ORION-1 Trial

Inclisiran lowers LDL-C and PCSK9 irrespective of diabetes status without worsening glycemia

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ORION-1: Diabetes status subgroups

Presented on behalf of the Steering Committee

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Disclosures for Lawrence A Leiter, MD

Research grants

- Astra Zeneca, Amgen, Esperion, Kowa, Merck, Sanofi/Regeneron, The Medicines Company

Advisory panels

- Astra Zeneca, Amgen, Merck, Sanofi/Regeneron

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Major progress in ASCVD - but challenges remain

PCSK9 inhibition is now a validated target for reducing LDL-C and ASCVD

- mAb therapy requires 12-26 injections per year
- Adherence with PCSK9 mAbs is not substantially better than that with statins[2]

1. Sabatine MS et al. N Engl J Med. 2017;376:1713-1722
2. Hines D et al. J Am Coll Cardiol. 2017;69 (11 Suppl):159

Poor adherence and LDL-C variability are associated with poor outcomes[3]

- Approximately 9% of ASCVD risk is attributable to poor adherence[4]
- Limitations are most relevant in high risk patients

3. Bangalore S et al. J Am Coll Cardiol. 2015;65:1539-48
4. Chowdhury R et al. EHJ 2013;34:2940-8

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Inclisiran: A novel agent to address unmet needs

RNAi harnessing

Viable option to inhibit PCSK9 and lower LDL-C[1]

Inclisiran

Synthetic siRNA that inhibits PCSK9 synthesis in the liver[2]

Phase I trial

300 mg inclisiran lowered LDL-C 50-60% for 84 days[3]

1. Wittrup A, Lieberman J. Nat Rev Genet. 2015;16:543-52..

2. Fitzgerald K et al. Lancet. 2014;383:60-68
3. Fitzgerald K et al. N Engl J Med. 2017;376:41-51

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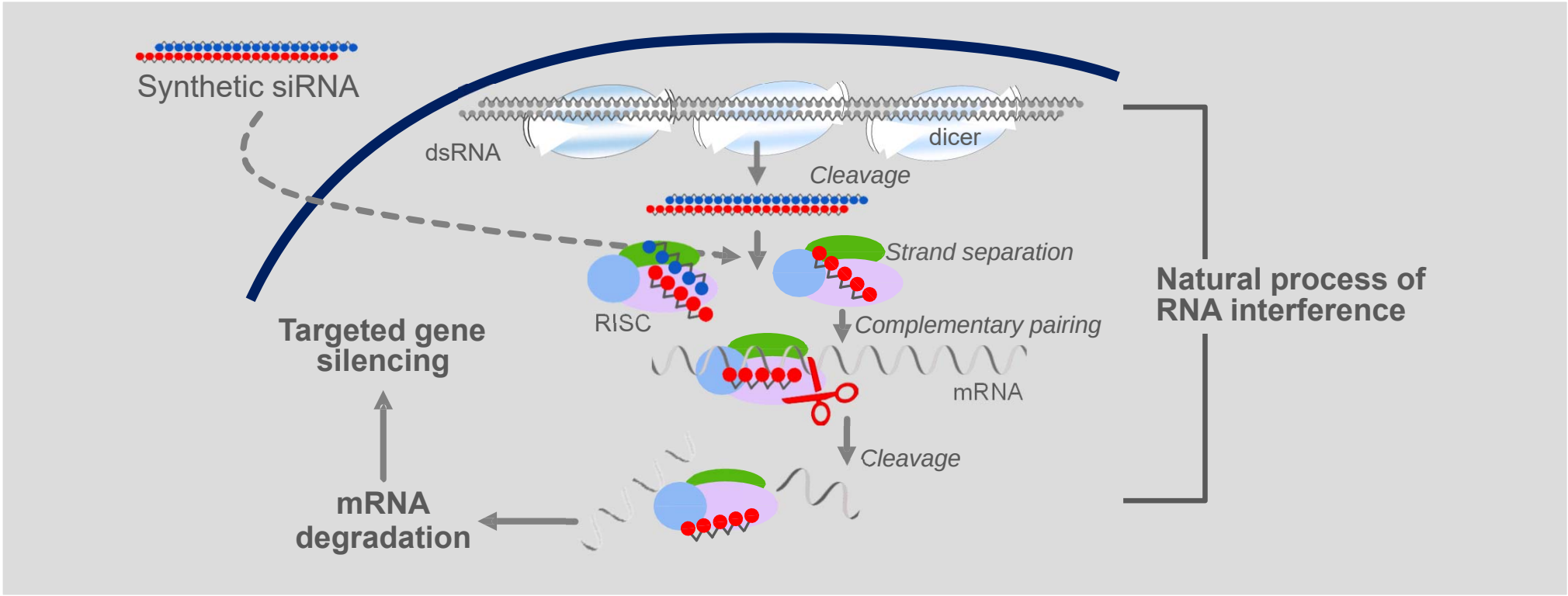
RNAi – A natural process for inhibiting mRNA



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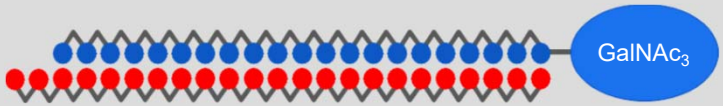
GalNAc-siRNA conjugate facilitates hepatic uptake

Asialoglycoprotein receptor

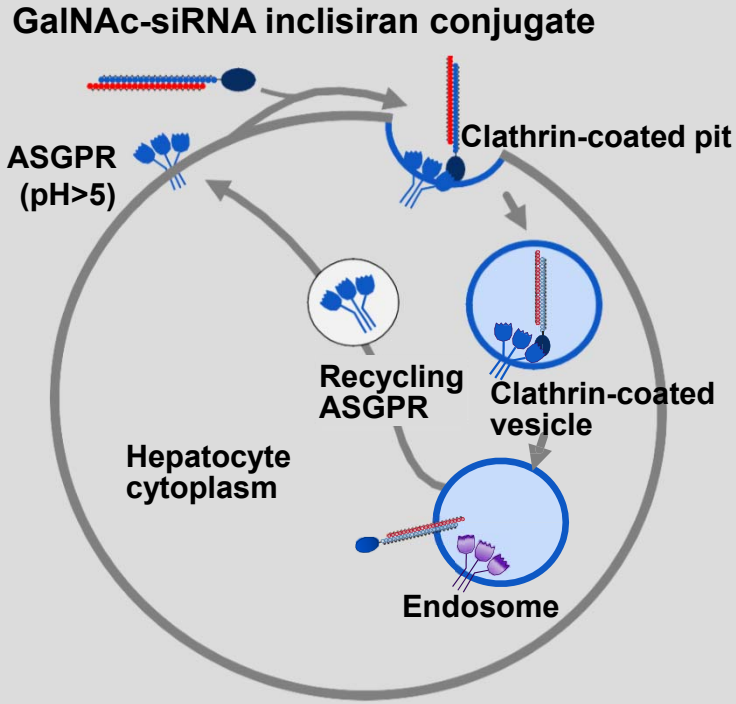
- Expressed only by hepatocytes
- High rate of ligand uptake

Inclisiran

- siRNA conjugated to N-acetylgalactosamine



- Subcutaneous administration
- Targeted delivery to hepatocytes



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Trial entry criteria

Phase II dose-finding trial

≥18 years old

ASCVD	all patients on maximally tolerated statin ± other lipid-lowering Rx	ASCVD risk equivalents
LDL-C >70 mg/dL (1.8 mmol/L)		LDL-C >100 mg/dL (2.6 mmol/L)

ASCVD = atherosclerotic cardiovascular disease

Ray KK et al. N Engl J Med. 2017;376:1430-1440 | ClinicalTrials.gov NCT02597127.

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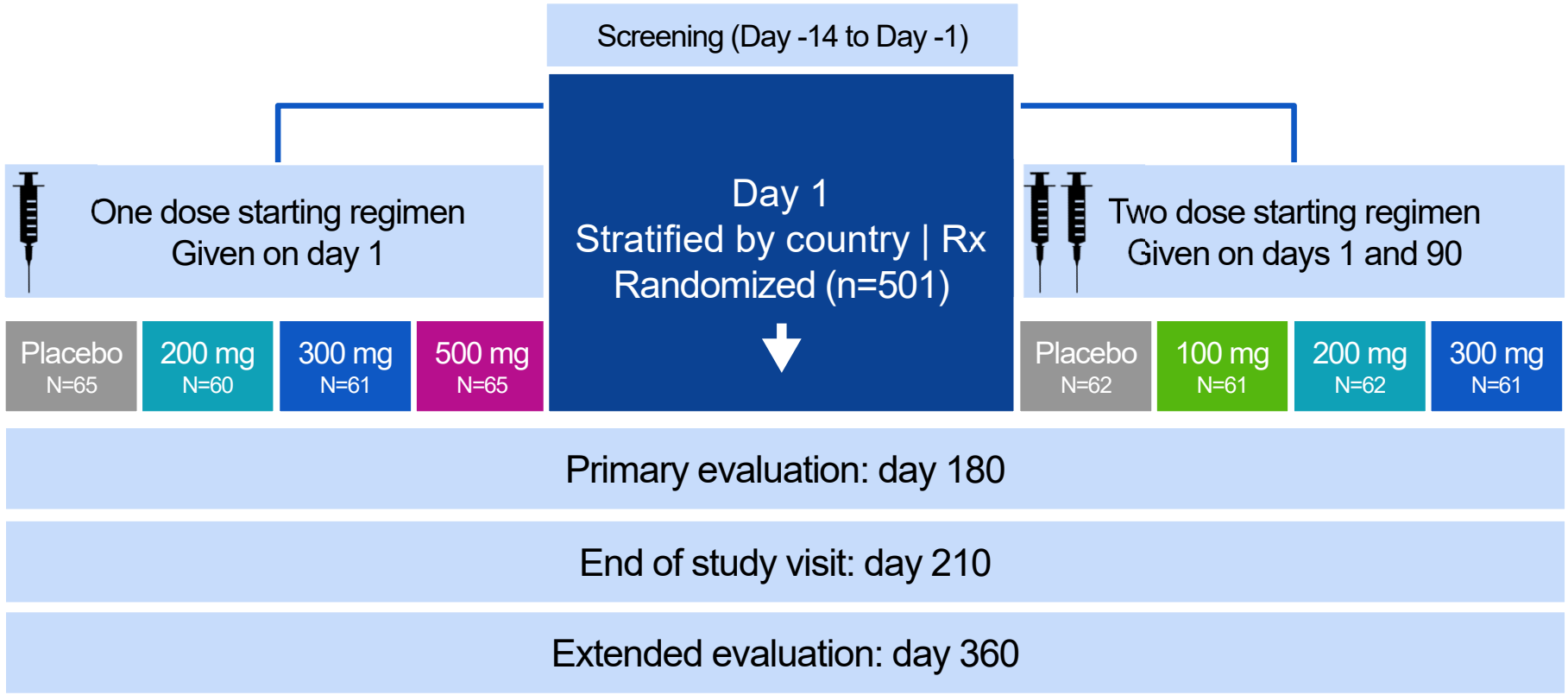
Overall trial design



Ray KK et al. N Engl J Med. 2017;376:1430-1440 | ClinicalTrials.gov NCT02597127

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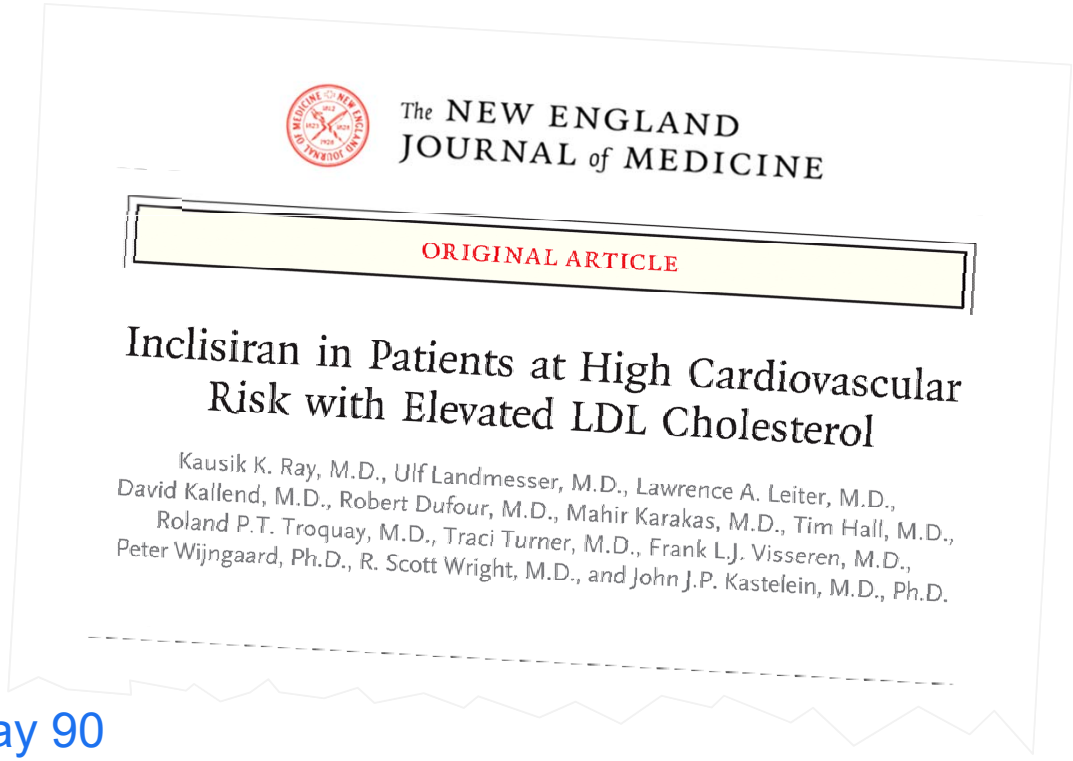
Overall trial results have been published

Safety data
- No concerns

Efficacy data
- All patients responded at 300 mg dose given 2x with significant LDL-C lowering
- Mean LDL-C↓ at 6 months: 53% (absolute reduction 64 mg/dL)
- Maximum LDL-C↓ at 6 months: 81%


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol

Kausik K. Ray, M.D., Ulf Landmesser, M.D., Lawrence A. Leiter, M.D., David Kallend, M.D., Robert Dufour, M.D., Mahir Karakas, M.D., Tim Hall, M.D., Roland P.T. Troquay, M.D., Traci Turner, M.D., Frank L.J. Visseren, M.D., Peter Wijngaard, Ph.D., R. Scott Wright, M.D., and John J.P. Kastelein, M.D., Ph.D.

Future studies will have dosing at Day 1, Day 90 and every 180 days thereafter

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

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Analysis of patients without versus with diabetes

Pre-specified protocol objective and methods

To compare the impact of inclisiran in patients with and without diabetes at baseline on:

- PCSK9 levels
- Lipid profile
- Glycemic control

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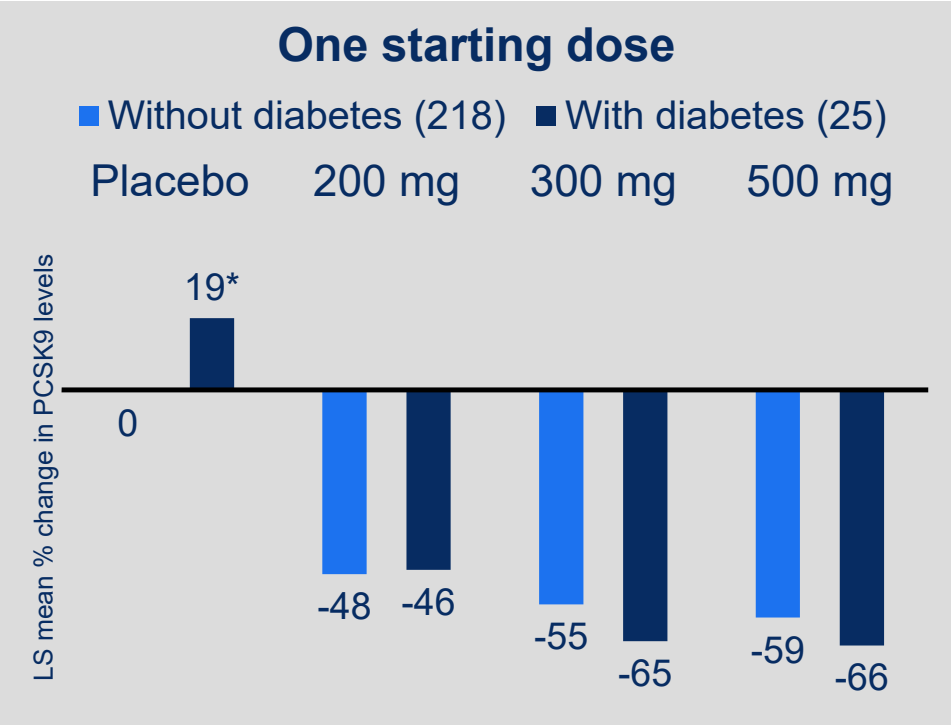
Patient baseline characteristics

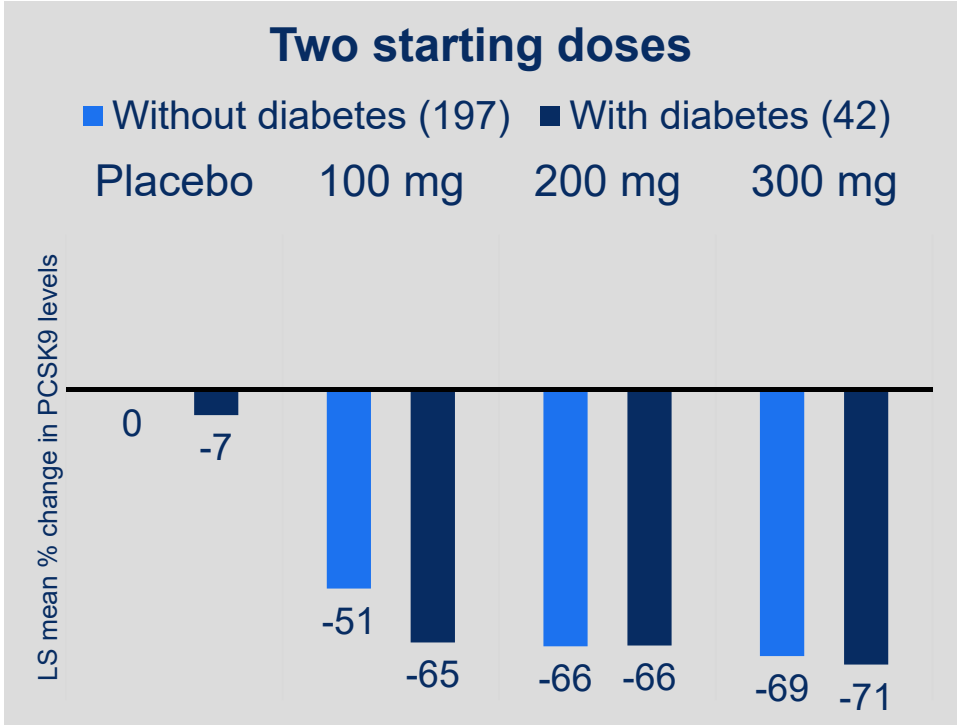
ITT	One starting dose				Two starting doses			
	Without diabetes (n=223)		**With diabetes (n=27)**		**without Diabetes (n=203)**		**with Diabetes (n=43)**	
	Placebo (n=57)	Inclisiran (n=166)	Placebo (n=7)	Inclisiran (n=20)	Placebo (n=53)	Inclisiran (n=150)	Placebo (n=9)	Inclisiran (n=34)

Data are presented as % or median for the intention-to-treat population, which consisted of all participants who underwent randomization

ORION-1: Diabetes status subgroups

PCSK9 levels – similar lowering from Day 1-180





*P = 0.0116 vs. group without diabetes; all others, P > 0.05 for the difference between participants with and without diabetes within each treatment arm at Day 180.

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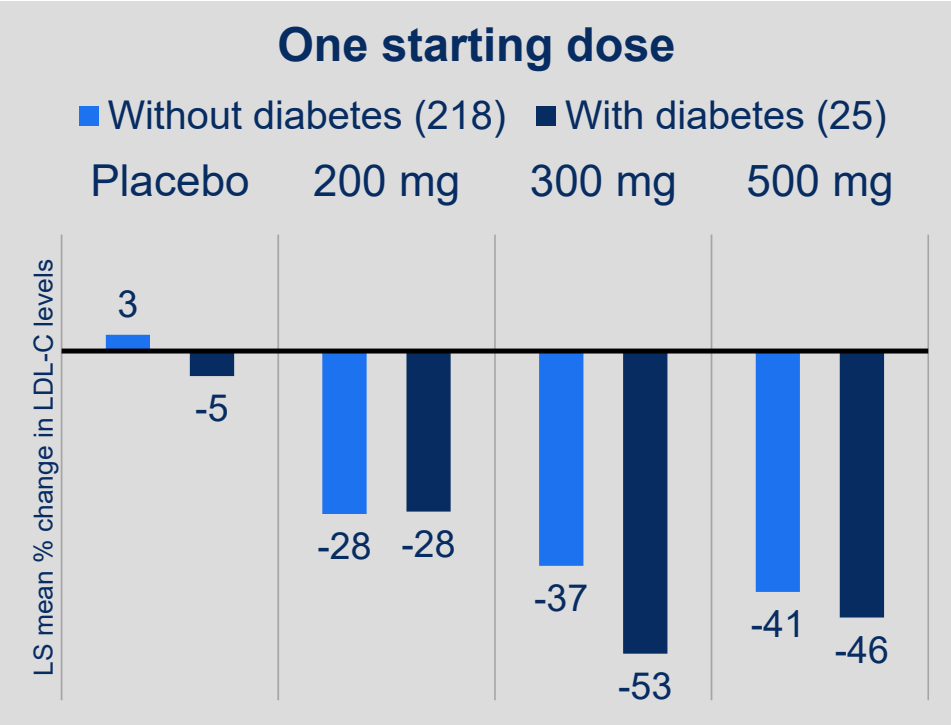
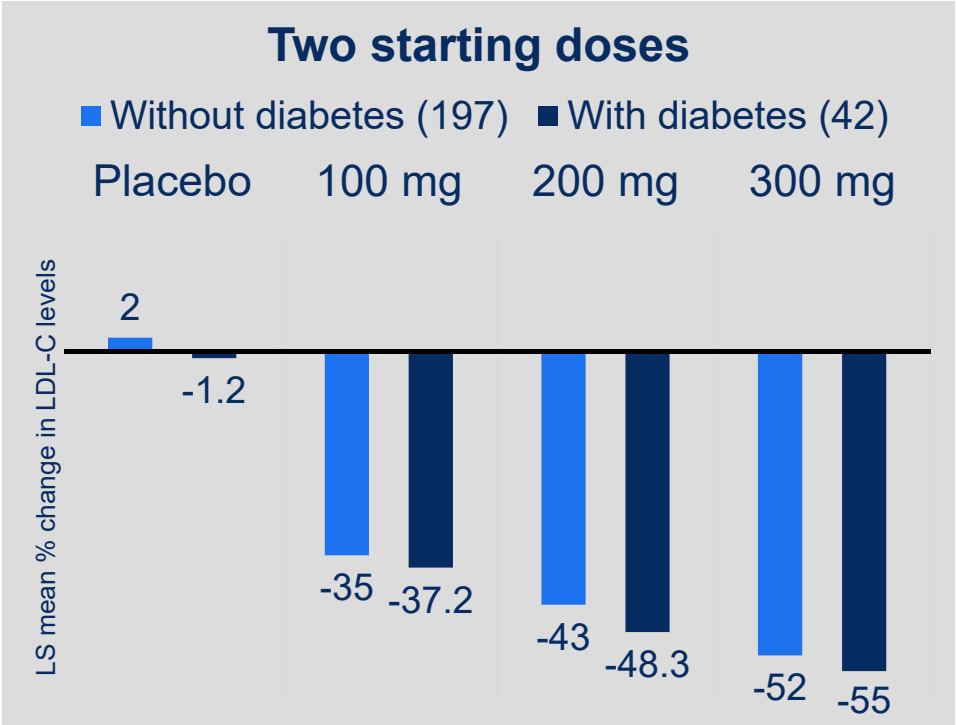
ORION-1: Diabetes status subgroups

LDL-C levels – similar lowering from Day 1-180





Primary endpoint evaluation. P > 0.05 for the difference between participants with and without diabetes within each treatment arm at Day 180.

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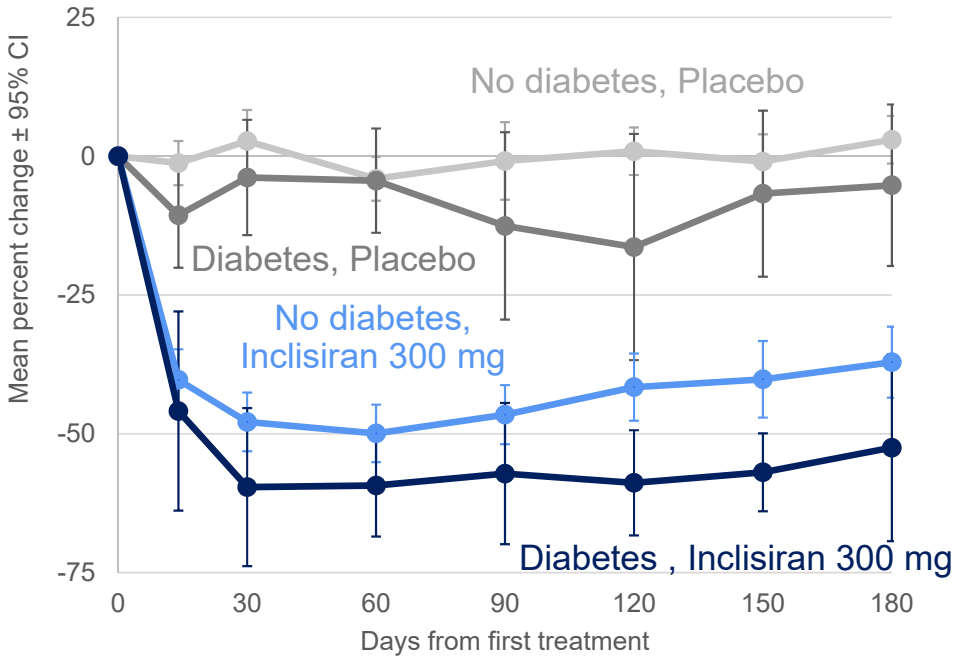
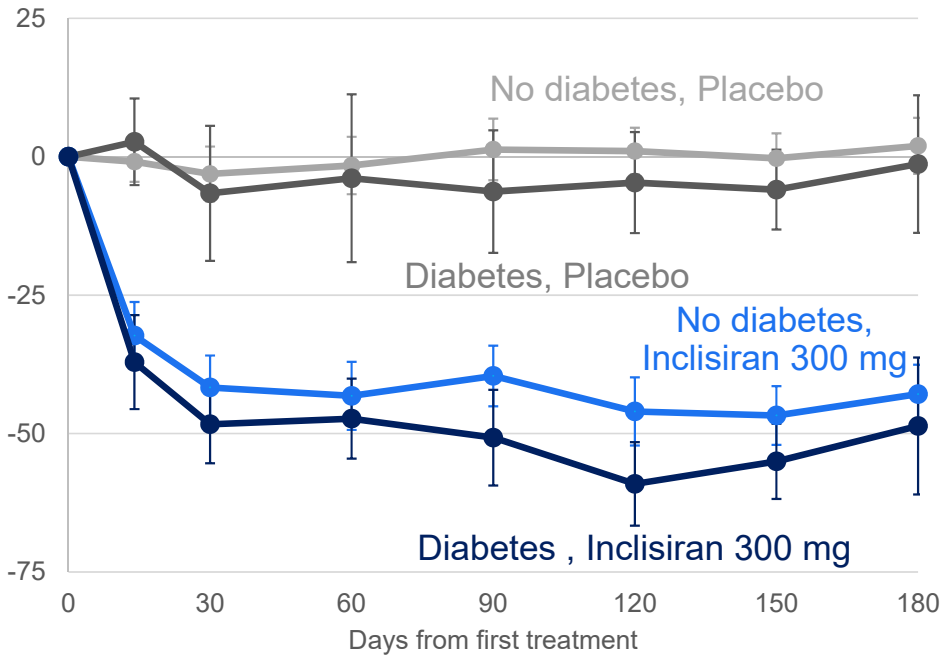
LDL-C lowering similar without versus with diabetes

Placebo or inclisiran 300 mg given Day-1
One starting dose



Placebo or inclisiran 300 mg given Day-1 and -90
Two starting doses



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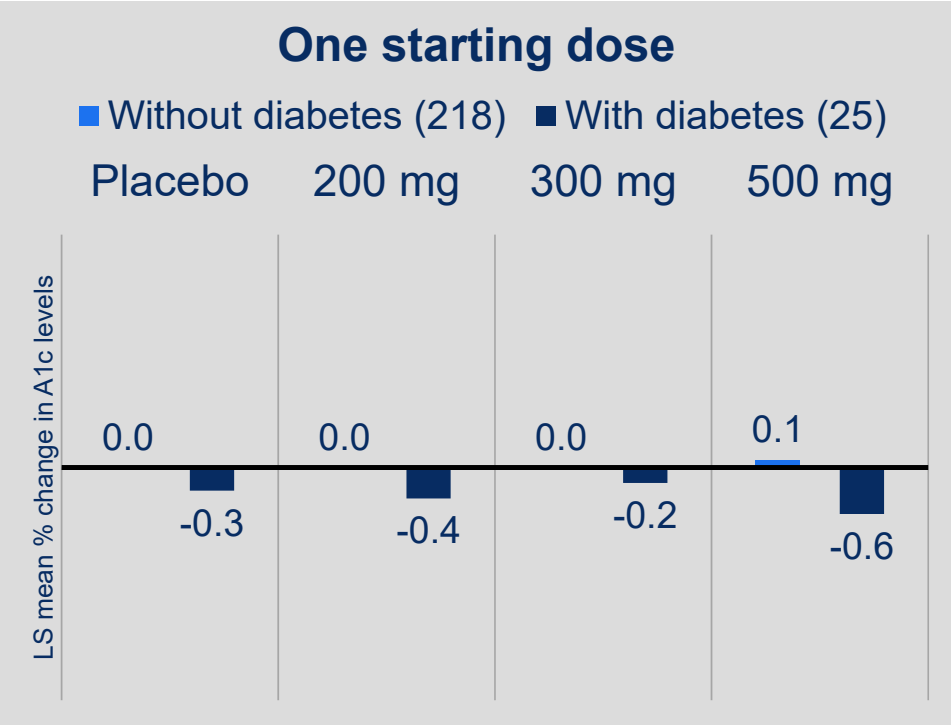
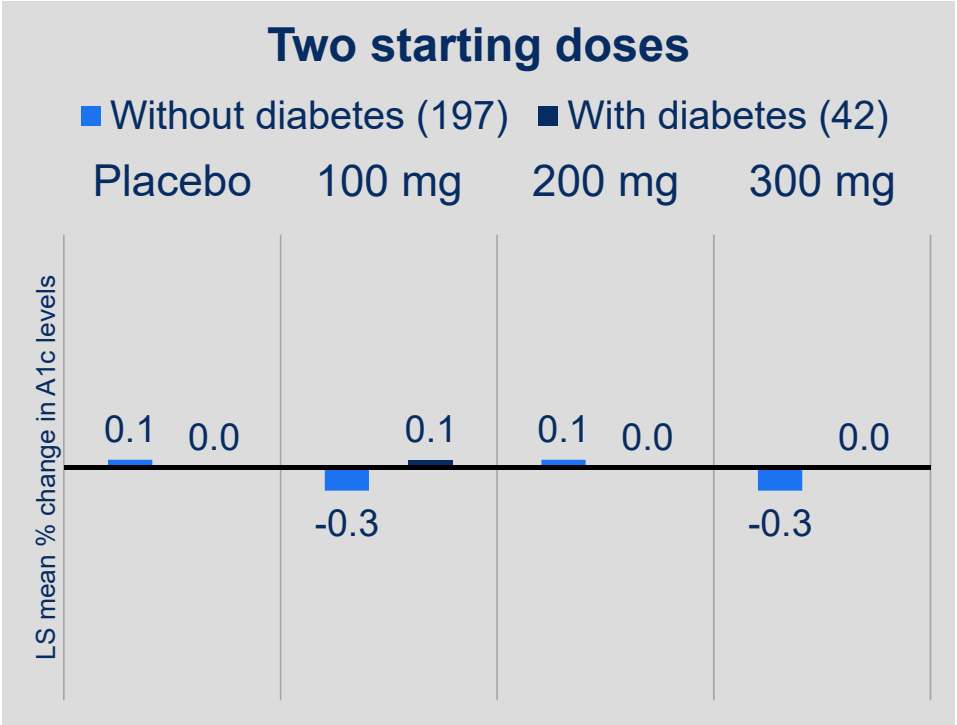
HbA1c levels – no differential change from Day 1-180





P > 0.05 for the difference between participants with and without diabetes within each treatment arm at Day 180.

ORION-1: Diabetes status subgroups

AE profile was similar in both groups

Pre-specified safety population

Doses	Treatment group	Without diabetes N	≥1 AE	≥1 SAE	Death	Myalgia	With diabetes N	≥1 AE	≥1 SAE	Death	Myalgia
1	Placebo	57	72%	5%	0%	5%	7	71%	0%	0%	0%
	Inclisiran (200 to 500 mg)	166	75%	10%	1%	5%	20	75%	10%	0%	5%
2	Placebo	53	81%	9%	0%	4%	9	89%	11%	0%	11%
	Inclisiran (100 to 300 mg)	150	79%	12%	1%	10%	34	71%	18%	0%	6%

No unexplained or persistent elevations in any liver parameter considered related to inclisiran
No symptomatic/clinically significant elevations of creatinine kinase in any inclisiran-treated group

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Summary

For the primary efficacy endpoint at 180 days, 300 mg inclisiran given at Day 1 and 90

- Lowered LDL-C by >50% in persons with ASCVD or ASCVD-risk equivalents, regardless of whether they had diabetes or not
- Had no effect on glycemia
- Displayed no clinically important safety signals

ORION-1: Diabetes status subgroups

Conclusions

Inclisiran may represent an excellent alternative to monoclonal antibodies to PCSK9 in individuals both with and without diabetes

Inclisiran is characterized by a much lower injection frequency and a clean safety profile to date, attributes that could help with therapeutic adherence and clinical efficacy for cardiovascular risk reduction