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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).

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.

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.

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