

NATIONAL LIPID ASSOCIATION

May 16-19



**SCIENTIFIC
SESSIONS**

**2019
MIAMI**





THE EXTENSION TRIAL FOR ORION-1

ORION-3

Long-term inclisiran in subjects with high CV risk and elevated LDL-C

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For the ORION-1 and 3 investigators



Research grants

- ORION-1, 2 and 3 were sponsored by MDCO with participation of AMC

Consultancy

- Advisor to The Medicines Company, Amgen, Sanofi, Pfizer

Safety & efficacy of inclisiran not known beyond 1-year



In ORION-1:

- 300mg inclisiran given on day 1 & 90 demonstrated safe lowering of LDL-C by $\geq 50\%$ and up to 88% — with minimal variability and at least 6-months persistence¹
- Subjects were followed up to 1-year

Could ORION-3 extend the treatment period for ORION-1 inclisiran subjects to enable the assessment of long-term safety and efficacy, and

Could a dose-PD response model from ORION-1 be validated using ORION-3 and offer insights for ongoing and future trials including Phase III?

1. Ray KK et al. N Engl J Med 2017; 376:1430-1440

OBJECTIVES

Investigate the long-term safety and efficacy of inclisiran



Safety: Incidence of adverse events and laboratory changes

Efficacy: LDL-C, PCSK9 and other lipid parameters on day 210 of ORION-3

LDL-C, PCSK9 over the time course of ORION-1 & 3 combined

Dosage: Build a dose-PD response model and validate its performance

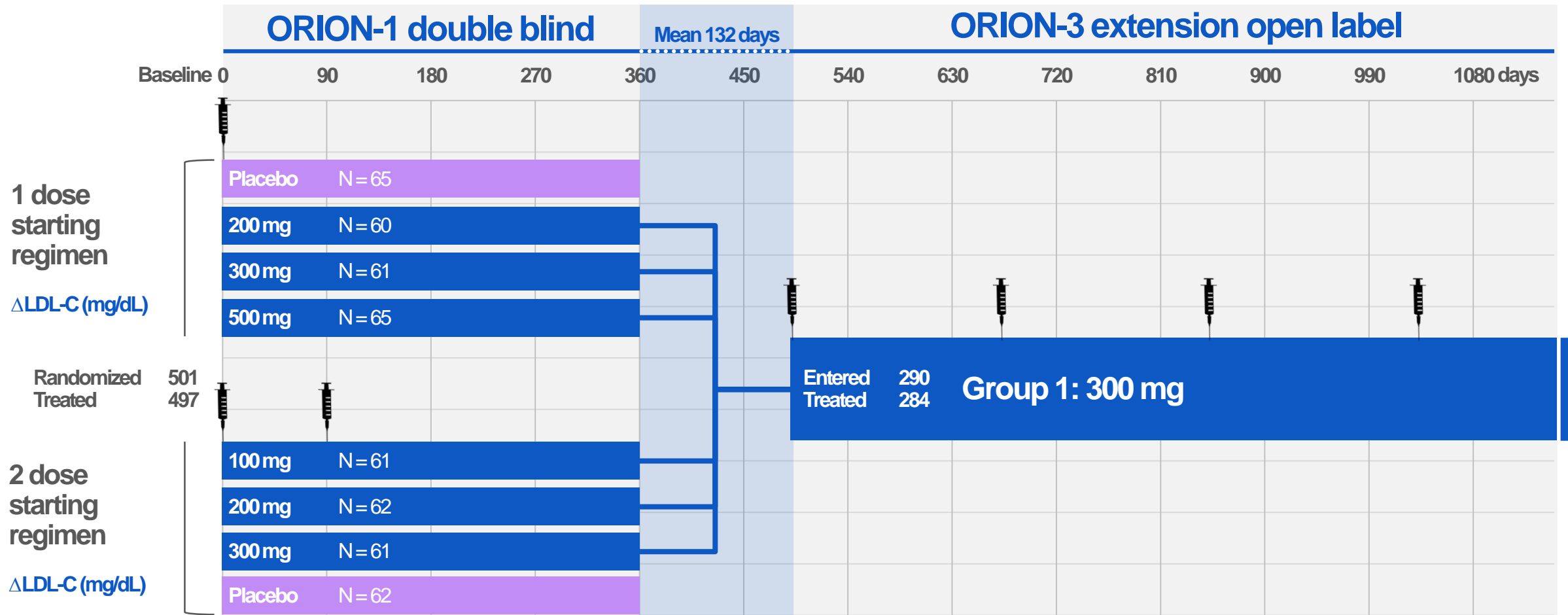
Simulation: Use the model to predict effects of inclisiran in Phase III

METHODS

Design of investigation



Total ~3 years treatment & observation



Data Sources: ORION-1 Table 5.10.1.1 final and ORION-3 Table 5.1.1.ORN3.calc ORION-3 09 May 2019

METHODS

ORION-3 Group-1 baseline¹ characteristics (N = 290)



Representative of a typical moderate/high-risk ASCVD population

Age	Mean years (SD)	63.3	(11.1)
Male	N (%)	188	(65%)
Diabetes	N (%)	70	(24%)
Prior PCI	N (%)	125	(43%)
MI	N (%)	104	(35%)
CABG	N (%)	47	(16%)
Hypertension	N (%)	193	(67%)
Current statin use	N (%)	232	(80%)
PCSK9	Mean ng/dL (\pm SD)	428.4	(128.5)
LDL-C	Mean mg/dL (\pm SD)	130.1	(57.3)

1. Baseline for ORION-1

RESULTS

Excellent tolerability and safety



Highly consistent profile throughout ORION-1 and ORION-3 over ~3 years

- Injection site reactions infrequent, mild-moderate and transient
- No LFT elevations considered related to inclisiran
- No myalgias or CPK elevations considered related to inclisiran
- No renal adverse events or thrombocytopenia considered related to inclisiran
- One cerebrovascular accident death in ORION-3 related to underlying ASCVD

RESULTS

Persistent and robust efficacy



Group-1 primary endpoint: Percent change in LDL-C on day 210 of ORION-3

ITT		Day 210 change from baseline ¹			p-value
LDL-C	All patients (N=290)	Mean (SD)	- 51%	(28)	< 0.001
		Mean (SD)	- 64 mg/dL	(39)	< 0.001
	Patients randomized to 300 mg 2 dose starting regimen (N = 61)	Mean (SD)	- 56%	(18)	< 0.001
		Mean (SD)	- 73 mg/dL	(31)	< 0.001
PCSK9	Mean (SD)	- 77%	(8)	< 0.001	
Non HDL-C	Mean (SD)	- 43%	(24)	< 0.001	
HDL-C	Mean (SD)	+ 9%	(15)	ns	
Triglycerides	Mean (SD)	- 6%	(42)	ns	

1. Average 22 months from baseline at the start of ORION-1

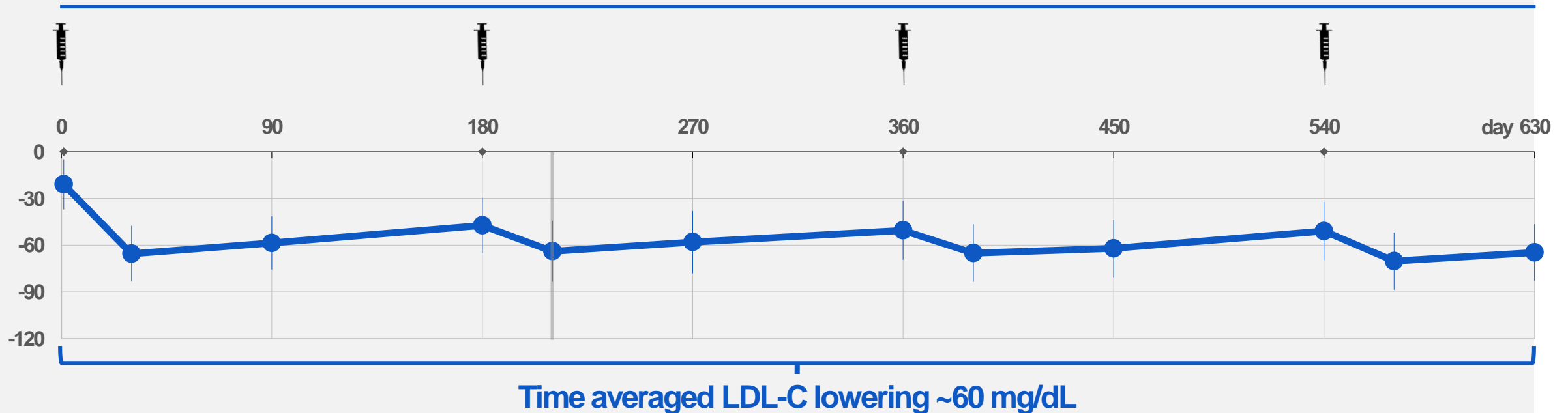
RESULTS

Consistent long-term effect of 300 mg inclisiran on LDL-C



LDL-C lowering in ORION-3 over 22 months

ORION-3 extension open label Group 1 (N=290) mean change in LDL-C (mg/dL [SD])

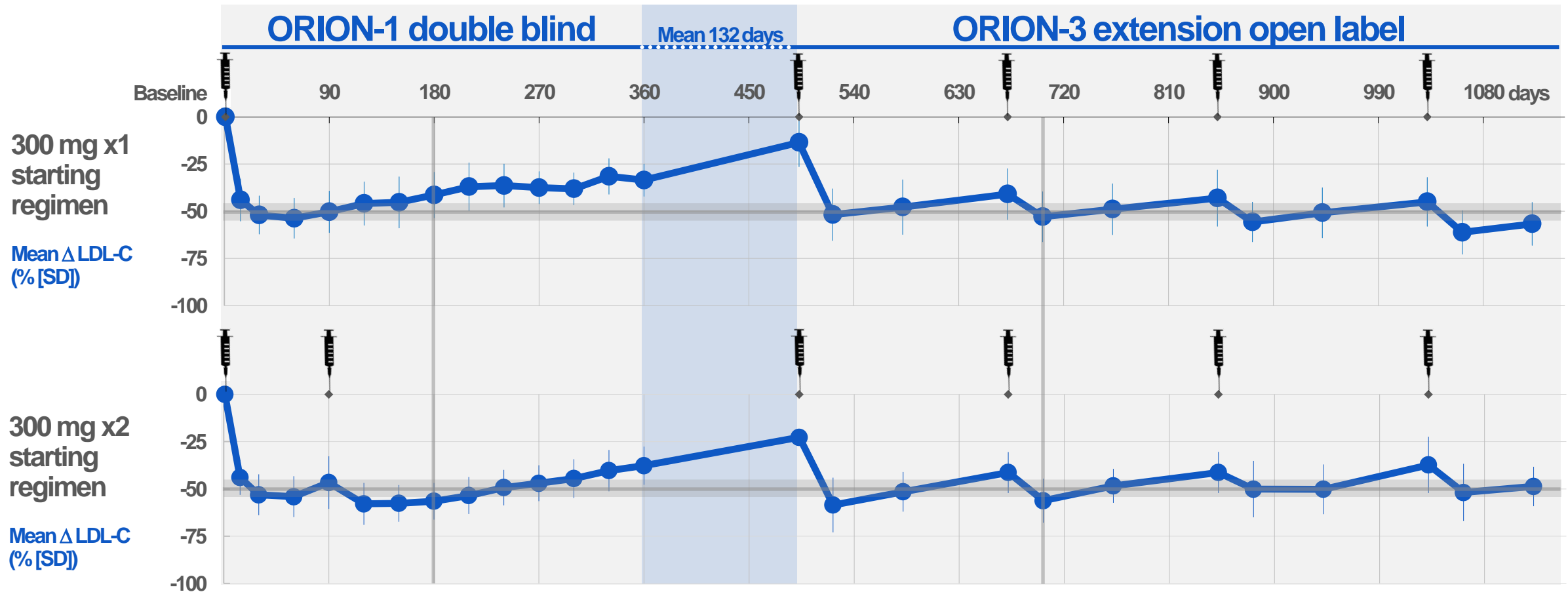


RESULTS

Long-term effect of 300 mg inclisiran on LDL-C



Consistent lowering of LDL-C >50% with no loss of effect over ~3 years



Data Sources: ORION-1 Table 5.10.1.1 final and ORION-3 Table 5.1.1.ORN3.calc ORION-3 09 May 2019

SUMMARY

Inclisiran given twice a year persistently lowers LDL-C



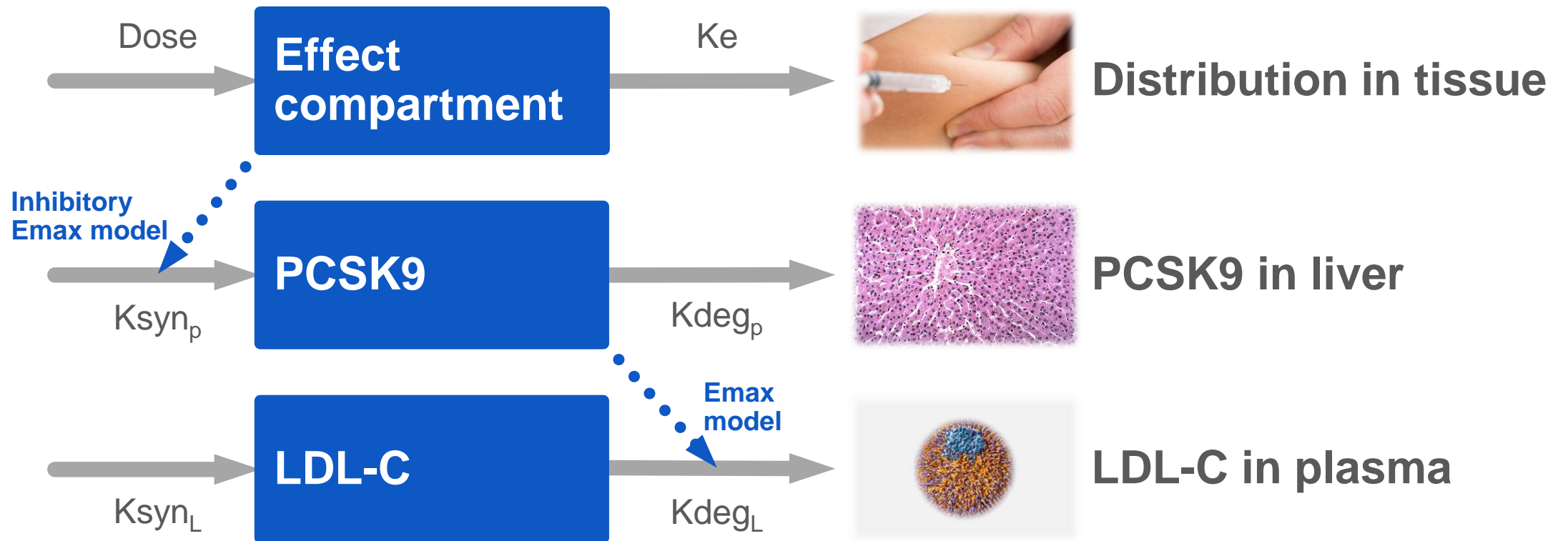
No material safety observations out to 3 years

- Primary endpoint at ~22 months from baseline showed 51% ↓LDL-C (p-value <0.001)
- Time-averaged lowering of LDL-C in ORION-3 was ~60 mg/dL
- Well tolerated and no Rx-related elevation of liver enzymes or changes in renal function

Dose response model



Describes relationship between dose, RNA interference of PCSK9, effect on LDL-C

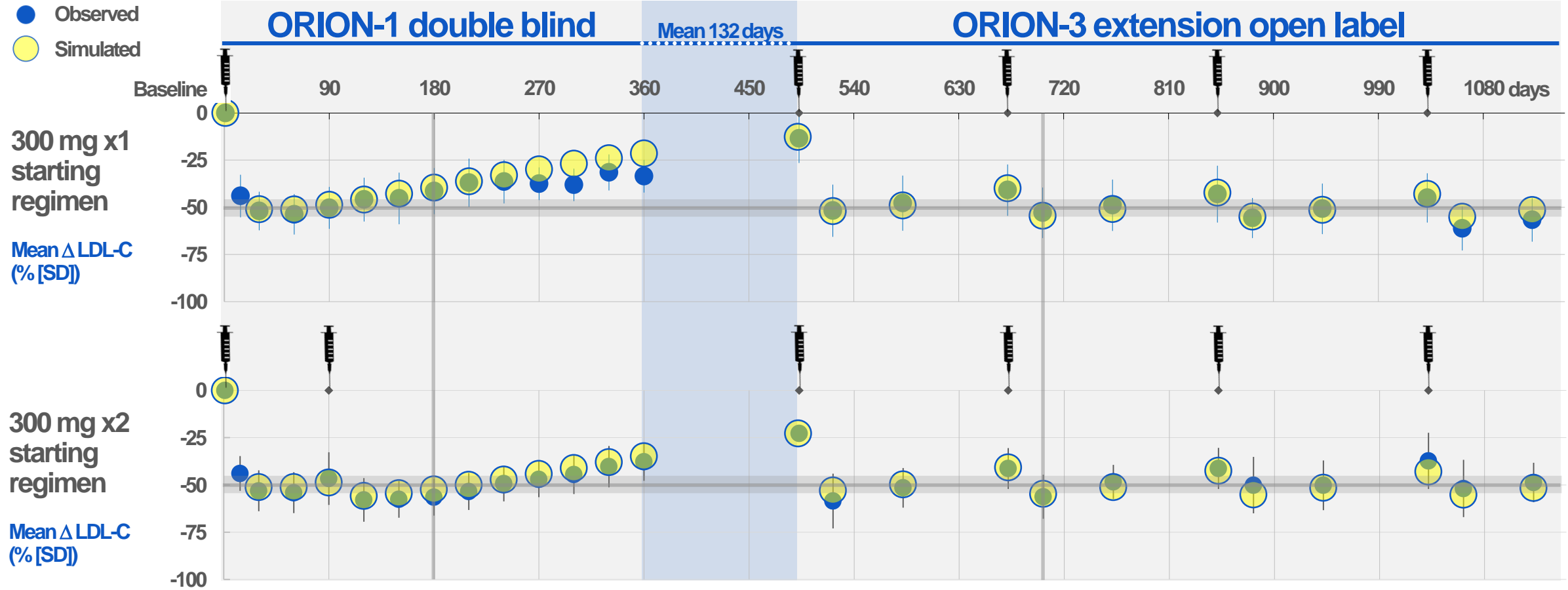


RESULTS

Model fit for percent reduction in LDL-C



Simulation closely matches observed results out to 3-years



Data Sources: ORION-1 Table 5.10.1.1 final and ORION-3 Table 5.1.1.ORN3.calc ORION-3 09 May 2019

What could this mean for ongoing blinded Phase III trials?



Inclisiran expected to lower LDL-C $\geq 50\%$ and MACE by $\geq 25\%$

	ORION-9 HeFH N = 482	ORION-10 U.S. ASCVD N = 1561	ORION-11 EU ASCVD/RE N = 1617
Baseline LDL-C	161 mg/dL	110 mg/dL	112 mg/dL
Simulation using dose-PD response model			
1 ^o endpoint: Day 510 % LDL reduction	54%	54%	54%
Time-averaged % LDL-C reduction	51%	51%	51%
LDL-C reduction calculated	82 mg/dL	56 mg/dL	57 mg/dL
Estimated 5 year MACE RRR¹	44%	30%	31%

1. MACE relative risk reduction estimate assumes 50% of effect year-1; 100% of effect thereafter; based on Cholesterol Treatment Trialists' (CTT) Collaboration (Baigent et al, 2005)

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