



**The HDL Company**

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## **Jean-Louis DASSEUX, PhD, MBA**

### **Founder and CEO**

- More than 25 years of experience in the pharmaceutical industry (Pfizer, Esperion Therapeutics, Fournier Laboratories)
- A leading world expert in lipid metabolism, atherosclerosis and cardiovascular diseases
- Inventor of more than 60 patent families relating to HDL and the treatment of cardiovascular diseases



## **Cyrille TUPIN, CPA**

### **CFO**

- Audit Director at Sygnatures, the largest private auditing and consulting company in Toulouse, France
- More than 7 years at PWC working on high-profile business transactions

## **CER-001: major potential in the treatment of patients post-ACS**

1. A therapy targeting the 2/3 of patients who are poorly served with available medical treatments
2. Advanced and promising clinical developments currently in Phase II (CARAT)
3. Compelling to big pharma (e.g., OMTHERA \$443 m; Esperion \$1.3 bn; KOS \$3.7 bn)<sup>1</sup>
4. A manufacturing process validated on an industrial level with proven clinical safety and tolerability

## **In the short term: CER-001, a drug for treating orphan diseases**

1. A potential of value creation in the short term, currently in Phase III (TANGO)
2. A major unmet medical need
3. Application for marketing approval before 2018

## **CER-209: major potential in the treatment of patients with atherosclerosis and NAFLD/NASH**

1. A significant unmet medical need
2. CER-209, a highly specific P2Y<sub>13</sub> receptor agonist promoting lipid elimination

**A WELL-CAPITALIZED (€33 MILLION), LISTED COMPANY WITH SUBSTANTIAL  
POTENTIAL IN HDL THERAPY**

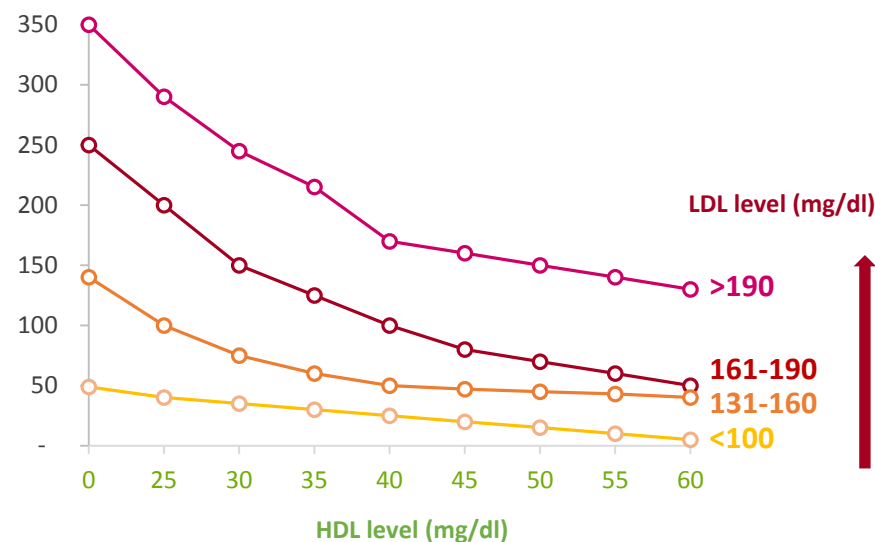
1. Press releases,  
OMTHERA: <http://www.astrazeneca.com/Media/Press-releases/Article/20130528-omthera>  
Esperion: <http://www.bloomberg.com/apps/news?pid=newsarchive&sid=apU2qcYCmkO4&refer=us>  
KOS: [http://www.bloomberg.com/apps/news?pid=newsarchive&sid=af\\_8tgk4fHE](http://www.bloomberg.com/apps/news?pid=newsarchive&sid=af_8tgk4fHE)

## Fundamental role of HDL in removing cholesterol

- At each LDL level, it is the HDL level that determines the cardiovascular risk
- An HDL therapy that increases the number of HDL particles is one of the best approaches for treating atherosclerosis
- No HDL medical treatment that can treat or eliminate atherosclerosis is yet available

## A major epidemiological study on HDL <sup>1</sup>

Incidence of cardiovascular events (per 1,000) over 10 years



**CERENIS IS THE COMPANY THAT OFFERS ONE OF THE MOST COMPREHENSIVE INNOVATIVE HDL SOLUTIONS FOR TREATING ATHEROSCLEROSIS**

1. PROCAM:  
7,152 men aged 35 to 65  
406 coronary events over 10 years

## Leading cause of death in the world

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- 1 out of 3 deaths worldwide (source: WHO)
- The disease category with the greatest health expenditure:
  - \$107 bn in the United States, in 2010
  - \$110 bn in Europe, in 2009

## A primary cause: atherosclerosis

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- Atherosclerosis: accumulation of cholesterol plaque in the arteries

Only 1/3 of cardiovascular patents receive benefit from the best current treatments

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**ONLY ONE REAL SOLUTION: ELIMINATE CHOLESTEROL PLAQUE WITH CERENIS**

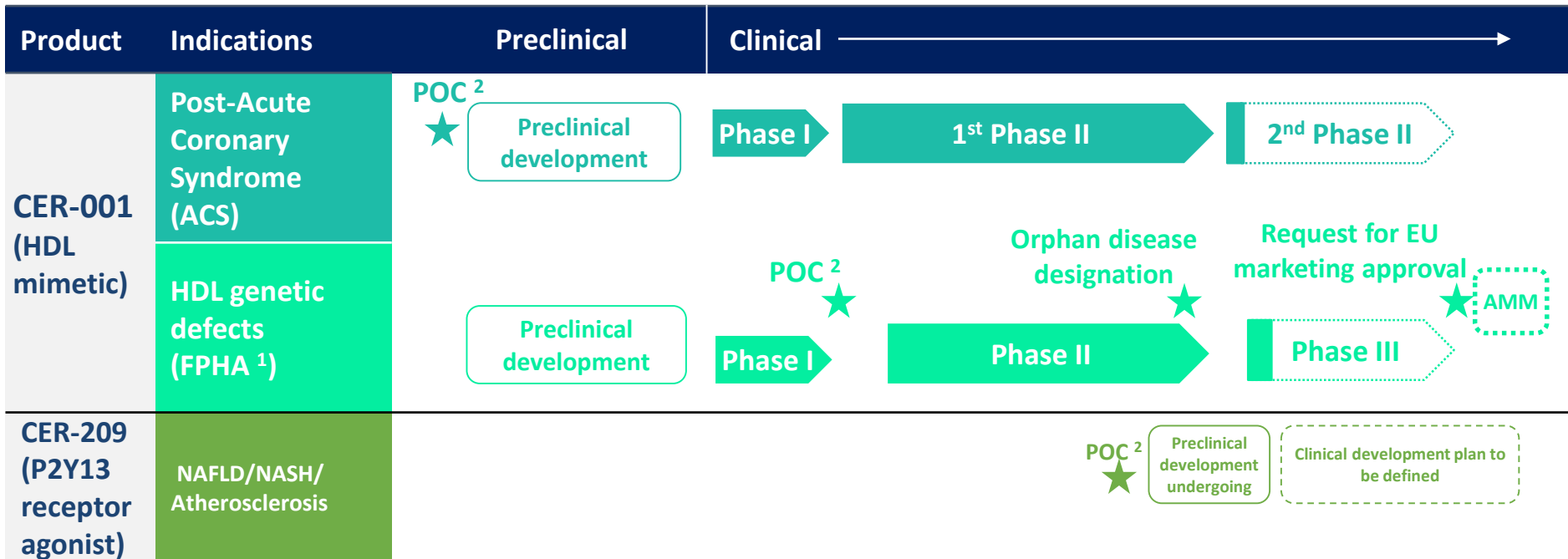
2005: creation of Cerenis

2015

2016

2017

2018



Financing to date

€25 m in 2005

€42 m in 2006

€50 m in 2010

IPO:  
€53.4 m in 2015

Investors

**SOFINNOVA**  
 PARTNERS  
 HealthCap **Daiwa** TVM|Capital

**IRDI**  
Institut Régional de Développement Industriel de Midi-Pyrénées  
**bpi france**  
**ixO** PRIVATE EQUITY  
**OrbiMed**  
 Healthcare Fund Management

**CERENIS**  
 LISTED  
 Euronext

## 3 TARGETED INDICATIONS: ACS, FPHA AND NAFLD/NASH/ATHEROSCLEROSIS

1. Familial Primary Hypoalphalipoproteinemia

2. Proof of Concept

## LDL APPROACH: reduces bad cholesterol

**No direct action on atherosclerotic plaque**



### AVAILABLE DRUGS:

**Statins:** inhibit cholesterol synthesis

**Resins and Inhibitors:** limit intestinal absorption of cholesterol

**Fibrates:** reduce the level of triglycerides containing LDL cholesterol

**Indirect long-term effect with no direct action on plaque: only 1/3 of patients get benefit**

## HDL APPROACH: reduces plaque

**Reduces atherosclerotic plaque**



### NO DRUGS YET AVAILABLE:

**CER-001:** Cerenis HDL mimetic candidate that reduces atherosclerotic plaque

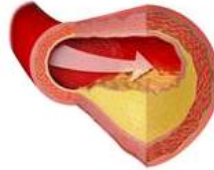
**Rapid direct effect: reduction in atherosclerotic plaque**

## LDL DRUGS HAVE A LIMITED EFFICACY ON PLAQUE REDUCTION



## Cardiovascular disease

### 2 main indications



#### Acute Coronary Syndrome

**2.8 million patients (US + EU)**

**1/3 of patients  
receive benefit**

– Stent  
– LDL therapies

**2/3 of patients do  
not receive benefit**

**No existing HDL  
treatment**

#### HDL genetic defect (FPHA)

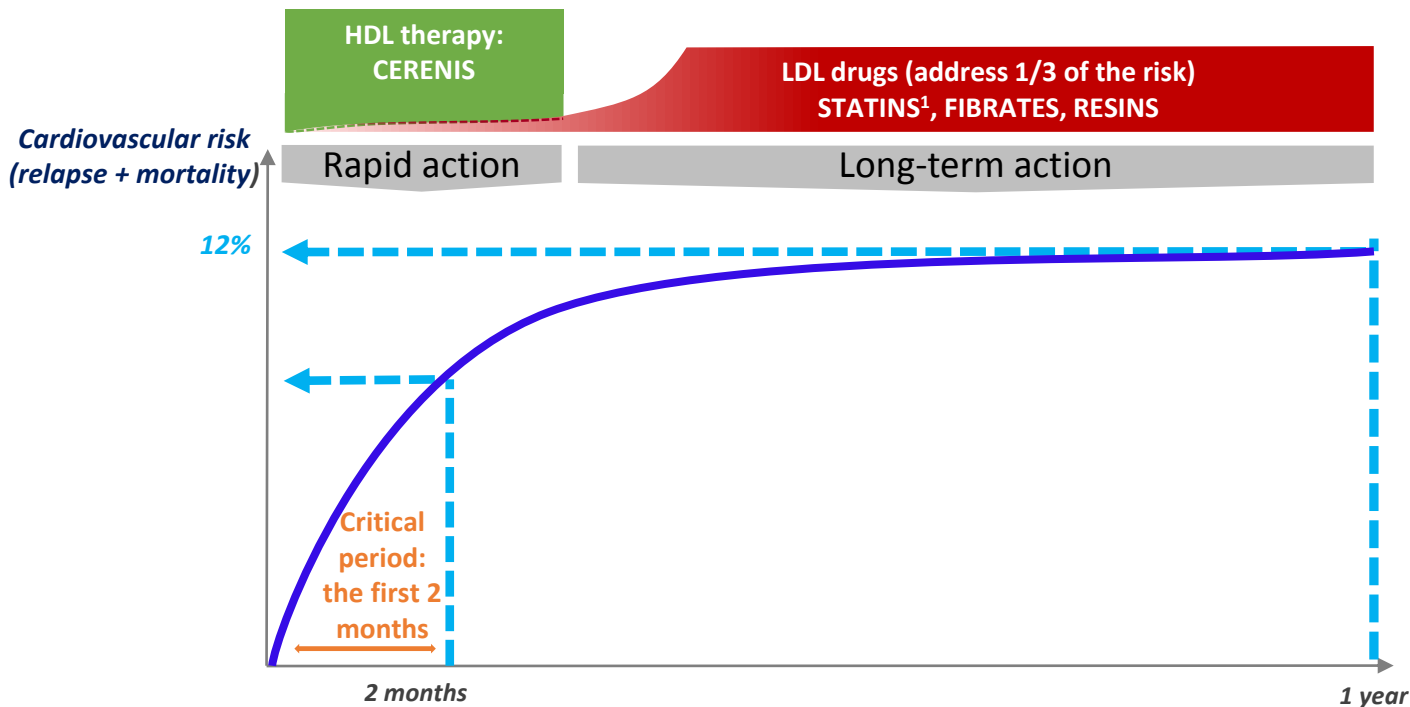
**100,000 – 150,000 patients (US + EU)**

**No existing HDL  
treatment**

**Cerenis™**  
THERAPEUTICS

**NO HDL DRUG IS CURRENTLY AVAILABLE FOR ALMOST 3 MILLION PATIENTS**

## HDL therapy is the only solution for post-ACS



- 12% <sup>2</sup> of patients relapse during the 12 months following an ACS, 2/3 of them during the first 2 months
- 19-26% <sup>3</sup> of patients over age 45 die during the 12 months that follow a cardiovascular event
- ACS hospitalization costs: \$20,000 - \$60,000 per patient per event

**HDL THERAPY IS THE ONLY SOLUTION ADDRESSING THE CRITICAL 2-MONTH POST-ACS PERIOD**

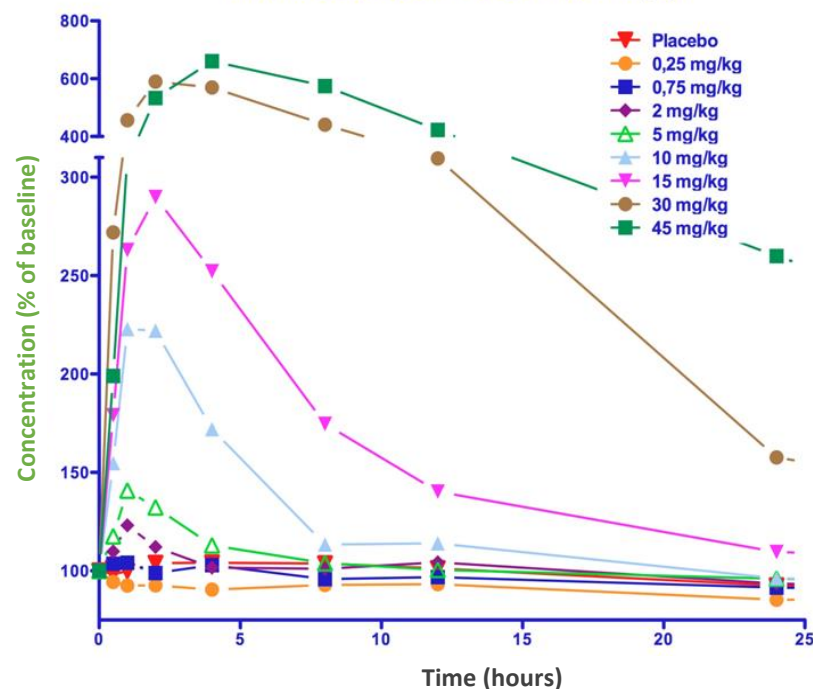
1. Vale N. et al Cochrane Database of Systematic Reviews 2014, Issue 9.  
2. PLATO clinical study, AstraZeneca  
3. Source: AHS

## Phase I showed:

### Mobilization of HDL cholesterol

- Increase in HDL cholesterol: +700% for 45 mg/kg dose
- Mobilization observed beginning with the 2 mg/kg dose
- No patient safety issues

### Concentration of HDL cholesterol following the infusion of CER-001



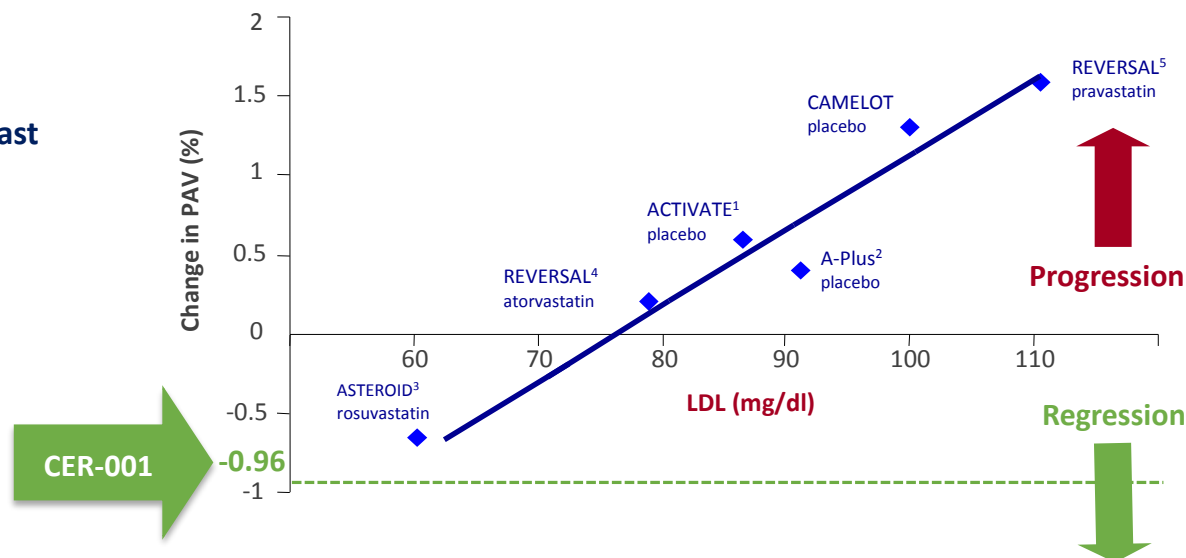
**A PROVEN SAFETY PROFILE AT ALL DOSES**

## CHI SQUARE: Phase II post-ACS study

### Effects on plaque

- Significant regression in the volume of atherosclerosis plaque, substantially better than existing treatments
- Rapid action in just 2 months vs. at least 2 years for other treatments

### Change in the percentage atherosclerosis volume (PAV)



## An independent analysis (SAHMRI) showed:

- A significant reduction in atherosclerotic plaque compared with the placebo

**CER-001 IS THE MOST EFFICIENT OF ALL TREATMENTS**

<sup>1</sup> Nissen S and al. *N Engl J Med* 2006;354:1253-1263. <sup>2</sup> Tardif J and al. *Circulation* 2004;110:3372-3377.

<sup>3</sup> Nissen S and al. *JAMA* 2006;295 (13):1556-1565 <sup>4</sup> Nissen S and al. *JAMA* 2004;292: 2217-2225.

<sup>5</sup> Nissen S and al. *JAMA* 2004; 291:1071-1080

## Conclusions of CHI-SQUARE, the 1<sup>st</sup> Phase II study:

- Cholesterol mobilization by CER-001 at every dose level
- Demonstrated patient safety profile
- Primary endpoint (reduction in plaque at 12 mg/kg dose vs. placebo) not achieved
- Reduction in the total volume of atherosclerosis vs. baseline was statistically significant at 3 mg/kg



## An independent analysis (SAHMRI) confirmed the optimal dose<sup>2</sup> :

### Change in the percentage atherosclerosis volume (PAV)

*Patients with PAV ≥30 at baseline*

Parameter	Placebo (n=69)	3 mg/kg (n=58)	6 mg/kg (n=78)	12 mg/kg (n=66)
PAV	-0.259	-0.963	-0.619	+0.177
P value		0.038 <sup>1</sup>	0.287	0.587

- Too high a concentration of HDL induces a down-regulation of ABCA1 transporter, which is necessary for cholesterol efflux. The 12 mg/kg dose caused such a down-regulation whereas 3 mg/kg did not resulting in the highest efficacy
- The optimal dose enabling a maximization of the plaque regression vs. placebo: 3 mg/kg
- Next study: number of infusions

**THE OPTIMAL DOSE HAS BEEN IDENTIFIED**  
**THE OPTIMAL NUMBER OF INFUSIONS STILL NEEDS TO BE DETERMINED**

1. Statistically significant result  
2. Greater regression of coronary atherosclerosis with the pre-beta high-density lipoprotein mimetic CER-001 in patients with more extensive plaque burden American Heart Association sessions 2015, S. Nicholls et al.

## The publication highlights CER-001 preclinical positive results:

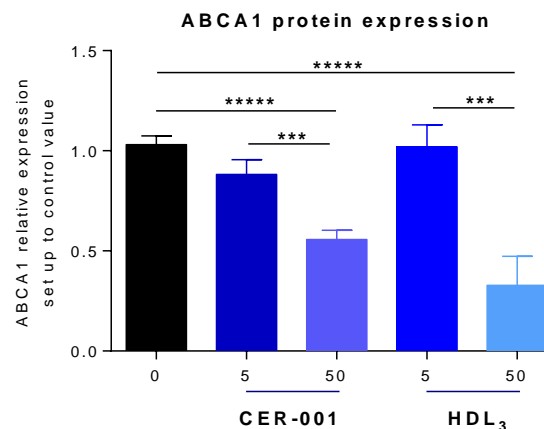
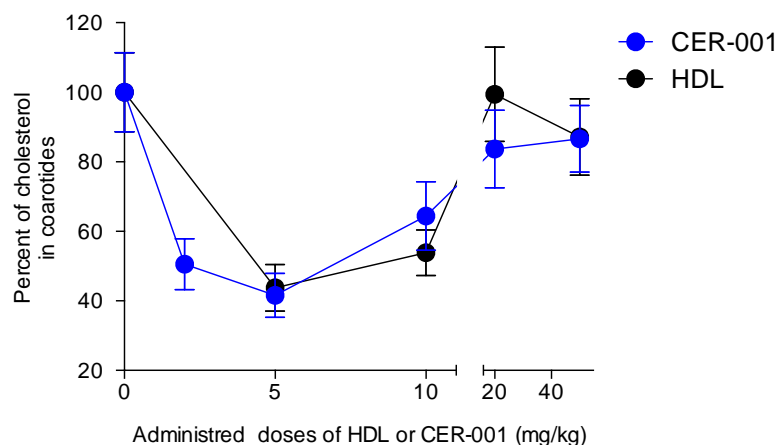
- CER-001 mimics native HDL
- Ability of CER-001 to inhibit the formation of atherosclerotic plaque with better efficacy at lower doses



## Dose-response mechanism follows a U-shaped curve

- At high dose see strong down-regulation of the ABCA1 transporter, the cellular gatekeeper for eliminating excess tissue cholesterol
- Confirmation of the optimal 3mg/kg dose of the Phase II CARAT clinical trial in the post-ACS indication

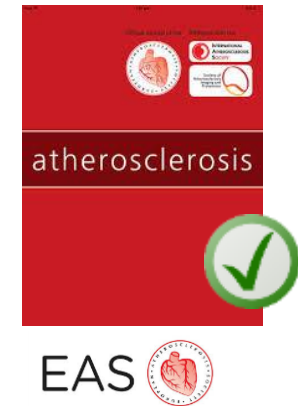
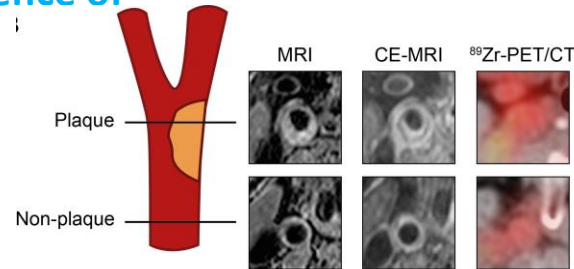
### Decrease percentage of an atherosclerotic plaque within carotids <sup>1</sup>



## CONFIRMATION OF OPTIMAL DESIGN FOR CARAT AND TANGO STUDIES

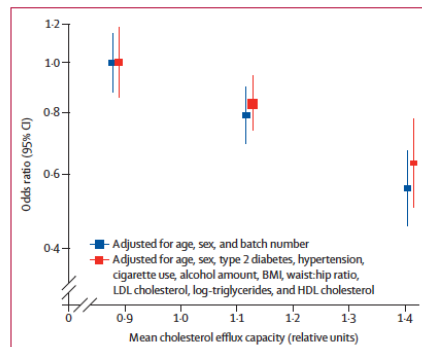
## The LOCATION study provides the first evidence of

- CER-001's ability to:
  - Penetrate atherosclerotic plaques
  - Preferentially target atherosclerotic plaques
- CER-001's capacity to increase cholesterol efflux

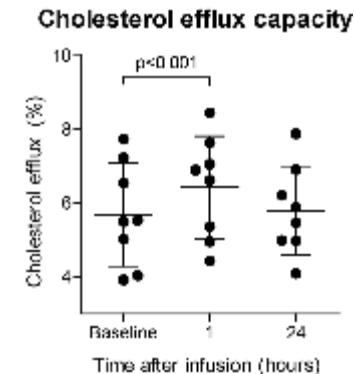


## Increased cholesterol efflux capacity is a predictive marker of a reduction in cardiovascular-related morbidity and mortality :

### Association between cardiovascular risk and cholesterol efflux capacity\*



\* Source : Lancet Diabetes Endocrinol 2015, Danish Saleheen, Robert Scott, Sundas Javad, Wei Zhao, Amrith Rodrigues, Antonino Picataggi, Daniya Lukmanova, Megan L Mucksavage, Robert Luben, Jeffery Billheimer, John J P Kastelein, S Matthijs Boekholdt, Kay-Tee Khaw, Nick Wareham, Daniel J Rader



\* Source: 17th SYMPOSIUM INTERNATIONAL DE L'ATHEROSCLEROSE (IAS), 23 au 26 mai 2015 à Amsterdam, Erik Stroes et al., Academic Medical Center of Amsterdam, The Netherlands

## THE LOCATION CLINICAL STUDY SUPPORTS CER-001'S PROOF OF CONCEPT

## A prestigious steering committee for the CARAT trial

- Dr. John Kastelein
- Dr. Béla Merkely
- Dr. Stephen Nicholls, **Principal Investigator**
- Dr. Steven Nissen
- Dr. Kausik Ray
- Dr. Gregory Schwartz
- Dr. Stephen Worthley

“

*I'm particularly enthusiastic about collaborating with Cerenis Therapeutics for the future Phase II CARAT clinical study of CER-001. On the basis of our convincing analyses of the Phase II CHI-SQUARE study highlighting the efficacy of the optimal 3mg/kg dose, I'm highly confident regarding the potential success of this important clinical step to establish CER-001 as the market benchmark in HDL mimetic.”*

**Professor Stephen Nicholls**

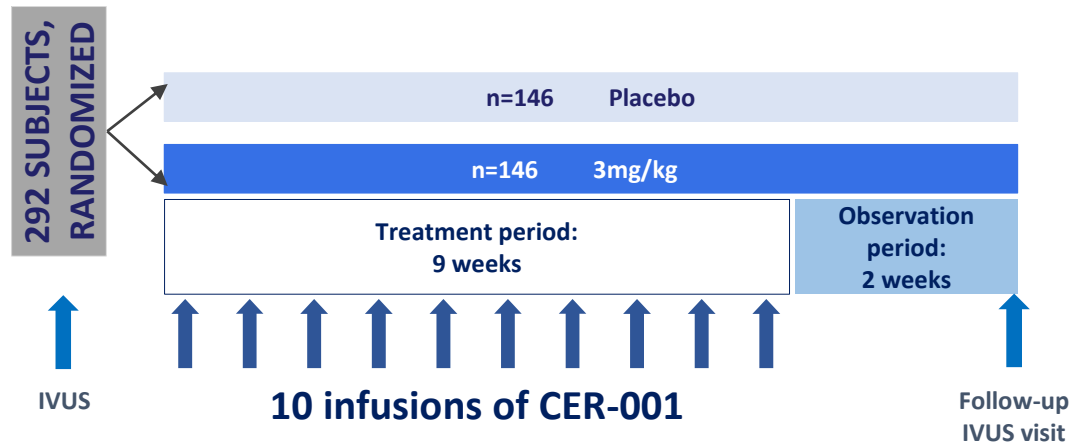




## The CARAT study should show:

- A significant reduction in the percentage atherosclerosis volume vs. placebo
- The superior efficacy of an increase in the number of doses
- Enrollment completed in August 2016

Study led by the South Australian Health and Medical Research Institute Limited (SAHMRI)



**IDENTIFICATION OF THE OPTIMAL TREATMENT AND  
ENROLLMENT OF PATIENTS WITH SUBSTANTIAL ATHEROSCLEROSIS PLAQUE**

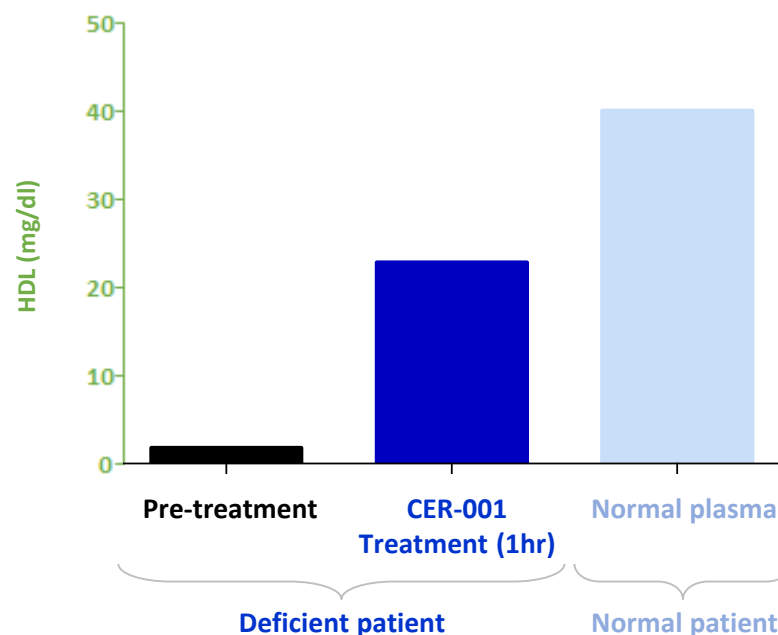
## FPHA: a rare syndrome of severe HDL deficiency

- Caused by mutations in the genes responsible for HDL synthesis/maturation
- Characterized by accelerated atherosclerosis

## CER-001 treatment

- CERENIS' solution restores the blood's ability to mobilize cholesterol into HDL to facilitate its elimination
- Two Orphan Drug designations obtained
  - HDL deficiency (no apoA-I synthesis)
  - Tangier disease (absence of ABCA1 )

## Mobilization of HDL cholesterol in the blood<sup>1</sup>



**CERENIS: A THERAPEUTIC SOLUTION TO MEET THE UNMET FPHA MEDICAL NEED**

1. Company: SAMBA study

## The Phase II SAMBA study:

### Evaluated the efficacy of CER-001

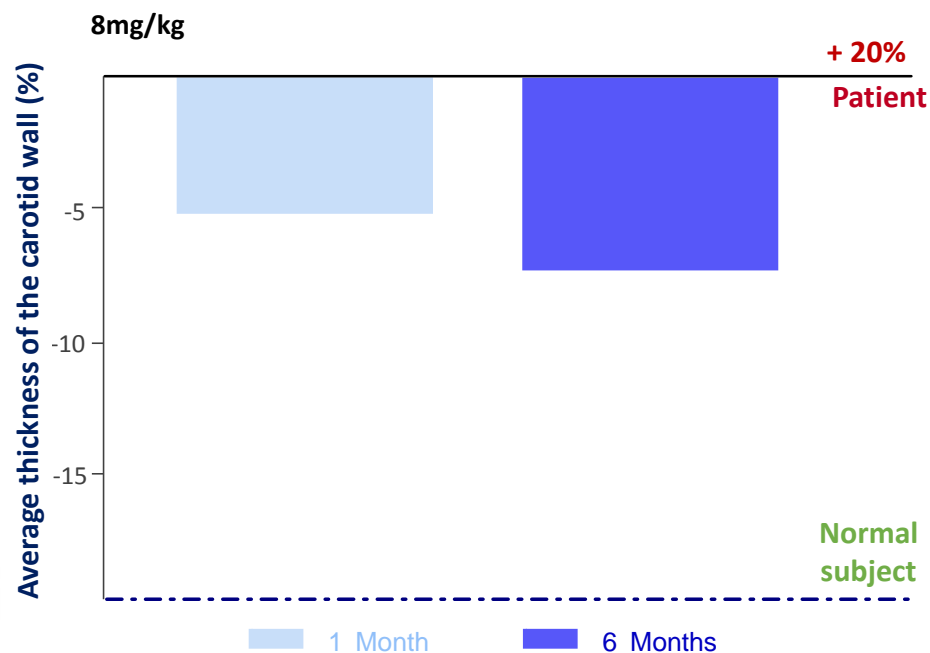
- 7 FPHA patients in an open-label, single-arm, active-treatment study for a one-month treatment of 9 doses
- Assessed the reconstitution of the endogenous reverse lipid transport pathway

Showed reduction  
of the vascular wall thickness

- Behaves like a natural HDL
- Eliminates cholesterol
- Reduces plaque



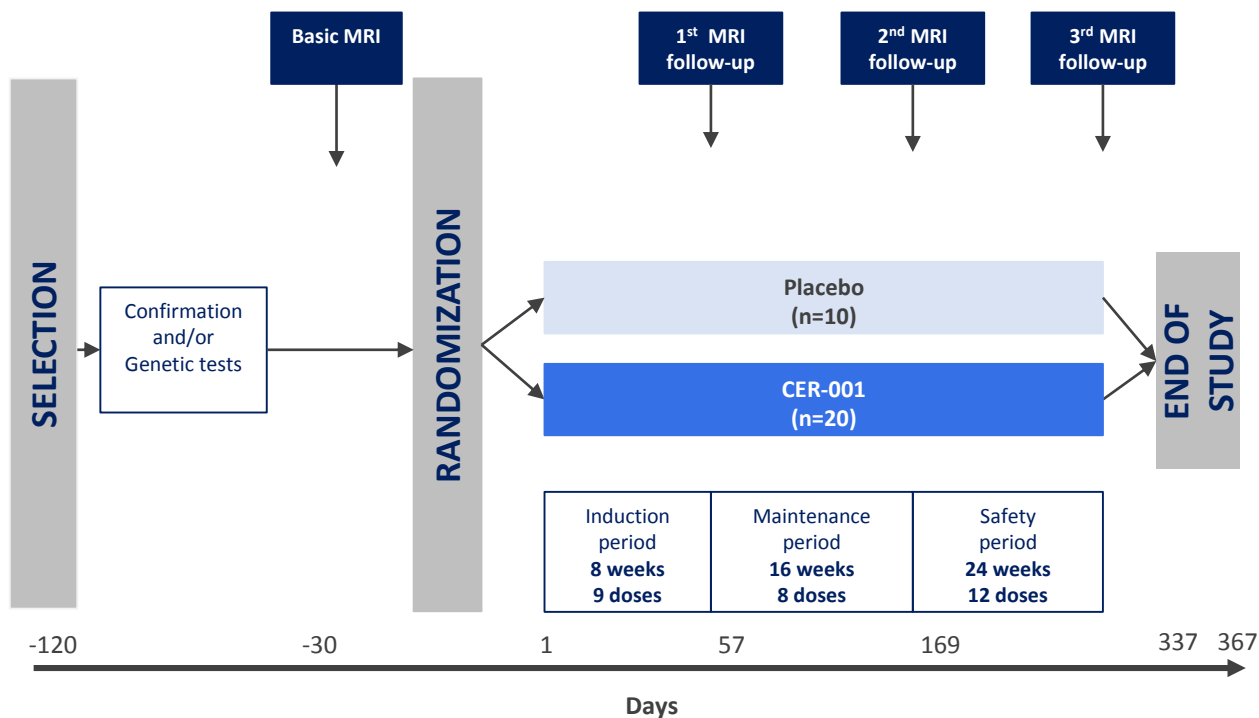
### Efficacy on carotid atherosclerosis<sup>1</sup>



**IN THE BODY, CER-001 RESULTED IN A STATISTICALLY SIGNIFICANT REDUCTION OF PLAQUE IN THE CAROTID ARTERY VESSEL WALL**

## The TANGO study should show:

- A reduction in coronary plaque in the carotid and aorta
- Enrollment began in December 2015



**THE TARGET OBJECTIVE IS TO OBTAIN MARKETING APPROVAL IN THE TWO IDENTIFIED GENETIC DEFECTS (APOA-I DEFICIENCY / TANGIER DISEASE)**

	<u>CERENIS</u>	<u>The Medicines Company</u>	<u>CSL</u>	
<b>Product specificity</b>	Only mimetic with the biological properties of natural HDL	Mutant protein produced in an <i>E. coli</i> bacteria	Protein extracted from plasma	
<b>Composition of the nanoparticle</b>	Natural HDL mimetic	Mutant form	Multiple forms of A-I apolipoprotein	
				<i>Competitive advantage of CER-001</i>
<b>Purity</b>	✓✓✓	✓	✗	Homogenous particle population
<b>Mobilization of cholesterol / Efficacy</b>	✓✓✓	✓	✓	Lower required dosage
<b>Side effects/Toxicity</b>	✓✓✓	✗	✗	No identified toxicity
<b>Intellectual property</b>	✓✓✓	✗	✗	Protection of the active principle blocking any reproduction of the nanoparticle
<b>Composition</b>	✓✓✓	✓	✓	Only charged-complex natural HDL mimetic
<b>Manufacturing process</b>	✓✓✓	✓	✓	Only 3 purification steps

# CER-209, a potential breakthrough treatment for atherosclerosis and nonalcoholic steatohepatitis (NASH)

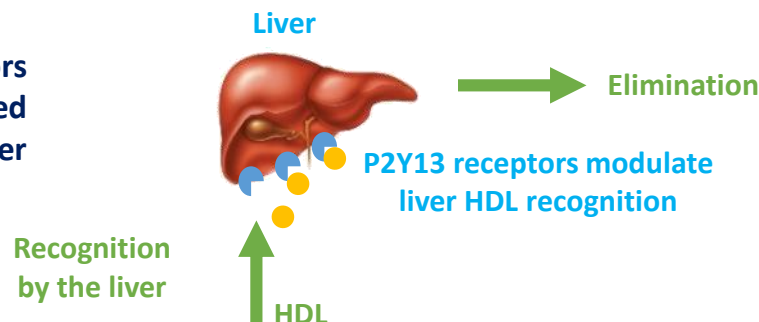
## HDL therapy enables to address atherosclerosis and NAFLD/NASH

- Atherosclerosis is frequently observed in patients with NASH, thus presenting high cardiovascular risk, in addition to steatohepatitis and liver inflammation
- Current treatments based on lipid-lowering drugs attempt to reduce LDL cholesterol but they often increase liver enzymes, thereby limiting the benefits for treating NASH patients
- Other treatments currently under development for NASH, such as targeting the nuclear receptor PPAR as well as FXR agents, may face problems associated with their multiple effects

### CER-209 increases HDL elimination by the liver...

- A new mechanism of action that involves the last steps of the RLT pathway
- Agonist activity of CER-209 on the liver P2Y13 receptors facilitates elimination of mature HDL particles loaded with lipids such as cholesterol, through better HDL liver recognition and increased bile secretion

### ...by stimulating the activity of HDL receptors

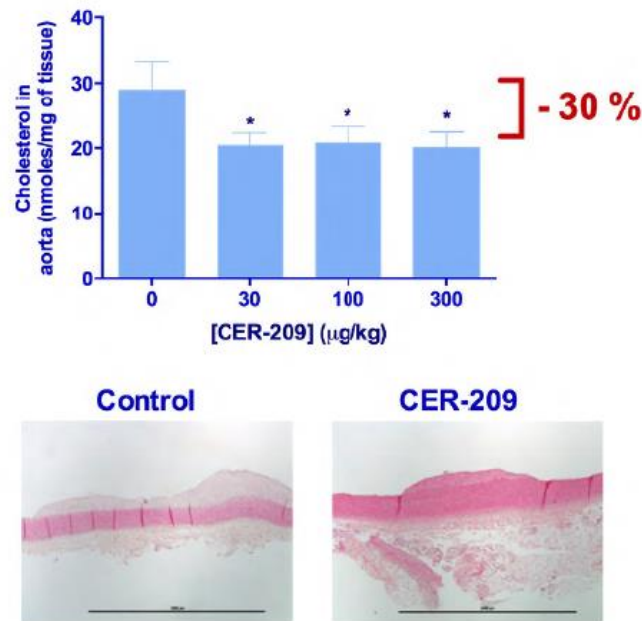


**CER-209, THE UNIQUE FIRST-IN-CLASS THERAPEUTIC SOLUTION TO ADDRESS BOTH NASH AND ATHEROSCLEROSIS**

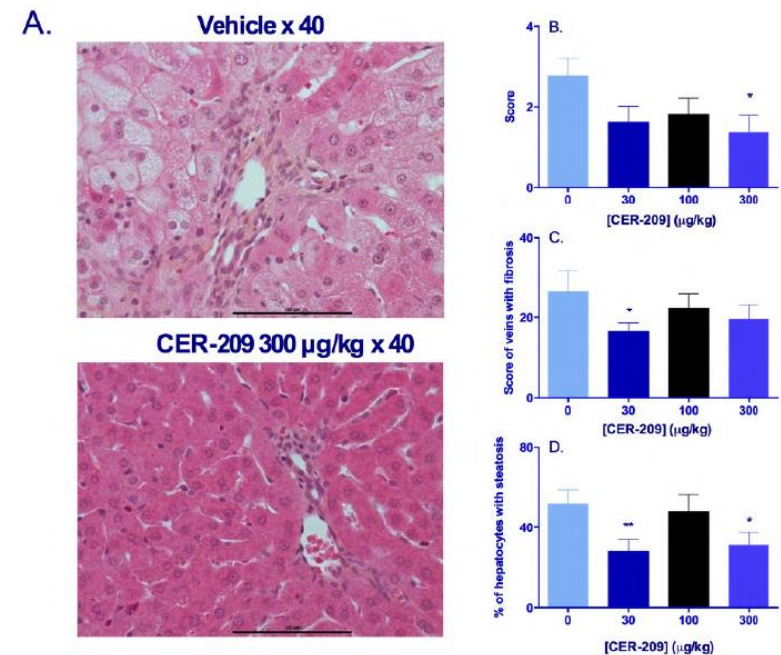


## CER-209, an agonist of the P2Y13, decreases both atherosclerosis and liver steatosis

### Plaque regression after treatment with CER-209\*



### Regression of liver steatosis after high-cholesterol diet and treatment with CER-209\*



**CER-209 HAS A STRONG POTENTIAL FOR THE TREATMENT OF NASH AND NAFLD**  
**CLINICAL DEVELOPMENT STRATEGY SHOULD BE FINALIZED IN 2016**

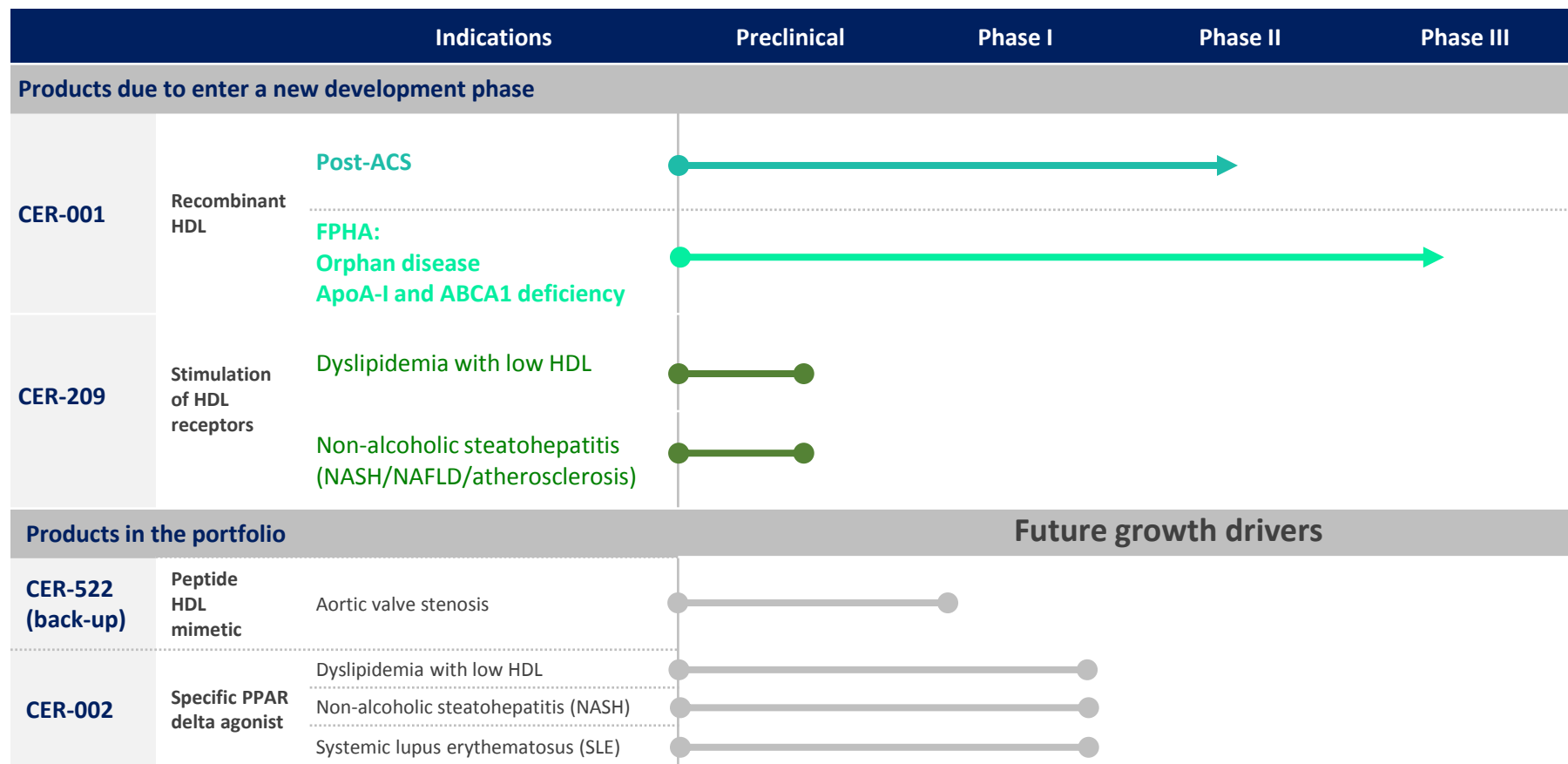
*\* P2Y13 receptor agonist CER-209 decreases both atherosclerosis and liver steatosis in vivo: Rudi Baron, Marine Goffinet, Nadia Boubekeur, Claudine Tardy, Guy Cholez, Daniela C. Oniciu, Narendra D. Lalwani, Jean-Louis H. Dasseux and Ronald Barbaras*

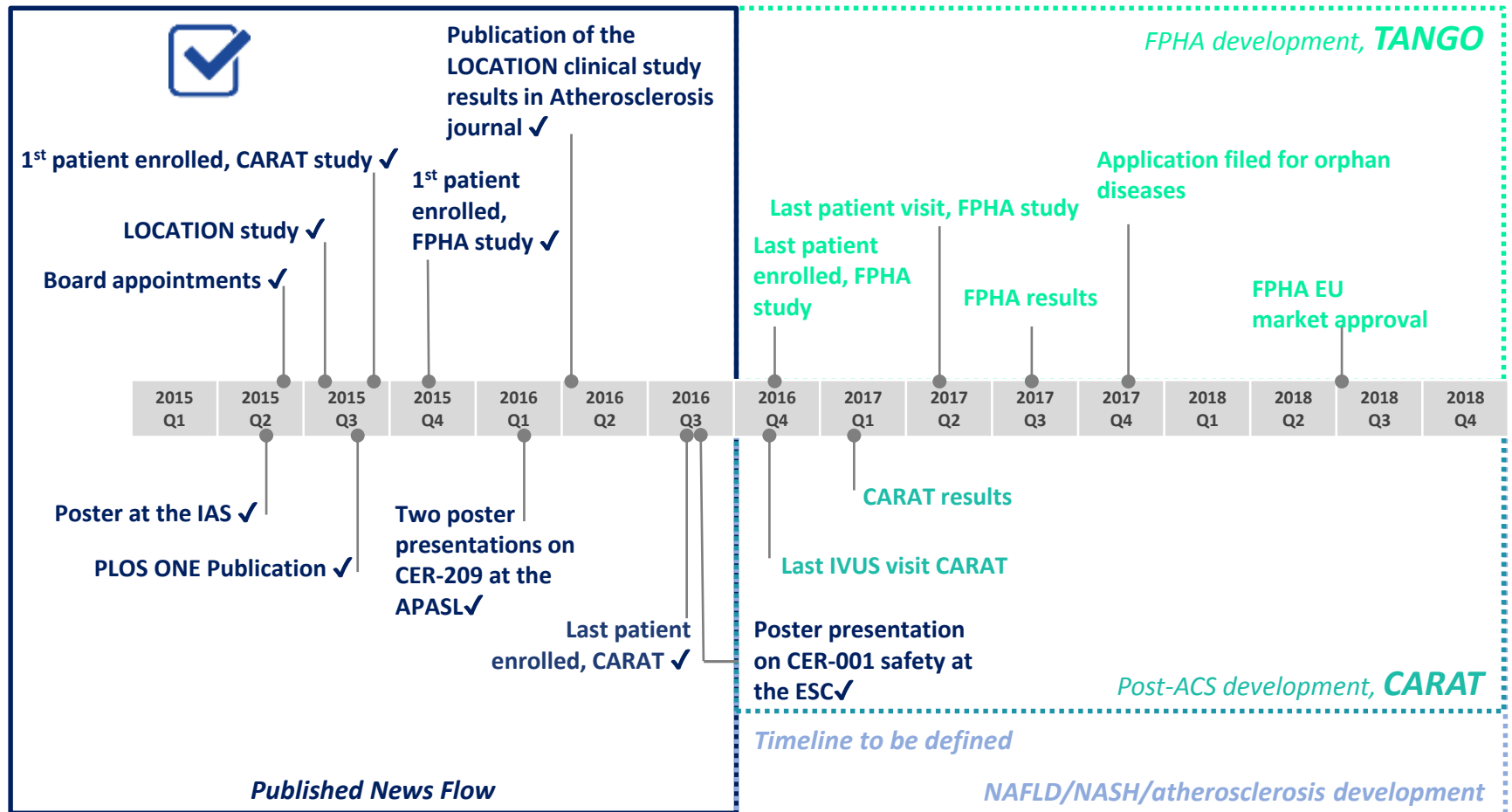
- 9 patent families protecting the products, indications and manufacturing / diagnostic methods

PRODUCT	INDICATION	MANUFACTURING/DIAGNOSTIC
<b>Family 1:</b> Formulation of CER-001 and its use		<b>Family 2:</b> Manufacturing methods for reconstituted HDL particles and highly-homogenous resulting populations of HDL particles
<b>Family 6:</b> HDL mimetic peptide including CER-522	<b>Family 4:</b> Treatment of dyslipidemias	<b>Family 3:</b> Companion diagnostics and dosage of CER-001
<b>Family 7:</b> P2Y13 receptor agonists (CER-209)		<b>Family 5:</b> Synthetic sphingomyelin synthesis / production methods
<b>Family 8:</b> PPAR agonists (CER-002)		<b>Family 9:</b> Carrier particles for administering drugs

**NO COMPETITOR CAN REPRODUCE THE CHARGED NANOPARTICLE, EVEN PARTIALLY**







**WEALTH CREATION PERSPECTIVE IN BOTH THE NEAR AND MEDIUM TERM**

## Consolidated accounts (IFRS)

BALANCE SHEET	31/12/2015	30/06/2016
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€ thousands

### ASSETS

Total non-current assets	446	340
Total current assets	45,661	37,152
<b>Total assets</b>	<b>46,107</b>	<b>37,492</b>

### LIABILITIES

Total shareholders' equity	33,198	22,359
Total non-current liabilities	7,120	7,082
Total current liabilities	5,790	8,051
<b>Total liabilities</b>	<b>46,107</b>	<b>37,492</b>

• Gross cash position of:

- €7.8 m on December 31, 2014
- €43.0 m on December 31, 2015
- €37.2 m on June 30, 2016

• Of which €6.6 m is linked to Bpifrance (OSEO) advance payment

• Of which €6.8 m is trade payables

INCOME STATEMENT	31/06/2015	30/06/2016
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€ thousands

Operational income	0	0
Marketing and Admin. costs	(1,064)	(3,828)
R&D costs	(5,239)	(10,213)
<b>Operating profit / loss</b>	<b>(6,303)</b>	<b>(14,041)</b>
<b>Financial profit / loss</b>	<b>(760)</b>	<b>(626)</b>
<b>Net profit / loss</b>	<b>(7,062)</b>	<b>(14,662)</b>

• Enrollment of clinical studies: CARAT, TANGO and LOCATION

• Affected by non-cash elements:  
-IFRS treatment of the BPI repayable advances

\* Unaudited

# Simplified cash flow table

CASH FLOW TABLE	30/06/2015	30/06/2016
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€ thousands

Cash flow from operations	(6,079)	(11,018)
Cash flow from investments	(25)	(2)
Cash flow from financing	48,924	940
<b>Change in cash position</b>	<b>42,820</b>	<b>10,079</b>
Cash position at start of period	7,843	42,951
Currency effect	(3)	0
<b>Cash position at end of period</b>	<b>50,660</b>	<b>32,872</b>

• March 2015 IPO

• Cash position as of June 30, 2016

## **CER-001: major potential in the treatment of patients post-ACS**

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2. Advanced and promising clinical developments currently in Phase II (CARAT)
3. Compelling to big pharma (e.g., OMThera \$443 m; Esperion \$1.3 bn; KOS \$3.7 bn)<sup>1</sup>
4. A manufacturing process validated on an industrial level with proven clinical safety and tolerability

## **In the short term: CER-001, a drug for treating orphan diseases**

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2. A major unmet medical need
3. Application for marketing approval before 2018

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**A WELL-CAPITALIZED (€33 MILLION), LISTED COMPANY WITH SUBSTANTIAL POTENTIAL IN HDL THERAPY**

<sup>1</sup> Press releases,  
OMThera: <http://www.astrazeneca.com/Media/Press-releases/Article/20130528-omthera>  
Esperion: <http://www.bloomberg.com/apps/news?pid=newsarchive&sid=apU2qcYcmkO4&refer=us>  
KOS: [http://www.bloomberg.com/apps/news?pid=newsarchive&sid=af\\_8tgk4fHE](http://www.bloomberg.com/apps/news?pid=newsarchive&sid=af_8tgk4fHE)