAPEUTICS HOLDING shares, representing 9.58% of the Company's capital and voting rights, broken down as follows:

	Shares and voting rights	% of equity capital and voting rights
HealthCap IV LP	940,563	5.26
HealthCap IV Bis LP	679,637	3.80
HealthCap IV KB	68,650	0.38
Ofco Club IV	25,715	0.14
<b>Total for concert party</b>	<b>1,714,565</b>	<b>9.58</b>

This threshold crossing was due to a sale of CERENIS THERAPEUTICS HOLDING shares on the open market.

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#### AMF Notice 216C2011

September 9, 2016

In letters received on September 9, 2016, **HealthCap IV Bis LP** (c/o HealthCap IV GP S.A., 18 avenue d'Ouchy, 1006 Lausanne, Switzerland) declared that individually it had **crossed below** CERENIS THERAPEUTICS HOLDING's **5% capital and voting rights** threshold on September 6, 2016 and

individually held **842,929** CERENIS THERAPEUTICS HOLDING shares, representing **4.71% of the Company's capital and voting rights**.

This threshold crossing was due to a sale of CERENIS THERAPEUTICS HOLDING shares on the open market.

At that time, the **concert party** comprising HealthCap IV KB (LP), HealthCap IV LP (LLP), HealthCap IV Bis LP (LLP) and Ofco Club IV (LLC) **had not crossed any thresholds** and held 2,126,501 CERENIS THERAPEUTICS HOLDING shares at September 6, 2016 representing the same number of voting rights, which is 11.88% of the Company's capital and voting rights, broken down as follows:

	Shares and voting rights	% of equity capital and voting rights
HealthCap IV LP	1,166,551	6.52
HealthCap IV Bis LP	842,929	4.71
HealthCap IV KB	85,127	0.48
Ofco Club IV	31,894	0.18
<b>Total for concert party</b>	<b>2,126,501</b>	<b>11.88</b>

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#### AMF Notice 216C2010

September 9, 2016

In a letter received on September 9, 2016, **JP Morgan Asset Management (UK) Limited** (60 Victoria Embankment, London, EC4Y 0JP, United Kingdom), acting on behalf and as representative of its clients, declared it had crossed **below** CERENIS THERAPEUTICS HOLDING's **5% capital and voting rights** threshold on September 7, 2016, and held **890,979** CERENIS THERAPEUTICS HOLDING shares on behalf of said clients, representing the same number of voting rights, which is 4.98% of the Company's share capital and voting rights.

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#### AMF Notice 216C1171

May 19, 2016

In a letter received on May 18, 2016, supplemented in particular by a letter received on May 19, 2016, the **concert party** composing HealthCap IV KB (LP), HealthCap IV LP (LLP), HealthCap IV Bis LP (LLP) and Ofco Club IV (LLC) declared that **for regulation purposes** it had crossed **below** CERENIS THERAPEUTICS HOLDING's **15% capital and voting rights** threshold on February 29, 2016 and held, at that date, 2,674,651 CERENIS THERAPEUTICS HOLDING shares, representing the same number of voting rights, which is 14.99% of the Company's capital and voting rights, broken down as follows:

	Shares and voting rights	% of equity capital and voting rights
HealthCap IV LP (LLP)	1,467,266	8.22
HealthCap IV Bis LP (LLP)	1,060,213	5.94
HealthCap IV KB (LP)	107,053	0.60
Ofco Club IV (LLC)	40,119	0.22
<b>Total for concert party</b>	<b>2,674,651</b>	<b>14.99</b>

This threshold crossing is due to the Company's capital increase.

The **concert party** stated that at May 18, 2016 it held 2,674,651 CERENIS THERAPEUTICS HOLDING shares, representing the same number of voting rights, which is 14.94% of the Company's capital and voting rights, broken down as follows:

	Shares and voting rights	% of equity capital and voting rights
HealthCap IV LP	1,467,266	8.20
HealthCap IV Bis LP	1,060,213	5.92
HealthCap IV KB	107,053	0.60
Ofco Club IV	40,119	0.22
<b>Total for concert party</b>	<b>2,674,651</b>	<b>14.94</b>

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#### AMF Notice 216C1943

August 31, 2016

In a letter received on August 31, 2016, the simplified limited liability company **Sofinnova Partners** (16-18 rue du 4 septembre, 75002 Paris, France), acting on behalf of the Sofinnova Capital V venture capital fund, which it manages, declared it had crossed **below** CERENIS THERAPEUTICS HOLDING's **15% capital and voting rights** threshold on August 30, 2016, and held 2,683,602 CERENIS THERAPEUTICS HOLDING shares on behalf of said fund, representing the same number of voting rights, which is 14.99% of the Company's share capital and voting rights.

This threshold crossing was due to a sale of CERENIS THERAPEUTICS HOLDING shares on the open market.



#### **21.1.7.4. Breakdown of capital and voting rights as of the filing date of the Registration Document**

To the Company's knowledge, there has not been any significant change in the distribution of the Company's share capital as of the filing date of the Registration Document compared to that presented above at December 31, 2016, except for where thresholds are exceeded as noted below.

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##### **AMF NOTICE 217C0604**

March 7, 2017

In a letter received on March 7, 2017, JP Morgan Asset Management (UK) Limited (60 Victoria Embankment, London, EC4Y 0JP, United Kingdom), acting on behalf and as representative of its clients, stated that its stake dropped below CERENIS THERAPEUTICS HOLDING's 5% capital and voting rights threshold on March 2, 2017, and that it no longer holds any CERENIS THERAPEUTICS HOLDING shares on behalf of said clients. This threshold crossing was due to a sale of CERENIS THERAPEUTICS HOLDING shares on the market.

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##### **AMF NOTICE 217C0627**

March 9, 2017

In a letter received on March 6, 2017, supplemented by a letter received on March 9, 2017, Alta California Management Partners IV, LLC (ACMP IV, LLC) (One Embarcadero Center, Suite 3700, San Francisco, California, United States), acting on behalf and as representative of the fund ACP IV, L.P., which it manages, stated that its stake dropped below CERENIS THERAPEUTICS HOLDING's 5% capital and voting rights threshold on March 2, 2017, and that it holds 824,701 CERENIS THERAPEUTICS HOLDING shares on behalf of said fund, which represent 4.51% of the company's share capital and voting rights. This threshold crossing was due to a sale of CERENIS THERAPEUTICS HOLDING shares on the market.

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##### **AMF NOTICE 217C0634**

March 10, 2017

In a letter received on March 9, 2017, the simplified joint stock company Sofinnova Partners (16-18 rue du 4 septembre, 75002 Paris), acting on behalf and as representative of FCPR Sofinnova Capital V, which it manages, stated that its stake dropped below CERENIS THERAPEUTICS HOLDING's 10% capital and voting rights threshold on March 6, 2017, and that it holds 1,535,605 CERENIS THERAPEUTICS HOLDING shares on behalf of said fund, which represent 8.39% of the company's share capital and voting rights. This threshold crossing was due to a sale of CERENIS THERAPEUTICS HOLDING shares on the market.

## **21.2. Articles of Incorporation and Bylaws**

### **21.2.1. Corporate purpose (Article 4 of the bylaws)**

The Company's purpose, both in France and abroad, includes the following:

- Research into and development of all pharmaceutical products for the purposes of their production and marketing, after obtaining, where appropriate, all the necessary authorizations;
- Participation, by any means, directly or indirectly, in all operations related to its purpose through the creation of new companies, provision of subscription or purchase of securities or corporate rights, merger or otherwise creation, acquisition, rental, lease-management of any businesses or establishments;
- And, more generally all commercial, industrial, financial, securities, and real estate operations related directly or indirectly to the corporate purpose.

## **21.2.2. Bylaws or other provisions relative to the administrative and management bodies**

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### **21.2.2.1. Board of Directors**

#### *21.2.2.1.1. Appointment of the members of the Board of Directors*

Subject to any exceptions provided for by law, the Company is managed by a Board of Directors composed of three to eighteen Directors, appointed by the General Shareholders' Meeting, who may be natural persons or legal entities.

Once appointed, legal entities are required to designate a natural person as a permanent representative. The term of office of the permanent representative is the same as that of the legal entity he/she represents. When the legal entity dismisses its permanent representative, it must immediately appoint a replacement. The same provisions shall apply in the event of death or resignation of the permanent representative.

The term of service of appointed Directors is three (3) years; it shall expire at the end of the General Shareholders' Meeting convened to approve the accounts for the year ended, and held in the year in which their mandate expires.

Directors may be re-elected. They may be removed at any time by the General Shareholders' Meeting, having duly assembled a quorum and reached the majority required for Annual General Shareholders' Meetings.

In the event of vacancy of one or more Director seat(s) due to death or resignation, the Board of Directors may, between two General Shareholders' Meetings, make provisional arrangements. These are subject to ratification at the next Annual General Shareholders' Meeting. The absence of ratification does not mean that previous deliberations carried out and resolutions passed by the Board may be any less valid.

No person shall be appointed Director if, having reached 79 years of age, his/her appointment results in more than one-third of Board members having reached this age. The number of Directors over 79 years of age may not exceed one-third of Board members, rounded up, if necessary, to the immediately higher number. When this limit is exceeded, the oldest Director is deemed to have resigned at the end of the Annual General Shareholders' Meeting called to approve the accounts of the year in which the limit was exceeded.

#### *21.2.2.1.2. Deliberations of the Board of Directors*

The Board of Directors shall meet as often as the Company's interests so require, and at least once a quarter and such meetings shall be called by the Chairman, to be held at the registered office or

venue indicated in the notice. The call to meeting notice is made by any means, five days in advance, and it may also be made verbally and without delay:

- If all of the Directors agree; or
- If the Board is called to meeting by the Chairman during a General Shareholders' Meeting.

Directors constituting at least one third of the Board members may, provided they specify the agenda, ask the Chairman to call a Board meeting if it has not met for more than two months. When the positions of Chairman and CEO are held by different parties, the Chief Executive Officer may also request that the Chairman call a Board meeting to discuss a specific agenda. The Chairman is bound by requests addressed to him as such.

The Board deliberates validly if at least half of its members are present.

Any Director may authorize, whether by letter, telegram, fax or email, another Director to represent him/her at a Board meeting, but each Director may represent only one other Director.

Except for matters falling exclusively to the Senior Management, resolutions are passed by a majority of the Directors present or represented, with each Director having one vote for himself/herself and one vote for the Director he/she represents. The Chairman does not have the casting vote in the event of deadlock.

Except when the Board has been called to meet in order to carry out the operations referred to in Articles L. 232-1 and L. 233-16, internal regulations may include as present, for calculation of the quorum and the majority, the Directors participating in the meeting by videoconference and telecommunications means allowing for their identification and ensuring their effective participation.

An attendance register is maintained, and minutes are prepared for each meeting of the Board.

The Directors as well as any person called to attend Board of Directors' meetings are held to discretion with respect to information of a confidential nature and qualified as such by the Chairman of the Board of Directors.

#### *21.2.2.1.3. Compensation of the members of the Board of Directors*

The General Shareholders' Meeting may allocate an annual fixed sum to Directors in respect of their activity, as attendance fees. Its distribution among Directors is determined by the Board of Directors.

The Board of Directors may allocate exceptional compensation for assignments or mandates entrusted to Directors. In this case, these earnings are subject to the provisions of Articles L. 225-38 to L. 225-42 of the Code of Commerce.

#### *21.2.2.1.4. Powers of the Board of Directors*

The Board of Directors determines the Company's business policies and ensures adherence to such policies. Subject to the powers expressly attributed to the Shareholders' Meetings and within the limits of the corporate purpose, it concerns itself with all issues affecting the Company's proper functioning and, by its deliberations, governs the matters with which it is concerned.

The Board of Directors proceeds with controls and inspections that it considers appropriate. Each Director must be provided with all the information required to perform his/her duties as well as any documents deemed useful to him/her.

#### *21.2.2.1.5. Chairman of the Board of Directors*

The Board of Directors elects a Chairman, who must be a natural person, from among its members. It determines the term of office, which may not exceed that of his or her mandate as Director, and may revoke it at any time. The Board shall determine the remuneration of the Chairman.

No one shall be appointed Chairman if he/she has attained 79 years of age. If the Chairman has reached this age while in office, he/she is deemed to have resigned from office. The mandate is extended, however, until the meeting during which the Board of Directors shall appoint of a new Chairman under the conditions stipulated in the bylaws. Subject to this provision, the Chairman is always eligible for re-election.

The Chairman of the Board of Directors organizes and directs the work of the Board, which he/she reports on at the General Shareholders' Meeting. He/she shall ensure the proper functioning of the Company's bodies, and in particular, ensure that Directors are able to accomplish their mission.

#### **21.2.2.2. Senior Management**

The Company's general management is taken on, under its responsibility, by the Chairman of the Board of Directors or by another natural person appointed by the Board of Directors and bearing the title of Chief Executive Officer.

The members of the Board of Directors may unanimously choose between two procedures for the Senior Management to follow.

When the Company's general management is assumed by the Chairman of the Board of Directors, the provisions relative to the Chief Executive Officer hereafter are applicable.

##### *21.2.2.2.1. Chief Executive Officer*

When appointing the Chief Executive Officer (CEO), the Board of Directors sets the term of office, which may not exceed the Chairman's term. The Board of Directors determines the CEO's compensation.

No one shall be appointed CEO if he/she has attained 79 years of age. When a CEO has reached this age limit, he/she shall be deemed to have resigned from office. The mandate extends, however, until the next meeting of the Board of Directors during which, where appropriate, a new CEO will be appointed.

The CEO is revocable at any time by the Board of Directors. When the CEO does not assume the functions of Chairman of the Board of Directors, his/her revocation may give rise to damages, if it is deemed to be without just cause.

The CEO is vested with the broadest powers to act in all circumstances on behalf of the Company. He/she exercises his powers within the limits of the corporate purpose and subject to those that the law and the present articles attribute specifically at the shareholders' and Board of Directors' meetings.

He/she represents the Company in his/her dealings with third parties. The Company is also bound by the CEO's acts that do not relate to the corporate purpose, unless it is able to prove that the third party was aware that the act exceeded this objective or that the third party could not be unaware of it considering the circumstances, being excluded that only publication of the bylaws is sufficient to constitute such evidence.

#### *21.2.2.2.2. Deputy Executive Officers*

At the request of the CEO, the Board of Directors may appoint one or more natural persons to assist the CEO, whose title is Deputy Executive Officer. The number of Deputy Executive Officers may not exceed five.

In agreement with the CEO, the Board of Directors determines the scope and duration of the powers conferred upon the Deputy Executive Officers. The Board of Directors sets their remuneration. Deputy Executive Officers have, with respect to third parties, the same powers as the CEO.

The Deputy Executive Officers must be under 79 years of age. When this age limit has been reached during the mandate, the Deputy Executive Officer shall be deemed to have resigned from office. His/her mandate extends, however, until the next meeting of the Board of Directors during which, where appropriate, a new Deputy Executive Officer will be appointed.

When the CEO steps down or is prevented from exercising his/her post, the deputy executive officers retain, unless otherwise decided by the Board of Directors, their posts and duties until the appointment of a new CEO.

#### **21.2.2.3. Observers**

The General Shareholders' Meeting may designate, for the Company, within the maximum limit of one, two or more observer(s), physical person(s), whether shareholder(s) or not, aged under 79 on the day of his/her (their) appointment.

Observers are appointed for a term of three (3) years. Their appointment ends at the end of the General Shareholders' Meeting called to approve the accounts for the previous fiscal year and held in the year in which their mandate expires.

Observer positions are non-remunerated. Observers may receive, as reimbursement for the costs incurred in connection with the normal performance of their duties, a compensation set by the Board of Directors. If the Board delegates a particular assignment to the observers, or to one of them, it may allocate them (him/her) compensation, in addition to a budget for its implementation, in relation to the significance of the entrusted task.

Observers are called upon to attend all Board of Directors' meetings and all Shareholders' Meetings, and to take part in deliberations in an advisory capacity. Observers hold within the Company a general and permanent advisory and monitoring role. They may not, however, in any way, interfere in the management of the Company, or generally substitute for their legal bodies.

They are bound by the same obligations of confidentiality and discretion as the members of the Board of Directors.

#### **21.2.2.4. Committees**

The Board of Directors may decide on the creation of one or more committees to study issues that the Board of Directors refers for their review. The Board of Directors sets the composition and powers of the committees that operate under its responsibility.

### **21.2.3. Rights, privileges and restrictions attached to Company shares**

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#### **21.2.3.1. Form of securities**

The shares may be registered or in bearer form, at the holder's discretion, subject to certain legal provisions relating to the form of the shares held by certain parties.

Shares are registered in individual accounts opened by the Company or any authorized intermediary in the name of each shareholder and kept according to the conditions and to the terms provided for by legal and regulatory provisions.

If the owner of the securities does not have his/her registered address on French territory, any intermediary may, pursuant to Article 102 of the Civil Code, be registered on behalf of that owner. This registration may be made in the form of a collective account or multiple individual accounts each with an owner.

The registered intermediary is required, at the time of opening his/her account with either the issuing Company or the authorized financial intermediary account holder, to declare his/her capacity as intermediary holding securities on behalf of others.

The Company may ask the central depository, at any time, at its expense, under current legal and regulatory requirements, for the following.

#### **21.2.3.2. Voting rights**

Each share gives the right to vote and be represented at General Shareholders' Meetings under legal and bylaws provisions. The right to vote attached to the shares is proportional to the percentage of share capital they represent. Each capital or use share gives the right to one vote.

#### **21.2.3.3. Rights to dividends and profits**

Each share entitles the bearer, as part of the equity income and assets, to a proportional share of capital it represents.

#### **21.2.3.4. Preferential subscription rights**

Shareholders have, proportionately to the amount of their shares, a preferential right to the subscription of cash shares to carry out a capital increase.

#### **21.2.3.5. Limitations on voting rights**

None.

#### **21.2.3.6. Identifiable Bearer Securities**

The Company may at any time make use of the provisions defined by law, and in particular in Article L. 228-2 of the Commercial Code, in relation to the identification of the holders of securities in bearer form and, to this end, it may, at any time, request from the central depository, at its expense, the information referred to in Article L. 228-2 of the Code of Commerce, the name, or company name, nationality, year of birth or year of incorporation and address of holders of securities granting, immediately or over time, the right to vote at shareholders' meetings and amount of securities held by each of them and, where appropriate, any restrictions applicable to these securities.

#### **21.2.3.7. Company buyback of treasury shares**

Refer to Section 21.1.3. “Number, book value and par value of shares held by the Company or on its behalf” of this Registration Document.

#### **21.2.4. Terms and conditions for modifying shareholder rights**

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Shareholders’ rights as set out in the Company bylaws may only be modified by the Company’s Shareholders at their Extraordinary General Meeting.

#### **21.2.5. General Shareholders’ Meetings**

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##### **21.2.5.1. Rules common to all General Meetings**

###### *21.2.5.1.1. Notice of meeting*

Meetings are convened by the Board of Directors. They may also be convened by the Statutory Auditor(s), by a court representative or by capital or voting right majority shareholders under the conditions and in the manner provided for by law.

During the liquidation period, General Meetings are convened by the liquidators.

The preceding provisions apply to special meetings. Shareholders acting on appointment of a judicial officer must together hold at least one-twentieth of the shares of the class in question.

The meetings are held at the registered office or any other venue indicated in the meeting notice.

The meeting notice is issued by publishing it in an official journal of record for the administrative department in which the registered office is located and in the Bulletin des Annonces Légales Obligatoires (the “BALO” or Bulletin of Mandatory Legal Notices). Shareholders holding shares for at least one month at the time of publication of the notice of meeting are also invited to attend all General Shareholders’ Meetings by ordinary post or, at their request and expense, by registered mail or any other means permitted by law.

Shareholders’ Meetings may not be held less than 15 days following publication of the notice or delivery of the letter to the registered shareholders.

If shareholders could not regularly deliberate, in the absence of the required quorum, the second meeting and, where appropriate, the second extended meeting are convened in the same manner as the first and the call to meeting notice recalls the date of the first one and reproduces its agenda.

###### *21.2.5.1.2. Agenda*

The agenda of the Shareholders’ Meeting is decreed by the author of the call to meeting notice.

One or more shareholders representing at least the proportion of the share capital set out by law and acting within legal provisions and terms are entitled to require, by registered mail with acknowledgment of receipt, the inclusion in the agenda of issues or draft resolutions.

The Shareholders gathered at their General Meeting may not deliberate on an issue that is not on the agenda, which may not be modified on second call. It may, however, in all circumstances, dismiss one or more members of the Board of Directors and proceed with their replacement.

#### *21.2.5.1.3. Shareholder participation at Shareholders' Meetings*

Unless attending the General Meeting in person, shareholders may:

- Be represented by granting a proxy to any natural person or legal entity of their choice, under the conditions set forth by law or in the regulations;
- Send a proxy to the Company without indication as to the mandate, as provided for by law or in the regulations; or
- Vote by mail via a form which may be sent to them under the conditions indicated in the meeting notice.

Participation in General Shareholders' Meetings, in any form whatsoever, is subject to corporate and trade-related registration and filing of shares under the conditions and time limits set forth by current legislation.

The postal voting form, duly completed, must reach the Company at least 3 days prior to the date of the meeting; otherwise it shall not be taken into account.

The shareholder having voted by mail will no longer be able to participate directly in the General Meeting or be represented.

In case of return of the proxy form and of the voting by mail form, the proxy form is taken into account, subject to the votes cast in the voting by mail form.

Shareholders who do not have their registered address on French territory may, pursuant to Article 102 of the Civil Code, be represented at General Shareholders' Meetings by an intermediary under the conditions laid down by current legislative and regulatory provisions. In this way, the shareholder is deemed to be present at this Shareholders' Meeting for the calculation of quorum and majority.

Any shareholder may also, if the Board of Directors so decides when calling a meeting, participate and vote at Shareholders' Meetings by videoconference or by any telecommunication means allowing for his/her identification and his/her effective participation in the meeting, under the conditions and in accordance with the procedures laid down in current legislative and regulatory provisions. Thus, he/she will be represented for the calculation of quorum and majority of the shareholders.

#### *21.2.5.1.4. Attendance sheet*

An attendance sheet is kept at each General Shareholders' Meeting containing the information required by law.

This attendance sheet, duly signed by the shareholders present and the proxies and shareholders participating via videoconference or by other means of telecommunication in accordance with legal and regulatory requirements and which are lined with the powers granted to each proxy, and, where appropriate, the voting by mail, is certified accurate by the General Committee of the Shareholders' Meeting.

Shareholders' Meetings are chaired by the Chairman of the Board of Directors. Otherwise, the meeting itself elects its Chairman.

The offices of tellers are filled by two shareholders, who are present and accept such, representing, both by themselves and as proxies, the largest number of votes.



The General Committee thus composed appoints a Secretary who may be chosen from outside the shareholders.

#### *21.2.5.1.5. Quorum*

During Annual and Extraordinary General Shareholders' Meetings, the quorum is calculated on all shares making up the share capital and, during Special Meetings, on all of the shares of the class concerned, minus any shares deprived of voting rights under the provisions of the law.

The right to vote attached to the shares is proportional to the percentage of share capital they represent. Each capital or use share gives the right to one vote. Under the special provision in the last section of Article L. 225-123 of the Commercial Code, the bylaws do not grant double voting rights to Company shares.

In the event of voting by mail, for the quorum calculation, only those forms completed and received by the Company at least three days before the Shareholders' Meeting are taken into account. However, electronic remote voting forms may be received by the Company until the eve of the General Shareholders' Meeting, no later than 3 pm, Paris time.

The forms not giving rise to a vote or expressing forbearance are considered as negative votes.

#### *21.2.5.1.6. Minutes*

The deliberations of the General Shareholders' Meetings are found in the minutes drawn up in a special register kept at the registered office and signed by the members of the General Committee.

Copies or transcripts of the minutes of the deliberations are certified, either by the Chairman of the Board of Directors, by the CEO if he/she is a Director, or by the Secretary of the General Shareholders' Meeting. In case of dissolution, they are validly certified by the liquidator(s).

#### **21.2.5.2. Provisions specific to Annual General Shareholders' Meetings**

The Annual General Shareholders' Meetings may make all decisions, other than those directly or indirectly amending the bylaws or those referred to in Articles 27 and 28 below.

It meets at least once a year, within six months of the end of each fiscal year, to approve the accounts for such period, subject to the extension of this period by order of the President of the Commercial Court acting at the request of the Board of Directors.

It meets extraordinarily, whenever it is deemed necessary for the best interests of the Company.

The Annual General Shareholders' Meeting deliberates validly on first call only if the shareholders present, represented or voting by mail hold at least one-fifth of the shares providing entitlement to vote.

On second call, no quorum is required provided that the original agenda has not changed.

The Annual General Meeting passes resolutions by majority of the votes available to the shareholders, represented or voting by mail.

#### **21.2.5.3. Provisions specific to Extraordinary General Shareholders' Meetings**

Extraordinary General Shareholders' Meetings are the only body empowered to amend the bylaws and decide, in particular, on the transformation of the Company into a company with another legal

form. However, it may not increase the shareholders' undertakings, subject to transactions resulting from a regularly performed consolidation of shares.

The Extraordinary General Shareholders' Meeting deliberates validly if the shareholders present, represented or voting by mail hold at least, on first call, one quarter of the shares providing entitlement to vote and, on second call, one-fifth of the shares providing entitlement to vote. Failing this last quorum, the second meeting may be extended to a date two months or more after that at which it was convened.

It shall pass resolutions by a majority of two-thirds of the votes of the shareholders present, represented or voting by mail or participating in the meeting by videoconference or by other telecommunications means in accordance with legal and regulatory provisions.

Notwithstanding the foregoing provisions, the General Shareholders' Meeting, which decides on a capital increase by way of incorporation of reserves, profits or premiums, may pass resolutions pursuant to the conditions of quorum and majority of a General Shareholders' Meeting.

In addition, when the Extraordinary Shareholders' Meeting is convened to deliberate on the approval of a contribution in kind or the grant of a particular advantage, the shares of the contributor or the beneficiary are not taken into account for the calculation of the majority. Neither the contributor nor the beneficiary has the right to deliberate or vote on his/her own behalf or as a proxy.

#### **21.2.6. Provisions for delaying, deferring, or preventing a change of control**

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The Company's bylaws contain no provisions for delaying, deferring, or preventing a change of control.

#### **21.2.7. Thresholds crossings as per the bylaws**

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Without prejudice to the obligations regarding disclosure in the event of crossing of legal thresholds provided for under Articles L. 233-7 *et seq.* of the Commercial Code, any natural person or legal entity, acting alone or in concert, coming to directly or indirectly own a number of shares representing a fraction at least equal to 2.5% of the Company's share capital or voting rights, is required to inform the Company, by registered mail with acknowledgment of receipt, of the total number of shares or voting rights he/she/it holds within four trading days as from the date of acquisition.

This declaration shall be made, under the same conditions, whenever a whole threshold of 2.5% is exceeded up to 50% inclusive of the total number of Company shares or of voting rights.

The aforementioned declaration must also be made when the capital interest becomes less than the thresholds referred to above.

In the event of failure to comply with this information requirement, the shares exceeding the fraction of 2.5% which should have been declared are deprived of voting rights, upon request, recorded in the minutes of the General Shareholders' Meeting, from one or several shareholders holding a fraction of the Company's capital or voting rights at least equal to the above fraction of 2.5% of this capital or of the voting rights, for any General Shareholders' Meeting which will be held until the expiration of a period of two years from the date of regularization of the notification.

#### **21.2.8. Special stipulations governing changes in share capital**

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There is no specific provision in the Company's bylaws governing the modification of its share capital that would be more stringent than the provisions laid down by law.

## 22. KEY AGREEMENTS

With the exception of the agreements outlined below, the Company has entered into agreements only as part of the normal course of business.

### 22.1. Catalent Pharma Solutions, LLC – Agreement to develop and manufacture GPEX dated October 20, 2008

On October 20, 2008, the Company signed a development and manufacturing agreement with Catalent Pharma Solutions, LLC (Catalent).

As of this date, the agreement has been fully executed.

Catalent held certain technologies to develop cell and gene expression lines for protein expression (GPEX Technology). Under this agreement, Catalent was supposed to design a cell line (“Cell Line”), using its GPEX technology that expresses the apolipoprotein A-I (apoA-I). Under the terms of the agreement, Catalent was required to perform services for the Company pursuant to the Specifications (SOWs). Each SOW described the services that had to be provided or the products that had to be manufactured by Catalent, the products to be provided by each party, and the costs for said services and manufacturing. All the product batches manufactured by Catalent were considered to be development batches until the manufacturing, test and storage methods had been validated or declared to be suitable.

Each party retained all the intellectual property rights and the confidential information it provided under the terms of this agreement. The Company holds all the intellectual property rights on its inventions (Client Improvements), subject to the Company’s award of a non-exclusive, free, global and perpetual license to Catalent for the Client Improvements for all usages, with the exception of those involving the Cerenis products. Catalent holds ownership of all inventions that are the intellectual property of Catalent (Catalent Improvements), other than the Client Improvements directly involving the products. Catalent grants the Company a non-exclusive, global and perpetual license without royalties, regarding the Catalent Improvements for usages relating to the Cerenis products.

During the full term of the agreement, and for a period of eighteen (18) month after expiration or termination of the agreement by the Company, Catalent grants the Company a research license, in consideration of the payment of an annual royalty, on a stem cell research bank in connection with the production of a cell line intended solely for non-cGMP usages by the Company and its affiliated companies. Catalent grants the Company a royalty-free, non-exclusive, global license on all process inventions held by Catalent and necessary for the Company to develop and conduct clinical trials, and formulate, manufacture, test and then request approval from the regulatory authority for the sale of any medical products that incorporate an expression product. The agreement requires Catalent to sell the GPEX Cell Lines (as defined in Section 22.2 below) to the Company under the cell line agreement described in Section 22.2 below, during the term of the agreement and for one (1) year after the expiration or termination of the agreement.

The term of the agreement was initially three (3) years, automatically renewable for successive periods of one (1) year, unless one party notified the other in writing of its intention to terminate the agreement within a period of ninety (90) days before the end of the current period. Either of the parties is entitled to terminate this agreement in the event of a significant breach of an obligation thereunder that has not been remedied when, after a formal notice to do so, the party in question remains in breach.

As of this date, all activities stipulated by the agreement have been performed. Catalent has produced a new CHO stem cell that expresses apoA-I and meets the requirements set by Cerenis for stability, quantity of apoA-I expression and secretion.

## **22.2. Catalent Pharma Solutions, LLC – Agreement to sell GPEX derived cell lines dated March 24, 2010**

On March 24, 2010, the Company signed a cell line sales agreement with Catalent for the sale of a GPEX cell line (“GPEX Cell Line”) in connection with the development and manufacturing agreement signed with Catalent. Catalent sold the GPEX Cell Line to the Company for a royalty, stipulating a usage of the GPEX Cell Line only for development, manufacture, the implementation of trials and the request for regulatory authorizations to market and commercially use a product containing a peptide, a polypeptide or a protein coded by a specific gene and expressed in the GPEX Cell Line. Catalent included a transfer of technology in the sale to the Company. The Company has no right, on its own, to manufacture or use the GPEX Technology or to modify or even obtain segments of the GPEX Cell Line for the development of products other than the product in question.

The GPEX Cell Line is used in the manufacture of CER-001, the Company’s main product.

Under the agreement, the Company has the right to sell or transfer its rights to the GPEX Cell Line to any third party, provided it informs Catalent and obtains its consent in the event that said third party does not meet certain criteria defined in the agreement and provided that said third party agrees in writing to comply with all restrictions and to assume the Company’s obligations.

As long as the Company meets its obligations and Catalent receives a certain annual commission threshold as of the commercial launch of the product in question, Catalent will refrain from providing the GPEX Cell Line to a third party, or from manufacturing any product intended for use in connection with the GPEX technology. In addition, Catalent will refrain from authorizing any third party to use the GPEX technology to develop, manufacture or distribute said product.

Under the terms of the agreement, the Company pays Catalent milestone payments based on the achievement of certain objectives, as well as annual maintenance costs and commissions calculated on the net sales.

The agreement will be in force until it is terminated. The Company has the right to terminate the agreement provided it issues a written notice sixty (60) days in advance. Either of the parties may terminate this agreement in the event of a significant breach of an obligation thereunder that has not been remedied when, after a formal notice to do so, the party in question remains in breach. Following termination of the agreement, the Company’s rights concerning the GPEX Cell Line end automatically; ownership is returned directly to Catalent, and the Company is required to destroy any GPEX Cell Line in its possession.

## **22.3. ImaSight Corp. Asset purchase agreement dated September 18, 2009**

On September 18, 2009, the Company and ImaSight Corp (ImaSight) entered into an asset sale agreement for the sale by ImaSight of its rights and interests regarding the CRD5 patent held by Liponex, and the patent of the Ottawa Heart Institute Research Corporation (OHIRC) also held by Liponex, as well as all documents relating to the rights to the Liponex patent.

The acquisition of the licenses on these patents was part of Cerenis’ strategy to secure a perimeter around its intellectual property rights to the lipoprotein complexes and their potential use.

Within the context of this sale, ImaSight agreed to grant an exclusive sublicense to the Company on its rights under the terms of the OHIRC agreement. This sublicense has been granted under a separate sublicense agreement (please see below).

In consideration of the sale of assets under this agreement, the Company made an initial payment to ImaSight and will pay royalties on future net sales.

The Company agreed to hold ImaSight harmless against third-party claims deriving from the use of the Liponex patent rights, or resulting from any violation of a warranty, undertaking, representation or agreement executed by the Company, or in the event of negligence or deliberate fault by the Company. ImaSight guarantees the Company in the event of claims by third parties resulting from the violation of any warranty, undertaking, representation or agreement executed by ImaSight, and against any limitation of liability, development, manipulation, or use of any product by ImaSight, its subsidiaries or sublicenses, or against any negligence or deliberate fault by ImaSight. ImaSight's obligation to indemnify is limited to the larger of either the amount paid by the Company under the terms of the agreement, or the amount of the insurance carried by ImaSight to cover such an obligation.

#### **22.4. ImaSight Corp. – Exclusive sublicense dated February 22, 2010**

In connection with the asset purchase agreement dated September 18, 2009 outlined in Section 22.3 above, the Company and ImaSight entered into an exclusive sublicensing agreement on February 22, 2010 within the framework of the OHIRC agreement.

Under the terms of the sublicense agreement, ImaSight granted the Company an exclusive sublicense and authorized the Company to grant other sublicenses on the patents and technology covered by the license in order to use said technology to (a) manufacture or commission the manufacture of, use, sell, offer for sale and import products or processes that fall within the scope of application of the patents covered by the license, including all of the products under license, and (b) make improvements relating to the technology and patents under license.

Although not included in the manufacturing of the Company's products, signing the licenses to these patents was part of Cerenis' strategy to securing a perimeter around its intellectual property rights to the lipoprotein complexes and their potential use.

The Company pays ImaSight a royalty on net sales, the amount of which is capped. Above this cap, the license automatically becomes an irrevocable, royalty-free license.

The Company has the exclusive right, but not the obligation, to file, maintain, abandon, defend and ensure compliance with all patents covered by the License, at its expense.

The agreement ends when there is no longer any valid claim for any of the Patents covered by the License. The Company has the right to terminate the agreement in its entirety subject to prior notice of thirty (30) days. Either of the parties may terminate this agreement in the event of a significant breach of an obligation thereunder that has not been remedied when, after a formal notice to do so, the party in question remains in breach. After the termination of the ImaSight licensing agreement with OHIRC, this sublicensing agreement will be automatically transferred to OHIRC under the conditions stipulated in accordance with the terms of said agreement.

#### **22.5. Nippon Chemiphar Co., Ltd.– Licensing agreement dated July 21, 2005**

On July 21, 2005, the Company signed a licensing agreement with Nippon Chemiphar Co., Ltd (Chemiphar) under which it obtained an exclusive license to certain patents for chemical compounds in connection with peroxisome, the receiver agonists activated by proliferation, the antagonists and ligands.

Entering into these licenses was part of Cerenis' strategy to strengthen its intellectual property rights concerning the molecules regulating lipid metabolism, in relation to the manufacturing of CER-002.

Chemiphar granted an exclusive license, including the right to assign sublicenses in all countries of the world, except in Asia, including the right for the Company to (a) analyze or commission the analysis of, conduct or commission research on, and develop or commission the development of the chemical compounds, the compounds selected and the compounds of the program, but also to (b) conduct or commission research on, develop and commission the development of, manufacture or commission the manufacture of, use or commission the use of, import or commission the importation of, market or commission the marketing of, and offer for sale, sell or commission the sale of the products. Chemiphar undertakes to refrain from bringing legal action against the Company, its affiliated companies, sub-contractors and sub-licensees for any type of violation or misuse in terms of the license granted. Chemiphar does not have the authorization to sell the compounds selected and the compounds of the program outside Asia for the terms of the agreement and for two (2) years after the end of the agreement.

In return, the Company grants Chemiphar a limited, non-exclusive license on the intellectual property of the program, only for the purpose of manufacturing activities by Chemiphar in order to supply the Company under this agreement. In addition, the Company grants Chemiphar an exclusive license (even relative to the Company), without royalties, on the right to assign sublicenses relating to intellectual ownership of the program for the purpose of conducting or commissioning research on, developing or commissioning the development of, manufacturing or commissioning the manufacture of, using or commissioning the use of, importing or commissioning the importation of, marketing or commissioning the marketing of, and offering for sale, selling or commissioning the sale of the products in all countries in Asia.

Development stages for the Company are set forth in the agreement. Chemiphar has an option to supply an active ingredient for non-clinical uses, preclinical development and clinical development studies. In case Chemiphar exercises its option, Chemiphar is required to provide the active principle to the Company for such uses. The parties agree to sign a supply agreement over a one-year period prior to the expected first commercial sale of a product.

The Company makes milestone payments to Chemiphar and pays royalties on the net sales (subject to reductions for third-party licenses).

The agreement has different expiration terms in each country and for each product, which is no later than (a) the expiration of the last valid claim in a given country for a given product or (b) the tenth (10th) anniversary of the first commercial sale of a product in a given country. The agreement may be terminated by the Company for a specific product, and for a specific country, provided it sends a notice to Chemiphar with reasonable justification based on the scientific, medical or regulatory level, or for reasons of freedom to operate, commercial feasibility, or other commercial factors, and provided that the Company notifies and provides written proof of such elements. Either of the parties may terminate this agreement in the event of a significant breach of an obligation thereunder that has not been remedied when, after a formal notice to do so, the party in question remains in breach. In the event of termination, the sublicenses of the Company have a right of substitution under this license.

#### **22.6. Nippon Chemiphar Co., Ltd – Agreement on the major clauses dated October 10, 2007 and Retrocession Agreement dated December 7, 2007**

On October 10, 2007, the Company and Chemiphar signed an agreement establishing the main clauses of the retrocession agreement. On December 7, 2007, the Company and Chemiphar signed a retrocession agreement under which the Company retroceded to Chemiphar its intellectual property rights regarding which a license had been exclusively granted to the Company in the area of topical ophthalmic products for humans, and for Chemiphar to grant an exclusive world license to Senju Pharmaceutical Co., Ltd. In consideration for the award of such a license, the Company waived the

rights in question, and obtained 45% of the revenues received by Chemiphar in the context of the award of the license to Senju.

To date, this agreement is still being performed.

#### **22.7. CordenPharma**

The Company signed an agreement with CordenPharma under the terms of which CordenPharma manufactured synthetic sphingomyelin and developed a synthetic process. All related intellectual property rights belong to Cerenis.

To date, this agreement is still being performed.

#### **22.8. Novasep Process SAS - Collaboration agreement dated June 10, 2010**

On June 10, 2010, the Company signed a collaboration agreement with Novasep Process S.A.S. (Novasep). The Company holds all the intellectual property rights to the CER-001 product. In this respect, it developed a process to manufacture CER-001 batches, in which third parties work to create the cell culture for the CER-001 protein, manufacture lipid complexes, and perform the purification and formulation activities on the Company's behalf. The collaboration agreement with Novasep was signed in order to develop an innovative process to manufacture the product CER-001 with nearly continuous fermentation of the apoA-I and a redefined purification process, so that the yield and productivity of the CER-001 are significantly improved in order to market it for certain specific therapeutic indications.

Under the terms of the agreement, the Company supplies Novasep, at no cost, the material necessary to execute the approved development plan, particularly a cell line appropriate for the production of the apoA-I used in the composition of the CER-001 product. This material remains the exclusive property of Cerenis. In addition, the Company transfers to Novasep, at no additional cost, the initial process and the specifications for the manufacturing process (protocols, methods, procedures) as well as reasonable and necessary assistance to conduct the development activities assigned to it in accordance with the plan.

Novasep, in compliance with the quantities and time frames set forth in the development plan, manufactures products that it then supplies to the Company for clinical development in accordance with the manufacturing and product specifications, which meet the quality standards defined by the parties. If the orphan drug project is successful, the Company undertakes to purchase a certain quantity of the CER-001 product from Novasep. If the post-SCA indication project is successful, the Company grants Novasep the right to refuse to manufacture the product. If Novasep refuses, the Company must pay a certain sum in consideration of Novasep's efforts, the licenses granted, and the loss of the commercial relations between the parties. However, the Company may alternatively purchase a certain quantity of material from Novasep at prices and conditions that may be no less favorable than those offered to other customers. If the Company finds suppliers that can manufacture the product with the same quality for a price of less than 10%, it may freely contract with them without paying compensation to Novasep. In this case, however, Novasep will have a priority right to make a new price proposal.

Each party retains its independent intellectual property rights developed outside of the partnership. Novasep grants the Company an exclusive, global, perpetual license, without royalties, relating to its intellectual property rights necessary for the research and development and the manufacture of the CER-001 product, giving the right to grant sublicenses, but limited to the right to manufacture the CER-001 product or apoA-I, or commission their manufacture. All rights developed in the context of the collaboration between the parties will be held jointly by the Company and Novasep. The Company will have exclusive ownership of the rights to the CER-001 product, including the exclusive right to grant sublicenses, and Novasep has exclusive ownership of the other rights. Finally, the Company retains



exclusive ownership of the rights that it develops on its own. Moreover, any agreement signed by Novasep with a third party in the context of the project must give Novasep a free and perpetual user's license with the right to sublicense, so that Novasep may transfer the technology to the Company without violating the agreement signed with the third party.

The agreement includes a commitment for Novasep not to file legal action against the Company, its affiliated companies, sub-licensees or sub-contractors for any infringement of the Company's rights related to the development of the CER-001 product. The Company agrees not to bring legal action against Novasep for infringement of its intellectual property rights, except those related to the CER-001 product. During the term of the agreement, and for the next ten (10) years, the parties agree to observe confidentiality of the information and protect business secrecy.

Novasep undertakes to hold the Company, its affiliated companies, employees, executives and corporate officers harmless against third-party claims deriving from (a) any violation of a warranty, undertaking, or representation of Novasep in the execution of the agreement or the development plan; (b) the lack of compliance of the products with the technical and quality requirements stipulated in the contract; (c) any violation of the regulations by the Company in the performance of the agreement; and d) negligence or willful misconduct on the part of Novasep. This undertaking does not apply if the Company fails to meet an obligation that could trigger its guarantee to Novasep.

The Company has agreed to hold Novasep, its affiliated companies, employees, executives and corporate officers harmless against third-party claims deriving from any violation of a warranty, undertaking, or representation or agreement signed by the Company, or in the case of the Company's negligence or willful misconduct in the performance of the agreement or the development plan, and any violation of regulations by the Company in the performance of the agreement. This guarantee does not apply if Novasep fails to meet an obligation that could trigger its guarantee to the Company.

The agreement ends once the Company has met its commitment to purchase a certain quantity of apoA-I from Novasep. Moreover, either party has the right to end the agreement in its entirety by issuing a prior written notice of ten (10) days in the event of a significant breach of an obligation that has not been remedied when, after a formal notice to do so, the party in question remains in breach at the end of a period of sixty (60) days. Each party may also end the agreement if the other party files for bankruptcy. The Company may also end the agreement, at its discretion, under the terms of a written notice of ninety (90) days in consideration of the payment of a certain sum. The agreement may also be ended following a prior notice of ninety (90) days if the project is still not completed and one of the financing agreements is terminated.

## **22.9. South Australian Health and Medical Research Institute Limited (SAHMRI) - Service provision master agreement dated May 29, 2013**

On May 29, 2013, the Company signed a master agreement with South Australian Health and Medical Research Institute Limited (SAHMRI) to provide research services to support its clinical development projects. In particular, these services include the review, screening, image analysis, raw data and statistical analysis of the data on the CER-001 product, as well as the effect on the load of coronary atherosclerosis.

Performance of the CARAT Phase II clinical trial in the post-SCA indication became the subject matter of a new contract signed under this Master Agreement.

The agreement stipulates that the parties will implement reasonable security measures so that the confidential information exchanged is not disclosed to third parties. At the Company's request, the research results must be transmitted to it. SAHMRI is required to inform the Company in writing of all the inventions and improvements revealed by the research, and to provide the Company with all



useful information to obtain the issuance of a patent in the United States and in all the countries in which the Company wants to protect its interests. The potential copyrights resulting from this research are the property *ab initio* of the Company. The parties mutually guarantee each other against all actions resulting from the violation of the agreement that is chargeable to them.

The Company may end the agreement at any time via a written notice of thirty (30) days and payment for the research work initiated by SAHMRI. Either of the parties may terminate the agreement in writing, in the event of a significant breach of an obligation that has not been remedied when, after a formal notice to do so, the party in question remains in breach at the end of a period of thirty (30) days.

#### **22.10. ICTA Project Management (ICTA SYSTEMS SAS) - Master agreement to provide services, dated June 8, 2015**

On June 8, 2015, the Company signed a master agreement with ICTA Project Management S.A.S represented by ICTA SYSTEMS S.A.S. (ICTA) to provide research services to support its clinical development projects. These services include the review, screening, image analysis, raw data and statistical analysis of the data on the CER-001 product.

Performance of the TANGO Phase III clinical trial in the indication of HDL deficiency (FPHA) became the subject matter of an agreement signed pursuant to this framework agreement.

The agreement stipulates that the parties will implement reasonable security measures so that the confidential information exchanged is not disclosed to third parties. At the Company's request, the research results must be transmitted to it. ICTA must inform the Company in writing of all inventions and improvements encountered in the research, and provide the Company with all useful information to obtain the patent issue in the United States and in all the countries in which the Company wants to protect its interests. The potential ICTA copyrights resulting from this research are assigned to the Company.

The Company may end the agreement at any time, having issued a prior written notice of at least thirty (30) days and the payment for the research work initiated by ICTA. Either of the parties may terminate the agreement in writing, in the event of a significant breach of an obligation that has not been remedied when, after a formal notice to do so, the party in question remains in breach at the end of a period of thirty (30) days.

## **23. INFORMATION FROM THIRD PARTIES, EXPERT STATEMENTS AND DECLARATIONS OF INTERESTS**

None.

## **24. DOCUMENTS ACCESSIBLE TO THE PUBLIC**

Copies of this Registration Document are available at no cost from the Company's registered office at 265, rue de la Découverte, 31670 Labège.

This Registration Document may also be consulted on the Company's website ([www.cerenis.com](http://www.cerenis.com)) and on the AMF website ([www.amf-france.org](http://www.amf-france.org)).

The bylaws, minutes of the shareholders' meetings and other corporate documents of the Company, as well as financial information and any assessment or statement prepared by an expert at the Company's request that must be made available to the shareholders, in accordance with the applicable legislation, may be consulted free of charge at the Company's registered office.

The regulated information as defined by the provisions of the General Regulation of the AMF is also available on the Company's website ([www.cerenis.com](http://www.cerenis.com)).

## **25. INFORMATION ON EQUITY ASSOCIATES**

The Company owns 100% of the shares of Cerenis Therapeutics Inc., located in the United States.

## 26. FINANCIAL COMMUNICATIONS TIMETABLE FOR 2017

February 3: the Company published its provisional financial communications timetable for 2017:

Event	Date *
Annual results 2016	17 February 2017
Treasury position and update on Q1 2017 activity	20 April 2017
General Meeting	9 June 2017
Treasury position and update on Q2 2017 activity	20 July 2017
Half Year Results 2017	12 September 2017
Treasury position and update on Q3 2017 activity	26 October 2017
Treasury position and update on Q4 2017 activity	25 January 2018

\* Indicative timetable subject to change

## 27. GLOSSARY

1. **18F – FDG:** fluorodeoxyglucose (18F), abbreviated as 18F-FDG, is a radiopharmaceutical glucose analog used as a tracer in medical imaging by Positron Emission Tomography (PET), a scintigraphy method.
2. **ABCA-I (ATP-Binding Cassette Transporter A1):** ATP designates adenosine triphosphate, which is the main carrier of energy in all cellular reactions. The ABCA-I protein plays a crucial role in HDL metabolism by allowing cellular cholesterol mobilization to pre- $\beta$  HDL particles. Rare mutations in the ABCA-1 gene cause the disappearance of HDL (pathologies: hypoalphalipoproteinemia, anaalphalipoproteinemia, Tangier disease).
3. **ABCG-I (ATP-Binding Cassette Transporter G1):** ATP designates adenosine triphosphate, which is the main carrier of energy in all of our cellular reactions. The ABCG-I protein is involved in the regulation of cholesterol mobilization.
4. **Acute coronary syndromes (ACS):** acute coronary syndrome (ACS) is a term used to describe any health problems resulting from the sudden reduction of blood supply to the heart.
5. **American Heart Association (AHA):** a U.S. non-profit organization, highly renowned in cardiovascular diseases and risk prevention. Most of the protocols and recommendations used in the United States and around the world are established, in large part, based on their research and publications.
6. **Angioplasty:** Angioplasty is a surgical act generally performed under local anaesthesia. Namely, it is recommended in the case of the narrowing of the coronary arteries (stenosis) during angiography of the vessels of the heart called coronary angiography. Angioplasty consists in inserting a catheter into the blood vessel to treat it. A small balloon is placed into the artery and then inflated to enlarge it. A device (stent) is left at the site of the narrowing so that the effect is permanent. Percutaneous coronary angioplasty via the femoral artery is the most commonly practiced.
7. **apoA-I (abbreviation of apolipoprotein A-I):** the apolipoprotein A-I is a protein manufactured by the intestines and liver, and constitutes 75-80% of the composition of HDL particles. It activates the LCAT enzyme, which enables the synthesis of cholesterol esters, a less mobile chemical form of cholesterol.
8. **Atherosclerosis:** degenerative disease of the artery due to the formation of atherosclerotic plaque (lipid deposit) in its wall. It occurs when the atherosclerotic plaque becomes significant enough to disrupt the blood flow or if there is a rupture of this plaque. Atherosclerosis can cause attacks of angina pectoris, transient neurological accidents (vertigo) or pain in the extremities. The symptoms depend on the location of the atherosclerotic plaque. Atherosclerosis especially concerns the areas close to the heart, intersections, bifurcations of the arteries. It affects, in order of frequency: the abdominal aorta, coronary arteries (the heart's feeder arteries), the internal carotid, which vascularizes the brain, the iliac and femoral arteries of the lower limbs.
9. **Atherosclerotic plaque:** the bad cholesterol is at the origin of the formation of atherosclerotic plaque also known as atherosclerosis. The atherosclerotic plaque is caused by an excess of cholesterol in an insidious manner over the years and can eventually obstruct one or more arteries. Fatty plaques thus accumulate over the years in the inner lining of the arteries (intima) causing thickening, hardening and decreased artery elasticity. The diameter of these arteries decreases, which can hinder blood circulation.

10. **Autologous:** the term autologous refers to the constituents of the body such as cells, tissues, which are specific to an individual.
11. **Blind or blinded clinical trial:** the treatments compared or placebo can be administered without the person knowing what kind of treatment he/she takes: it is referred to as blind or blinded trial. The physician who administers the treatment may also not know it: in this case it is referred to as a double-blind or double-blinded trial.
12. **Carcinoma:** cancer developed from epithelial tissue (skin, mucosa).
13. **Catheterization:** cardiac catheterization is an exploration method used to perform various tests and interventions. A small flexible probe referred to as a catheter is inserted into an artery or a vein in the groin or arm, in order to reach the heart. X-rays are then used to visualize the blood vessels and the heart. This catheter measures the pressure within the heart and blood vessels, thus allowing determining if blood flows from one side to the other of the heart.
14. **Chelating resins:** these are substances whose role it is to prevent the intestinal absorption of bile salts contained in bile and cholesterol from food. Thus, the bile is used, among other things, for the absorption of various lipids by the intestines. The bile acid chelating resins limit the entry of cholesterol into the body.
15. **Chest angina or angor:** there are two forms of angina, stable angina and unstable angina. The latter is more serious because unlike the first, it also appears at rest and can result in myocardial infarction. Unstable angina manifests itself with chest pain that occurs in the form of attacks. Electrocardiogram, ultrasound, scintigraphy and angiography aid in confirming the diagnosis.
16. **Cholesterol esterification:** natural process by which the cholesterol molecule is made totally insoluble in water by the addition of a fatty acid. There are two chemical forms of cholesterol, one free (not linked to another substance), the other esterified (linked to a fatty acid). The cholesterol that is found in the blood is the sum of these two forms.
17. **Cholesterol lowering drug:** a cholesterol-lowering drug is a drug whose therapeutic action is aimed at reducing the LDL cholesterol) circulating in the blood.
18. **cIMT (Carotid Intima-Media Thickness):** intima-media thickness (IMT) of the carotid artery. IMT is closely correlated with the occurrence of cardiovascular events: an increased IMT multiplies the risk of myocardial infarction and stroke by 2 to 5 times.
19. **Coronary artery bypass:** coronary bypass is used to solve the problem of blood supply to the heart muscle caused by the build-up of plaque (atherosclerosis) inside the coronary arteries. This procedure involves the use of a segment of blood vessel (artery or vein) collected elsewhere in the body in order to create a detour or bypass intended to circumvent the obstructed section of a coronary artery. Another choice of treatment called percutaneous cardiac intervention (also referred to as angioplasty), a non-surgical technique performed using a catheter and small structures called stents (or springs), intended to keep the arteries open.
20. **Coronary Heart Disease or CHD:** coronary artery disease, also called cardiac disease, corresponds to the narrowing of the arteries of the heart (coronary arteries), caused by atherosclerosis.
21. **Dyslipidaemia:** abnormally high or low concentration of lipids in the blood.

22. **EMA:** European Medicines Agency.
23. **HDL:** high density lipoproteins.
24. **Iliac arteries:** these are arteries located near the groin.
25. **Investigator:** the person who directs and monitors the implementation of the clinical trial. A physician who must provide proof of appropriate experience for clinical trials of medication.
26. **Ischemia:** Ischemia corresponds to a decrease in arterial vascularization, or the blood supply at the level of a more or less extended area of tissue or an organ. Ischemia may be reversible and cause only limited discomfort. It may be irreversible and can lead to organ failure, namely the death of some or all of it. The two most critical cases are obviously ischemia affecting the brain or the heart muscle.
27. **IVUS Imaging:** an endovascular ultrasound technique that allows high-resolution imagery of the vascular walls in real time. This technique provides qualitative and quantitative information that allowed for development of in vivo work on atherosclerotic pathology.
28. **Heterozygote:** an organism is heterozygous for a gene when it has two different forms of this gene.
29. **Homozygote:** an organism is homozygous for a gene when it has two identical forms of this gene.
30. **LCAT:** lecithin-Cholesterol Acetyltransferase is an enzyme that enables activation of the transfer of a fatty acid from the lecithin on the cholesterol within the context of its esterification.
31. **LDL:** low density lipoproteins.
32. **LDL Apheresis:** LDL removal technique by extracorporeal circulation of the blood. The LDL to eliminate are separated and extracted, while the components that are not collected are re-injected into the patient.
33. **Lipid lowering drug:** a lipid-lowering drug is a drug whose therapeutic action is aimed at reducing lipids (triglycerides and/or LDL cholesterol) circulating in the blood.
34. **Lipoproteins:** lipoproteins are large complexes of water soluble proteins and lipids, which massively carry lipids in the body.
35. **Marketing authorization (MA):** to be sold, any industrially manufactured drug must obtain an MA. The MA is issued by the relevant European authorities (European Commission, following consultation with the European Medicines Agency) or national authorities (in France: ANSM).
36. **Myocardial infarction (MI):** is triggered by the obstruction of an artery that feeds blood to the heart muscle (coronary artery) and therefore oxygen. Deprived of oxygen, the heart muscle cells die quickly on a more or less extended area. This causes contraction of the heart muscle (myocardium) issues, manifested by rhythm disorders, heart failure, or even heart stoppage. The only solution is to unclog the artery as soon as possible after the onset of symptoms. This rapid revascularization reduces mortality and complications associated with myocardial infarction. With age and under the influence of various risk factors, including plaque composed of cholesterol is formed along the wall of the arteries. They are



called atherosclerotic plaques. When one of these plaques ruptures, a clot forms and blocks circulation. It can then suddenly reduce blood flow or even totally interrupt it: this is what is referred to as ischemia. If this phenomenon continues, the induced hypoxia (lack of oxygen) causes the death of muscle cells.

37. **Mortality rate:** the mortality rate (gross) is the ratio of the number of yearly deaths to the average yearly population.
38. **Morbidity rate:** percentage of sick individuals in a population, at a given time, from a specific disease or from all diseases.
39. **mPP Population (modified per protocol):** statistical analysis of the results taking into account patients with very slight differences in inclusion criteria for a clinical trial and who participated in the trial from the beginning to the end, and strictly complying with the trial protocol.
40. **MVWT:** mean vessel wall thickness or percentage of the total of the vascular wall taken over by atherosclerotic plaque.
41. **NSTEMI:** acronym for “Non-ST segment Elevation Myocardial Infarction” is a type of acute coronary syndrome similar to unstable angina (characteristic chest pain that occurs unexpectedly and generally at rest) with the difference that blood test results are abnormal and indicate that cardiac cells are damaged.
42. **Open-label clinical trial:** the investigator and the person on whom the clinical trial is carried out are aware of the treatment.
43. **PAV:** percentage of atheroma volume.
44. **PCSK9:** the proprotein convertase subtilisin/kexin 9 is an enzyme. The PCSK9 inactivates the LDL receptors in the liver. These receptors are necessary to transport the LDL cholesterol into the liver for metabolization and elimination. The lack of receptors results in more LDL cholesterol circulating in the blood. Thus the inhibition of PCSK9 leads to a reduction of LDL cholesterol in the blood.
45. **PCSK9 inhibitors, such as Repatha® and Praluent®:** are a newer class of injectable antibodies that have been shown to dramatically lower LDL cholesterol levels, by up to 60% when combined with a statin. PCSK9 inhibitors are monoclonal antibodies (MABs), a type of biologic drug. They bind to and inactivate a protein in the liver called proprotein convertase subtilisin kexin 9 (PCSK9).
46. **PET-CT Imaging:** the positron emission tomography (PET), referred to as PET or PET scan is a medical imaging method practiced by nuclear medicine specialists for measuring the body's metabolic or molecular activity in three dimensions thanks to the emissions produced by positrons from previously injected radioactive material.
47. **Pharmacokinetics:** a pharmacokinetic study is designed to study the fate of an active substance after administration in the body.
48. **Phospholipid:** a lipid containing a phosphoric acid group.
49. **pre-β HDL:** pre-β HDL particles are part of HDL (high density lipoprotein). It is a very dense subclass of high density lipoprotein, very small (less than 7 nm in diameter), discoid shaped

and negatively charged. They are also known as nascent HDL, composed of a few molecules of apolipoprotein A-I complexed with phospholipids. The pre- $\beta$  HDL particles initiate the reverse cholesterol transport from the cells to the liver.

50. **Randomized clinical trial:** we refer to trials as randomized when patients are distributed randomly into different groups receiving different treatments.
51. **Serum transaminase:** transaminase dosage in the blood. Transaminases are enzymes located within the cells. Their increase reflects a cellular lesion (cellular toxicity), particularly at the level of the liver, heart, kidney, or muscle.
52. **Stent:** medical device also referred to as a “spring”. It is a small metal tube that is introduced into an artery in order to facilitate blood circulation. It is mainly used during angioplasty to treat stenosis (narrowing of an artery). The stent may be stainless steel or alloy and rests on the artery walls.
53. **STEMI:** acronym for “ST segment elevation myocardial infarction,” which is one of the three main forms of heart attack (or acute coronary syndrome). Myocardial infarction with ST-segment elevation is a severe heart attack due to the generally complete obstruction of an artery supplying the heart.
54. **Stroke:** stroke is an obstruction or the rupture of a vessel that transports blood to the brain.
55. **TAV (Total Atheroma volume):** measurement of the total volume of the atheroma of the vascular wall.
56. **Thrombosis:** formation of a clot or thrombus at the level of a blood vessel or heart chamber. The risk of thrombosis is the complete obstruction of the vessel.
57. **VLDL (Very Low Density Lipoproteins):** lipoproteins of very low density.

## 28. CROSS REFERENCE TABLE BETWEEN THE MANAGEMENT REPORT AND ANNUAL FINANCIAL REPORT

Headings	Sections of the Registration Document	Information on
<b>1. CORPORATE FINANCIAL STATEMENTS</b>	20.3	<b>AFR*</b>
<b>2. CONSOLIDATED FINANCIAL STATEMENTS</b>	20.1	<b>AFR</b>
<b>3. MANAGEMENT REPORT</b>		
<b>3.1. Information about the Company's business</b>		
<ul style="list-style-type: none"> <li>List of employee shareholders in the Company, including shares held under a PEE or FCPE, as well as registered shares granted to employees under Art. L. 225-197-1 of the French Commercial Code which have vested (applicable to bonus shares authorized by the SM of August 7, 2015).</li> </ul> <p>Art. L. 225-23, L. 225-102, subsection 1, L. 225-180 of the French Commercial Code</p>	3, 6, 9, 10 and 20	
<ul style="list-style-type: none"> <li>Analysis of changes in the business, results, financial position and notably the Company and Group's debt</li> </ul> <p>Art. L. 233-26, L. 225-100, subsection 3, L. 225-100-1 and/or L. 225-100-2 of the French Commercial Code</p>	3, 9 and 20	<b>AFR</b>
<ul style="list-style-type: none"> <li>Foreseeable changes in the Company and/or Group</li> </ul> <p>Art. L. 232-1, R. 225-102 and/or L. 233-26, R. 225-102 of the French Commercial Code</p>	12	
<ul style="list-style-type: none"> <li>Key financial and non-financial indicators for the Company and Group</li> </ul> <p>L. 225-100, subsections 3 and 5, L. 225-100-1, L. 223-26 and/or L. 225-100-2 of the French Commercial Code</p>	3	<b>AFR</b>
<ul style="list-style-type: none"> <li>Company and Group post-balance sheet events</li> </ul> <p>Art. L. 232-1 and/or L. 233-26 of the French Commercial Code</p>	20.1 (Note I.C) 20.3 (Note II)	
<ul style="list-style-type: none"> <li>Indicators on using financial instruments, including financial risks, pricing risks, credit risks, liquidity risks, cash flow risks for the Company and Group</li> </ul> <p>Art. L. 225-100, subsection 6, L. 225-100-1 and/or L. 225-100-2, L. 223-26 of the French Commercial Code</p>	4.4	<b>AFR</b>

Headings	Sections of the Registration Document	Information on
<ul style="list-style-type: none"> <li>Main risks and uncertainties for the Company and Group</li> </ul> <p>Art. L. 225-100, subsections 4 and 6, L. 225-100-1 and/or L. 225-100-2 subsections 2 and 4 of the French Commercial Code</p>	4	AFR
<ul style="list-style-type: none"> <li>Information on the Company and Group's R&amp;D</li> </ul> <p>Art. L. 232-1 and/or L. 233-26 of the French Commercial Code</p>	6, 11 and 20	
<b>3.2. Legal, financial and tax information of the Company</b>		
<ul style="list-style-type: none"> <li>Choice made between two executive management methods in the event of changes</li> </ul> <p>Art. R. 225-102 of the French Commercial Code</p>	N/A	
<ul style="list-style-type: none"> <li>Identity of individuals holding more than 5, 10, 15, 20, 25, 33.33, 66.66, 90, or 95% of capital or voting rights, either directly or indirectly, and changes made during the year</li> <li>Name of controlled companies holding treasury stock in the Company and share of capital that they hold</li> </ul> <p>Art. L. 233-13 of the French Commercial Code</p>	21.1.7.2 N/A	
<ul style="list-style-type: none"> <li>Interests of 5, 10, 20, 33.33, 50 or 66.66% in capital or voting rights during the fiscal year or controlling interests in companies with registered offices in French territory</li> </ul> <p>Art. L. 233-6, subsection 1 of the French Commercial Code</p>	N/A	
<ul style="list-style-type: none"> <li>Notice of holding more than 10% of the share capital in another limited liability company; transfer of cross-shareholdings</li> </ul> <p>Art. L. 233-29, L. 233-30 and R. 233-19 of the French Commercial Code</p>	N/A	
<ul style="list-style-type: none"> <li>Acquisition and sale by the Company of its treasury shares (share buyback)</li> </ul> <p>Art. L. 225-211 of the French Commercial Code</p>	21.1.3.	AFR

Headings	Sections of the Registration Document	Information on
<ul style="list-style-type: none"> <li>List of employee shareholders in the Company, including shares held under a PEE or FCPE, as well as registered shares granted to employees under Art. L. 225-197-1 of the French Commercial Code which have vested (<i>applicable to bonus shares authorized by an Extraordinary General Meeting since August 7, 2015</i>).</li> </ul> <p>Art. L. 225-23, L. 225-102, subsection 1, L. 225-180 of the French Commercial Code</p>	21.1.7.2	
<ul style="list-style-type: none"> <li>Report of items that may impact a public tender offer:</li> </ul> <p>Art. L225-100-3 of the French Commercial Code</p> <ul style="list-style-type: none"> <li>The Company's share capital structure;</li> <li>The bylaw limitations on exercising voting rights and share transfers or clauses in agreements brought to the Company's attention pursuant to Article L. 233-11 of the French Commercial Code;</li> <li>Direct or indirect investments in the Company's share capital of which the Company is aware by virtue of Articles L. 233-7 and 233-12 of the French Commercial Code;</li> <li>A list of parties holding any securities that have special control rights and a description of them;</li> <li>The control mechanisms defined in a potential employee shareholding system, when control rights are not exercised by the latter;</li> <li>Agreements between shareholders of which the Company is aware which could lead to restrictions in share transfers and exercising of voting rights;</li> <li>Rules applicable for appointing and replacing members of the Board of Directors as well as modifying the Company's bylaws;</li> <li>The powers of the Board of Directors, in particular regarding issuing or buyback of shares;</li> <li>Agreements signed by the Company that were modified or expire in the event of a change in control of the Company, unless this disclosure</li> </ul>	21.1.7.2. 21.2.7 21.1.7.2. N/A 17.4 (N/A) 18.4 21.2.2 21.1.3 and 21.1.5 N/A 15 (table 11) and 15.3	AFR

Headings	Sections of the Registration Document	Information on
<p>were to seriously undermine its interests (excluding cases involving legal disclosure obligations),</p> <ul style="list-style-type: none"> <li>○ Agreements providing for the payment of indemnities to members of the Board of Directors or employees, if they resign or their posts are terminated without a real, justified cause, or their employment is ended due to a public tender offer</li> </ul>		
<ul style="list-style-type: none"> <li>• Table summarizing delegation of powers granted by the General Shareholders' Meeting regarding capital increases being approved</li> </ul> <p>Art. L. 225-100, subsection 7 of the French Commercial Code</p>	21.1.5	AFR
<ul style="list-style-type: none"> <li>• Note on potential adjustments: <ul style="list-style-type: none"> <li>○ for securities representing share capital and stock options in the event of share buybacks</li> <li>○ for securities representing share capital in the event of financial transactions</li> </ul> </li> </ul> <p>Art. R. 228-90, R. 225-138 and R. 228-91 of the French Commercial Code</p>	N/A  N/A	
<ul style="list-style-type: none"> <li>• Amounts of dividends that have been distributed over the last three years</li> </ul> <p>Art. 243 bis of the French General Tax Code</p>	20.6.1.	
<ul style="list-style-type: none"> <li>• Amount of non-tax deductible expenses and costs</li> </ul> <p>Art 223(4) of the French General Tax Code</p>	N/A	
<ul style="list-style-type: none"> <li>• Payment terms and breakdown of outstanding trade payables and receivables by due date</li> </ul> <p>Art. L. 441-6-1, D. 441-4 of the French Commercial Code</p>	9.2.2.5.	
<ul style="list-style-type: none"> <li>• Injunctions or fines for anti-competitive practices</li> </ul> <p>Art. L.464-2 I, subsection 5 of the French Commercial Code</p>	N/A	

Headings	Sections of the Registration Document	Information on
<ul style="list-style-type: none"> <li>Agreements made between an officer or shareholder holding more than 10% of the voting rights and a subsidiary (excluding current agreements)</li> </ul> <p>Art. L. 225-102-1, subsection 13 of the French Commercial Code</p>	N/A	
<ul style="list-style-type: none"> <li>Amount of intercompany loans</li> </ul> <p>Art. L. 511-6 of the French Monetary and Financial Code</p>	N/A	
<ul style="list-style-type: none"> <li>Table of results for last five fiscal years</li> </ul> <p>Art. R. 225-102 of the French Commercial Code</p>	20.9	
<ul style="list-style-type: none"> <li>Existing branches</li> </ul> <p>Art. L. 232-1 of the French Commercial Code</p>	N/A	
<b>3.3 Information on corporate officers</b>		
<ul style="list-style-type: none"> <li>List of all terms of offices and posts held in any company by each corporate officer during the year</li> </ul> <p>Art. L. 225-102-1, subsection 4 of the French Commercial Code</p>	14.1.1 14.1.2	
<ul style="list-style-type: none"> <li>Compensation and benefits of any kind paid during the year to each corporate officer by the Company, companies it controls or company that controls it, including commitments of any kind corresponding to compensation components, payments or benefits due or likely to become due as a result of taking up, terminating or changing office, or subsequently, and in particular pension commitments and other lifetime benefits.</li> </ul> <p>Art. L. 225-102-1, subsection 1, 2 and 3 of the French Commercial Code</p>	15.1 and 15.2	
<ul style="list-style-type: none"> <li>Commitments related to acquiring, ending or changing posts</li> </ul> <p>Art. L. 225-102-1, subsection 3 of the French Commercial Code</p>	15.1 (Table 11) and 15.3	

Headings	Sections of the Registration Document	Information on
<ul style="list-style-type: none"> <li>In the event that stock options are granted to executive officers, mention of information the Board used to make the decision: <ul style="list-style-type: none"> <li>Either to prohibit executives from exercising their options before ending their posts;</li> <li>Or requiring them to keep all or part of their shares from already exercised options in registered form until their posts end (and specify the amount set)</li> </ul> </li> </ul> <p>Art. L. 225-185, subsection 4 of the French Commercial Code</p>	21.1.4.3.	
<ul style="list-style-type: none"> <li>In the event a grant of bonus shares or stock options to executives, mention of information on which the Board based its decision: <ul style="list-style-type: none"> <li>Either to prohibit executives from selling the shares that were granted to them free of charge or that were issued from the exercise of stock options before their posts end;</li> <li>or set the quantity of these shares that they must keep in registered form until their posts end (and specify the amount set)</li> </ul> </li> </ul> <p>Art. L. 225-197-1-II, subsection 4 and L. 225-185 of the French Commercial Code</p>	15.1 (table 10)	
<ul style="list-style-type: none"> <li>Table summarizing transactions of executives and related parties on the Company's securities</li> </ul> <p>Art. L. 621-18-2, R. 621-43-1 French Monetary and Financial Code; Art. 223-22 and 223-26 of the General Regulation of the AMF</p>	14.1.6.	
<b>3.4. Company CSR Information</b>		
<ul style="list-style-type: none"> <li>Consideration of the social and environmental consequences of the Company's business, including the consequences on climate change of its activities and its use of the goods and services it produces, and its corporate commitments to promote sustainable development and the circular economy, to combat food waste discrimination, and to promote diversity.</li> </ul> <p>Art. L. 225-102-1, subsection 5 to 8, R. 225-104, R. 225-105, R. 225-105-1 and R. 225-105-2-II of the French Commercial Code</p>	8 and 17	



Headings	Sections of the Registration Document	Information on
<ul style="list-style-type: none"> <li>Information on hazardous business activities</li> </ul> <p>Art. L. 225-102-2 of the French Commercial Code</p>	N/A	
<ul style="list-style-type: none"> <li>Collective agreements signed within the Company and their impact on the Company's economic performance as well as on working conditions for employees</li> </ul> <p>Art. L. 225-102-1 of the French Commercial Code</p>	N/A	
<b>4. Declaration of the individuals assuming responsibility for the annual financial report</b>	1.2	<b>AFR</b>
<b>5. Statutory Auditors' report on the corporate financial statements</b>	20.4	<b>AFR</b>
<b>6. Statutory Auditors' report on the consolidated financial statements</b>	20.2	<b>AFR</b>
<b>Additional documents (the inclusion of which does not require separate disclosure)</b>		
Description of the share buyback program	21.1.3.3	
Chairman's report on corporate governance, and internal audit and risk management procedures	16.5	
Statutory Auditors' report on the Chairman's report on corporate governance, and internal audit and risk management procedures	16.6	

\* AFR: Annual Financial Report