

A Subcutaneously Administered Investigational RNAi Therapeutic (ALN-PCSSc), Targeting PCSK9 for the Treatment of Hypercholesterolemia: Initial Phase I Study Results



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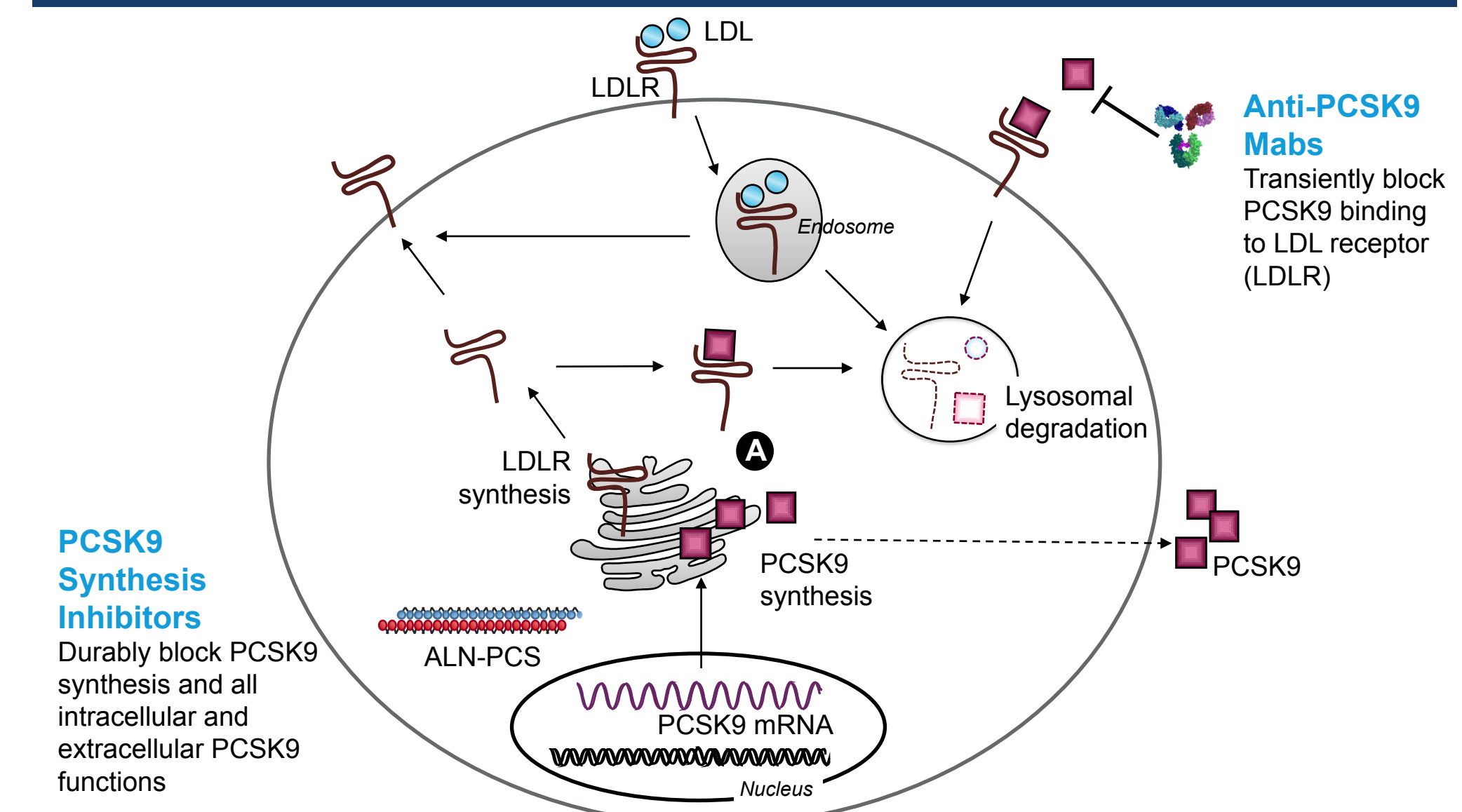
Declaration of Interest: Employees of Alnylam Pharmaceuticals¹
Employees of The Medicines Company²

A Phase 1, Randomized, Single-Blind, Placebo-Controlled, Single Ascending Dose and Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Subcutaneously Administered ALN-PCSSc in Subjects with Elevated Low-Density Lipoprotein Cholesterol

Abstract

ALN-PCSSc is an investigational RNAi therapeutic targeting PCSK9 protein synthesis. We report here a positive interim analysis of our ongoing Phase 1 trial of ALN-PCSSc. In this trial, we have tested the ability of single subcutaneous doses of ALN-PCSSc to lower both PCSK9 protein and LDL-C in healthy volunteer subjects with baseline LDL-C >100mg/dl. In addition, subjects with LDL-C >100mg/dl on and off of stable statin co-medication, were treated with two subcutaneous injections of ALN-PCSSc given 28 days apart (qM X2). Our results to date demonstrate a robust lowering of both PCSK9 protein and LDL-C. Moreover, a single dose of ALN-PCSSc achieved a highly durable response, supporting a quarterly or potentially bi-annual dosing frequency. ALN-PCSSc was generally well tolerated, all treatment emergent adverse events (TEAE's) were mild or moderate in severity. No serious adverse events or discontinuations due to adverse events occurred.

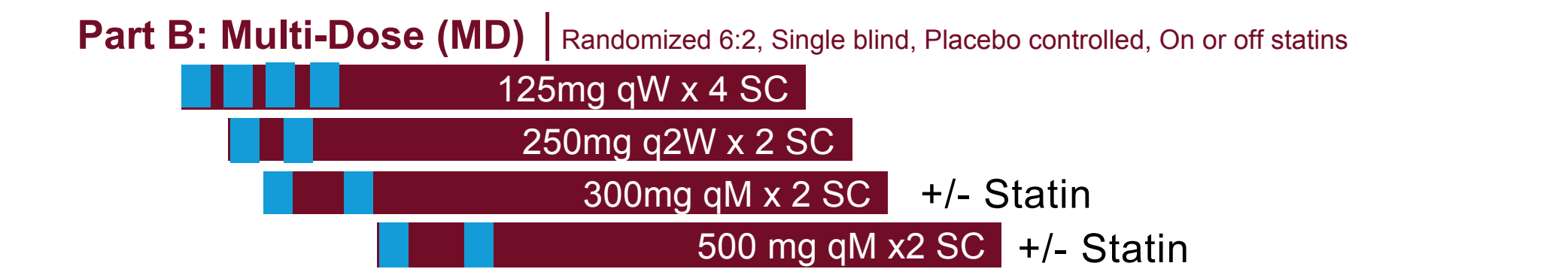
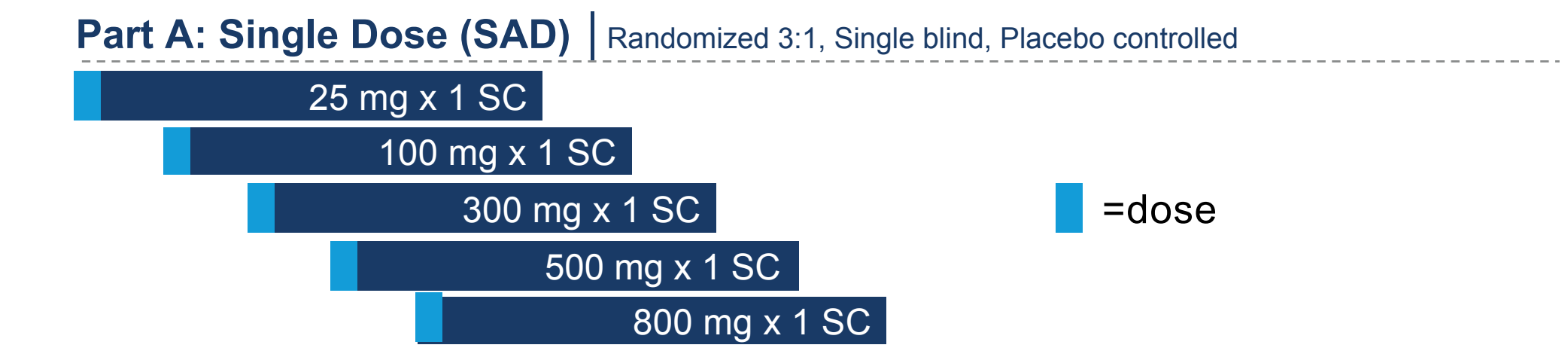
PCSK9 Therapeutic Hypothesis



ALN-PCSSc Phase I Study

Healthy subjects with LDL-C > 100mg/dl, on or off statins

- Primary objectives**
- Safety, tolerability
- Secondary objectives**
- PK, PCSK9 and LDL-C reduction



Initial ALN-PCSSc Phase I Study Results

SAD Cohort demographics and baseline characteristics

24 SAD subjects dosed with ALN-PCSSc or placebo (3:1)

	Placebo N=6	25 mg N=3	100 mg N=3	300 mg N=3	500 mg N=3	800 mg N=6	Total (excluding Placebo) N=18
Age (years), Mean (Min, Max)	47.5 (20, 59)	47.3 (31, 56)	48.0 (41, 53)	48.3 (34, 58)	39.3 (25, 53)	48.7 (37, 56)	46.7 (25, 58)
Gender: Male (%)	33.3%	100%	100%	100%	83.3%	94.4%	94.4%
BMI (kg/m ²), Mean	25.0	27.6	25.7	26.8	23.4	25.8	25.8
Race (%)							
Asian	0%	0%	0%	33.3%	0%	16.6%	11.1%
Black African or African American	33.3%	33.3%	0%	33.3%	0%	0%	11.1%
Caucasian	66.7%	66.7%	100%	33.3%	100%	50%	66.7%
Other	0%	0%	0%	0%	0%	33.3%	11.1%
Time on study, Mean (months)	2.9	3.3	5.2	5.4	4.2	3.7	4.2

Data in database as of 04 August 2015

MD Cohort demographics and baseline characteristics

45 MD subjects dosed with ALN-PCSSc or placebo (3:1)

	Placebo N=12	125 mg qW x4 N=6	250 mg q2W x2 N=6	300 mg qM x2 N=6	300 mg qM x2 S ^a N=4	500 mg qM x2 N=6	500 mg qM x2 S ^a N=5	Total (excluding placebo) N=33
Age (years), Mean (Min, Max)	53.3 (25, 71)	54.7 (42, 67)	60.5 (54, 70)	47.3 (37, 58)	51.8 (20, 68)	42.2 (25, 59)	56.4 (38, 69)	52.0 (20, 70)
Gender: Male (%)	66.7%	66.7%	66.7%	100%	50%	50%	40%	63.6%
BMI (kg/m ²), Mean	26.6	28.2	27.1	25.4	27.2	23.0	25.6	25.6
Race (%)								
Asian	0%	16.7%	0%	0%	25%	16.7%	20%	12.1%
Black African or African American	0%	0%	16.7%	0%	0%	0%	20%	6.1%
Caucasian	91.7%	83.3%	50%	100%	75%	83.3%	60%	75.8%
Other	8.3%	0%	33.3%	0%	0%	0%	0%	6.1%
Time on study, Mean (months)	2.8	2.9	2.4	4.7	3.1	3.3	2.7	3.2

S^a = On a stable statin dose
Data in database as of 04 August 2015

Baseline values for PCSK9 and LDL-C

SAD phase		Placebo (6)	25 mg (3)	100 mg (3)	300 mg (3)	500 mg (3)	800 mg (6)	Overall (24)
Mean (SEM) PCSK9 (ng/mL)		278.9 (40.53)	342.7 (39.2)	233.8 (22.61)	253.8 (12.91)	263.2 (14.42)	279.6 (13.94)	276.3 (15.56)
Mean (SEM) LDL-C (mg/dL)		142.2 (11.35)	154.0 (26.99)	161.7 (16.06)	173.2 (29.48)	135.0 (3.33)	161.3 (10.25)	157.6 (6.61)

MD phase		Placebo (12)	125 mg qW x4 (6)	250 mg q2W x2 (6)	300 mg qM x2 (6)	300 mg qM x2 S ^a (4)	500 mg qM x2 (6)	500 mg qM x2 S ^a (5)	Overall (45)
Mean (SEM) PCSK9 (ng/mL)		333.3 (28.95)	380.0 (20.67)	288.7 (21.86)	308.0 (25.62)	474.7 (86.65)	288.1 (28.2)	433.4 (47.98)	347.9 (15.56)
Mean (SEM) LDL-C (mg/dL)		137.0 (11.09)	150.2 (7.58)	129.2 (10.16)	145.4 (12.86)	158.1 (15.62)	131.7 (20.20)	131.3 (11.24)	139.4 (4.89)

S^a = On a stable statin dose
Data in database as of 04 August 2015

SAD safety and tolerability

ALN-PCSSc generally well tolerated

- No SAEs and no discontinuations due to AEs
- All AEs mild or moderate in severity
 - At highest dose group (800 mg), one subject with mild localized injection site reaction
 - No clinically significant changes in laboratory parameters

Common AEs (≥10% of more of ALN-PCSSc subjects)*

AE Preferred Term	Placebo N=6	25 mg N=3	100 mg N=3	300 mg N=3	500 mg N=3	800 mg N=6	Total ALN-PCSSc N=18
Cough	0	0	1	0	1	0	2
Musculoskeletal pain	0	1	0	0	0	1	2
Nasopharyngitis	0	1	0	1	0	0	2
Rash	0	0	0	0	0	2**	2

*Subjects with one or more AEs 2/6 placebo; 9/18 ALN-PCSSc
**1 mild injection site reaction; 1 mild facial rash not associated with drug
Data in database as of 04 August 2015

MD safety and tolerability

ALN-PCSSc generally well tolerated

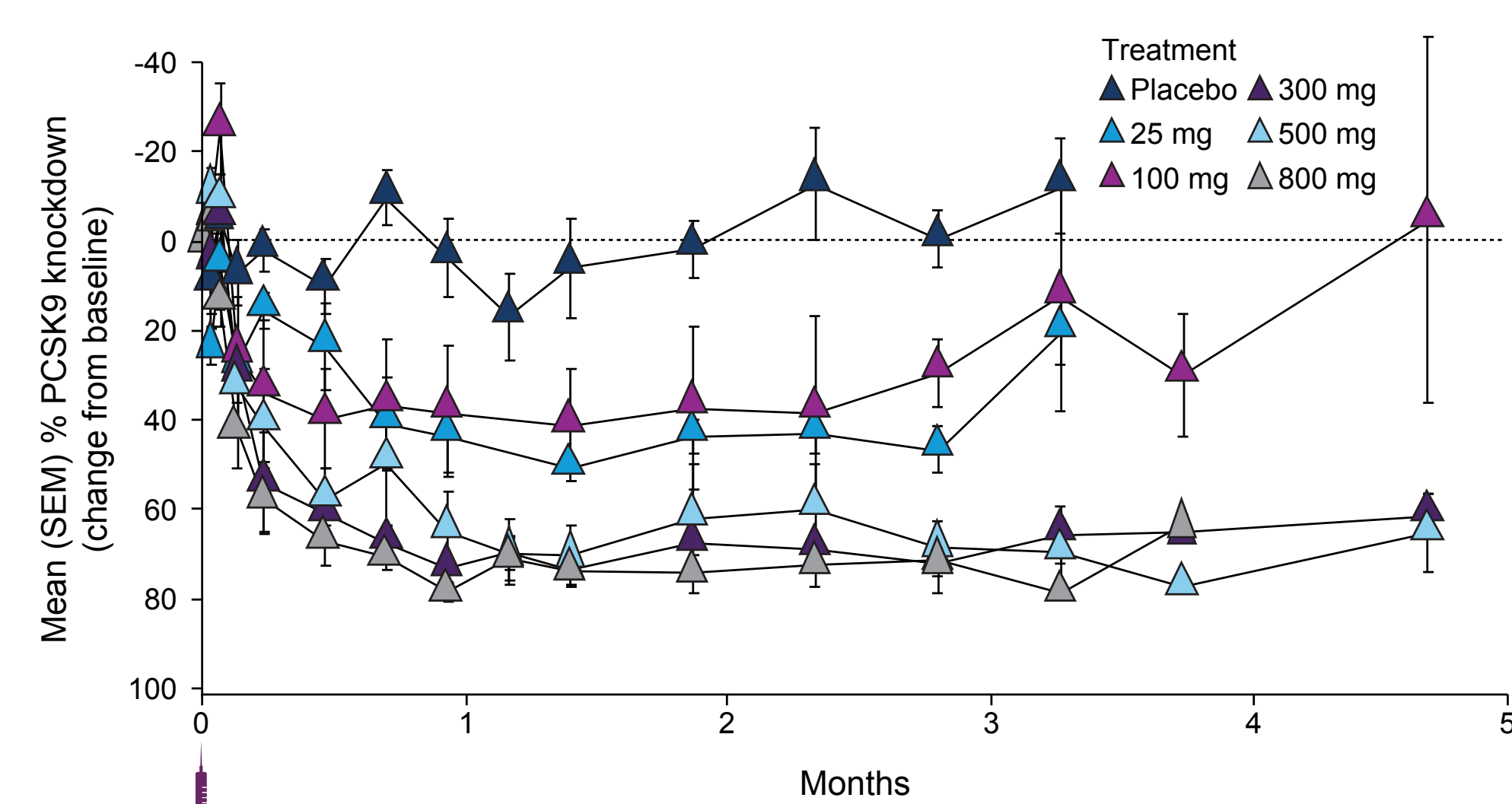
- No SAEs and no discontinuations due to AEs
- All AEs mild or moderate in severity
 - AE profile generally similar with or without statins
 - At higher drug exposures 3 subjects with mild, localized injection site reaction
 - One at 500 mg qM x2 with statin; two at 250 mg q2W x2
 - One subject with clinically significant change in LFTs
 - Subject receiving 500 mg ALN-PCSSc developed ALT ~4x ULN without rise in bilirubin; attributed to concomitant statin therapy

Common AEs (≥10% or more of ALN-PCSSc subjects)*

AE Preferred Term	Placebo N=12	125 mg qW x4 N=6	250 mg q2W x2 N=6	300 mg qM x2 N=6	300 mg qM x2 S ^a N=4	500 mg qM x2 N=6	500 mg qM x2 S ^a N=5	Total ALN-PCSSc N=33
Headache	2	1	1	1	1	2	1	6
Back pain	2	1	0	0	0	2	1	4
Diarrhea	3	2	0	0	1	0	1	4
Nausea	0	2	0	0	0	2	0	4

**Subjects with one or more AEs 9/12 placebo; 22/33 ALN-PCSSc
S^a = On a stable dose of statin
Data in database as of 04 August 2015

SAD PCSK9 knockdown relative to baseline

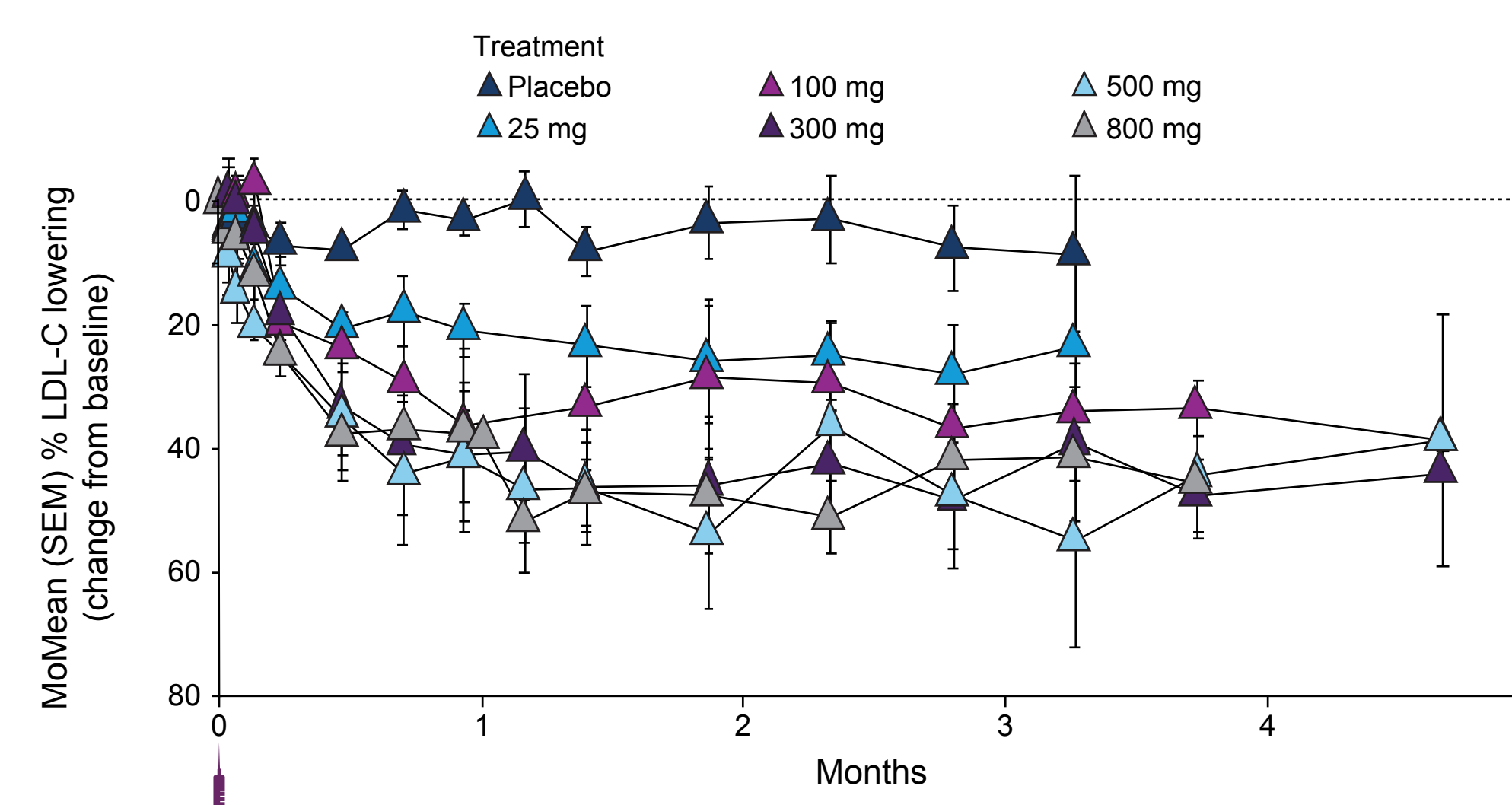


Day/Treatment combinations where N=1 not displayed
Data in database as of 04 August 2015

Dose Group	Mean Max % KD (SEM)		Max % KD	Mean % KD Day 84 (+/- SEM)*	N at Day 84*	Mean % KD Day 140 (+/- SEM)*	N at Day 140*
	Day 84	Day 140					
Placebo	29.4 (3.89)	38.4	0.1 (6.41)	5	NA	0	
25 mg	54.3 (2.74)	59.7	47.3 (5.12)	2	14.4 (-)	1	
100 mg	48.9 (15.5)	72.6	29.9 (7.44)	3	-4.1 (40.83)	2	
300 mg	77.9 (2.01)**	81.7	72.6 (6.99)**	3	62.1 (4.76)*	3	
500 mg	75.7 (6.79)**	85.7	68.7 (5.68)**	3	65.7 (6.92)	2	
800 mg	81.6 (1.61)**	85.9	72.2 (3.47)**	6	On-going	On-going	

Mean maximal knockdown compared via ANOVA
Mean knockdown per day for Days 1-84 compared via mixed effects ANCOVA
*Pairwise comparisons vs. Placebo examined via Tukey's tests under the ANOVANCOVA models
**Pairwise comparisons vs. Placebo examined via Tukey's tests under the ANOVANCOVA models
*Mean knockdown at Day 140 compared via pairwise t tests vs. baseline
*P<0.05; **P<0.01; ***P<0.001
Data in database as of 04 August 2015

SAD LDL-C lowering relative to baseline



Day/Treatment where N=1 not displayed
LDL-C analyzed by Beta-Quantification
Data in database as of 04 August 2015

Dose Group	Mean Max % Reduction (+/- SEM)*		Max % Reduction	Mean % Reduction Day 84 (+/- SEM)*	N at Day 84*	Mean % Reduction Day 140 (+/- SEM)*	N at Day 140*
	Day 84	Day 140					
Placebo	18.6 (2.27)	25.1	7.4 (6.99)	5	NA	0	
25 mg	34.4 (5.0)	44.2	27.9 (8.02)	2	15.2 (-)	1	
100 mg	43.0 (8.9)	59.8	36.6 (3.57)	3	38.7 (1.49)*	2	
300 mg	53.1 (7.02)	66.5	48.4 (10.99)**	3	44.0 (0.98)**	3	
500 mg	55.1 (11.56)*	78.1	47.6 (8.77)**	3	38.7 (20.42)	2	
800 mg	58.0 (4.27)**	69.1	41.8 (5.49)**	5	On-going	On-going	

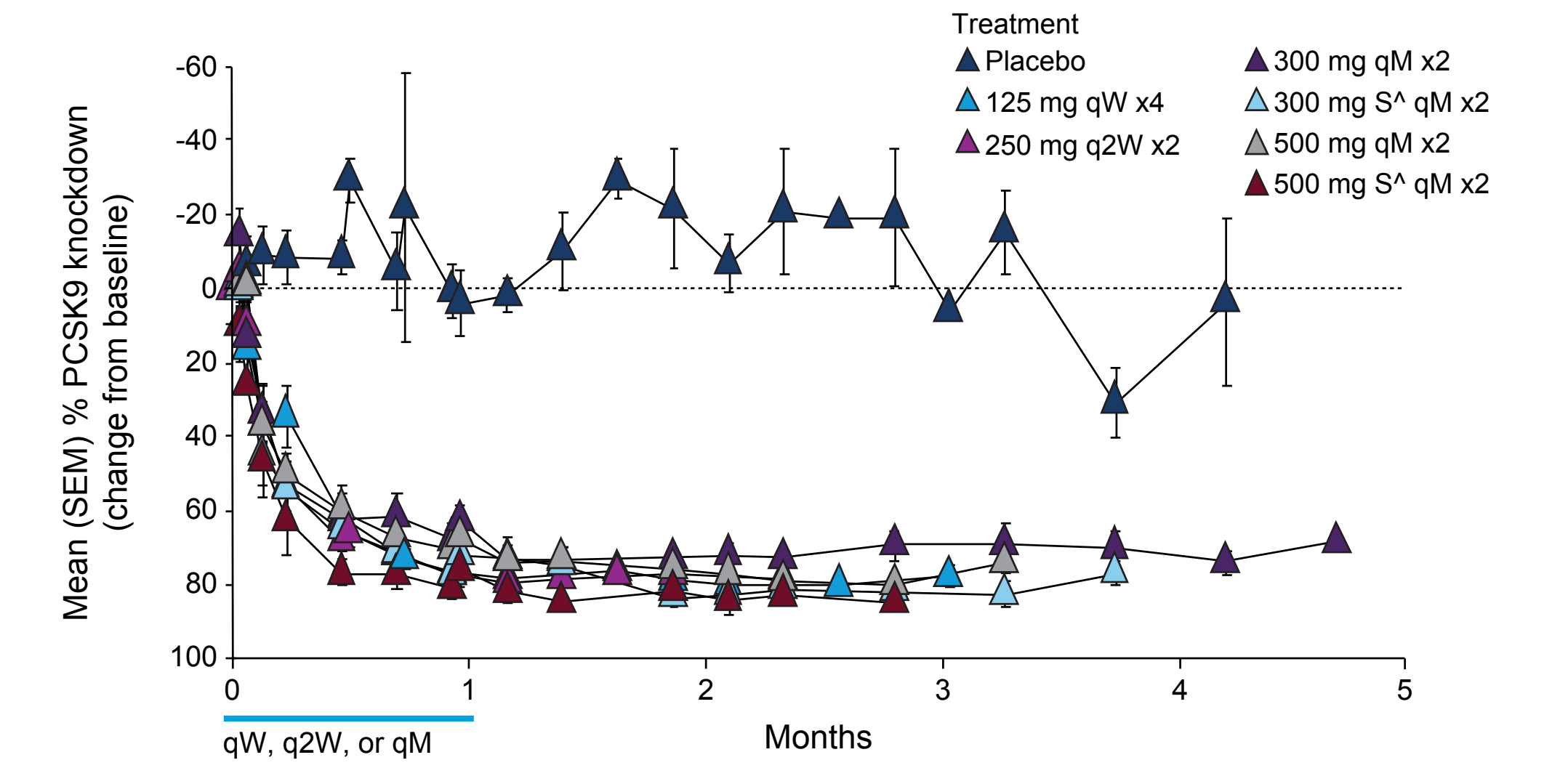
Mean maximal knockdown compared via ANOVA
Mean knockdown per day for Days 1-84 compared via mixed effects ANCOVA
*Pairwise comparisons vs. Placebo examined via Tukey's tests under the ANOVANCOVA models
**Pairwise comparisons vs. Placebo examined via Tukey's tests under the ANOVANCOVA models
*Mean lowering at Day 140 compared via pairwise t tests vs. baseline
*P<0.05; **P<0.01; ***P<0.001
*Subjects leave study when LDL-C recovers to 80% of baseline
Data in database as of 04 August 2015

Summary and Next Steps

ALN-PCSSc is promising first-in-class PCSK9 synthesis inhibitor

- Generally well tolerated
 - No SAEs and no discontinuations due to AEs
 - All AEs mild or moderate in severity
- Similar LDL-C reduction to published data reported for anti-PCSK9 mAbs* in subjects with and without statin co-medication
 - Single subcutaneous injection of ALN-PCSSc resulted in up to 86% maximal PCSK9 knockdown and up to 78% maximal reduction LDL-C lowering, with up to mean maximal LDL-C reduction of 58%
 - Two monthly doses of ALN-PCSSc resulted in up to 94% maximal knockdown of PCSK9 and up to 83% maximal reduction of LDL-C, with up to mean maximal LDL-C reduction of 64%
- Similar effects with or without concomitant statin

MD PCSK9 knockdown relative to baseline

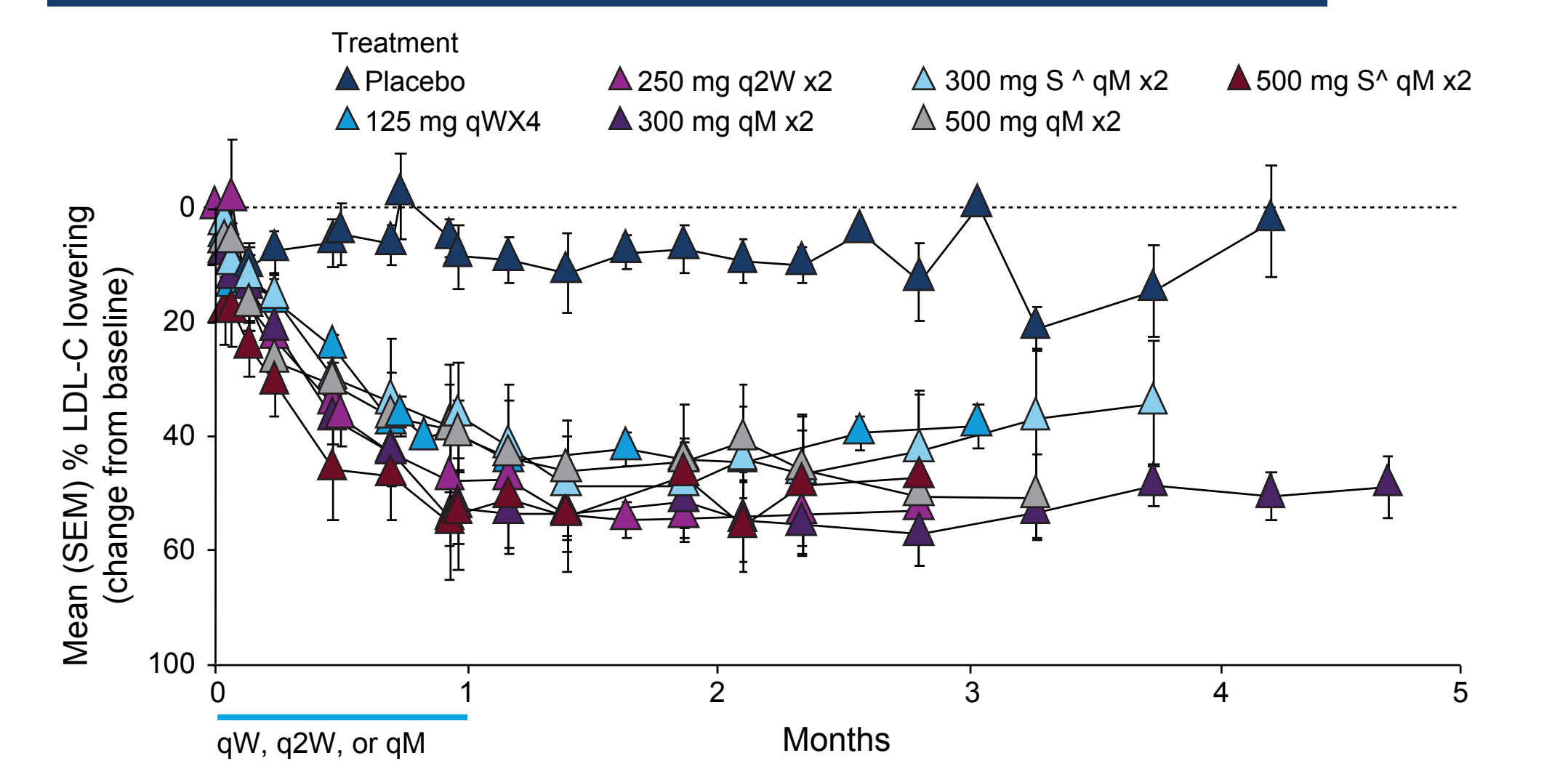


S^a = On a stable dose of statin
Two subjects excluded from all MD analyses:
One placebo subject elected to discontinue;
One subject in 300 mg statin group was incarcerated on Day 14
Data in database as of 04 August 2015

Dose Group	Mean Max % KD (SEM)*		Max % KD
	Day 84	Day 140	
Placebo	28.7 (5.70)	82.3 (1.12)**	63.2
125 mg qW x4	80.8 (1.30)**	79.6 (3.08)**	84.6
250 mg q2W x2	86.1 (1.19)**	81.3 (2.25)**	88.1
300 mg qM x2	88.1 (1.19)**	88.1 (1.19)**	88.1
300 mg S ^a qM x2	88.1 (1.19)**	88.1 (1.19)**	88.1
500 mg qM x2	88.1 (1.19)**	88.1 (1.19)**	88.1
500 mg S ^a qM x2	88.1 (1.19)**	88.1 (1.19)**	88.1

Mean maximal knockdown compared via ANOVA
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S^a = On a stable dose of statin
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Data in database as of 04 August 2015

MD LDL-C lowering relative to baseline



S^a = On a stable dose of statin
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
Data in database as of 04 August 2015

Dose Group	Mean Max % KD (SEM)*		Max % KD
	Day 84	Day 140	
Placebo	21.5 (3.26)	51.2 (1.91)	42.6
125 mg qW x4	51.2 (1.91)	80.4 (4.51)**	59.6
250 mg q2W x2	84.4 (5.41)**	55.2 (6.49)**	79.3
300 mg qM x2	84.4 (5.41)**	55.2 (6.49)**	79.3
300 mg S ^a qM x2	84.4 (5.41)**	55.2 (6.49)**	79.3
500 mg qM x2	84.4 (5.41)**	55.2 (6.49)**	79.3
500 mg S ^a qM x2	84.4 (5.41)**	55.2 (6.49)**	79.3

Mean maximal knockdown compared via ANOVA
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- Durability supports once-quarterly and possibly bi-annual, low volume SC dose regimen
 - Knockdown of PCSK9 and lowering of LDL-C for over 4 months after single SC dose
 - LDL-C significantly (P<0.001) reduced by mean 44% at day 140 after single dose
 - Lowest maximal effect dose of 300 mg administered in 1.5 mL volume
- Results support continued development of ALN-PCSSc in ORION Development Program
 - Phase 2 study expected to start by YE-2015

* Zhang XL, et al. BMC Med., 2015