# Targeting PCSK9

## Expanding knowledge and targeting new frontiers

John JP Kastelein, MD, PhD, FESC
University of Amsterdam
The Netherlands

# DISCLOSURES
# John JP Kastelein

**Professor Kastelein is a consultant for Akcea, AstraZeneca, CiVi Biopharma, Corvidia, CSL Behring, Daiichi Sankyo, Draupnir, Esperion Therapeutics, Gemphire, Madrigal Pharma, Matinas Bio, The Medicines Company, NorthSea Therapeutics, Novartis, Novo, Regeneron, REGENXBIO, Staten Bio**

# 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 ≥50% and up to 88% — with minimal variability and at least 6-months persistence[1]
- 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?**

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

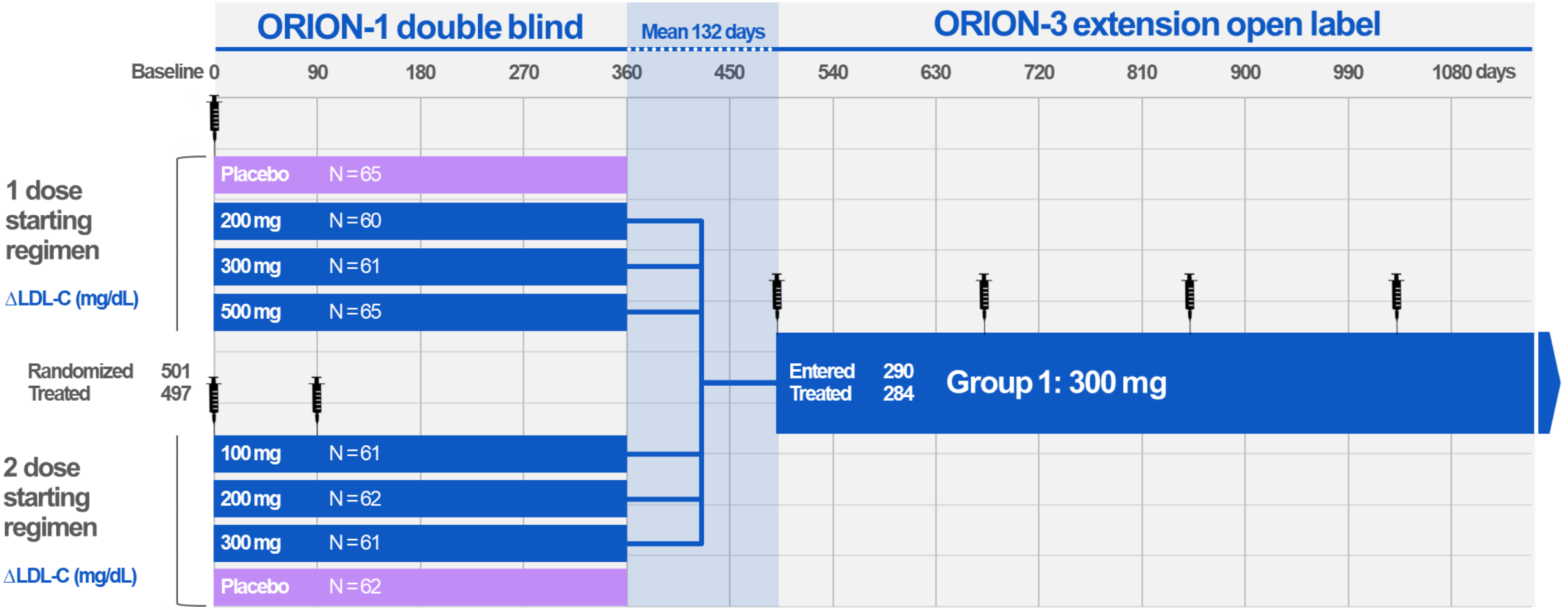
**Efficacy:** LDL-C, PCSK9 and other lipid parameters on day 210 of ORION-3

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

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 baseline[1] 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 (±SD) | 428.4 | (128.5) |
| LDL-C | Mean mg/dL (±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

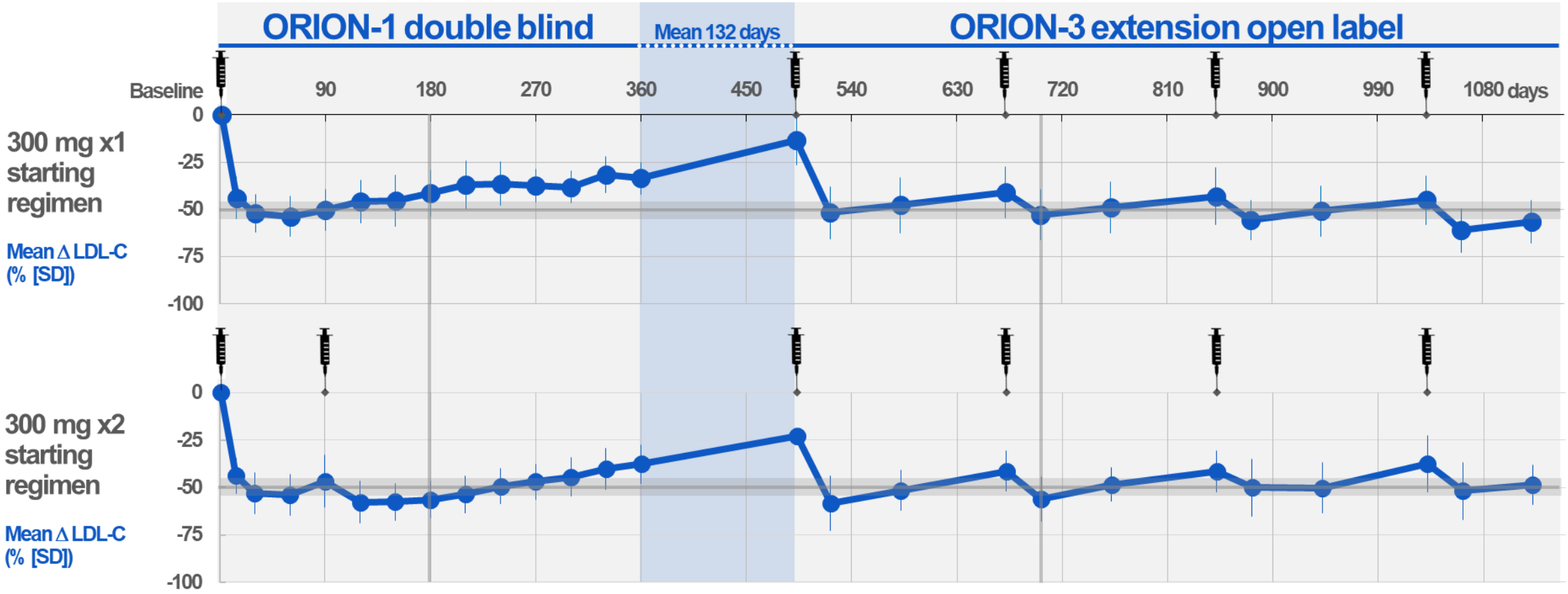
| ITT | | Day 210 change from baseline[1] | | | p-value |
|---|---|---|---|---|---|
| LDL-C | All patients (N=290) | Mean (SD) | - 51% | (28) | < 0.001 |
| | | Mean (SD) | - 64 mg/dL | (39) | < 0.001 |
| | Patients randomized to 300 mg 2 dose starting regimen (N = 61) | Mean (SD) | - 56% | (18) | < 0.001 |
| | | 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

# 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

POTENTIAL IMPLICATIONS

# What could this mean for ongoing blinded Phase III trials?

## Inclisiran expected to lower LDL-C ≥50% and MACE by ≥ 25%

| | ORION-9<br>HeFH<br>N = 482 | ORION-10<br>U.S. ASCVD<br>N = 1561 | ORION-11<br>EU ASCVD/RE<br>N = 1617 |
|---|---|---|---|
| **Baseline LDL-C** | 161 mg/dL | 110 mg/dL | 112 mg/dL |
| **Simulation using dose-PD response model** | | | |
| 1º 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 RRR[1]** | 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 at al, 2005)

Research

JAMA Cardiology | Original Investigation

# Low-Density Lipoprotein Cholesterol Reduction Following 1 or 2 Doses of Inclisiran

## One-Year Follow-up of the ORION-1 Randomized Clinical Trial

Kausik K. Ray, FRCP; Robert M. Stoekenbroek, MD; David Kallend, FRCS; Toshiyuki Nishikido, PhD; Lawrence A. Leiter, MD; Ulf Landmesser, PhD; R. Scott Wright, MD; Peter L. J. Wijngaard, PhD; John J. P. Kastelein, PhD

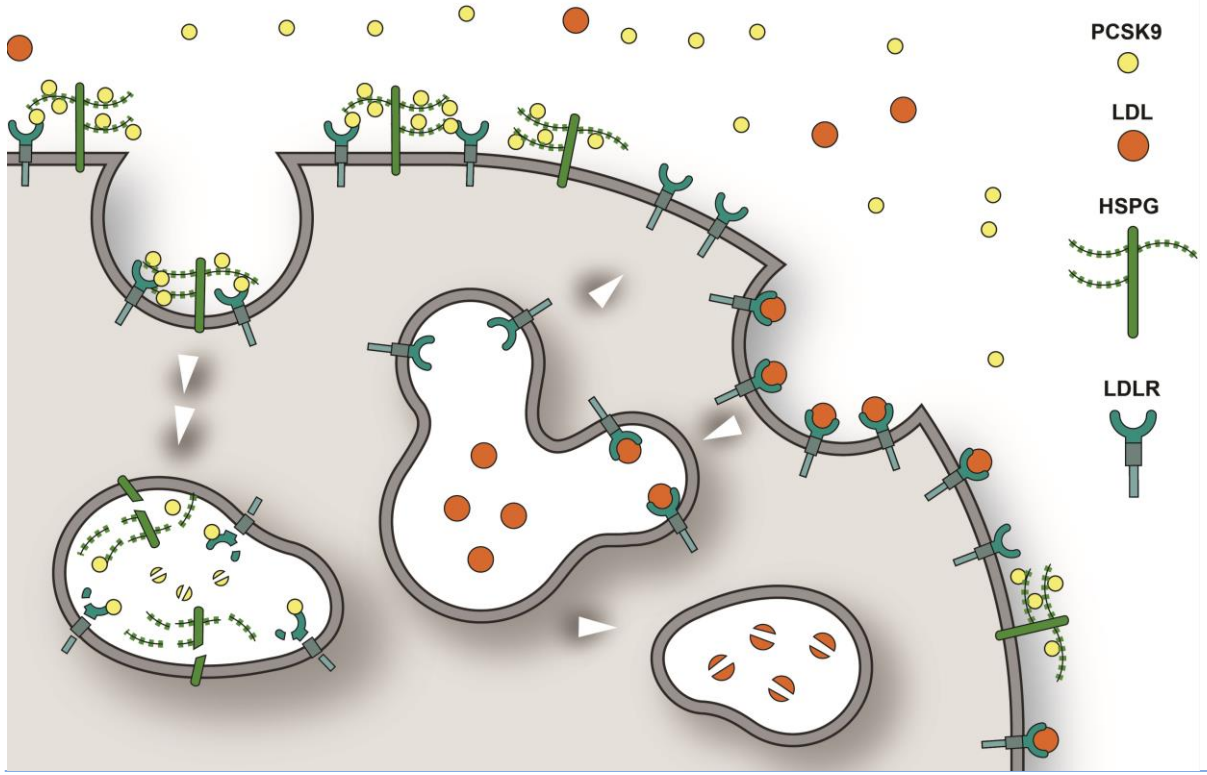
# ORAL PCSK9 INHIBITION

## Promises and challenges of oral PCSK9 inhibition

- A small molecule oral PCSK9i is expected to reduce costs and confer convenience to patients
- A cost effective pricing will significantly reduce the barriers for patient access to PCSK9i
- Development of small molecule PCSK9i has proven very challenging from a medicinal chemistry perspective
- Draupnir Bio is developing  the first orally available PCSK9 inhibitor

# ORAL PCSK9 INHIBITION

## PCSK9 activity depends on heparan sulfate proteoglycans (HSPG)

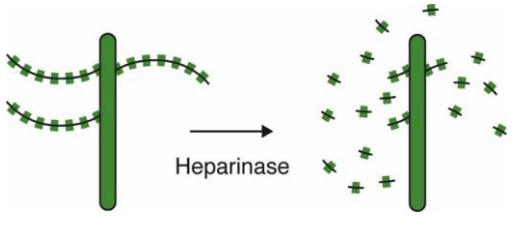


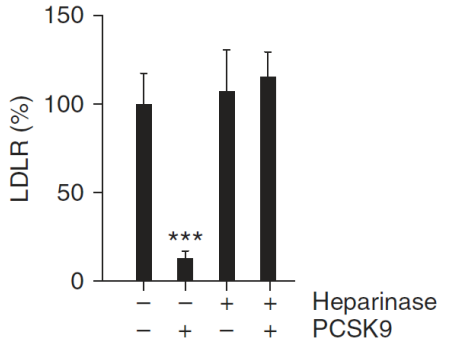

- In the absence of PCSK9, LDLR removes LDL particles by endocytosis
- LDL is metabolized in lysosomes while LDLR recycles
- PCSK9 binds to HSPG on hepatocytes and the PCSK9/HSPG complex hijacks LDLR for degradation

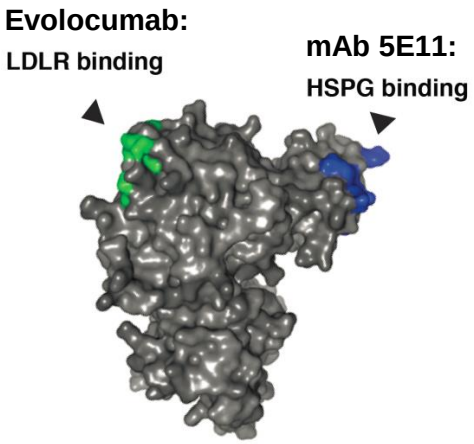
# ORAL PCSK9 INHIBITION

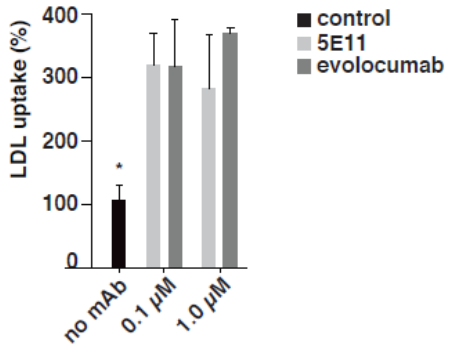
## Removal of HSPG/blocking PCSK9/HSPG binding protects the LDL receptor

- Enzymatic removal of heparan sulfate 5 min before PCSK9 injection, results in complete LDLR protection in the liver of mice.
- mAb 5E11 restores PCSK9-induced reductions in LDL uptake to a similar extent as evolocumab

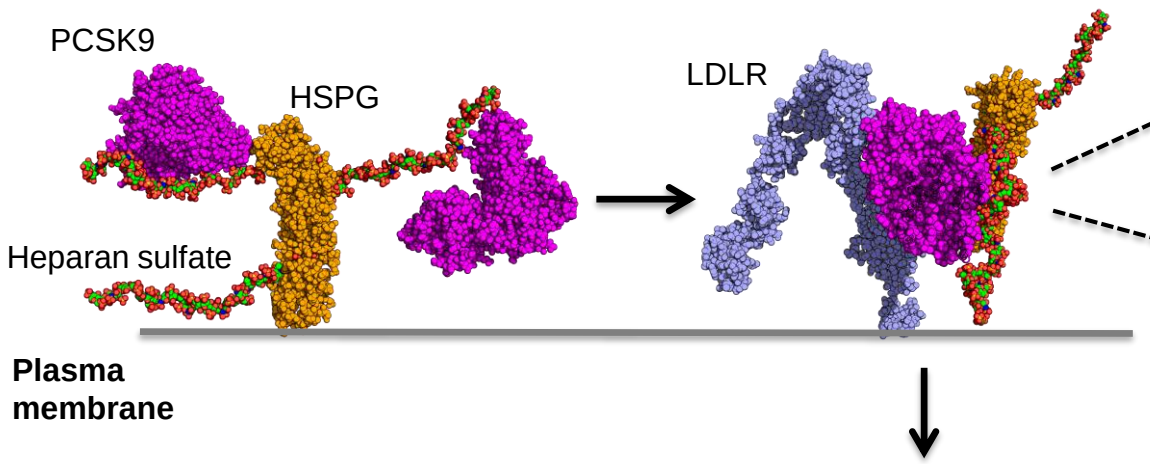


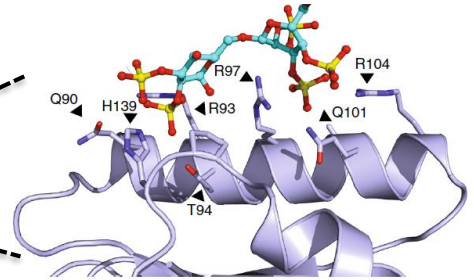



# ORAL PCSK9 INHIBITION
## Structure-based design of small molecule PCSK9i



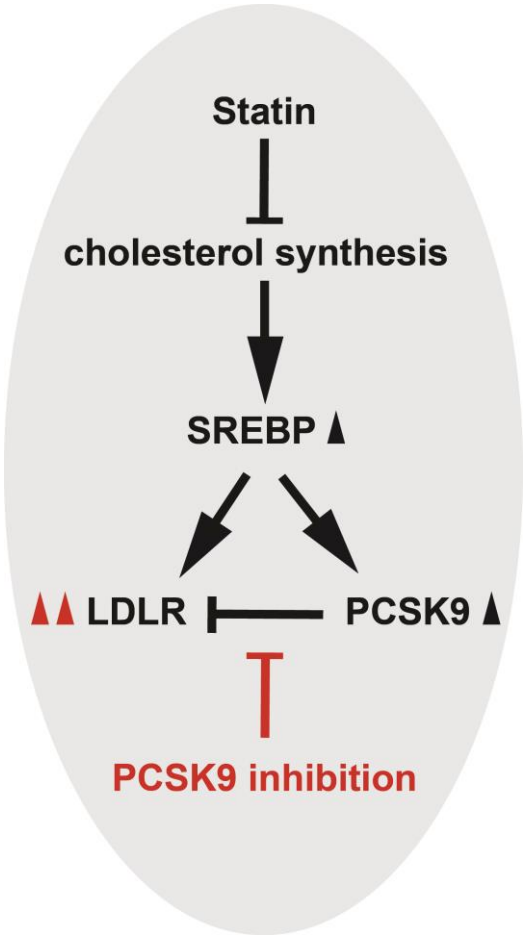

**PCSK9/HSPG binding involves several residues known from PCSK9 LOF variants**

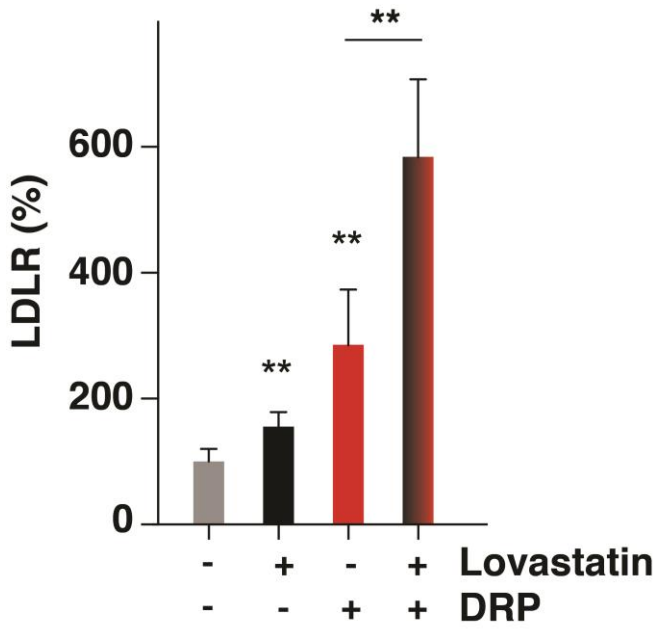


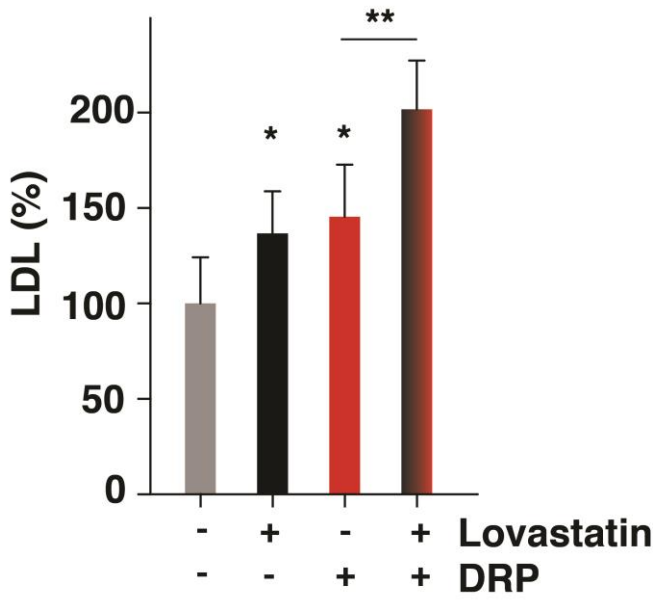

**R93C LOF variant confers 50% reduction in risk of CAD**
*Tang et al. Nature Commun 2017*

# ORAL PCSK9 INHIBITION

## Draupnir PCSK9i increases LDL uptake and acts in synergy with statins

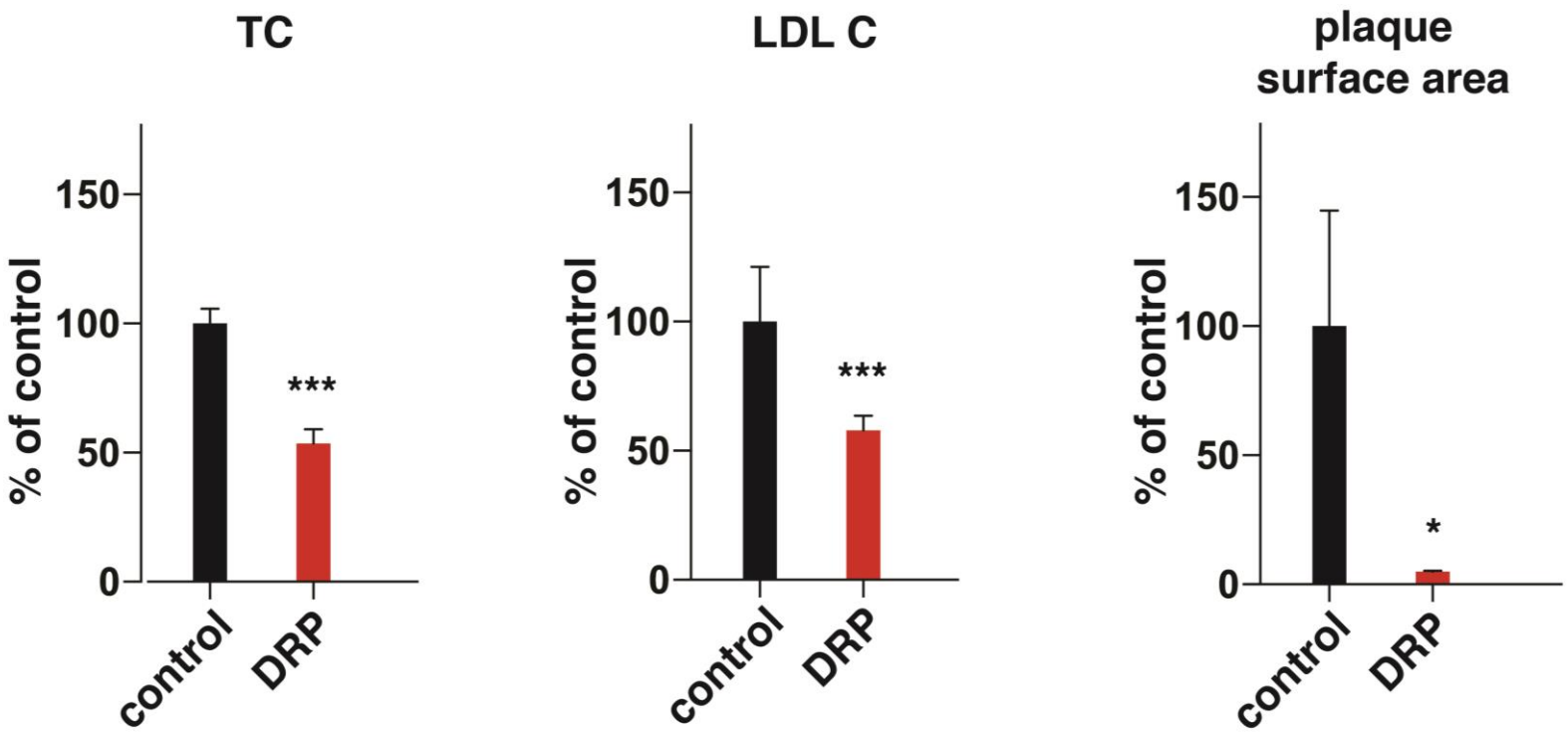


# ORAL PCSK9 INHIBITION

## Draupnir PCSK9i reduces cholesterol and plaque burden in mice



# ORAL PCSK9 INHIBITION
## Clinical development of oral PCSK9i

- **Draupnir is moving lead compound towards first in-human trials**

- **Lead compound has unique mechanism of action and may provide therapeutic benefits by conferring additional protection of the vascular endothelium**

# Conclusion

## Exciting times ahead!

Acknowledgements:
Thanks to  the Medicines Company and Draupnir Bio for providing the data