The Medicines Company

Alnylam® PHARMACEUTICALS

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

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Introduction

John Maraganore PhD
Chief Executive Officer
Alnylam 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.

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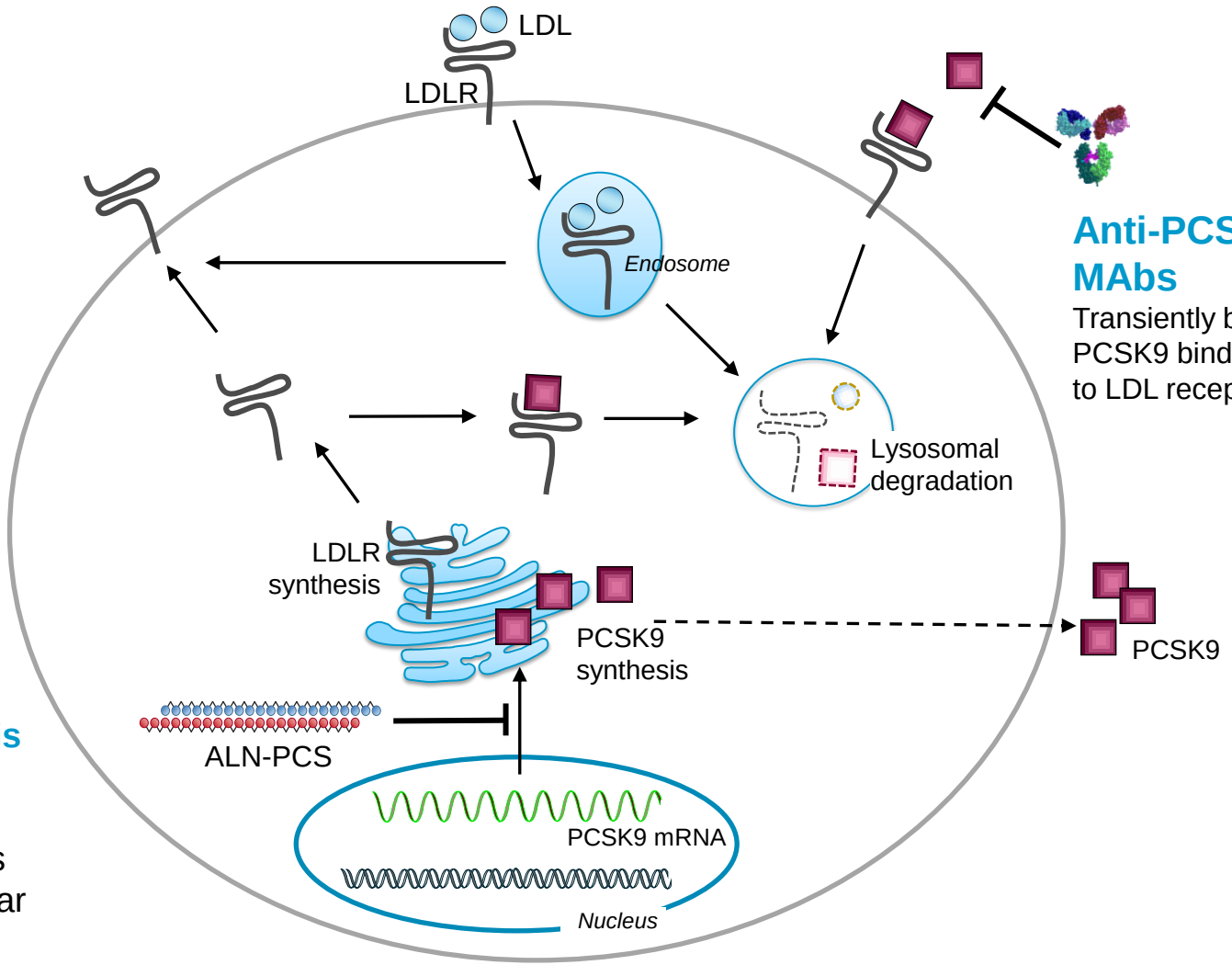
New data on ALN-PCSsc presented at AHA

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



Anti-PCSK9 MAbs
Transiently block PCSK9 binding to LDL receptor (LDLR)

PCSK9 synthesis inhibitors
Durably block PCSK9 synthesis and all intracellular and extracellular PCSK9 functions

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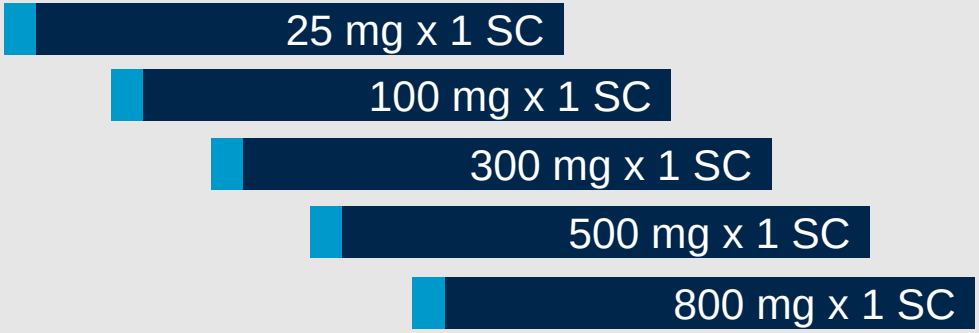
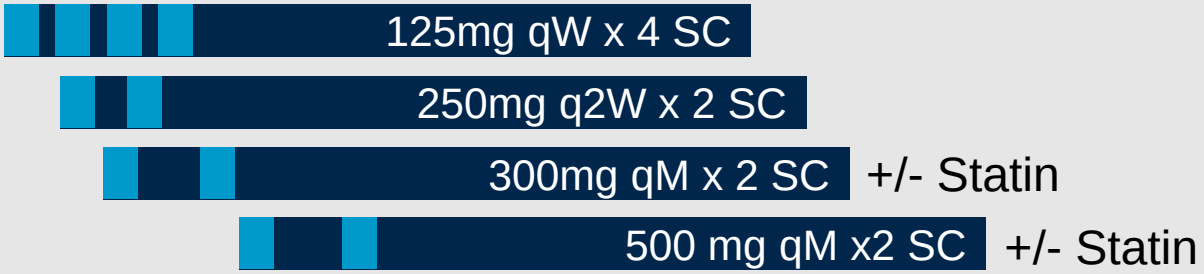
New data on ALN-PCSsc presented at AHA
Study design

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

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New data on ALN-PCSsc presented at AHA
Safety and tolerability

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

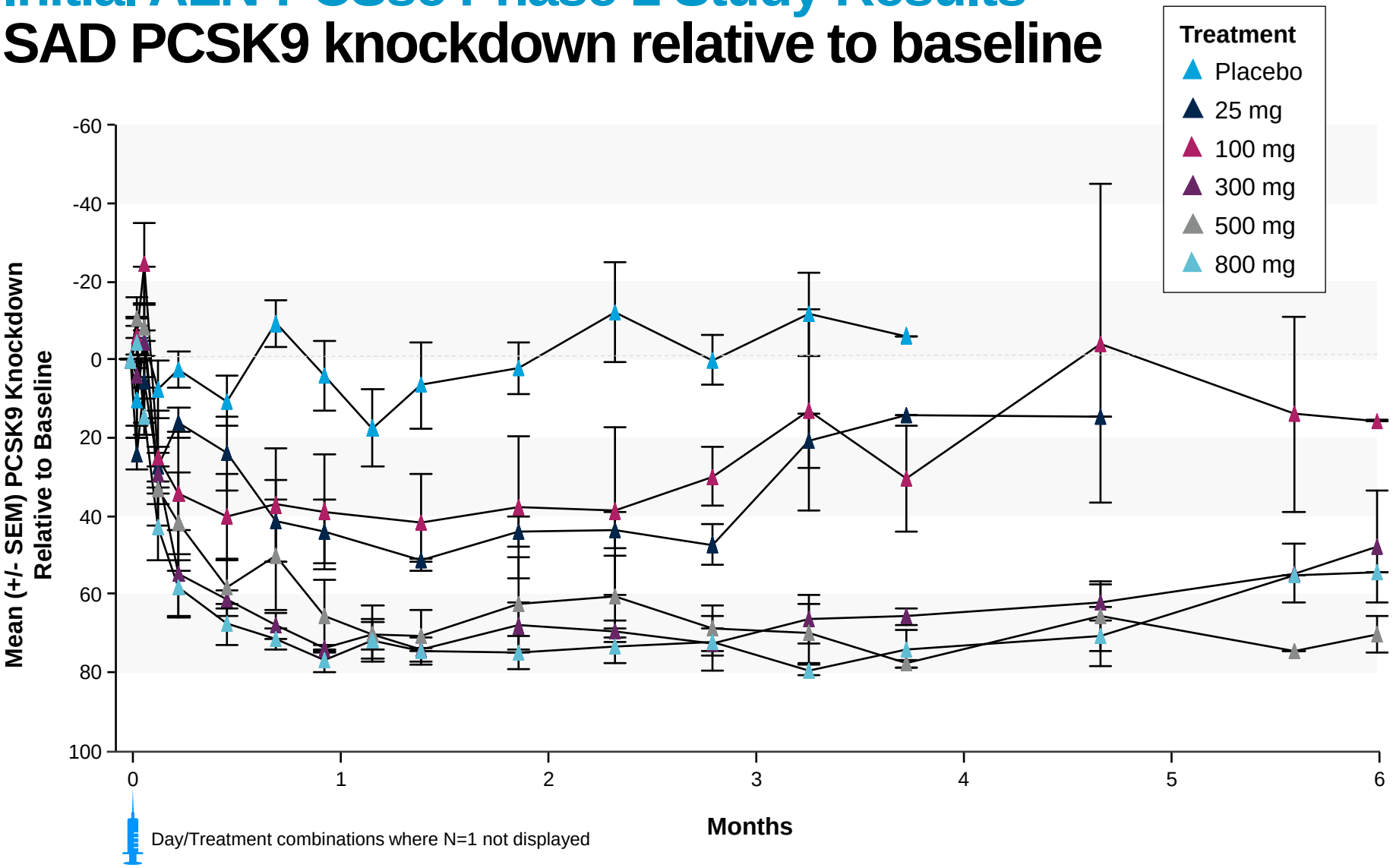
All AEs mild or moderate

- 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-PCSsc Phase 1 Study Results

SAD PCSK9 knockdown relative to baseline

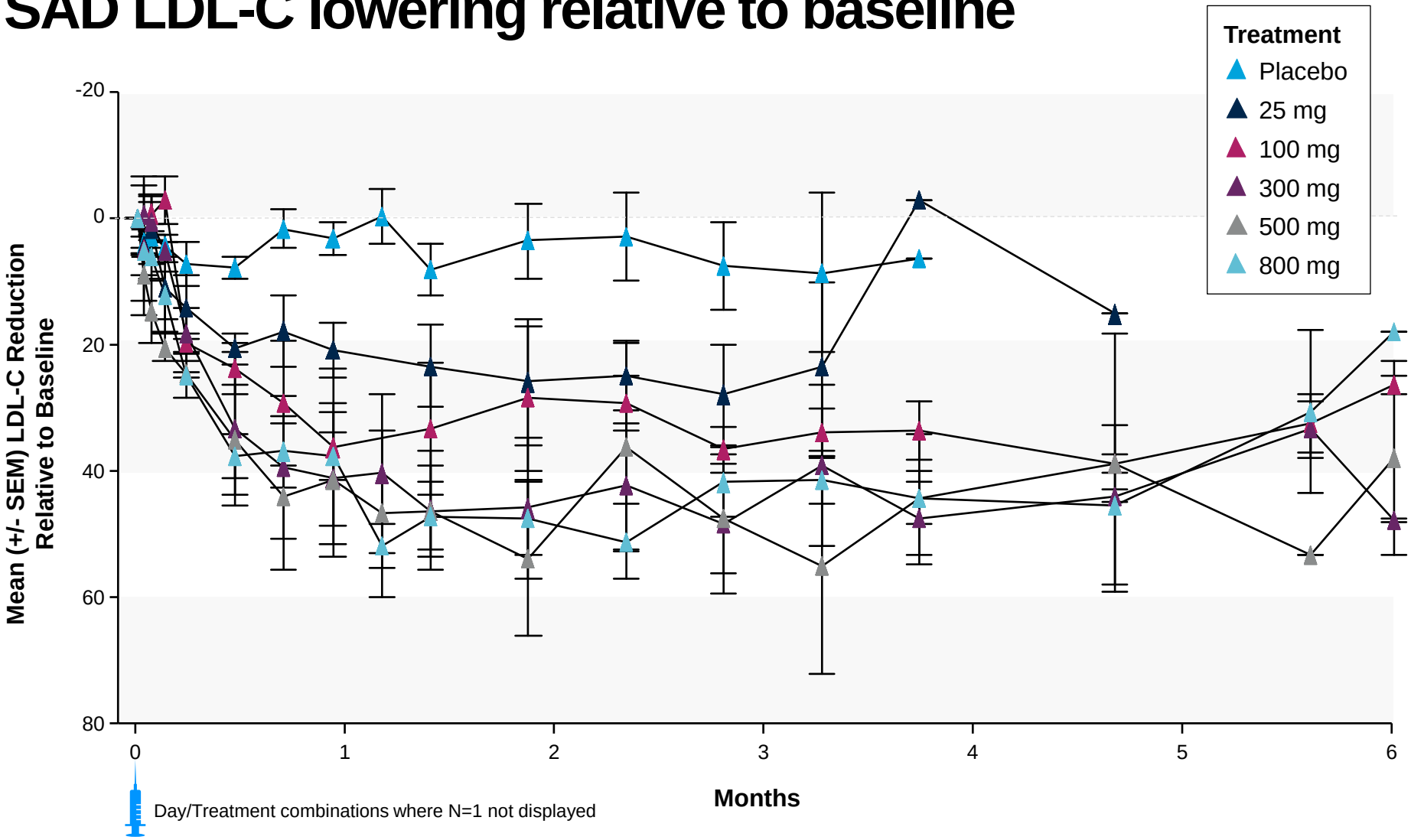


Max PCSK9 inhibition of 88.7% with mean max of 82.3% (+/- 2.0)

Data reported is from database transfer Sept. 24th 2015

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)

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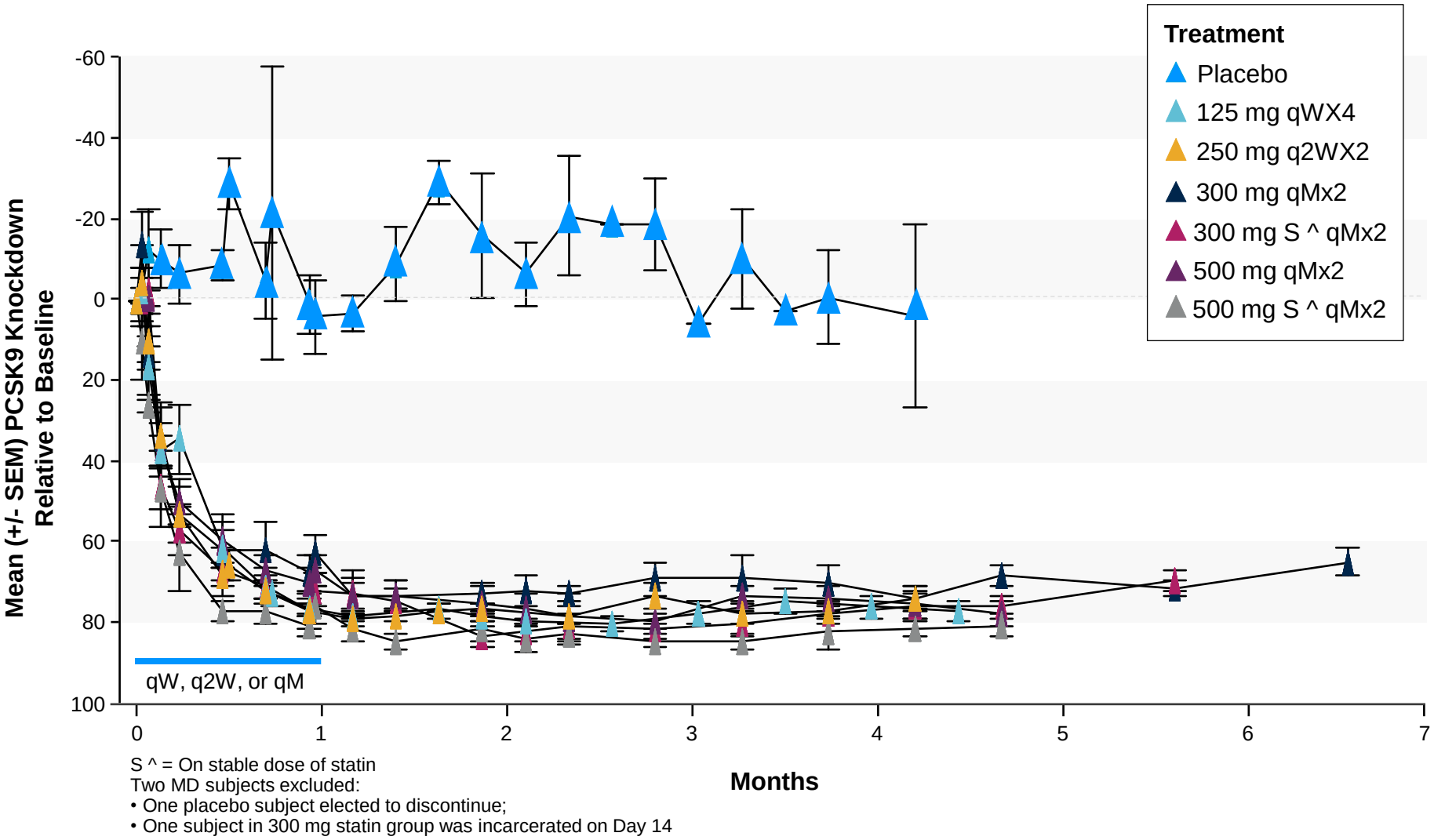
Initial ALN-PCSsc Phase 1 Study Results

MD PCSK9 knockdown relative to baseline



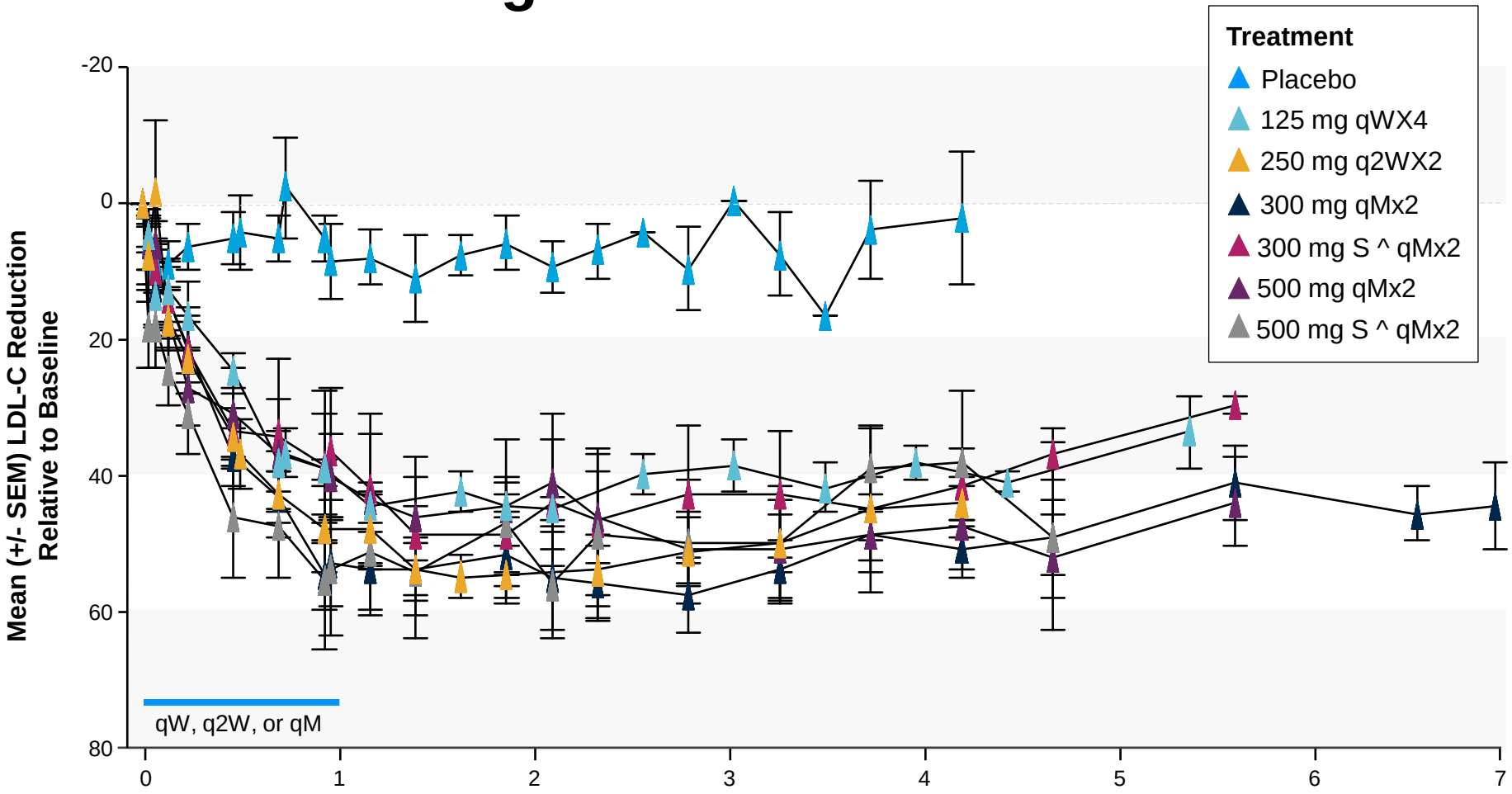
S ^ = On stable dose of statin
Two MD subjects excluded:
- One placebo subject elected to discontinue;
- One subject in 300 mg statin group was incarcerated on Day 14

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

Data reported is from database transfer Sept. 24th 2015

Initial ALN-PCSsc Phase 1 Study Results

MD LDL-C lowering relative to baseline



S ^ = On stable dose of statin
Two MD subjects excluded:
- One placebo subject elected to discontinue;
- One subject in 300 mg statin group was incarcerated on Day 14

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

Data reported is from database transfer Sept. 24th 2015

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%)

Data reported is from database transfer Sept. 24th 2015

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 is from database transfer Sept. 24th 2015

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

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The ORION Development Program

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

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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

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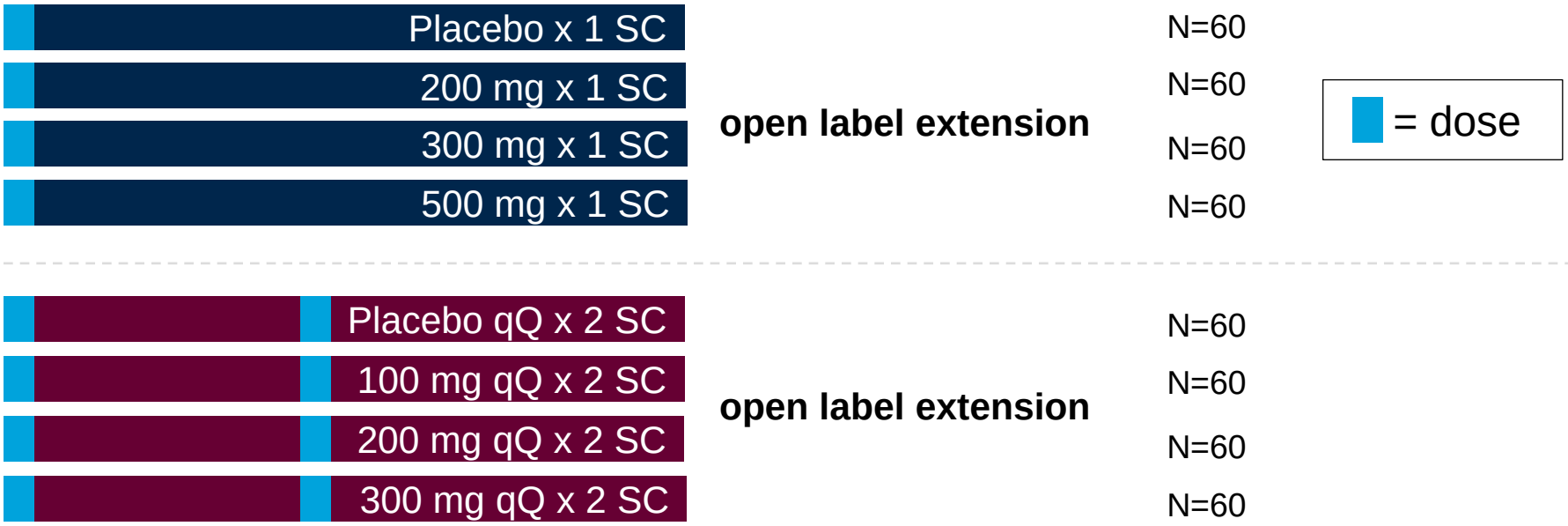
Primary objectives

- 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



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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

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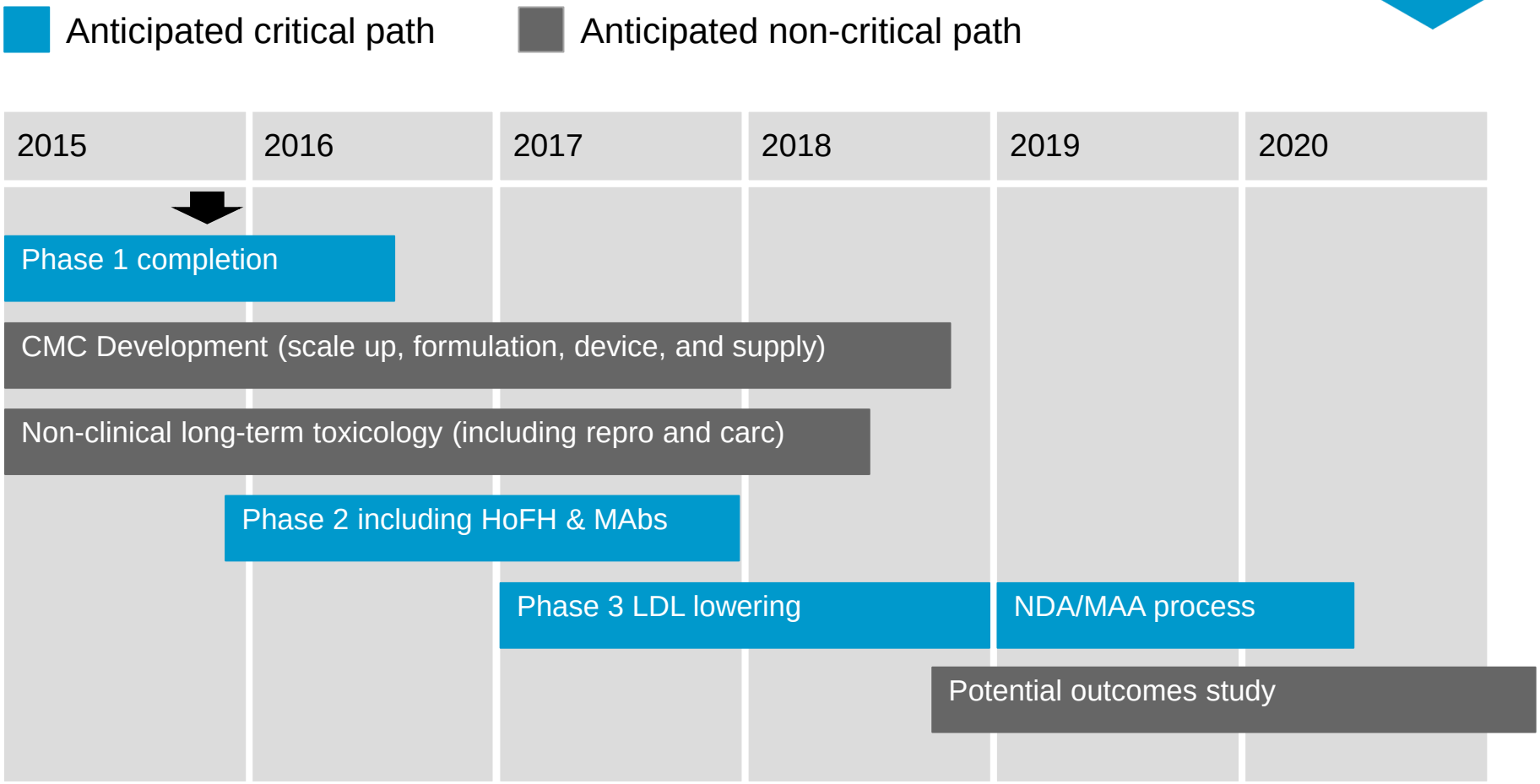
Estimated sequence of events



Timelines are estimates based on current assumptions

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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
Chief Executive Officer
The Medicines Company

A vision for innovation in ACVD

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

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Q&A