Validation of an in-silico knowledge-based mechanistic model of atherosclerotic cardiovascular disease for the SIRIUS study

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BACKGROUND

- **Goal:** validate an atherosclerotic cardiovascular disease (ASCVD) model before its use to conduct the SIRIUS study (NCT05974345). Model validation is a critical step to establish reliability of predictions.
- **SIRIUS study:** in silico program comparing the effect of inclisiran vs. standard lipid-lowering therapies (LLT) on major adverse cardiovascular events (MACE) and cardiovascular (CV) death in virtual patients with established ASCVD over 5 years.

METHODS

- **Validation**: compare model predictions of (i) LDL-C evolution under inclisiran to ORION-11 RCT data (N=1,617) and of (ii) the impact of changes in LDL-C levels under alirocumab on CV events to ODYSSEY-OUTCOMES RCT data (N=18,924) using 2 dedicated Virtual Populations (VPop), of 10,479 and 84,046 patients respectively, matching patients' characteristics of each RCT.
- **Validation criteria**: (1) predicted values of mean LDL-C relative change within a 5-percentage points error margin, (2) HR precision corresponding to proportion of the predicted 95% prediction percentile interval (PPI) included in the observed 95% confidence interval (CI) above 30%, (3) predicted HR value in the observed 95% CI, and (4) observed HR value in the 95% PPI.
- **In silico specificities: 95% PPI** obtained with 100 bootstrap repetitions of 808 and 9,462 patients sampled among the 10,479 and 84,046 virtual patients for ORION-11 and ODYSSEY-OUTCOMES VPop respectively. No p-value since there are no sampling fluctuation.

RESULTS

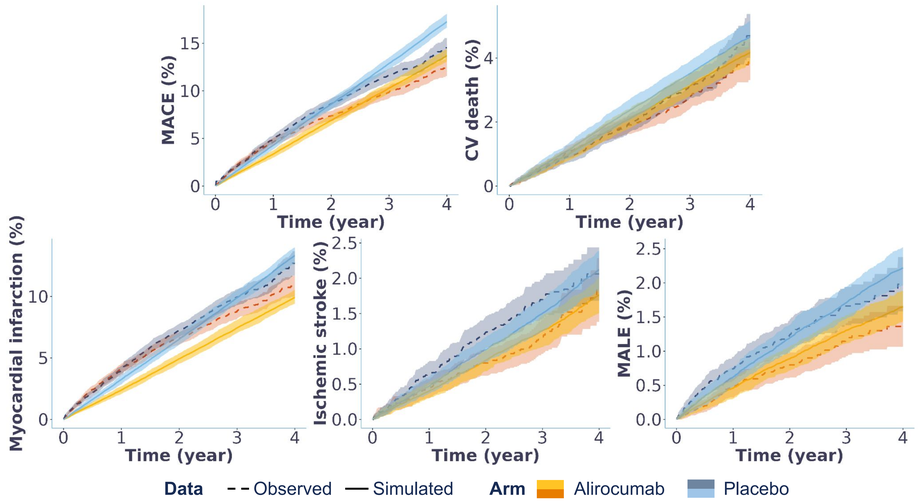
The model adequately predicted:

- mean **LDL-C relative decrease** from baseline following inclisiran treatment observed in ORION-11 RCT (right panel),
- impact of alirocumab vs. placebo on **CV events** observed in ODYSSEY-OUTCOMES at 2.8 yrs, related to the correct LDL-C decrease (central panel)
- **correlations** between **CV risk factors** (eg. age, sex and diabetes) and incidence of **CV events** and clinical impact of treatments depending on CV risk factors observed in ODYSSEY-OUTCOMES, IMPROVE-IT and CANTOS RCT (results not shown).

The ASCVD model was successfully validated to predict PCSK9i efficacy on CV events

The ASCVD model reproduces the effect of alirocumab on MACE, CV death, fatal or nonfatal MI, fatal or nonfatal IS and MALE observed in ODYSSEY-OUTCOMES RCT

CV events	Observed HR [95%CI]	Simulated HR [95%PPI]	Validation criteria		
	Median follow-up time of 2.8 years		n°2	n°3	n°4
MACE	0.85 [0.78-0.93]	0.79 [0.72-0.86]	59.8 %	TRUE	TRUE
CV Death	0.88 [0.74-1.05]	0.90 [0.76-1.06]	97.5 %	TRUE	TRUE
Fatal or nonfatal MI	0.86 [0.77-0.96]	0.74 [0.66-0.83]	33.9 %	FALSE	FALSE
Fatal or non fatal IS	0.73 [0.57-0.93]	0.84 [0.65-1.09]	64.2 %	TRUE	TRUE
MALE	0.69 [0.54-0.89]	0.77 [0.60-0.98]	76.0 %	TRUE	TRUE



Observed data are shown as mean and 95% CI; simulated data are shown as mean and 95% PPI.

The model simulates time to first occurrence of fatal or nonfatal MI, fatal or nonfatal IS, MALE, CV death and 3P-MACE defined as the first occurrence of CV death, nonfatal MI or nonfatal IS. It does not simulate unstable angina as clinical outcome nor as prior medical history due to model architecture and calibration. Nonetheless, due to lack of perfectly comparable data, observed MACE (coronary heart disease (CHD) death, nonfatal MI, fatal and nonfatal IS and unstable angina requiring hospitalization) of ODYSSEY-OUTCOMES are compared to simulated 3P-MACE and observed CHD death and nonfatal MI are compared to simulated fatal or nonfatal MI.

References: Bootstrap by Jacob et al (PMID: 37667175), ODYSSEY-OUTCOMES by Schwartz et al. (PMID 30403574), ORION-11 by Ray et al. (PMID 32187462), IMPROVE-IT by Cannon et al. (PMID 26039521), CANTOS by Ridker et al. (PMID 28845751)

For detailed information on SIRIUS in silico study on ClinicalTrials.gov, scan the QR code (NCT05974345).

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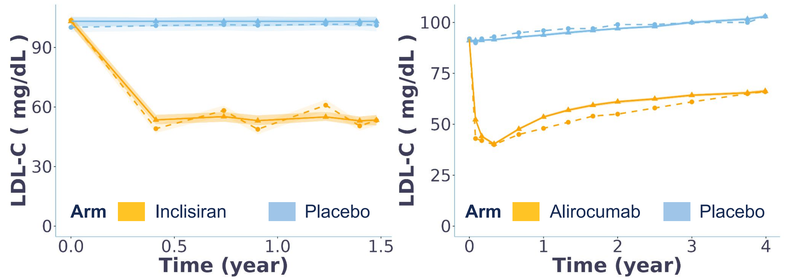
The ASCVD model reproduces inclisiran/alirocumab effects on LDL-C reduction observed in ORION-11/ODYSSEY-OUTCOMES RCT

LDL-C measure	Treatment	Observed Mean [95% CI]	Simulated Mean [95% PPI]	Validation criteria n°1
Mean relative change from baseline to 48 weeks (%)	Inclisiran	-52.8 % [-54.6; -50.9]	-49.7 % [-50.3; -49.1]	3.1 %
Mean relative change from placebo at 4 years (%)	Alirocumab	-36%	-36.2% [-36; -36.6]	-0.2 %



Observed data are shown as mean and 95% CI; simulated data as mean and 95% PPI. ODYSSEY-OUTCOMES LDL-C dynamics is a goodness-of-fit result since data were used to generate the VPop.

DISCUSSION

- Discrepancies between observed and predicted MACE and MI incidence and HR data are explained by differences in the definition of these events (see main panel) and in inclusion criteria (patients with prior unstable angina and recent acute coronary events included in ODYSSEY-OUTCOMES RCT vs. the VPop only included patients with a prior MI and no event 4 weeks prior trial start).
- **CV death** predictions are coherent with data observed in ODYSSEY-OUTCOMES (2.8 years median follow-up). However, no data were available to assess the predicted effect of PCSK9 inhibitors on CV death compared to placebo after 5 years of treatment as it will be simulated in SIRIUS study.

Limitation: CV deaths are not modeled mechanistically but using a statistical Cox models. Moreover, the model does not simulate recurrent events in the same vascular bed, which could contribute to CV death. No mechanistic hypothesis was implemented in the model regarding potential effect of LLT on other causes of CV death than fatal MI and IS.

Impact: By lowering the risk of recurrent CV events, LLT could reduce the risk of other CV death causes. The current ASCVD model does not capture this potential beneficial effect and could therefore underestimate the impact of LLT on CV death for longer follow-up durations.

CONCLUSION

The ASCVD model credibility assessment demonstrated its ability to reproduce a wide range of qualitative and quantitative behaviors in terms of effect of standard LLT (statin/ezetimibe) and PCSK9 inhibitors (inclisiran/alirocumab) on lipoproteins and on incidence of CV events, allowing its use to conduct the SIRIUS study.

DISCLOSURE INFORMATION

The SIRIUS study is funded by Novartis Pharma SAS. DA reports having received payments for consulting, speaking, or educational events from Amgen, Alnylam, Amarin, Astrazeneca, Boehringer, BMS, Bouchara Recordati, Pfizer, Novartis, Novo Nordisk, Organon, Sanofi, Servier, Vifor. PGS is the CSO of Bioquantis and reports having received research grants or payments for consulting or speaking from Amarin, Amgen, BMS, Novo-Nordisk, Sanofi.

***Abbreviations**: ASCVD, atherosclerotic CV disease; CI, confidence interval; coronary heart disease, CHD; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; Lp(a), lipoprotein a; MACE, major adverse cardiovascular event; MALE, major adverse limb event; MI, myocardial infarction; PCSK9i, PCSK9 inhibitor; PPI, prediction percentile interval; RCT, randomized clinical trials; VPop, Virtual Population.*