

**Next generation
LDL-C management
with ALN-PCSsc, an
investigational PCSK9
synthesis inhibitor**

11th November 2015

Next generation LDL-C management with ALN-PCSsc, an investigational PCSK9 synthesis inhibitor

Agenda

Topic

Speaker(s)

Introduction

John Maraganore PhD
Clive Meanwell MD PhD

New Phase 1 data with ALN-PCSsc

Akshay Vaishnaw MD PhD

Comments

David Kallend MBBS

The Orion Development Program

Peter Wijngaard PhD

Q&A

All

Legal notices

Forward-looking statements

Statements contained in these slides about The Medicines Company and Alnylam Pharmaceuticals, Inc., each Company's products and product candidates, clinical trial results, regulatory submissions, product or indication launches, each Company's future financial and operating results, and future opportunities for each Company, that are not purely historical, and all other statements that are not purely historical, may be deemed to be forward-looking statements for purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. Without limiting the foregoing, the words "believes," "anticipates," "plans," "expects," "intends," "potential," "estimates," "outlook" and similar expressions are intended to identify forward-looking statements. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include each Company's ability to discover and develop novel drug candidates and delivery approaches, successfully demonstrate the efficacy and safety of its drug candidates, obtain, maintain and protect intellectual property, enforce patents and defend its patent portfolio, obtain regulatory approval for products, establish and maintain business alliances; dependence on third parties for access to intellectual property; and the outcome of litigation, as well as those risks detailed from time to time in each Company's periodic reports filed with the Securities and Exchange Commission ("SEC") including, without limitation, the risk factors detailed in each Company's most recent quarterly report on Form 10-Q under the caption "Risk Factors." If one or more of these factors materialize, or if any underlying assumptions prove incorrect, actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. Each Company specifically disclaims any obligation to update these forward-looking statements. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this presentation. All forward-looking statements are qualified in their entirety by this cautionary statement.

Introduction

John Maraganore PhD
Chief Executive Officer
Anylam Pharmaceuticals, Inc.

Clive Meanwell MD PhD
Chief Executive Officer
The Medicines Company

Introduction

Next generation LDL-C management with ALN-PCSsc, an investigational PCSK9 synthesis inhibitor

ALN-PCSsc achieved sustained duration of effect supporting bi-annual sc dosing

Up to 83% maximal and 64% mean maximum LDL-C lowering

LDL-C reduction clamped at 180 days after single dose, with up to 53% and 47% least squares mean LDL-C lowering

Robust reductions in total cholesterol and other atherogenic lipoproteins such as Lp(a) and Apo B

Generally well tolerated with no clinically significant AEs to date

The ORION Development Program moving forward quickly

- Phase 2 study initiating with CTA approvals and FPI anticipated in Dec 2015
- Study completion anticipated in Q4/16 with full data presentation at ACC 2017
- Start of comparative HoFH study anticipated in H1/2016

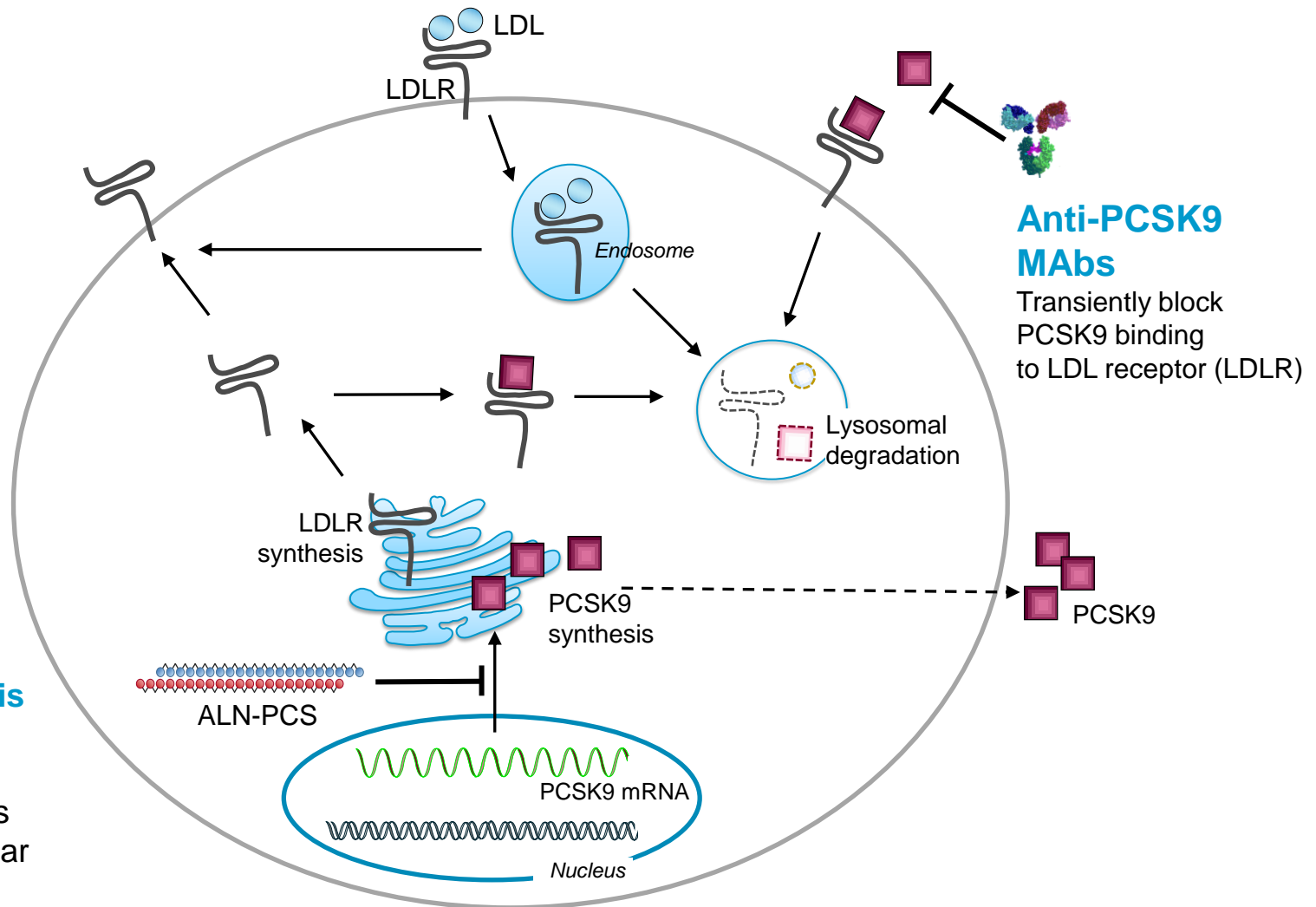
New data on ALN-PCSsc presented at AHA

Akshay Vaishnaw MD PhD
Executive VP of R&D,
Chief Medical Officer
Alnylam Pharmaceuticals, Inc.

RNAi therapeutics:
Ground-breaking biotechnology
with extensive clinical proof-of-
concept for the platform and for
the therapeutic concept

New data on ALN-PCSsc presented at AHA

PCSK9 synthesis inhibition through RNAi



PCSK9 synthesis inhibitors

Durably block PCSK9 synthesis and all intracellular and extracellular PCSK9 functions

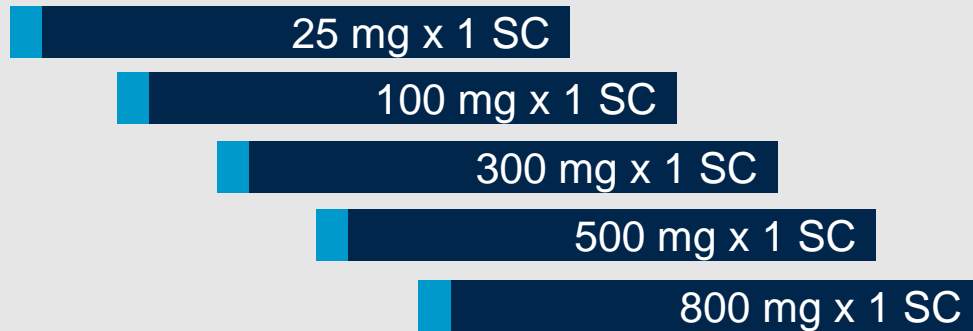
Anti-PCSK9 MAbs

Transiently block PCSK9 binding to LDL receptor (LDLR)

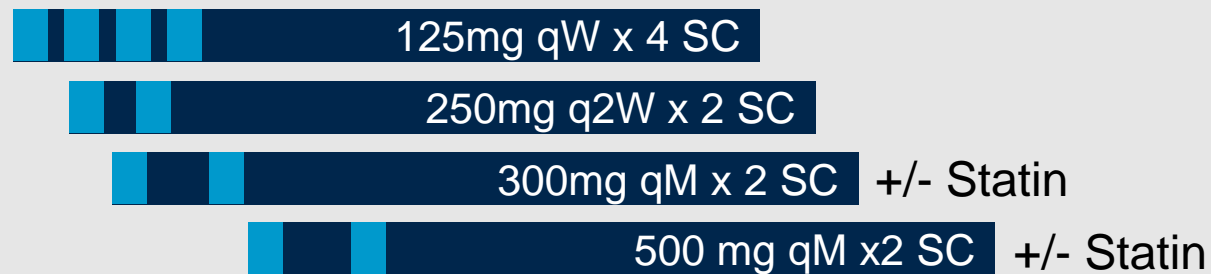
New data on ALN-PCSsc presented at AHA

Study design

Part A: Single Dose (SAD) | Randomized 3:1, Single blind, Placebo controlled



Part B: Multi-Dose (MD) | Randomized 6:2, Single blind, Placebo controlled, On or off statins



■ Subcutaneous injection of ALN-PCSsc

New data on ALN-PCSsc presented at AHA

Safety and tolerability

Generally well tolerated; no SAEs, no drug-related discontinuations to date

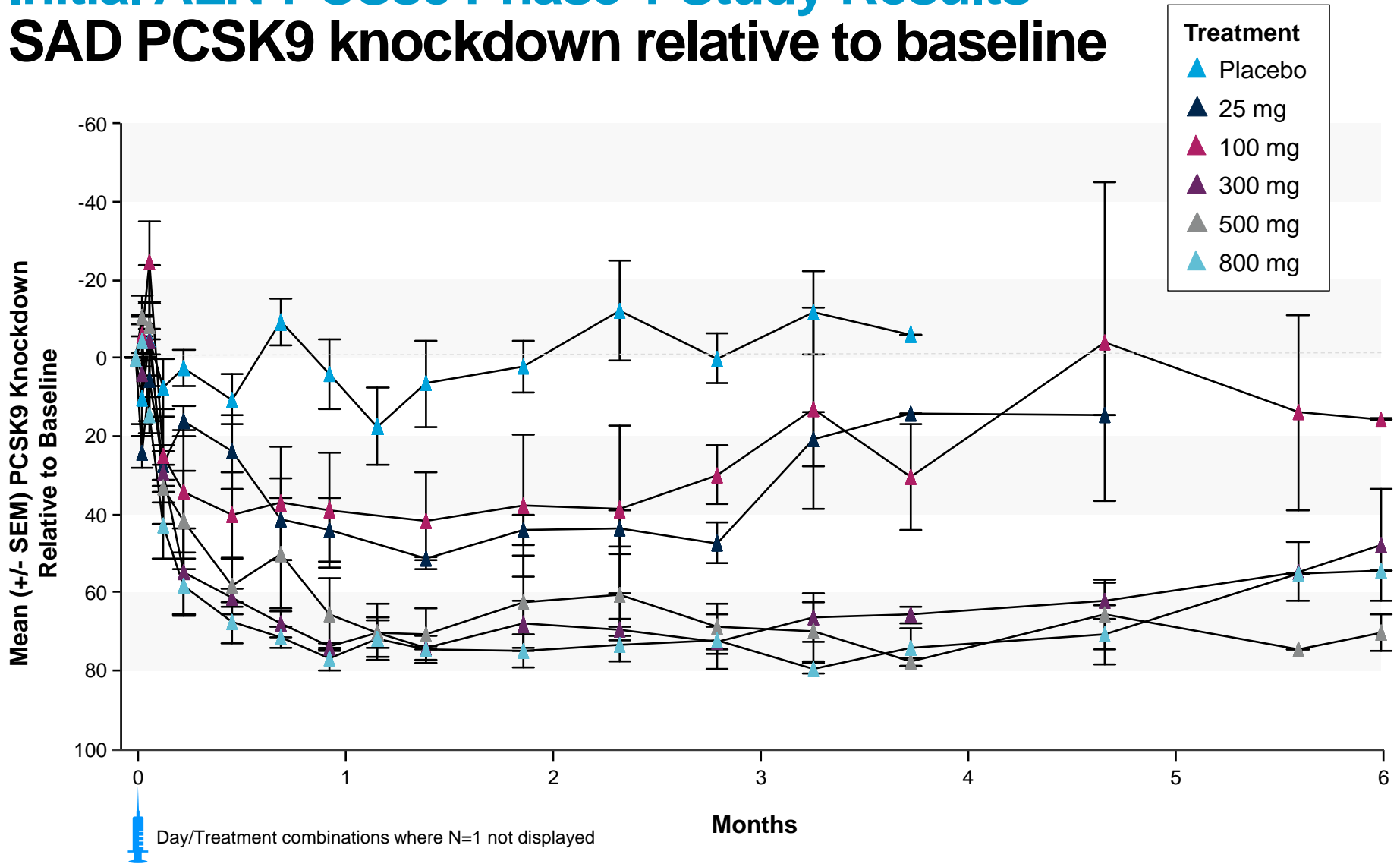
All AEs mild or moderate

- Part A single dose
 - 1 subject (800mg) with mild, localized injection site reaction (ISR)
- Part B multiple dose
 - AE profile similar with or without statins
 - 3 subjects with mild, localized ISRs at higher drug exposures
 - 1 subject at 500mg qM x2 with statin
 - 2 subjects at 250mg q2W x2

1 subject (500mg qM x2 + statin) experienced ALT elevation ~4x ULN without rise in bilirubin – related to concomitant statin therapy

Initial ALN-PCSc Phase 1 Study Results

SAD PCSK9 knockdown relative to baseline



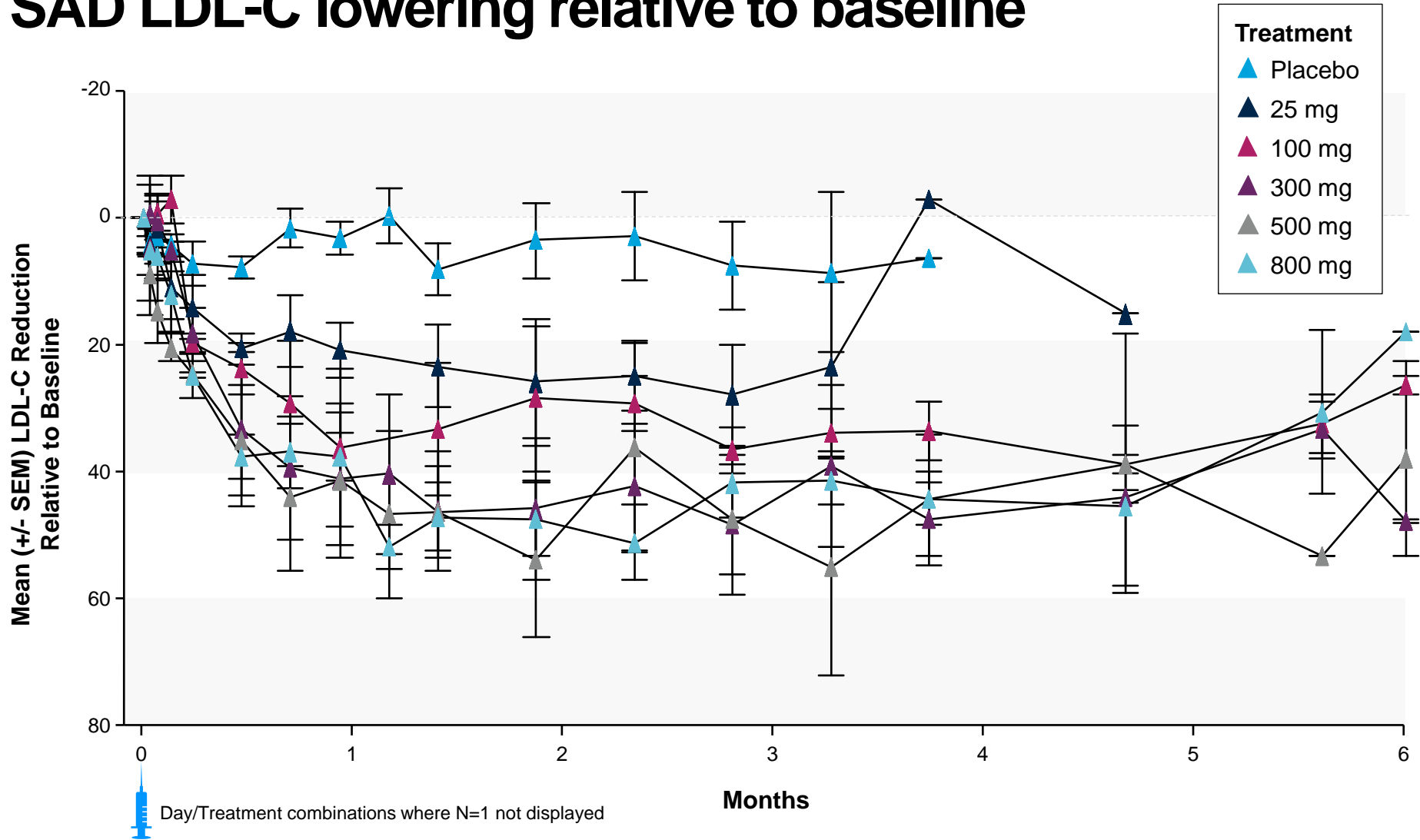
Max PCSK9 inhibition of 88.7% with mean max of 82.3% (+/- 2.0)

Data reported are from database transfer Sept. 24th 2015

Strictly Confidential

Initial ALN-PCSSc Phase 1 Study Results

SAD LDL-C lowering relative to baseline



Max LDL-C reduction of 78.1% with mean max of 59.3% (+/-5.0)

Data reported are from database transfer Sept. 24th 2015

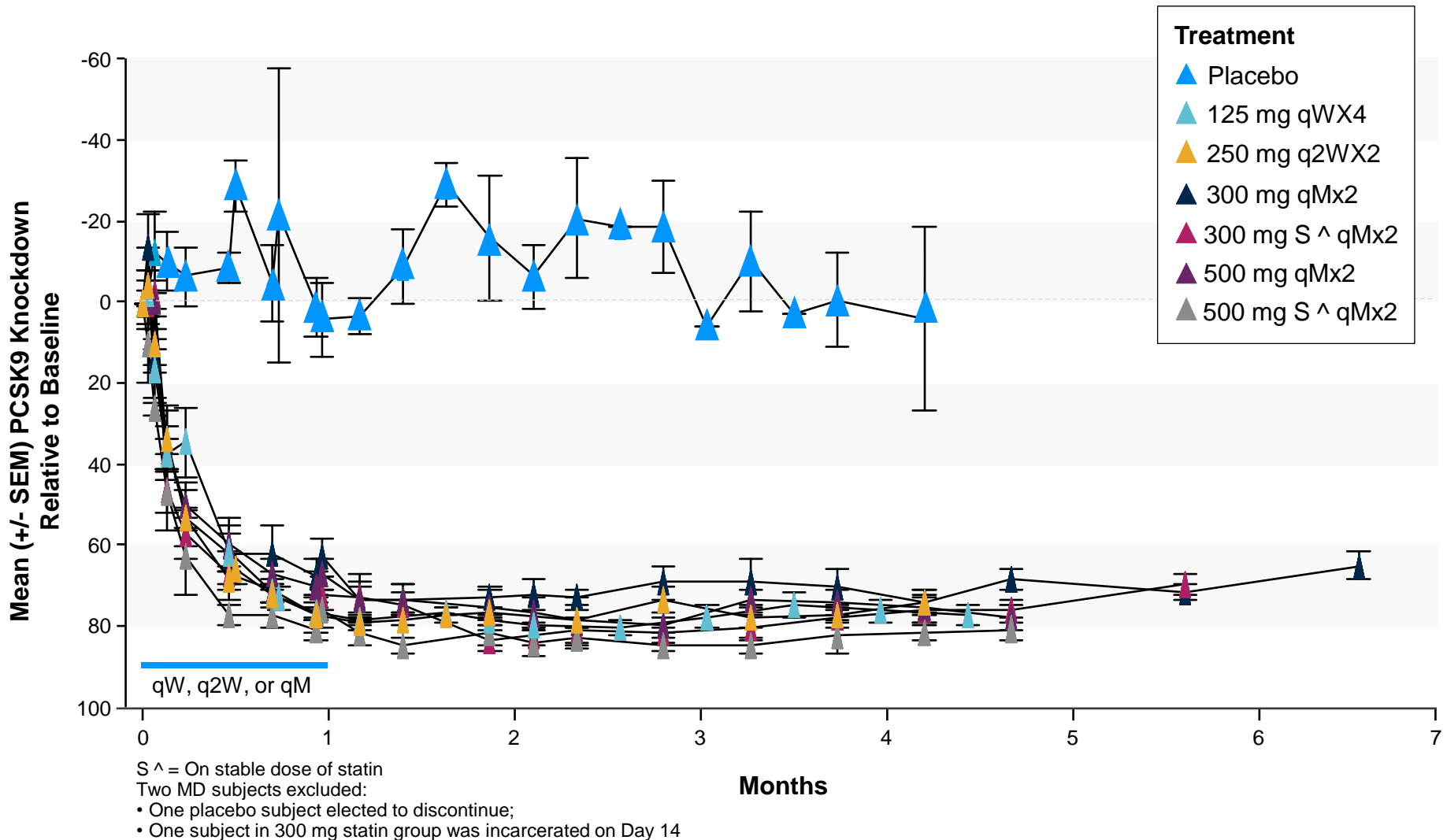
Strictly Confidential

The Medicines Company

Alnylam
PHARMACEUTICALS

Initial ALN-PCSSc Phase 1 Study Results

MD PCSK9 knockdown relative to baseline



Max PCSK9 inhibition of 94.4% with mean max of 88.5% (+/- 1.6)

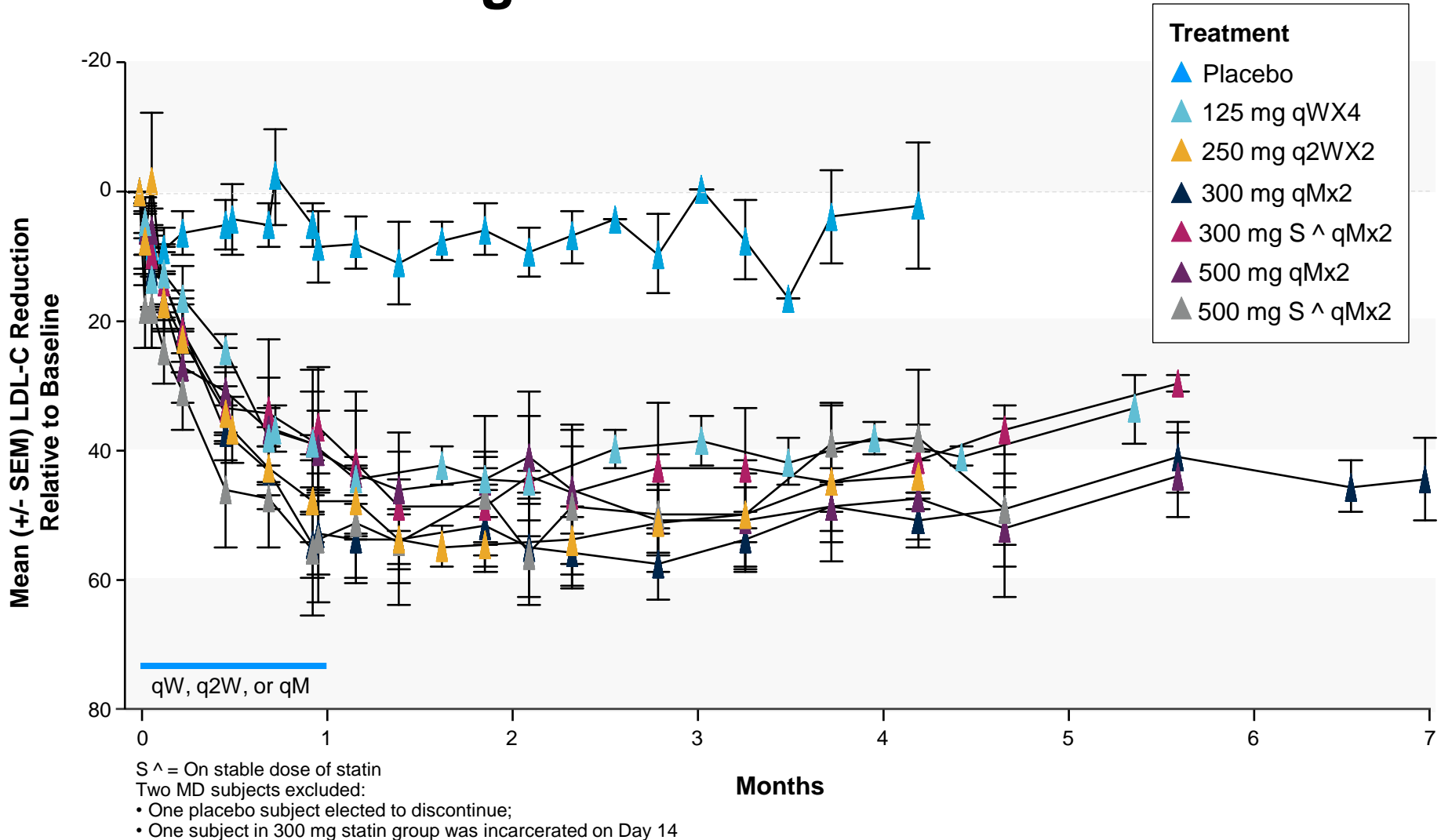
Data reported are from database transfer Sept. 24th 2015

Strictly Confidential



Initial ALN-PCSSc Phase 1 Study Results

MD LDL-C lowering relative to baseline



Max LDL-C reduction of 83.0% with mean max of 64.4% (+/- 5.4)

Data reported are from database transfer Sept. 24th 2015

Strictly Confidential

The Medicines Company

Alnylam
PHARMACEUTICALS

Initial ALN-PCSsc Phase 1 Study Results

Least square mean % change of other lipid parameters: Day 84

SAD Group (N)	LP(a)	Total Chol	ApoB	Non-HDL-C	HDL-C
Placebo (5)	+ 2.2	- 4.7	- 15.0	- 10.6	+ 12.7
25mg (2)	+ 2.2	- 16.8	- 16.5	- 23.5	+ 8.0
100mg (3)	- 20.2	- 17.8	- 26.9	- 28.3	+ 18.6
300mg (3)	- 44.7	- 30.8**	- 47.3**	- 48.9***	+ 39.5
500mg (3)	- 34.7	- 26.1	- 39.2	- 36.3	+ 6.9
800mg (6)	- 24.5	- 28.8**	- 37.5	- 37.0*	+ 0.6

*, P < 0.05; **, P < 0.01; ***, P < 0.001 (pairwise comparisons vs. Placebo)
LSMs and P values from baseline-adjusted ANCOVA model

Max. reductions: LP(a) (-77%); Total-C (-48%); ApoB (-72%); Non-HDL (-68%)

Initial ALN-PCSsc Phase 1 Study Results

Least square mean % change of other lipid parameters: Day 84

MD Group (N)	LP(a)	Total Chol	ApoB	Non-HDL-C	HDL-C
Placebo (10)	– 3.2	– 5.5	– 12.1	– 7.1	– 0.8
125mg qWx4 (6) #	– 22.7	– 23.6	– 33.3	– 36.8	+ 13.5
250mg q2Wx4 (6)	– 27.1	– 34.5***	– 46.4***	– 45.3***	+ 3.9
300mg (6)	– 21.3	– 40.4***	– 52.5***	– 56.9***	+ 11.2
300mg S (3)	– 26.6	– 25.9	– 36.8	– 36.7*	+ 9.1
500mg (6)	– 28.4	– 27.1**	– 46.4***	– 45.3***	+ 13.2
500mg S (5)	– 39.5*	– 30.5***	– 41.7**	– 46.4***	+ 5.8

S = On stable dose of statin

*, P < 0.05; **, P < 0.01; ***, P < 0.001 (pairwise comparisons vs. Placebo)

LSMs and P values from baseline-adjusted ANCOVA models

Day 91

Max. reductions: LP(a) (–76%); Total-C (–55%); ApoB (-68%); Non-HDL (–73%)

Data reported are from database transfer Sept. 24th 2015

Strictly Confidential

The
Medicines
Company

 Alnylam
PHARMACEUTICALS

New data on ALN-PCSsc presented at AHA

Summary

ALN-PCSsc is promising investigational first-in-class PCSK9 synthesis inhibitor

- Generally well tolerated to date
- Potent and dose-dependent knockdown of PCSK9 and lowering of LDL-C
- Durability sustained up to 6 months supporting bi-annual, low volume SC dose regimen
- Robust reductions in total cholesterol and other atherogenic lipoproteins such as Lp(a)
- Phase 1 results support continued development of ALN-PCSsc in ORION Development Program

Perspectives on data and opportunity

David Kallend MBBS

The ORION Development Program

Peter Wijngaard PhD
Senior Vice President,
Acute Cardiovascular Care
The Medicines Company



The ORION Development Program

Goal to make ALN-PCSsc available quickly with appropriate information for regulators and, upon approval, for prescribers, patients & payers



Objectives:

- Complete chronic toxicology studies by QX/16
- Optimize dose, formulation, administration, and device – small volume, infrequent, easy
- Transition to Phase 2 imminently
- Start of comparative HoFH study in H1/2016

ORION-1 Phase 2 Clinical Study

480 ASCVD subjects with elevated LDL-C on maximal lipid lowering therapy



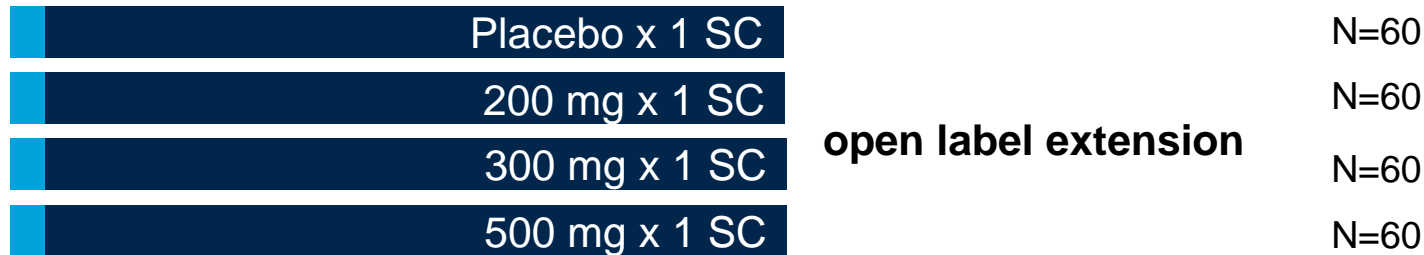
Primary objectives

- LDL-C levels at day 180


Secondary objectives

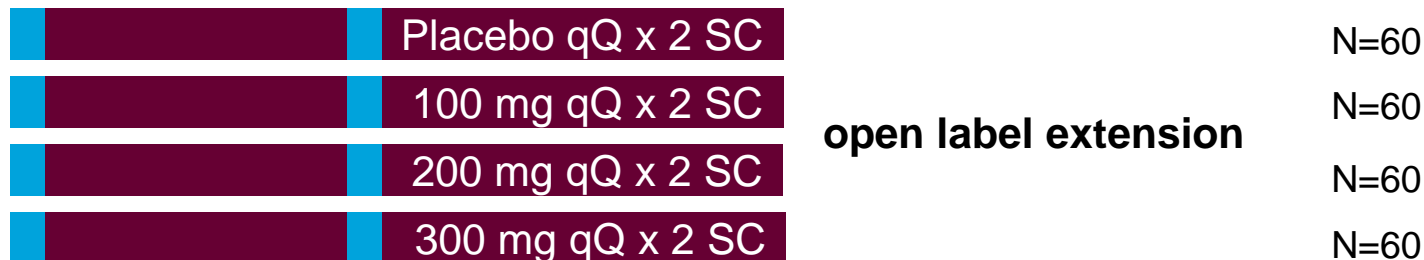
- Safety and tolerability, PCSK9 and LDL-C reduction and duration of effect qQ vs Bi-annual, proportion of patients reaching global lipid guidelines, changes in other lipoprotein levels

Randomized 1:1:1:1, Double blind, Placebo controlled



open label extension

 = dose



open label extension

The ORION Development Program

Benchmarking programs with approval on LDLc endpoints (US approval)



Parameter	Lipitor®	Crestor®	Praluent®	Repatha®
Initial US approval (YR)	1996	2003	2015	2015
Comparator in pivotal trials	Statins or Placebo	Statins or Placebo	Placebo or Ezetemibe	Placebo or Ezetimibe
Primary Endpoint	LDL-C % change	LDL-C % change	LDL-C % change	LDL-C % change
Efficacy database (N)	2502 (active) 1020 (control)	2873 (active & control)	3182 (active) 1792 (control)	2928 (active & control)
Safety database (N)	3092 (HV's & Pts)	11,210 (due to additional safety requirements)	3340 (active) 1894 (control)	4971 (active & control)
Long term treatment ≥12 months (N)	1749 (active)	2471 (active)	3627 (active & control)	1797 (active & control)
FH patients (N)	491 He 59 Ho	776 He 44 Ho	735 He	329 He 99 Ho

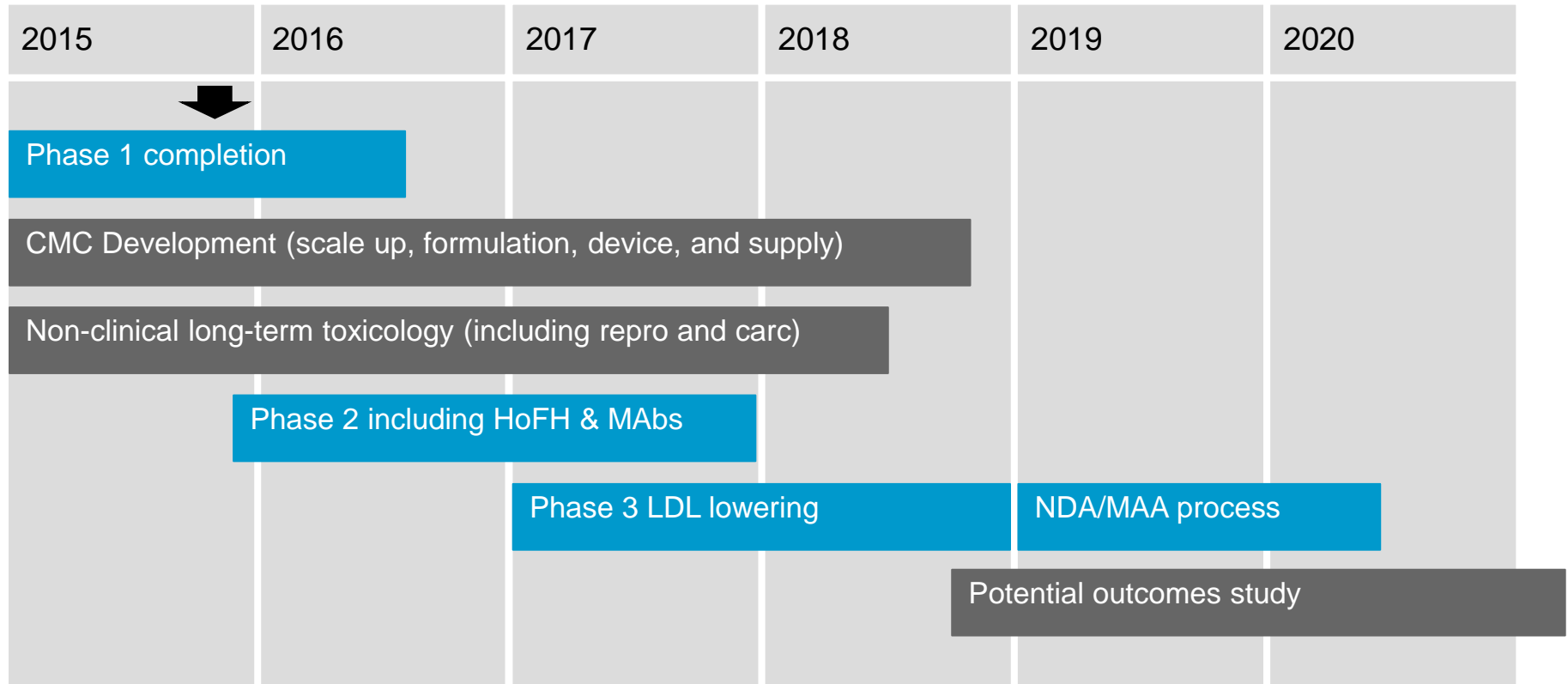
Source: FDA website

The ORION Development Program

Estimated sequence of events



■ Anticipated critical path
 ■ Anticipated non-critical path



Timelines are estimates based on current assumptions

The ORION Development Program Summary



Clear path forward leading to applications for approval for LDL-C lowering indication

Immediate next steps:

- Phase 2 starting up and FPI anticipated in Dec 2015
- Start of comparative HoFH study anticipated in H1/2016
- Scale up manufacturing and formulation development
- Complete long term toxicology program

Ensure only the clinical program remains on the critical path

Perspective

Clive Meanwell MD PhD
Chairman and Chief Executive Officer
The Medicines Company

Think what's possible if LDL-C monitoring and treatment were synchronous

A vision for innovation in ACVD

Potential to revolutionize the Dx-Rx cycle

- Quarterly or potentially bi-annual dosing of ALN-PCSSc would uniquely align monitoring and treatment cycle
- 3-6 monthly cholesterol check
- 3-6 monthly sc injection
- Oversight by physician with treatment monitored, or given by physician or retail pharmacy 24/7
- Adherence, patient satisfaction and value improvement potential



Q&A