In Silico Clinical Trials Using Mechanistic Knowledge-Based Model, an Innovative Approach to Accelerate Data Generation and Support Health Technology Assessment

E. Pham1*, S. Porte1, E. Courcelles1, E. Peyronnet1, Y. Wang1, A. Diatchenko1, G. Gomez1, P. Amarenco2, D. Angoultvant3, F. Boccara4, B. Cario1, G. Mahé1, N. Marquet1, A. Bastien1, L. Porta1, J.P. Boisserie1, E. Bechet1, S. Granjean-Noriot1, P.G. Stég1

1 Novadiscovery, Lyon, France; 2 Department of Medicine and Stroke Center, APHP, Bichat Hospital, Paris-Cité University, Paris, France and McMaster University, Population Health Research Institute, Hamilton, Ontario, Canada; 3 Cardiology department, Tourouse Hospital, CHRU Tours, EA2485, Tours University, Tours, France; 4 Sorbonne University, GIRC n°722, C2MV, INSERM U938, Saint-Antoine Research Center, ICAN, Cardiology, Saint Antoine Hospital APHP, Paris, France; 5 Nantes University, CHU Nantes, CNRS, Inserm, thorax institute, Nantes, France; 6 Vascular Medicine Unit, CHU Rennes, Rennes University CIIC44, Rennes, France; 7 Paris-Cité University, APHP, Bichat Hospital, and INSERM U9497 LTS, Paris, France; 8 Novartis, Rueil Malmaison, France.

* Corresponding author: emmanuel.pham@novadiscovery.com

OBJECTIVES

Demonstrating cardiovascular (CV) benefits with lipid-lowering therapy (LLT) requires long-term randomized clinical trials (RCT) with thousands of patients. Innovative approaches such as in silico trials applying a disease computational model to virtual patients receiving multiple treatment combinations provide a valuable option to complement RCTs by rapidly generating supplementary comparative effectiveness data and reinforce data package for drug value demonstration to health technology assessment (HTA) bodies.

Here, we present calibration results of a computational model of atherothrombotic cardiovascular disease (ASCVD) built with the aim to predict the benefit of inclisiran, an siRNA targeting PCSK9 mRNA, vs other LLT on CV events.

RESULTS

The model is calibrated to reproduce inclisiran effect on LDL-C levels

- CV outcomes incidence in both placebo and evolocumab arms reported in FOURIER trial [2] are well reproduced in the calibrated Vpop.
- MALE includes acute lower limb ischemia, lower limb amputation due to ischemia, or urgent lower limb revascularization for ischemia. Median follow-up duration is 2.5 yrs for MALE and 2.2 yrs for other events.

The calibrated model and Vpop reproduce evolocumab effect on CV outcomes at the population-level

Figure 2 - Comparison of population-mean percentage change in LDL-C levels following inclisiran (orange) or placebo (blue) administered as add-on to background LLT (statin with or without ezetimibe) as observed in ORION-10 [1] (solid lines; N=780 per arm) vs simulated by the model (dotted lines; N=780).

Figure 3 - CV outcomes incidence in both placebo and evolocumab arms reported in FOURIER trial [2] are well reproduced in the calibrated Vpop. MALE includes acute lower limb ischemia, lower limb amputation due to ischemia, or urgent lower limb revascularization for ischemia. Median follow-up duration is 2.5 yrs for MALE and 2.2 yrs for other events.

The calibrated model and Vpop reproduce 3P-MACE event rates with evolocumab and placebo at the subgroup-level

Figure 4 - (a) 3P-MACE and CV death rates observed in FOURIER trial [2] vs simulated in the calibrated Vpop. Median follow-up duration is 2.2 yrs, except for diabetes 3 yrs. Numbers of patients in each subgroup in the Vpop are similar to the ones in FOURIER. (b) 3P-MACE incidence in diabetics vs non diabetics.

REFERENCES


SA1

In Silico Clinical Trials Using Mechanistic Knowledge-Based Model, an Innovative Approach to Accelerate Data Generation and Support Health Technology Assessment


1 Novadiscovery, Lyon, France; 2 Department of Cardiology and Stroke Center, APHP, Bichat Hospital, Paris-Cité University, Paris, France and McMaster University, Population Health Research Institute, Hamilton, Ontario, Canada; 3 Cardiology department, Tourouse Hospital, CHRU Tours, EA2485, Tours University, Tours, France; 4 Sorbonne University, GIRC n°722, C2MV, INSERM U938, Saint-Antoine Research Center, ICAN, Cardiology, Saint Antoine Hospital APHP, Paris, France; 5 Nantes University, CHU Nantes, CNRS, Inserm, thorax institute, Nantes, France; 6 Vascular Medicine Unit, CHU Rennes, Rennes University CIIC44, Rennes, France; 7 Paris-Cité University, APHP, Bichat Hospital, and INSEM U9497 LTS, Paris, France; 8 Novartis, Rueil Malmaison, France.

* Corresponding author: emmanuel.pham@novadiscovery.com

METHODS

- A knowledge-based mechanistic model of ASCVD was built (Fig 1). Every piece of knowledge extracted from the literature was awarded a strength of evidence grading to allow tracking of uncertainty in the model.
- A panel of 6 multidisciplinary clinical experts reviewed knowledge models and subsequent modelling hypotheses to validate their relevance. They also contributed in defining the calibration and validation strategy by selecting relevant RCTs and registry data, that the model should be able to reproduce and assessed the model credibility by analyzing simulation results.
- A secondary prevention ASCVD Virtual Population (Vpop) was generated (N=6446) to account for inter-patient variability and calibrated at the population and subgroup levels to reproduce ORION-10 [1] and FOURIER [2] RCTs data.

A Virtual Population is a collection of virtual patients. Each virtual patient is generated by drawing randomly a value for each parameter of the model (eg age, sex, reaction rate constants) from the parameter distributions derived from available data sets and literature, or determined during calibration.

CONCLUSION

- An ASCVD model and secondary prevention Vpop were built and successfully calibrated to reproduce observed trial data including FOURIER and ORION-10 results at the level of both the whole population and subgroups.
- Next steps are:
  - Credibility assessment of the ASCVD model to demonstrate its ability to predict data that were not used for its conception or calibration.
  - Use the model to predict inclisiran effect compared to the current recommended therapeutic strategy on CV events in an ASCVD secondary prevention population in the upcoming SIRIUS in silico trial (NCT059794345).
- The acceptance of in silico approaches by the HTA bodies could accelerate patient access to this innovative drug.