American Heart Association. life is why™ | SCIENTIFIC SESSIONS

ORION-1

Inclisiran inhibits PCSK9 synthesis by RNA interference

Planned interim analysis of a multi-center randomized controlled dose-finding trial

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On behalf of the ORION-1 investigators

Background and rationale
Inclisiran: Under investigation for LDL-C lowering

- ASCVD remains a challenge to global health[1]
- LDL-C reduction is a proven strategy to prevent ASCVD[2]
- Statins are the cornerstone of treatment but with limitations[2]
- mAbs that block PCSK9 have demonstrated significant LDL-C lowering with or without statins[3,4]
- mAbs that block PCSK9 require 12-24 s.c. injections per year (totaling ~2-5 grams)[5,6]
- Administrative and financial burdens leave room for more efficient agents
- RNAi a highly efficient approach to inhibit PCSK9 synthesis in the liver[7,8]
- Phase I 300 mg s.c. inclisiran lowered LDL-C ~50% for 4-6 months (n=69)[9]

1: World Health Organization
2: AHA guidelines on dyslipidemia
3: Sabatine MS et al. N Engl J Med 2015;372:1500-9
4: Robinson JG et al. N Engl J Med 2015;372:1489-99
5: https://www.repathahcp.com/dosing
6: https://www.praluenthcp.com/dosing
7: Wittrup A & Lieberman J Nature Rev Gen 2015;16: 543-52
8: Fitzgerald K et al. Lancet 2013;9911:60-8
9: Fitzgerald K et al. N Engl J Med online publication 2016:November 13

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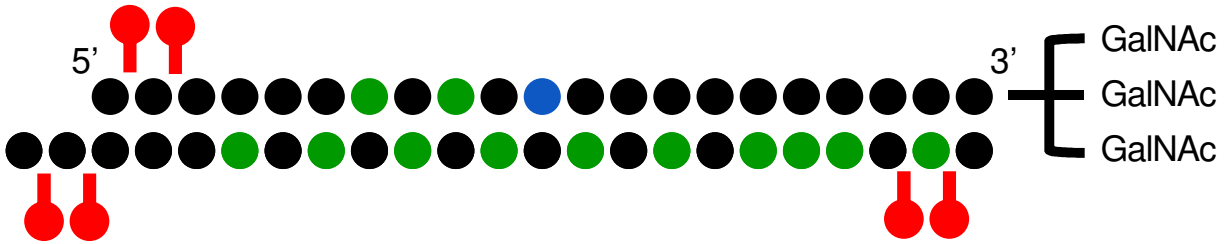
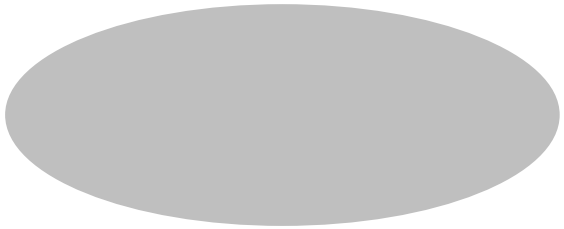
PCSK9 synthesis inhibition via RNA interference
Inclisiran harnesses a natural catalytic process

- Synthetic double strand 21-23mer oligonucleotide
- 3x GalNAc at sense 3' end enables hepatic-specific uptake via ASGP receptor
- Chemically modified to prevent RNAse degradation
- Dicer separates antisense strand – and incorporates it into RISC
- RISC degrades PCSK9 mRNA catalytically to halt PCSK9 protein synthesis in the liver



RISC - RNA induced silencing complex



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Objectives
Dosage selection for Phase III

- Primary endpoint
  - Percent change in LDL-C levels from baseline at day 180
- Secondary endpoint
  - LDL-C levels at day 90 and other lipid parameters
  - LDL-C and PCSK9 levels over time
  - Safety and tolerability
- **Interim analysis**
  - Pre-specified and pre-defined endpoints
  - Interim analysis endpoints up to 90 days
  - Change and % change from baseline in LDL-C, PCSK9, other lipids and lipoproteins
  - Safety and tolerability

Patient population
High cardiovascular risk and elevated LDL-C

Inclusion criteria

- Age ≥18 years
- With ASCVD - LDL-C >70 mg/dL
- High risk primary prevention LDL-C >100
- TG <400 mg/dL
- eGFR ≥30 mL/min
- Maximally tolerated statin
- Stable lipid Rx for ≥30 days

Exclusion criteria

- Significant comorbidity
- HbA1c ≥10%
- NYHA Class II-IV HF
- MACE <6 months
- Uncontrolled BP
- Active liver disease
- Pregnancy or risk | nursing
- Cognitive impairment

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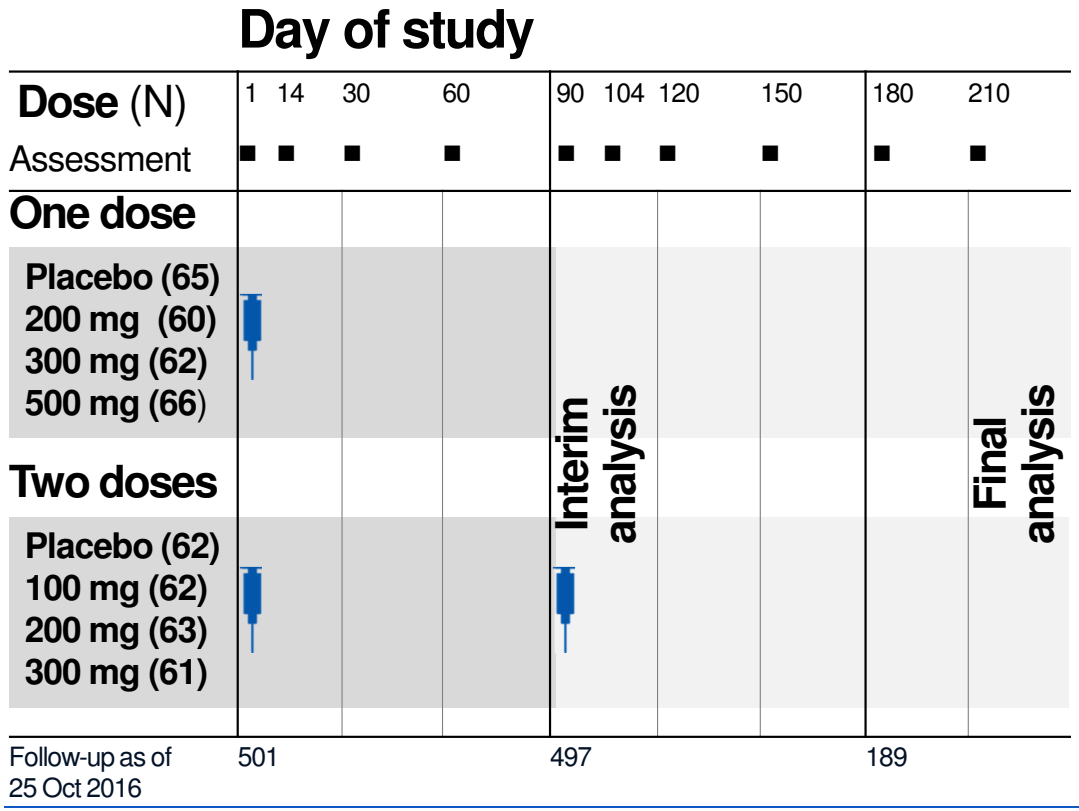
Study design and statistics
Dose finding - placebo controlled



Statistics

Sample size of 480 patients allowed for

- 15% drop out rate
- ≥90% power to detect ↓30% LDL-C in at least 1 treatment group

Pre-specified interim analysis plan

Follow-up cut-off 25 Oct 2016

- 497 patients followed to 90 days
- 189 patients followed to 180 days

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Patient characteristics
Baseline demographics well balanced

Total=501			Inclisiran			
	Placebo N=127	Pooled N=374	100 mg N=62	200 mg N=123	300 mg N=123	500 mg N=66
Age mean (years)	62	64	65	63	64	62
BMI (kg/m^2)	30	29	29	29	29	28
White	117 (93%)	357 (93%)	57 (92%)	114 (93%)	114 (93%)	63 (95%)
Male	75 (59%)	251 (67%)	39 (63%)	78 (63%)	87 (71%)	47 (71%)
Cardiovascular disease	91 (72%)	254 (68%)	43 (69%)	84 (68%)	91 (74%)	36 (55%)
Lipid lowering treatment	99 (78%)	307 (82%)	50 (81%)	103 (84%)	102 (83%)	52 (79%)
Statin treatment	94 (74%)	271 (72%)	44 (71%)	91 (74%)	91 (74%)	45 (68%)
LDL-C (beta quant) (mg/dL)	125	129	128	129	126	135
PCSK9 (ng/mL)	427	427	410	448	420	418

Safety of inclisiran to day 90
Treatment emergent adverse events (TEAE)

Total=497			Inclisiran			
Day 1-90	Placebo N=127	Pooled N=370	100 mg N=61	200 mg N=122	300 mg N=122	500 mg N=65
Any TEAE	69 (54%)	198 (54%)	38 (62%)	64 (52%)	68 (56%)	28 (43%)
Serious	5 (4%)	22 (6%)	8 (13%)	6 (5%)	6 (5%)	2 (3%)
Severe	5 (4%)	12 (3%)	3 (5%)	3 (2%)	4 (3%)	2 (3%)
Related	24 (19%)	67 (18%)	11 (18%)	20 (16%)	27 (22%)	9 (14%)
Death	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	1 (1.5%)

Most common TEAEs (>2%) were myalgia, headache, fatigue, nasopharyngitis, back pain, hypertension, diarrhea, dizziness (similar incidence to placebo)

Safety of inclisiran to day 90
Liver and muscle TEAE[1]

Total=497			Inclisiran			
Day 1-90	**Placebo**	**Pooled**	**100 mg**	**200 mg**	**300 mg**	**500 mg**
	N=127	**N=370**	**N=61**	**N=122**	**N=122**	**N=65**
ALT >3x ULN	0	1 (0.3%)	0	0	1 (0.8%)	0
AST >3x ULN	0	1 (0.3%)	0	0	1 (0.8%)	0
ALP >2x ULN	0	3 (0.8%)	1 (1.6%)	0	2 (1.6%)[2]	0
Bilirubin >2x ULN[3]	0	0	0	0	0	0
CK >5x ULN	0	2 (0.6%)	0	1 (0.8%)[4]	1 (0.8%)	0
Myalgia	6 (4.7%)	21 (5.7%)	5 (8.2%)	7 (5.7%)	8 (6.6%)	1 (1.5%)

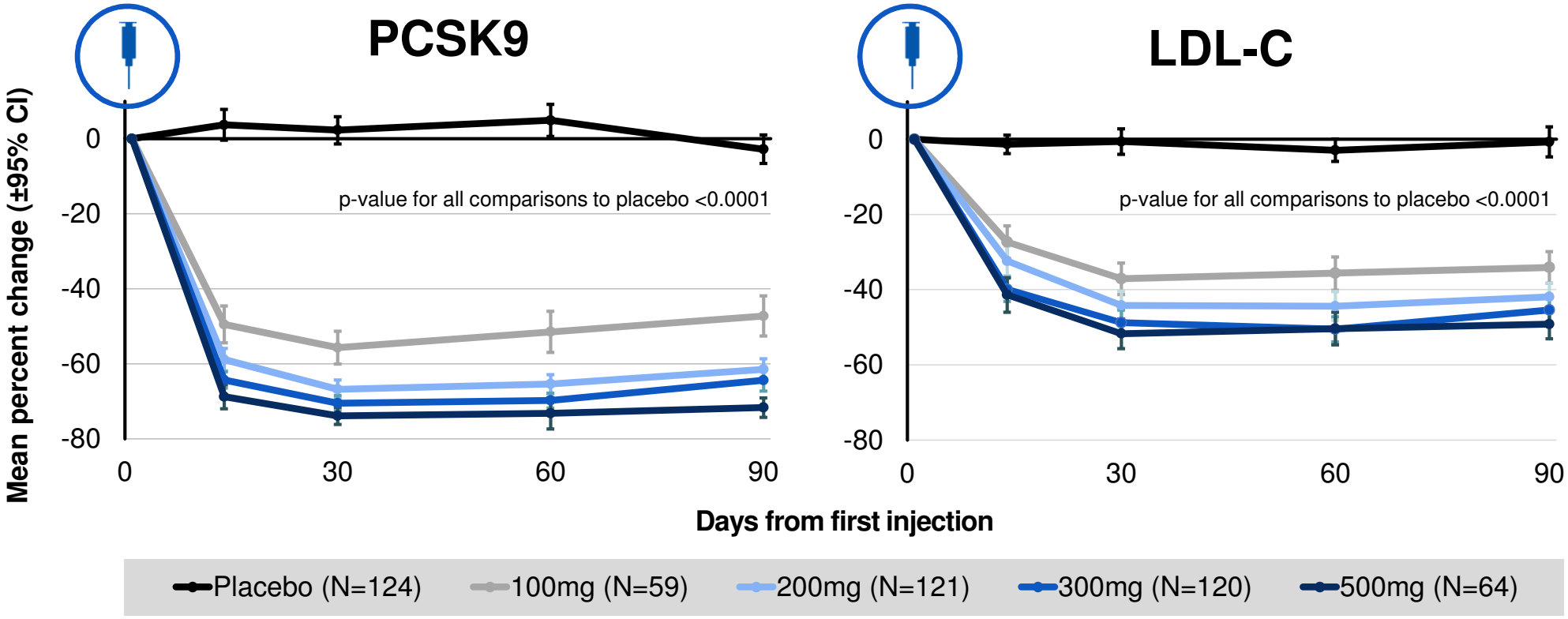
1: Crossing above threshold for significance at any time after randomization regardless of baseline
2: One patient above ULN at baseline
3: No patient met the criteria for Hy's law
4: Patient >3x ULN at baseline

Safety of inclisiran to day 90
First injection TEAE[1,2]

Total=497			Inclisiran			
AE terms	Placebo N=127	Pooled N=370	100 mg N=61	200 mg N=122	300 mg N=122	500 mg N=65
Injection site erythema	0	4 (1.1%)	0	2 (1.6%)	1 (0.8%)	1 (1.5%)
Injection site pruritus	0	1 (0.3%)	0	0	1 (0.8%)	0
Injection site rash	0	0	0	0	0	0
Injection site reaction	0	7 (1.9%)	1 (1.6%)	1 (0.8%)	3 (2.5%)	2 (3.1%)
Total (observed any time)	0	12 (3.2%)	1 (1.6%)	3 (2.5%)	5 (4.1%)	3 (4.6%)
Total (observed >4 hours)	0	9 (2.4%)	1 (1.6%)	3 (2.5%)	4 (3.3%)	1 (1.5%)

1: Number of patients with adverse event classified by preferred term – each patient is counted only once
2: Pre-defined histaminic/allergic type adverse events

Efficacy of one dose of inclisiran up to day 90
Significant, durable PCSK9 and LDL-C lowering



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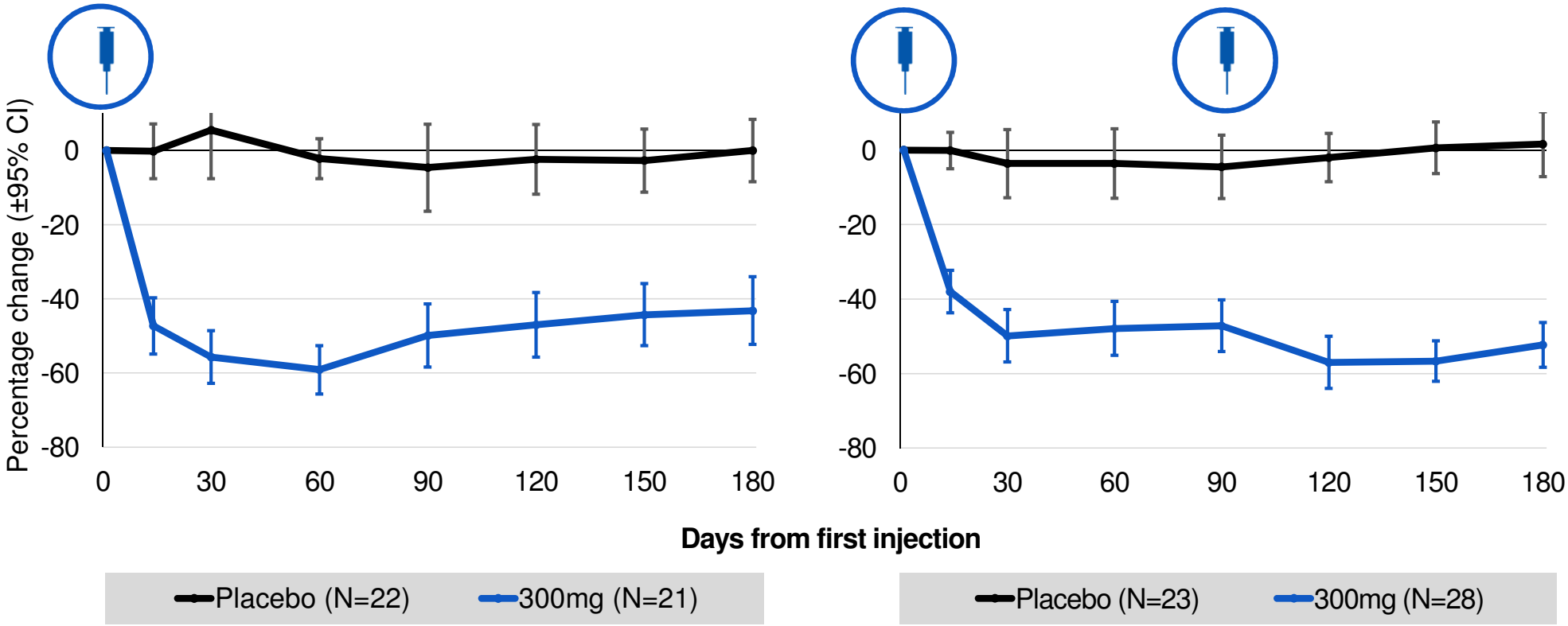
Efficacy of one dose of inclisiran up to day 90
Other lipid parameters - change from baseline

Total=494[1]			Inclisiran			
Day 90		Placebo	100 mg	200 mg	300 mg	500 mg
		N=124	N=61	N=122	N=122	N=65
Total cholesterol	mean (SD)	-1% (16)	-22% (12)	-26% (14)	-28% (15)	-30% (11)
Triglyceride	median	3%	1%	-11%	-10%	0%
HDL-C	mean (SD)	-2% (14)	5% (11)	8% (12)	9% (16)	8% (15)
Non-HDL-C	mean (SD)	0% (20)	-30% (13)	-37% (18)	-40% (19)	-42% (15)
Apo-B	mean (SD)	-2% (16)	-28% (12)	-34% (15)	-37% (16)	-40% (13)
Lp(a)	median	-1%	-18%	-21%	-23%	-22%

1: Includes patients with baseline and day-90 measurement for all parameters

One dose and two doses of inclisiran up to day 180
Efficacy of 300 mg versus placebo on LDL-C



Available data as of 25 Oct 2016

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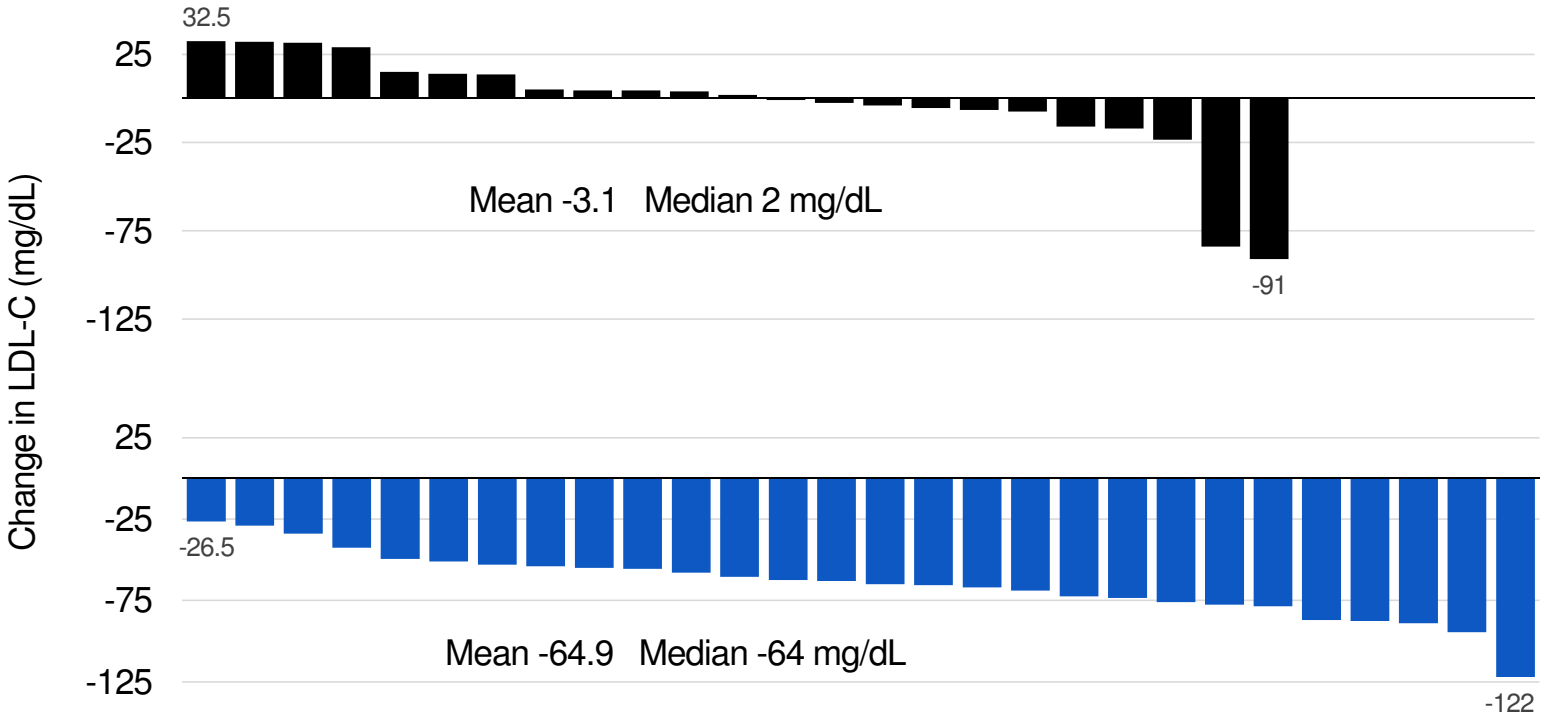
Individual patient response at day 180
Absolute change in LDL-C from baseline



Placebo
Two doses
(N=23)

300 mg
Two doses
(N=28)

Available data as of 25 Oct 2016

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Conclusions
Inclisiran: Phase III-ready investigational compound

- Inclisiran inhibits PCSK9 synthesis by RNA interference and lowers LDL-C significantly
  - One dose of 300 mg achieves mean 51% LDL-C reduction
  - Two doses of 300 mg achieve mean 57% LDL-C reduction
- Inclisiran is well tolerated with no material safety issues
- Potential for biannual or triannual dosing affirmed
- Results of ORION-1 support start of Phase III
- The efficacy, safety and dosing profile of inclisiran are likely to ensure significant and durable reductions in LDL-C and thus potentially impact cardiovascular outcomes