The Medicines Company

Alnylam® PHARMACEUTICALS

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

30th August 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
Medical and economic needs	Scott Johnson MD
New Phase 1 data with ALN-PCSsc	Akshay Vaishnaw, MD PhD
The Orion Development Program	Peter Wijngaard PhD
A vision for innovation in ACVD	Ray Russo MBA
Perspectives on data and opportunity	Prof. John J.P. Kastelein MD PhD
Q&A	All

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Introduction

John Maraganore PhD
Chief Executive Officer
Alnylam Pharmaceuticals, Inc.

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

Introduction

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

ALN-PCSsc achieved quarterly and potentially bi-annual sc dosing

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

Comparable LDL-C lowering to previously published results with anti-PCSK9 monoclonal antibodies

LDL-C reduction clamped for more than 140 days after single dose

Generally well tolerated with no clinically significant AEs to date

Program lead transitions to MDCO

Launch of The Orion Development Program, which will include comparative studies with anti-PCSK9 monoclonal antibodies

Medical and economic needs

Scott Johnson, MD
Chief Medical Advisor
The Medicines Company

Medical and economic needs

The job to be done is continuous, life-protecting lowering of LDL-C for people at risk of ACVD – in an economically sustainable manner

Medical and economic needs

Atherosclerotic cardiovascular disease (ACVD) is the leading cause of death worldwide

More people (~18M) die annually from cardiovascular diseases than from any other cause[1]

More than 14M are due to ACVD (coronary, cerebral, peripheral)[1]

Behavioral risk factors are well known and benefits of diet, exercise and smoking cessation have been demonstrated repeatedly[2]

Medical risk factors include hypertension, diabetes, obesity, and dyslipidemia

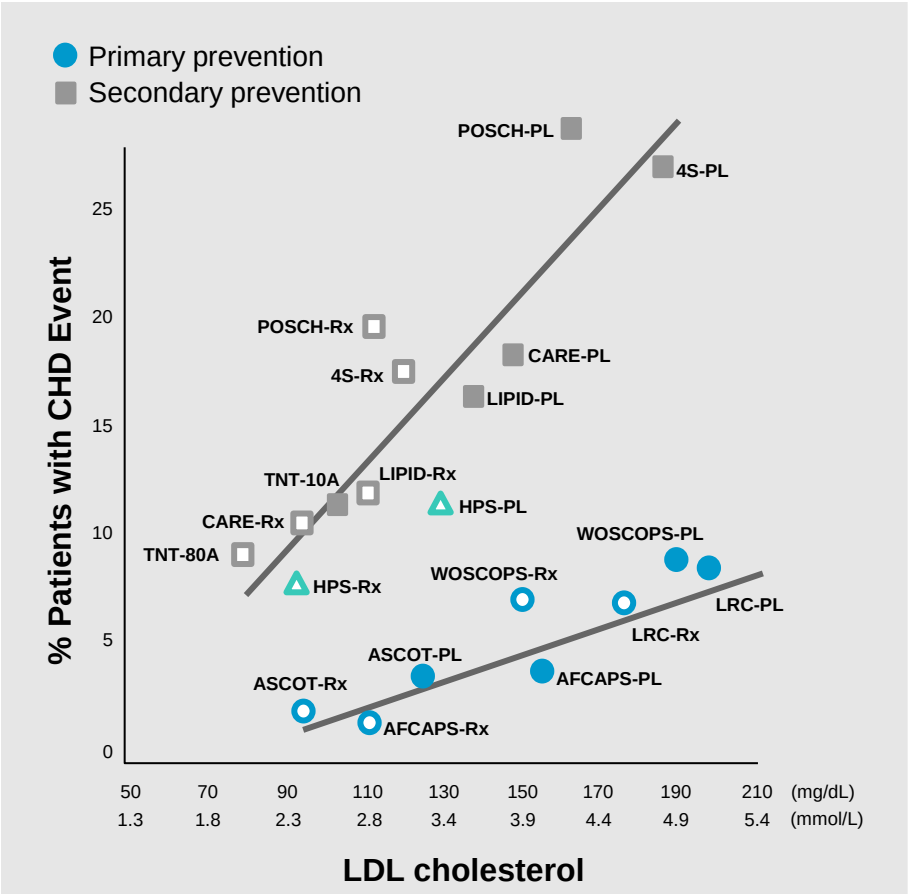
- dyslipidemia is the most important modifiable risk factor
- 39% of adults worldwide have elevated cholesterol[3]

1. Global Status Report on Noncommunicable Diseases WHO 2014.
2. Kotseva K, et al. *Eur J Cariovasc Prev Rehabil* 2009;16:121-137.
3. Global Status Report on Noncommunicable Diseases WHO 2010.

Medical and economic needs

Lowering of LDL-C for people at risk of ACVD is a proven strategy to prevent morbid events and deaths

- Linear association of risk reduction with LDL-C lowering[1]
- Primary and (especially) secondary prevention
- Risk reduced regardless of mechanism of LDL-C lowering
- Statins have proven themselves to be the mainstay of medical therapy



Source: Kastelein JJP. Slides presented at ESC 2014

1. CTT Collaboration. *Lancet* 2010;376:1670-81.

Medical and economic needs
Unresolved issues with statins

Efficacy	Tolerance	Adherence (60% off therapy within 1 year)[4]
<40% of patients achieve goals[1]	Myalgia / myopathy[3]	Asymptomatic disease
~30% CV event[2] risk reduction if goals and adherence are consistently achieved	Elevated LFTs	Frequency of dosing
		Human behavior

1. *MMWR* 2011:60(04);109-114.
2. CTT Collaborators *Lancet* 2012; 380:581–90.
3. McKenney JM, et al. *Am J Cardiol* 2006;97(8A):89c-94c.
4. Benner et al. *JAMA* 2002;228:455-461.

New data on ALN-PCSsc presented at ESC

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

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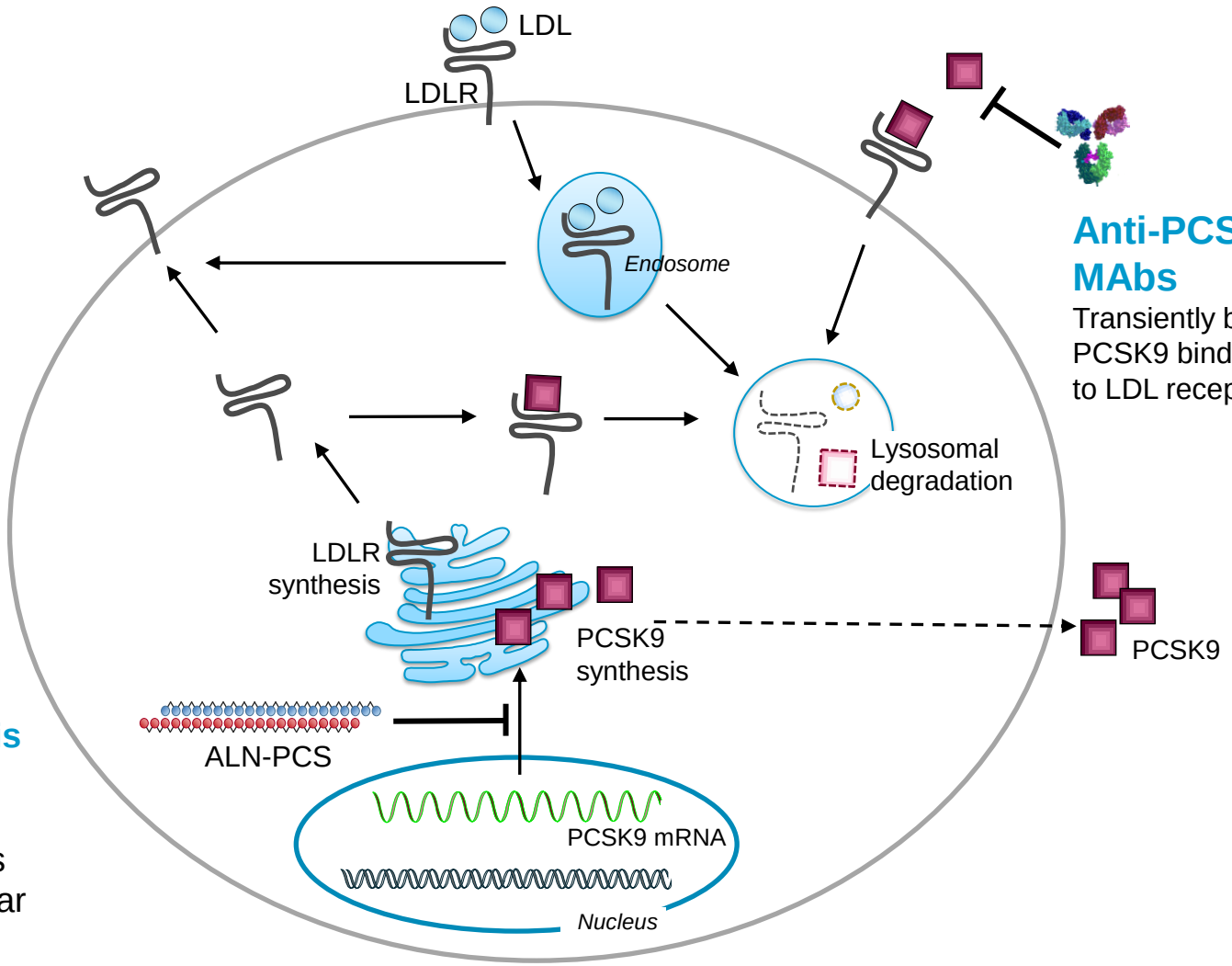
New data on ALN-PCSsc presented at ESC

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 ESC
PCSK9 synthesis inhibition through RNAi

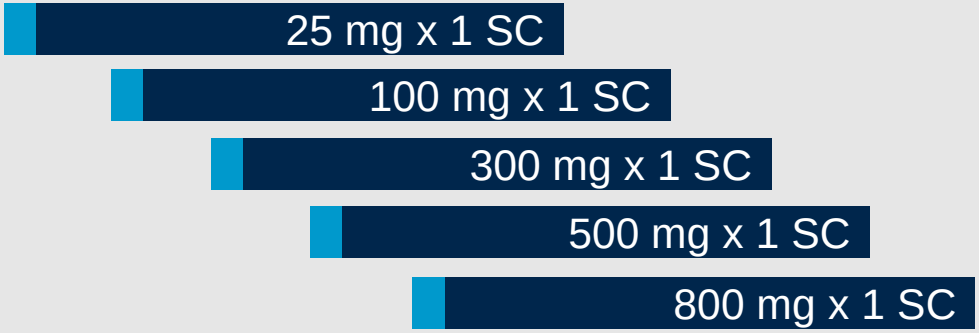


Anti-PCSK9 MAbs
Transiently block PCSK9 binding to LDL receptor (LDLR)

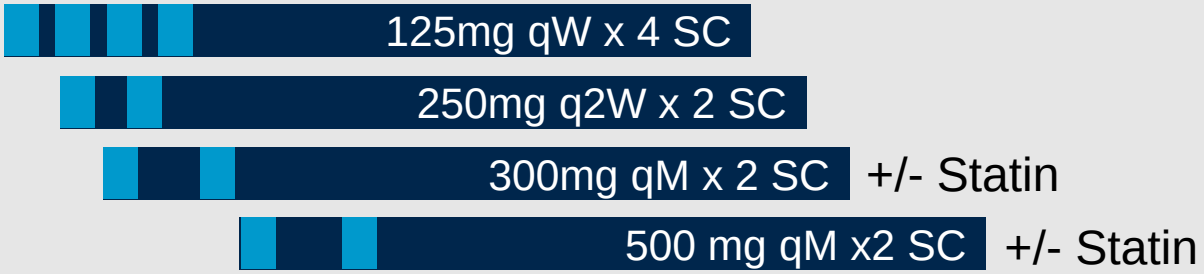
PCSK9 synthesis inhibitors
Durably block PCSK9 synthesis and all intracellular and extracellular PCSK9 functions

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

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

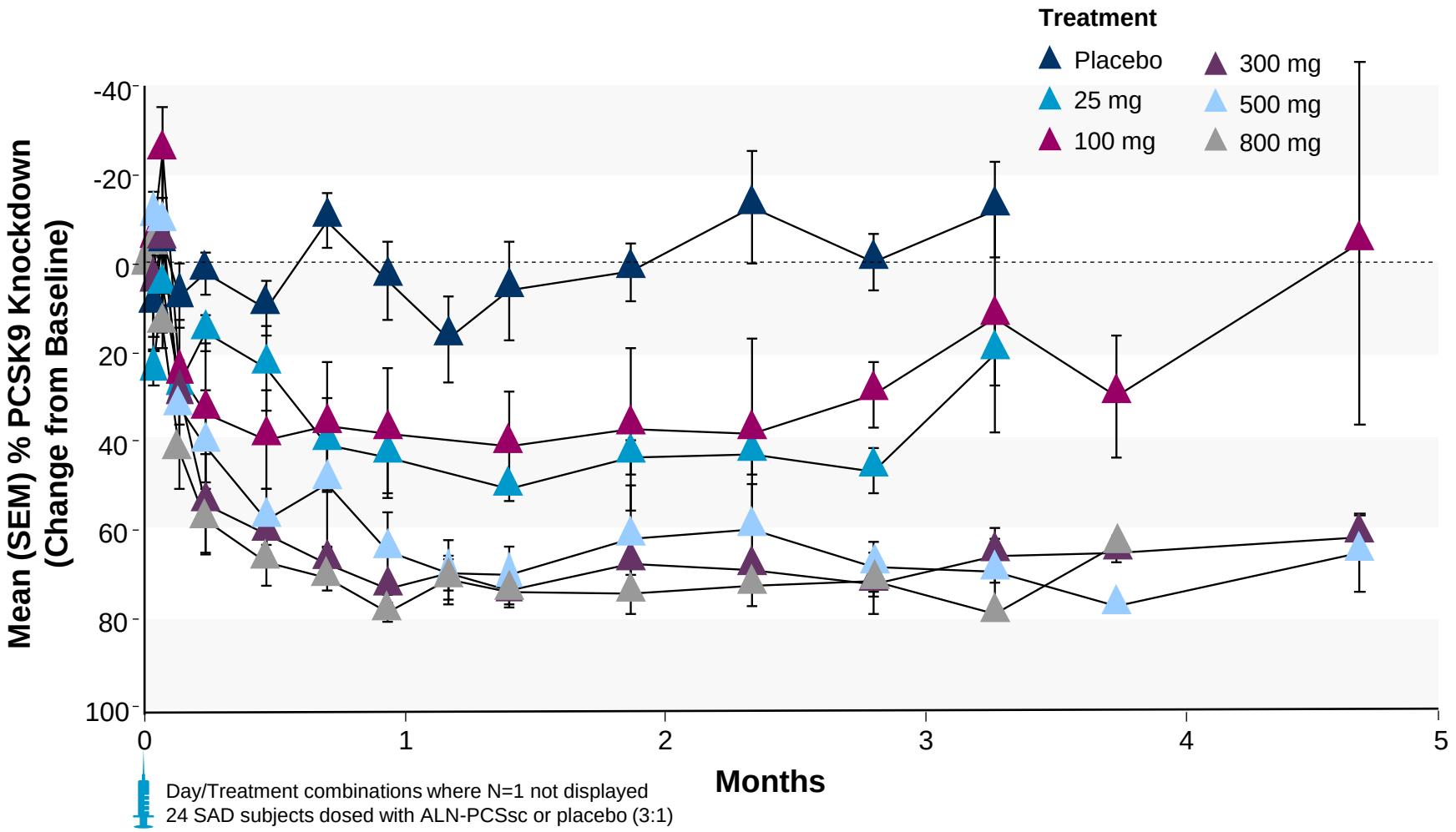
All AEs mild or moderate

- 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 – attributed to concomitant statin therapy

New data on ALN-PCSsc presented at ESC
PCSK9 inhibition Part A Single Dose (SAD)

Up to 86% maximal and up to 82% mean maximal knockdown of PCSK9



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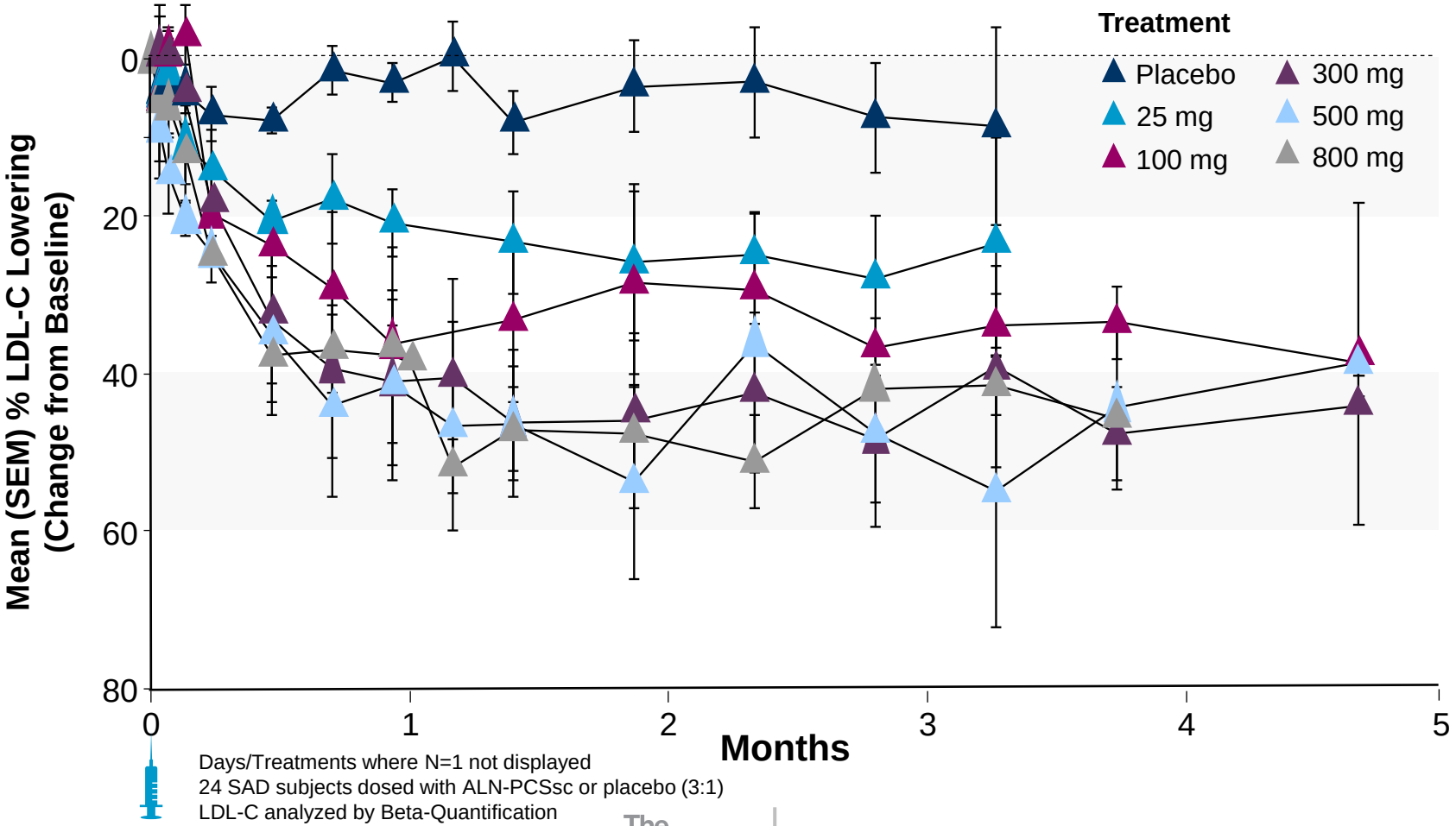
New data on ALN-PCSsc presented at ESC
LDL-C reduction Part A Single dose (SAD)

Up to 78% maximal and up to 58% mean maximal lowering of LDL-C

- LSM %LDL-C reduction from baseline at 12 weeks of 50.1% at 300 mg dose



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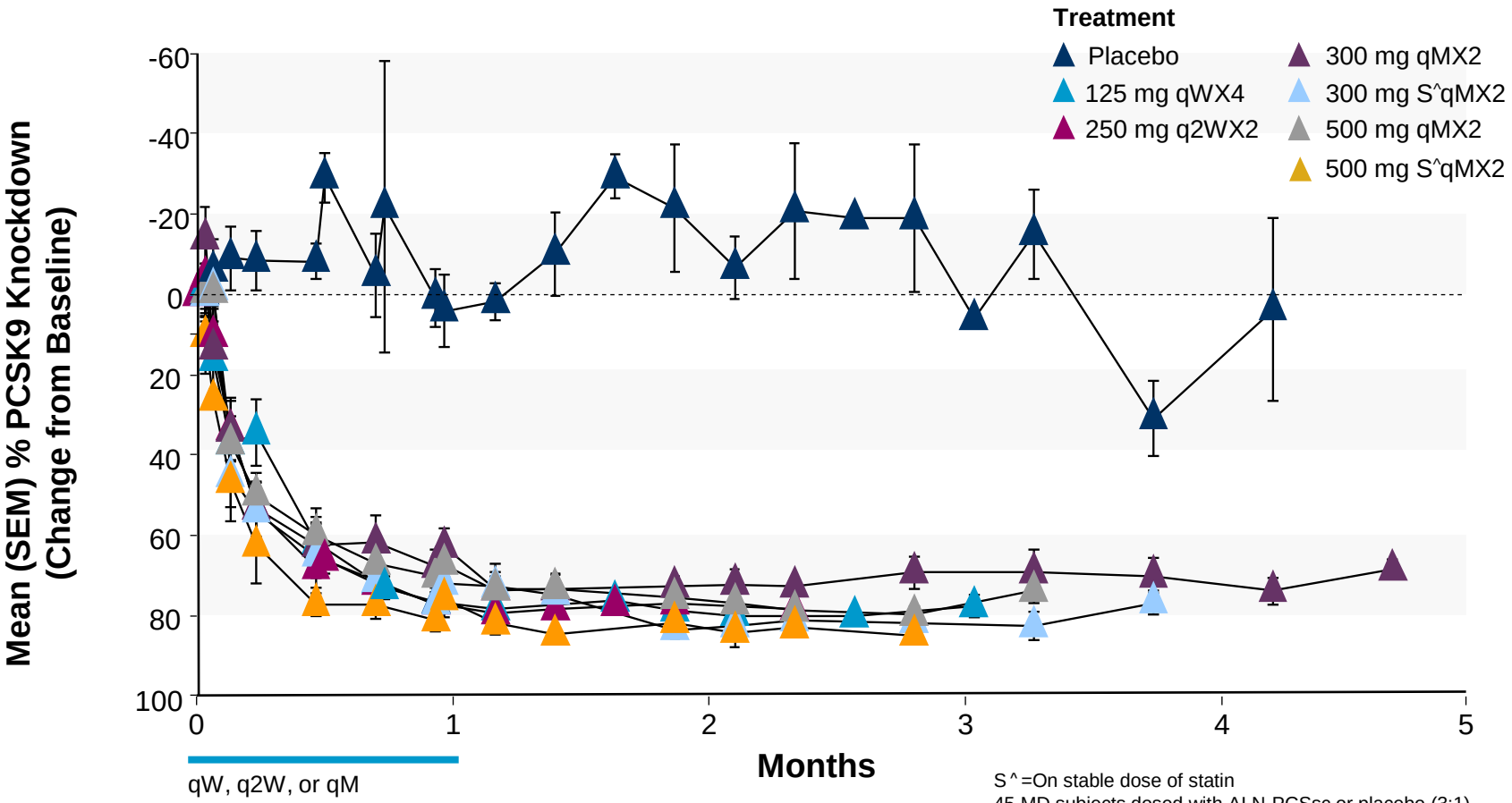
New data on ALN-PCSsc presented at ESC
PCSK9 inhibition Part B Multiple Dose (MD)

Up to 94% maximal and up to 88% mean maximal knockdown of PCSK9



S^=On stable dose of statin
45 MD subjects dosed with ALN-PCSsc or placebo (3:1)
Two subjects excluded from all MD analyses:
One placebo subject elected to discontinue;
One subject in 300 mg statin group was incarcerated on Day 14

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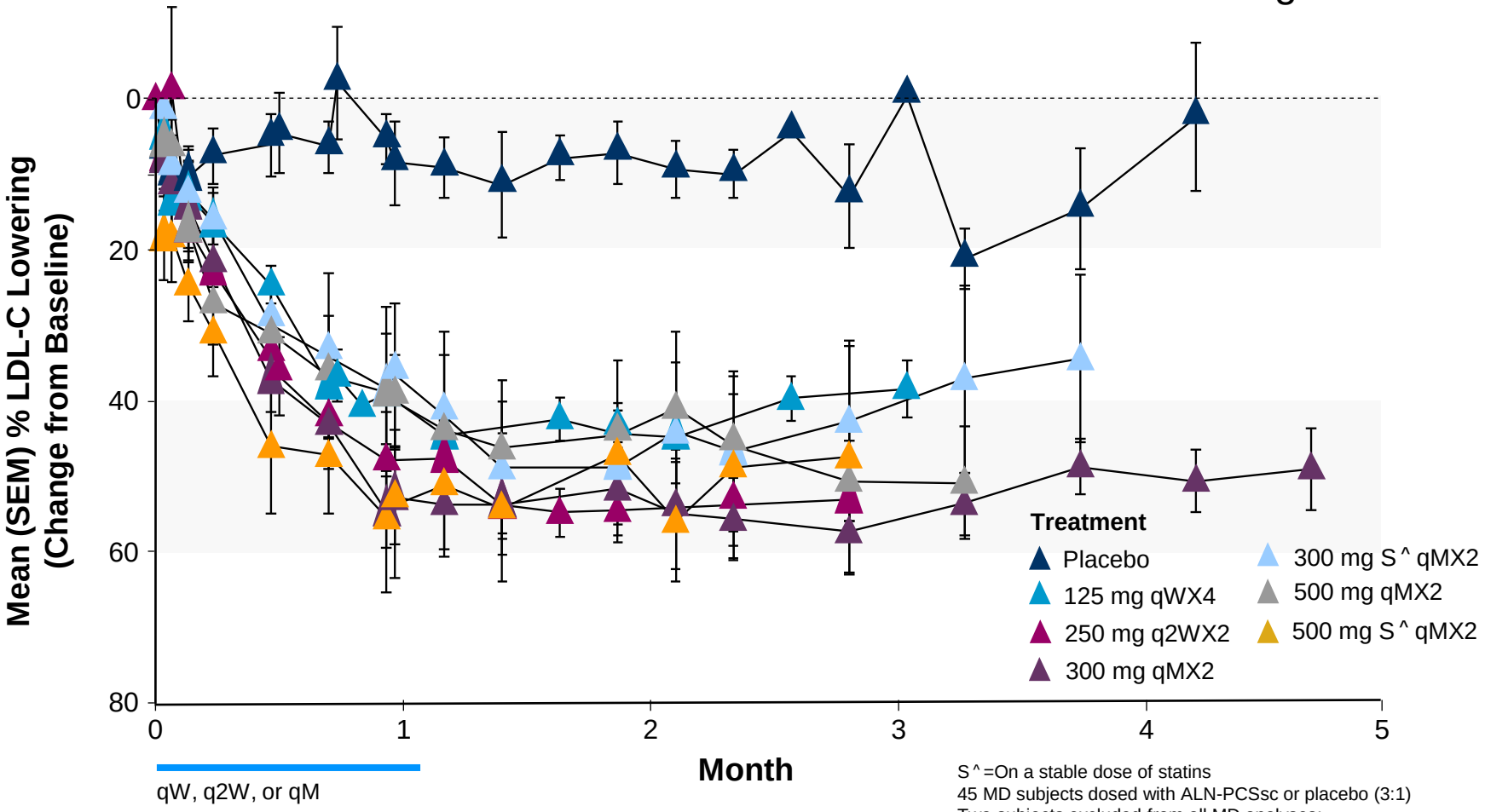
New data on ALN-PCSsc presented at ESC
LDL-C reduction Part B Multiple Dose (MD)

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

- LSM %LDL-C reduction from baseline at 12 weeks of 59.4% at 300 mg dose



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New data on ALN-PCSsc presented at ESC
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 supports once-quarterly and possibly bi-annual, low volume SC dose regimen
- Initial Phase 1 results support continued development of ALN-PCSsc in ORION Development Program

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:

- Keep chronic toxicology studies off the critical path
- Optimize dose, formulation, administration, and device – small volume, infrequent, easy
- Execute efficient phase III program based on LDL-C efficacy endpoint
  - Broad population of patients with ACVD
  - Focused FH studies
  - Compare head-to-head to monoclonal antibodies where appropriate
- Anticipate outcomes data and design phase IIIb/IV accordingly

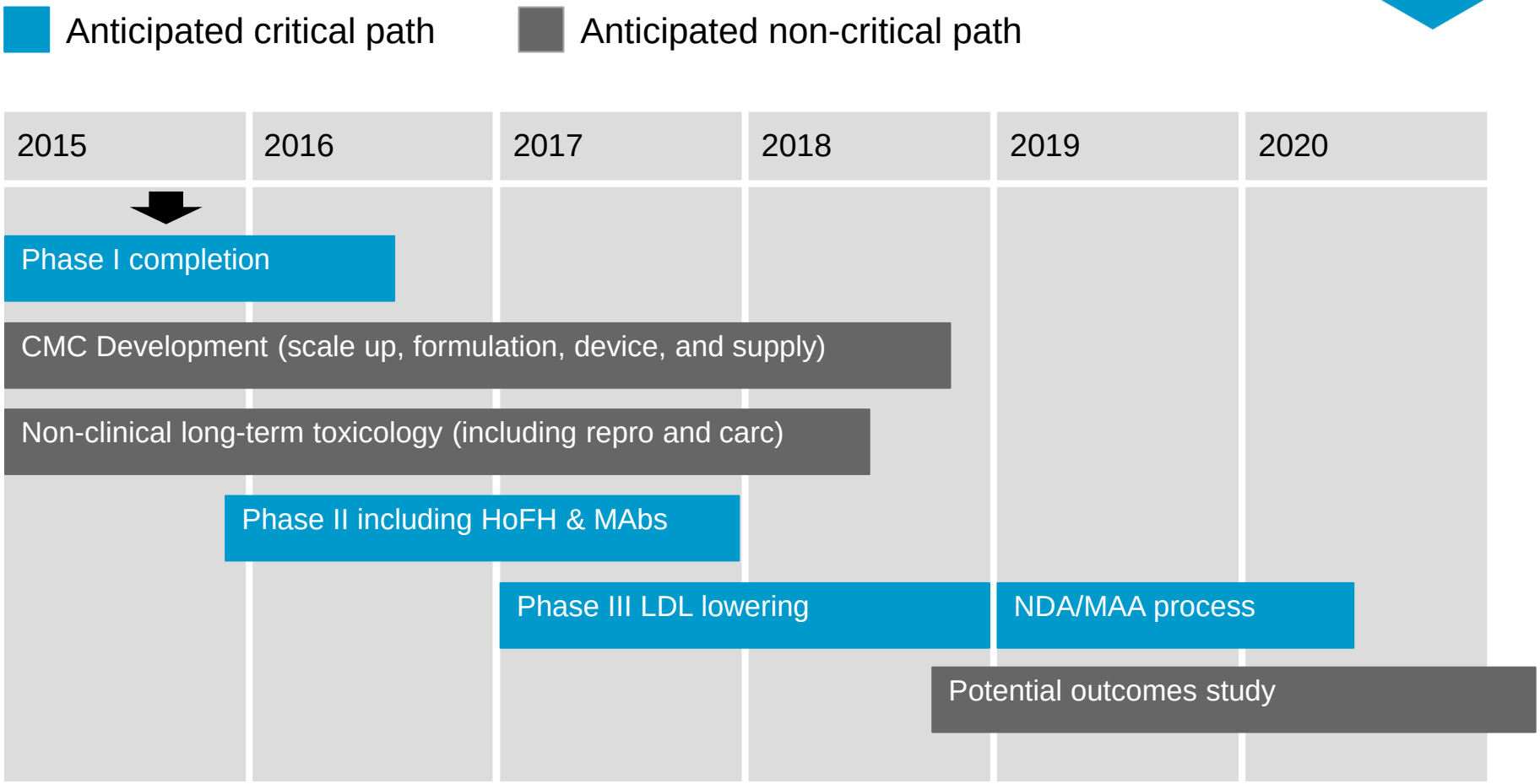
The Orion Development Program

Benchmarking programs with approval on LDLc endpoints (US approval)

Parameter	Lipitor®	Crestor®	Praluent®	Repatha®
Initial US approval (YR)	1996	2003	2015	2015 (est.)
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



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:

- Complete Phase I observations
- Start Phase II imminently
- Scale up manufacturing and formulation development
- Complete long term toxicology program

Ensure only the clinical program remains on the critical path

A vision for innovation in ACVD

Ray Russo MBA
Senior Vice President,
Acute Cardiovascular Care
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
Critical issues in LDL-C lowering

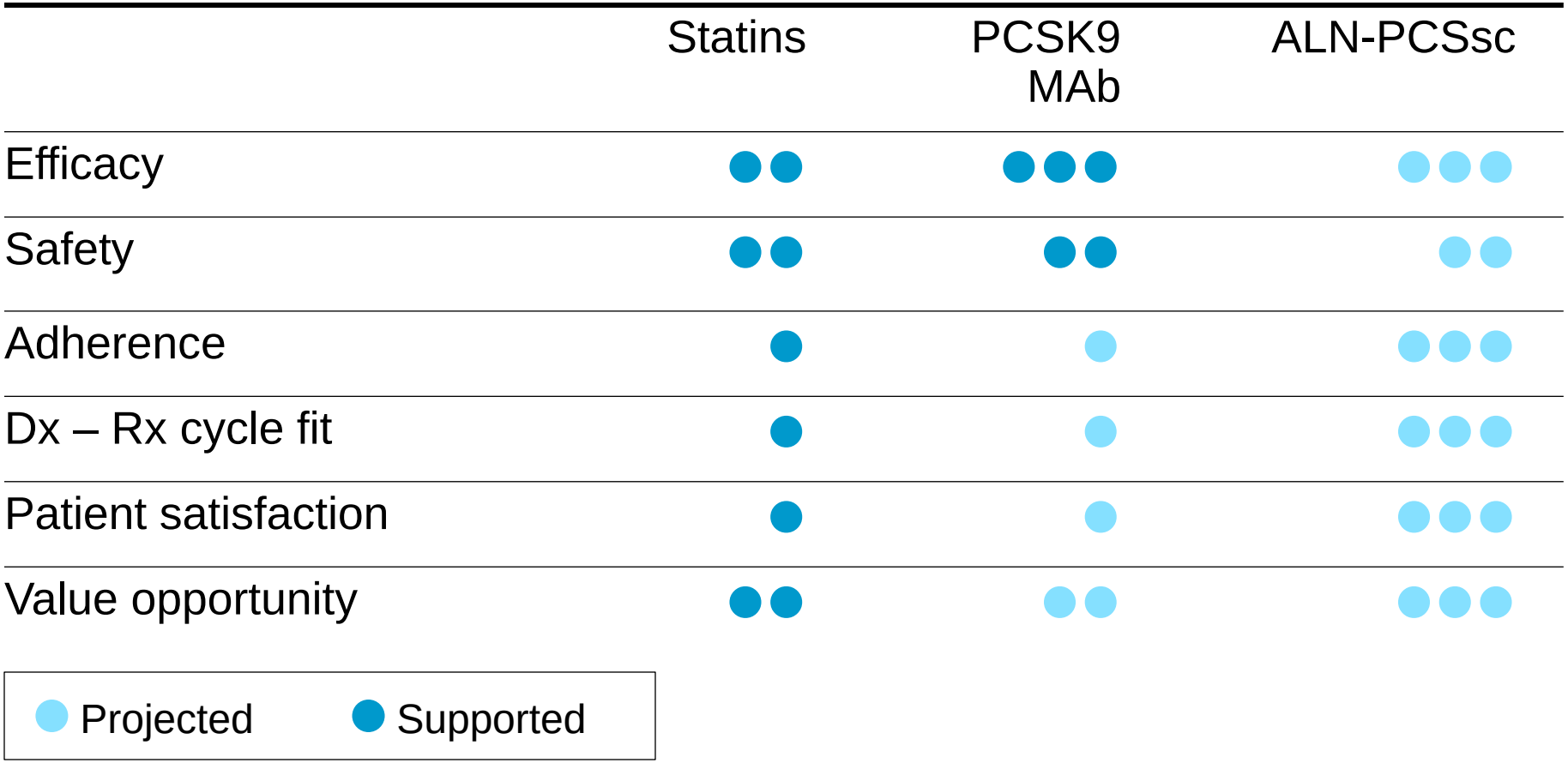
Adherence

Dx-Rx cycle fit

Patient satisfaction

Value

A vision for innovation in ACVD
Anticipated product profile



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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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Perspectives on data and opportunity

Prof. John J.P. Kastelein MD PhD
Professor of Medicine and Chairman of the Department of Vascular Medicine at the Academic Medical Center (AMC) of the University of Amsterdam

Q&A