A Quantitative Systems Pharmacology PhysioPD™ Platform to Investigate the Impact of Cholesterol-Lowering Therapies on Lipid Profiles and Plaque Characteristics: Insights for the Clinical Application of PCSK9 Inhibitors

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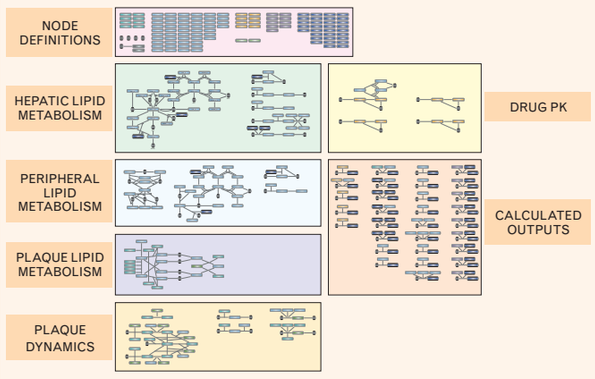
Background

- Reduction of low-density lipoprotein cholesterol (LDL-C) following treatment with statins or ezetimibe plus statins has been shown to lower morbidity and mortality from cardiovascular disease (CVD).
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, such as alirocumab, significantly reduce LDL-C and can enable patients poorly controlled on statins to reach LDL-C goals (Stein, et al., 2012). Their impact on CVD outcomes is under clinical investigation.
- Here, we describe the development of a Cardiovascular (CV) PhysioPD™ Research Platform to investigate mechanisms underlying LDL-C changes with therapy and their potential impact on atherosclerotic plaque dynamics.

Methods

- The Platform (Figure 1) is a quantitative systems pharmacology model that incorporates cholesterol metabolism and transport including LDL receptor (LDLR) trafficking, reverse cholesterol transport (RCT), and sterol regulatory element-binding proteins (SREBP) regulation of cholesterol synthesis, LDLR expression, and PCSK9 expression.
- The Platform includes a representation of mechanistic hypotheses linking plasma LDL-C to atherosclerotic lipid core deposition, fibrosis, inflammation and plaque volume in a representative coronary plaque.
- Simulated treatments include PCSK9 antibodies, statins, fibrates, and ezetimibe.
- Virtual Patients (VPs; alternate parameterizations of the Platform) were created to evaluate the effects of mechanistic and phenotypic variability on response.
- The Platform was developed and calibrated using published data in accordance with Rosa's Model Qualification Method (Friedrich, et al., 2011).

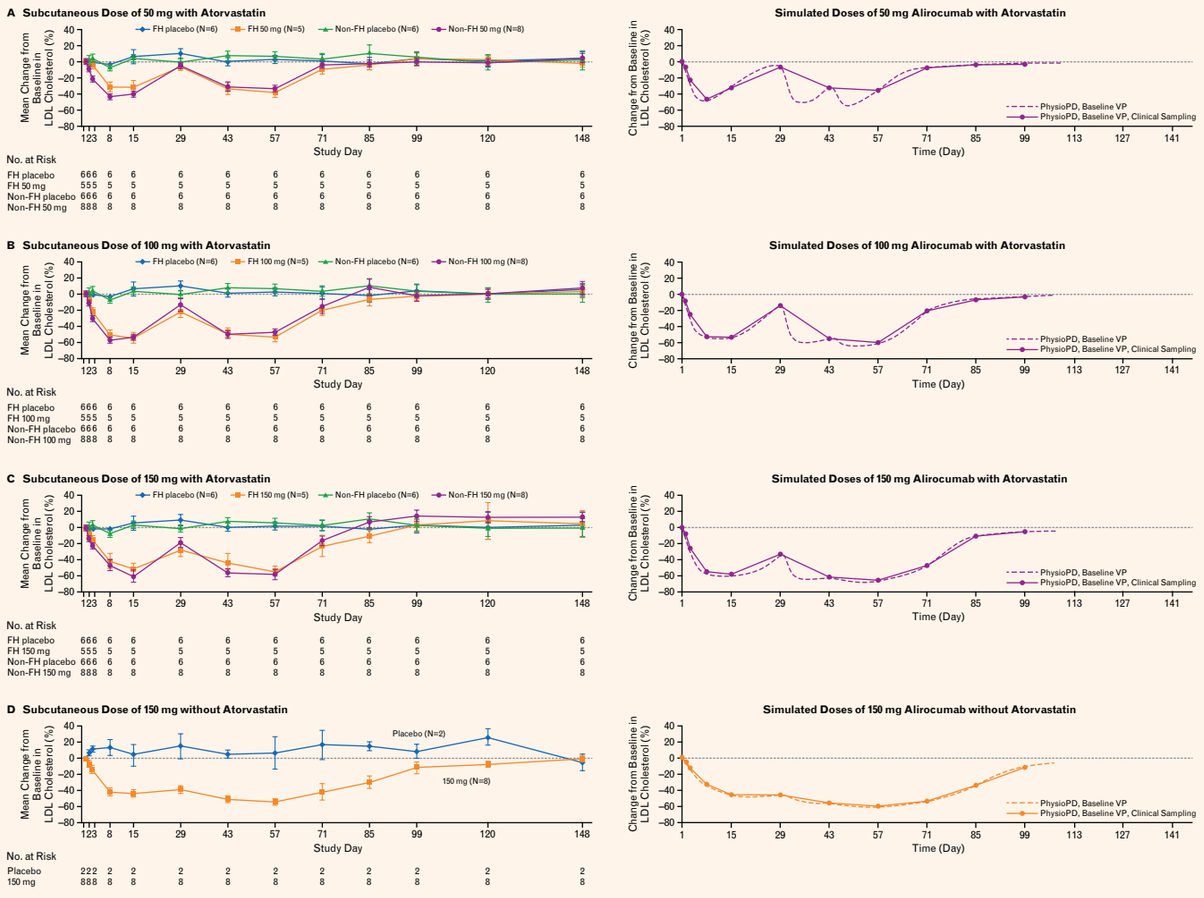
Figure 1. CV PhysioPD Research Platform



Results

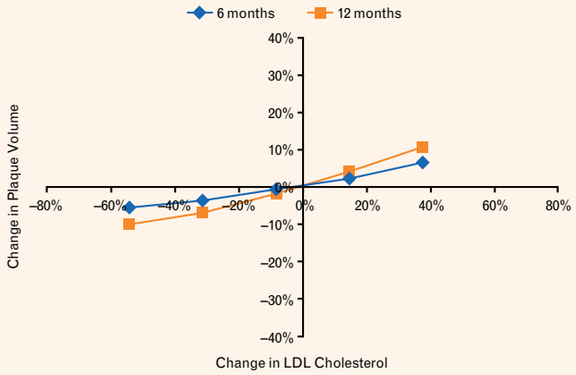
- Simulated changes in lipid profiles and plaque volume following therapy were consistent with published clinical data (Figures 2 and 3, Table 1).
- Platform research will be used to explore the impact of patient variability on the response to alirocumab and may potentially be used upon further updating and calibration to evaluate treatment-related changes in plaque size, composition, and stability.

Figure 2. Alirocumab Multiple Dose in Hypercholesterolemic Patients with and without Atorvastatin



- The Platform simulations in a representative virtual patient (Figure 2, right) were consistent with the magnitude and duration of LDL-C reduction reported in Stein, et al., 2012 following multiple doses of alirocumab in hypercholesterolemic patients (Figure 2, left). "Clinical Sampling" indicates matched sampling schedule.
- The Platform simulations were also consistent with reported data for ApoB, HDL-C and total cholesterol concentrations, and for lipid changes following statin, fibrate and ezetimibe monotherapy and background therapy (not shown).

Figure 3, Table 1. Effects of LDL-C Changes on Plaque Volume in Hypercholesterolemic Patients



Reference	Therapy	LDL	Plaque Volume
Okazaki S 2004	Atorvastatin, 6 months (statin-naïve)	–42%	–8 mm^3 (69.6–>61.4 mm^3) –12%
Hattori K 2012	Pitavastatin, 9 months (statin-naïve)	–34%	–1.4 mm^3/mm (8.1–>6.7 mm^3/mm) –17%
Kovarnik T 2012	Atorvastatin + ezetimibe, 12 months (mix)	–29%	–12 mm^3/mm (414–>402 mm^3/mm) –3%
Sipahi I 2006	Rosuvastatin, 24 months (statin-naïve)	–53%	–6 mm^3 (65–>59 mm^3) –9%

- Long-term platform simulations with fixed LDL reductions in a representative virtual patient (Figure 3) show a change in atheroma volume that is consistent with the ranges reported in multiple studies (Table 1).

Conclusions

- A CV PhysioPD Research Platform was developed to investigate the mechanisms by which cholesterol-lowering therapies affect lipid profiles, plaque size and plaque composition and stability.
- This Platform, upon further development and qualification, is intended to support dose optimization and clinical trial design for PCSK9 inhibitors and other lipid-modulating drugs for the treatment of CVD.

Acknowledgements

Study funded by Sanofi and Regeneron Pharmaceuticals, Inc. Typesetting provided by Prime Medica, Knutsford, UK, funded by Sanofi and Regeneron Pharmaceuticals, Inc.

Disclosures

D.W.B, K.K., A.K., C.M.F., and M.J.R. work for a company that has received payments from Sanofi/Regeneron for work involved in this study. All other authors are employees of either Sanofi or Regeneron.

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