A Subcutaneously Administered Investigational RNAi Therapeutic (ALN-PCSsc), Targeting PCSK9 for the Treatment of Hypercholesterolemia: Initial Phase 1 Study Results

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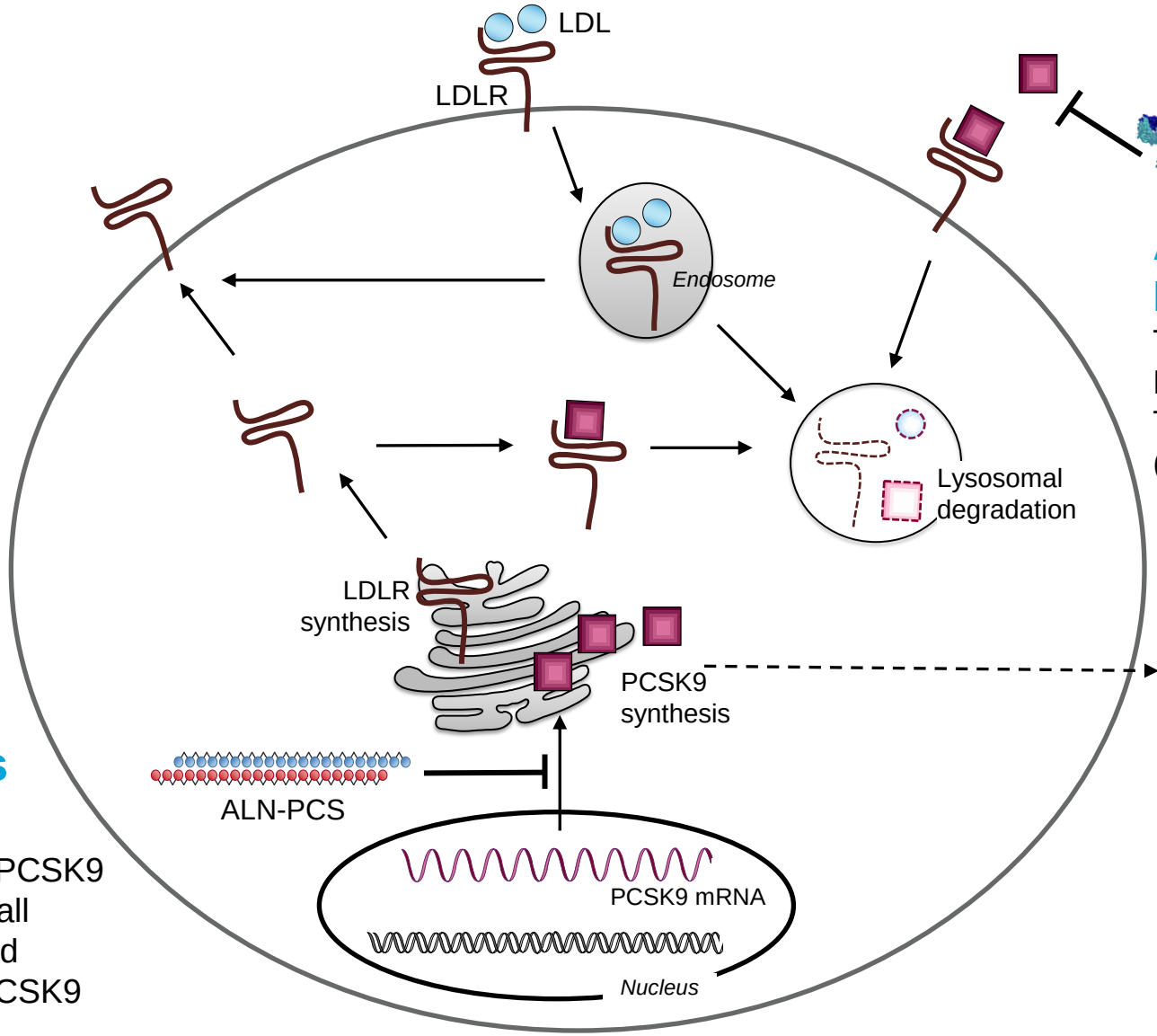
A Phase 1, Randomized, Single-Blind, Placebo-Controlled, Single Ascending Dose and Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Subcutaneously Administered ALN-PCSsc in Subjects with Elevated Low-Density Lipoprotein Cholesterol

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



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

ALN-PCSsc Phase 1 Study

Healthy Subjects with LDL-C >100mg/dl, On or Off Statins

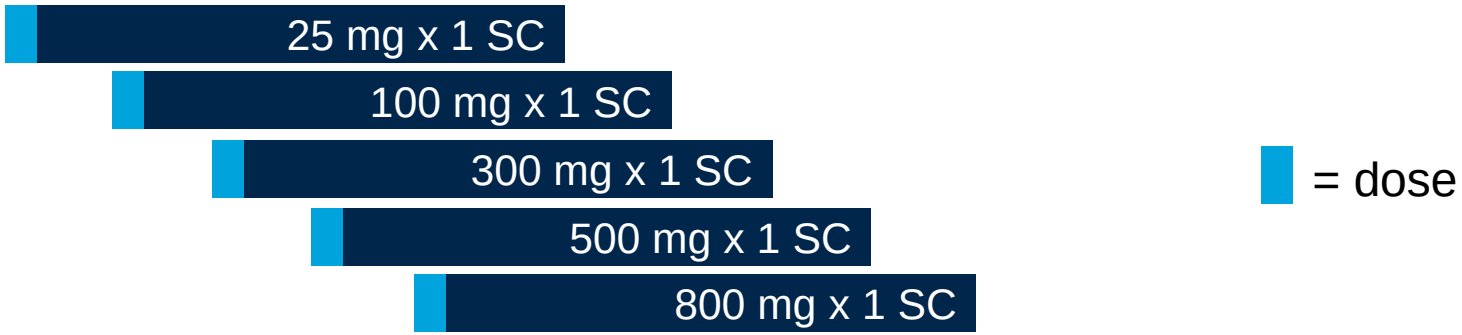
Primary objectives

- Safety, tolerability

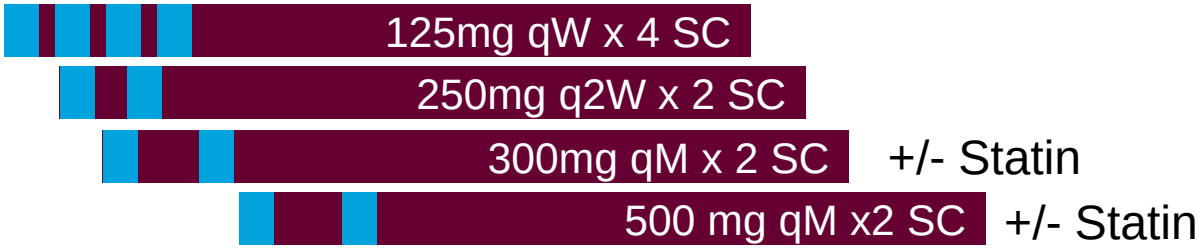
Secondary objectives

- PK, PCSK9 and LDL-C reduction

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**



Initial ALN-PCSsc Phase 1 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%	100%	83.3%	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%	16.7%	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

Initial ALN-PCSsc Phase 1 Study Results
MD Cohort Demographics and Baseline Characteristics

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

	Placebo N=12	125mg qW x4 N = 6	250mg q2W x2 N=6	300 mg qM x2 N=6	300 mg qM x2 S^ N=4	500 mg qM x2 N=6	500 mg qM x2 S^ 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%	50.0%	50.0%	40.0%	63.6%
BMI (kg/m^2), Mean	26.6	26.2	27.1	25.4	27.2	23.0	25.6	25.6
Race (%)								
-Asian	0%	16.7%	0%	0%	25.0%	16.7%	20.0%	12.1%
-Black African or African American	0%	0%	16.7%	0%	0%	0%	20.0%	6.1%
-Caucasian	91.7%	83.3%	50.0%	100%	75.0%	83.3%	60.0%	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 ^ = On a stable statin dose

Data in database as of 04 August 2015

Initial ALN-PCSsc Phase 1 Study Results

Baseline Values for PCSK9 and LDL-C

SAD phase							
Treatment (N)	**Placebo (6)**	**25mg (3)**	**100 mg (3)**	**300 mg (3)**	**500 mg (3)**	**800 mg (6)**	**Overall (24)**
Mean (SEM) PCSK9 (ng/mL)	278.9 (40.63)	342.7 (39.20)	233.8 (22.61)	253.8 (12.91)	263.2 (14.42)	279.6 (27.31)	276.3 (13.94)
Mean (SEM) LDL-C (mg/dL)	142.2 (11.35)	184.0 (26.99)	161.7 (16.06)	173.2 (29.48)	135.0 (3.33)	161.3 (10.25)	157.6 (6.61)

MD phase								
Treatment (N)	**Placebo (12)**	**125 mg qWx4 (6)**	**250 mg q2Wx2 (6)**	**300 mg qM x2 (6)**	**300 mg qM x2 S^ (4)**	**500 mg qM x2 (6)**	**500 mg qM x2 S^ (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 (10.18)	145.4 (12.86)	158.1 (15.62)	131.7 (20.20)	131.3 (11.24)	139.4 (4.89)

S ^ = On a stable statin dose

Data in database as of 04 August 2015

Initial ALN-PCSsc Phase 1 Study Results
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% or 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

Initial ALN-PCSsc Phase 1 Study Results
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)*

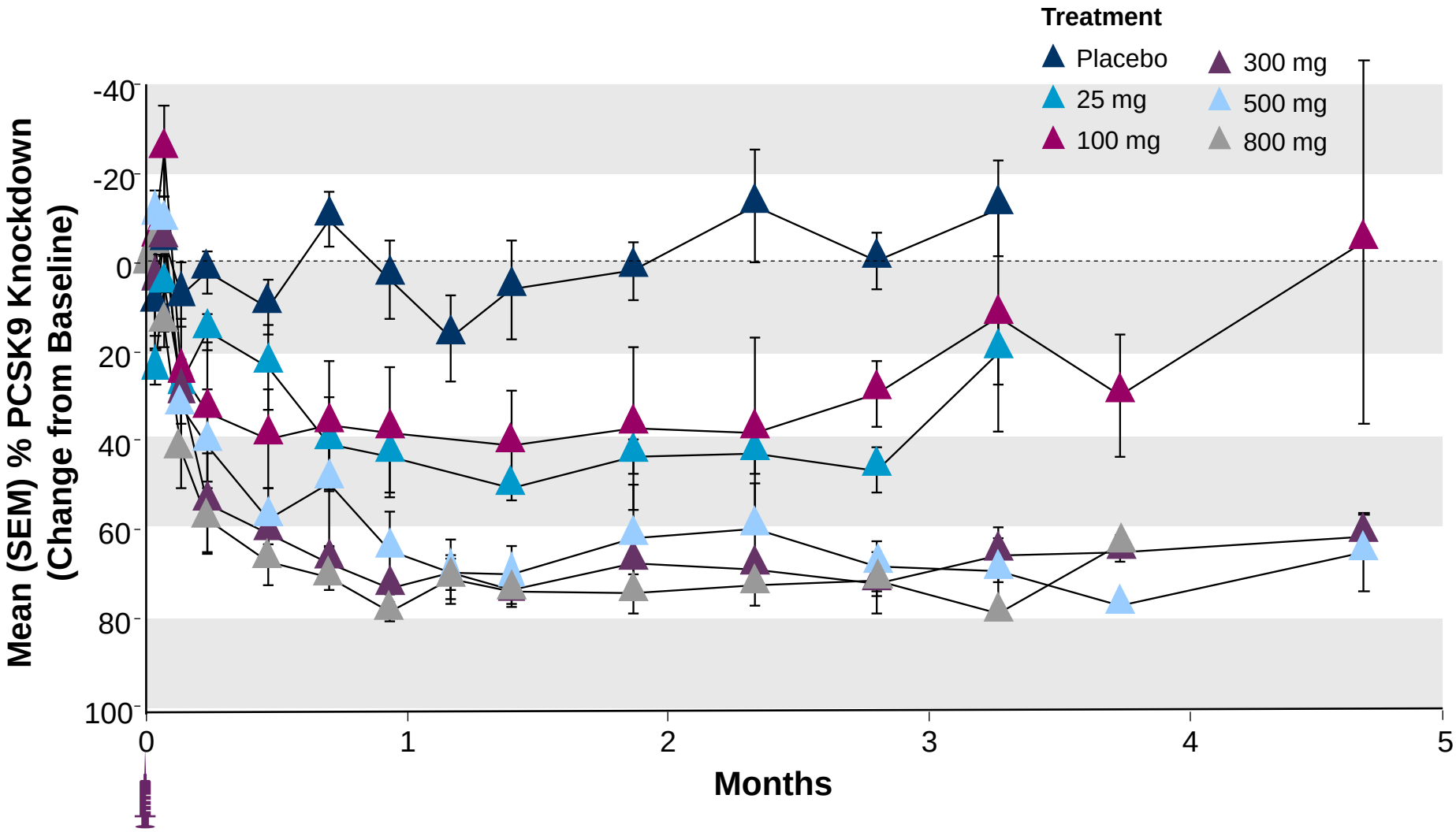
AE Preferred Term	Placebo N=12	125 mg qWx4 N=6	250 mg q2Wx2 N=6	300 mg qMx2 N=6	300 mg qMx2 S^ N=4	500 mg qMx2 N=6	500 mg qMx2 S^ N=5	Total ALN-PCSsc N=33
Headache	2	1	1	1	1	2	0	6
Back pain	2	1	0	0	0	2	1	4
Diarrhea	3	2	0	0	1	0	1	4
Nausea	0	2	0	0	0	2	0	4

*Subjects with one or more AEs 9/12 placebo; 22/33 ALN-PCSsc
S ^ =On stable dose of statin

Data in database as of 04 August 2015

Initial ALN-PCSsc Phase 1 Study Results

SAD PCSK9 Knockdown Relative to Baseline



Day/Treatment combinations where N=1 not displayed

Data in database as of 04 August 2015

Initial ALN-PCSsc Phase 1 Study Results
SAD PCSK9 Knockdown Relative to Baseline

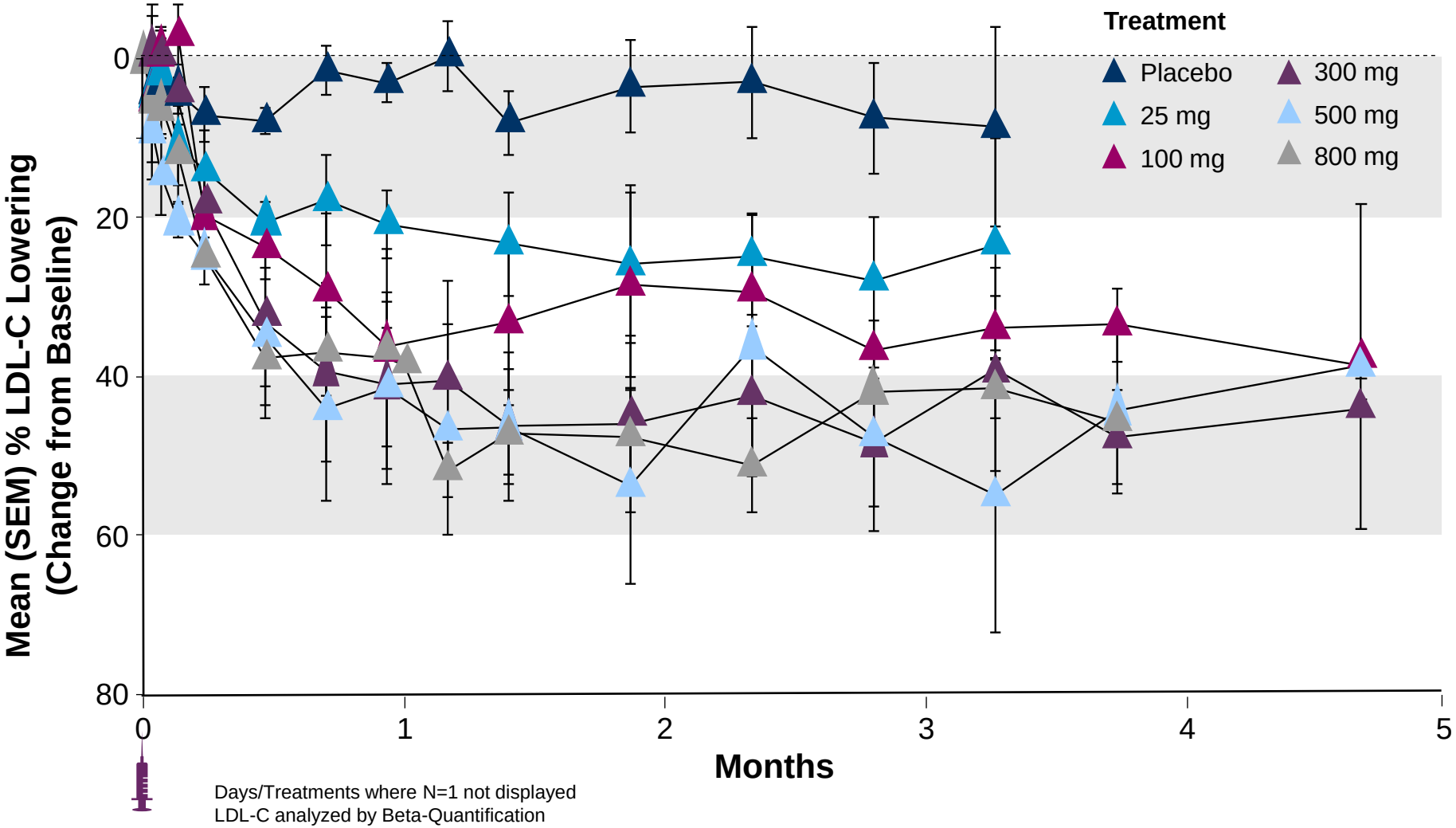
PCSK9 % Knockdown (KD) SAD Phase						
Dose Group	Mean Max % KD (+/- SEM)@	Max % KD	Mean % KD Day 84 (+/- SEM)@	N at Day 84#	Mean % KD Day 140 (+/- SEM)^	N at Day 140@
Placebo	29.4 (3.89)	38.4	0.1 (6.41)	5	NA	0
25 mg	54.3 (2.74)	59.7	47.3 (5.12)	2	14.4 (-)	1
100 mg	48.9 (15.80)	72.6	29.9 (7.44)	3	-4.1 (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 (8.92)	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 ANOVA/ANCOVA 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

Initial ALN-PCSsc Phase 1 Study Results

SAD LDL-C Lowering Relative to Baseline



Data in database as of 04 August 2015

Initial ALN-PCSsc Phase 1 Study Results
SAD LDL-C Lowering Relative to Baseline

LDL-C % Reduction SAD Phase						
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#
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 ANOVA/ANCOVA 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

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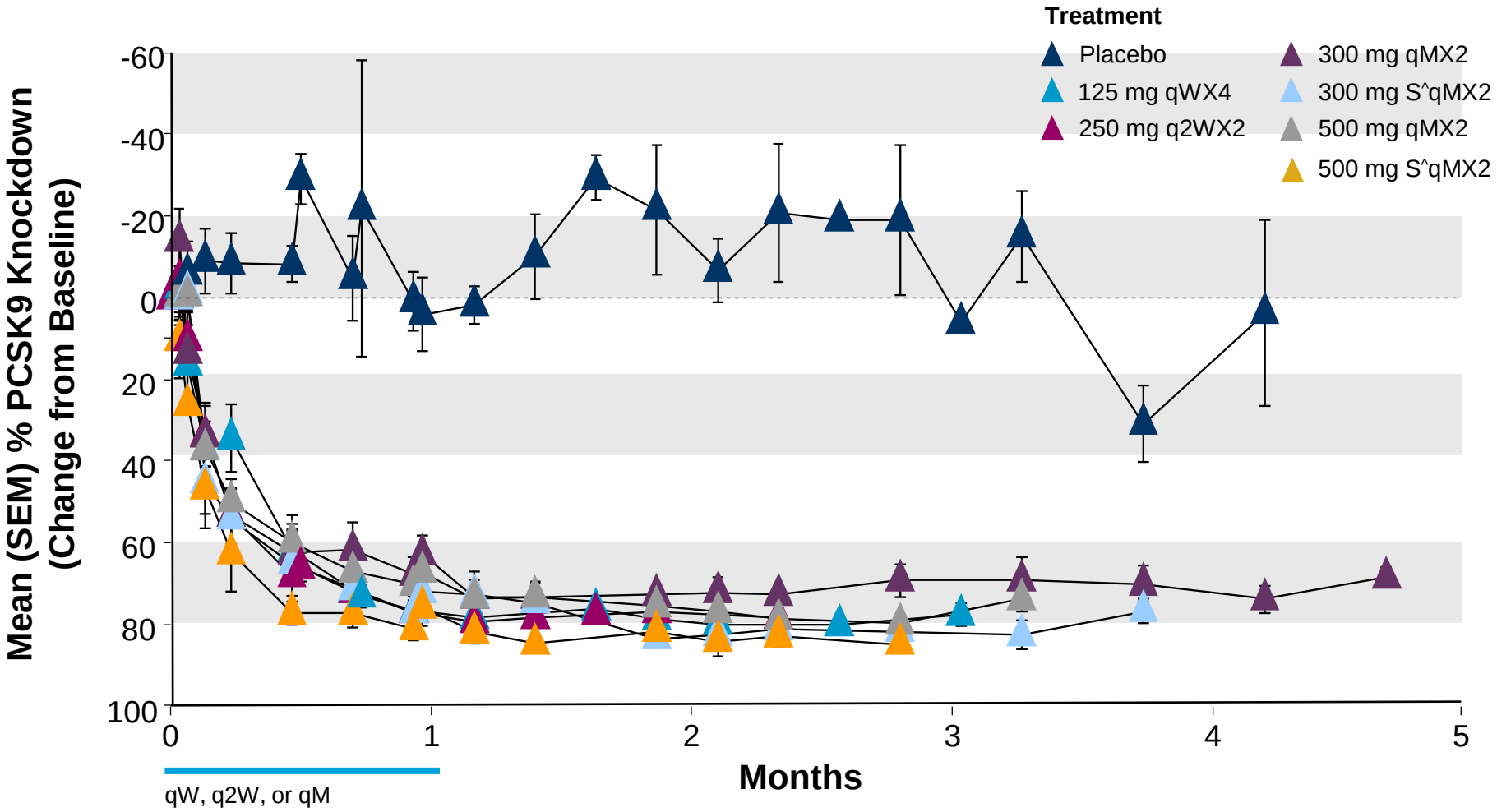
Initial ALN-PCSsc Phase 1 Study Results

MD PCSK9 Knockdown Relative to Baseline



S ^ =On 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

Initial ALN-PCSsc Phase 1 Study Results

MD PCSK9 Knockdown Relative to Baseline

PCSK9 % KD MD Phase		
Dose Group	Mean Max % KD (SEM)[@]	Max % KD
Placebo	28.7 (5.70)	63.2
125 mg qwX4	82.3 (1.12)***	85.7
250 mg q2wX2	80.9 (1.38)***	84.6
300 mg qMX2	78.6 (3.08)***	86.9
300 mg S^ qMX2	86.1 (1.19)***	88.1
500 mg qMX2	81.3 (2.25)***	86.4
500 mg S^ qMX2	88.0 (1.66)***	94.4

Mean maximal knockdown compared via ANOVA
[@] Pairwise comparisons *vs.* Placebo examined via Tukey's tests under the ANOVA/ANCOVA models
*, P < 0.05; **, P < 0.01; ***, P < 0.001
S^ = On 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

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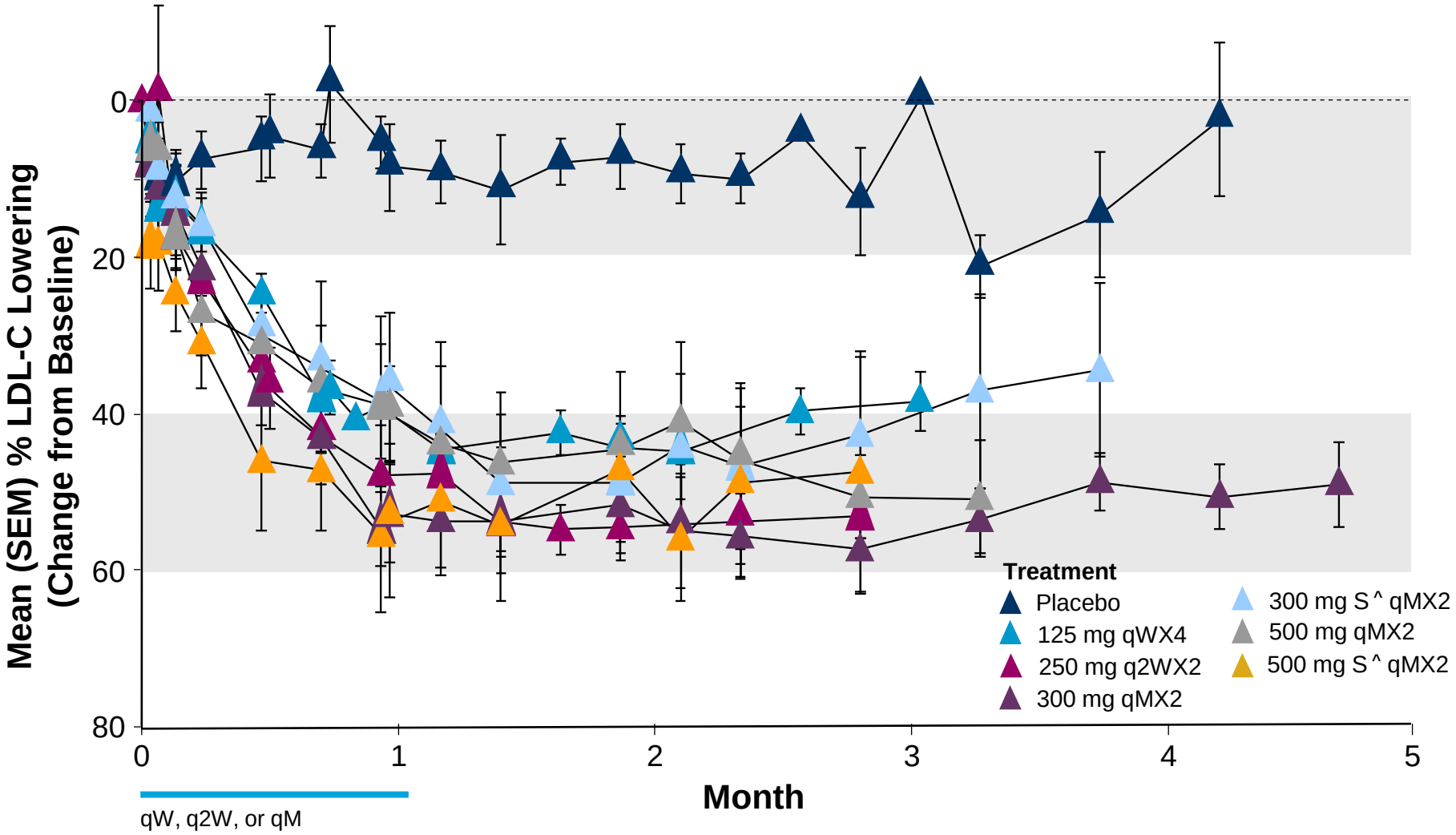
Initial ALN-PCSsc Phase 1 Study Results

MD LDL-C Lowering Relative to Baseline



S ^ =On a stable dose of statins
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

Initial ALN-PCSsc Phase 1 Study Results

MD LDL-C Lowering Relative to Baseline

LDL-C % Reduction MD Phase		
Dose Group	Mean Max % Reduction (+/- SEM)@	Max % Reduction
Placebo	21.5 (3.26)	42.6
125 mg qWX4	51.2 (1.91)	59.6
250 mg q2WX2	60.4 (4.51)***	70.3
300 mg qMX2	64.4 (5.41)***	79.3
300 mg S^ qMX2	51.8 (10.11)	69.4
500 mg qMX2	55.2 (6.49)**	69.3
500 mg S^ qMX2	59.6 (8.43)***	83.0

Mean maximal knockdown compared via ANOVA
@ Pairwise comparisons *vs.* Placebo examined via Tukey's tests under the ANOVA/ANCOVA models.
*, P < 0.05; **, P < 0.01; ***, P < 0.001
S^ = 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

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
- 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