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ANTICOAGULANT PRIMARY PROPHYLAXIS

MECHANISTIC POPULATION PHARMACOKINETIC/PHARMACODYNAMIC MODELING OF FACTOR XI-TARGETING MONOCLONAL ANTIBODIES SUPPORTS DURABLE ANTICOAGULANT COVERAGE AND TRANSLATIONAL DOSE AND REGIMEN SELECTION

O. Milberg[1], H. Abdallah[1], R. K. Lokken[2], R. Dingman[1], K. A. Meagher[1], M. E. Burczynski[1], E. Marin[1], A. P. Kithcart[1], D. E. Gutstein[1]

[1]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [2]Allucent, Cary, NC, USA

Introduction. Factor XI (FXI) inhibition is a promising anticoagulant strategy with potential for reduced bleeding risk versus standard of care therapies. With small-molecule and antibody (Ab)-based approaches such as abelacimab in clinical development, it is important to understand how pharmacokinetic/pharmacodynamic (PK/PD) properties and dose and regimen selection influence FXI inhibition durability.

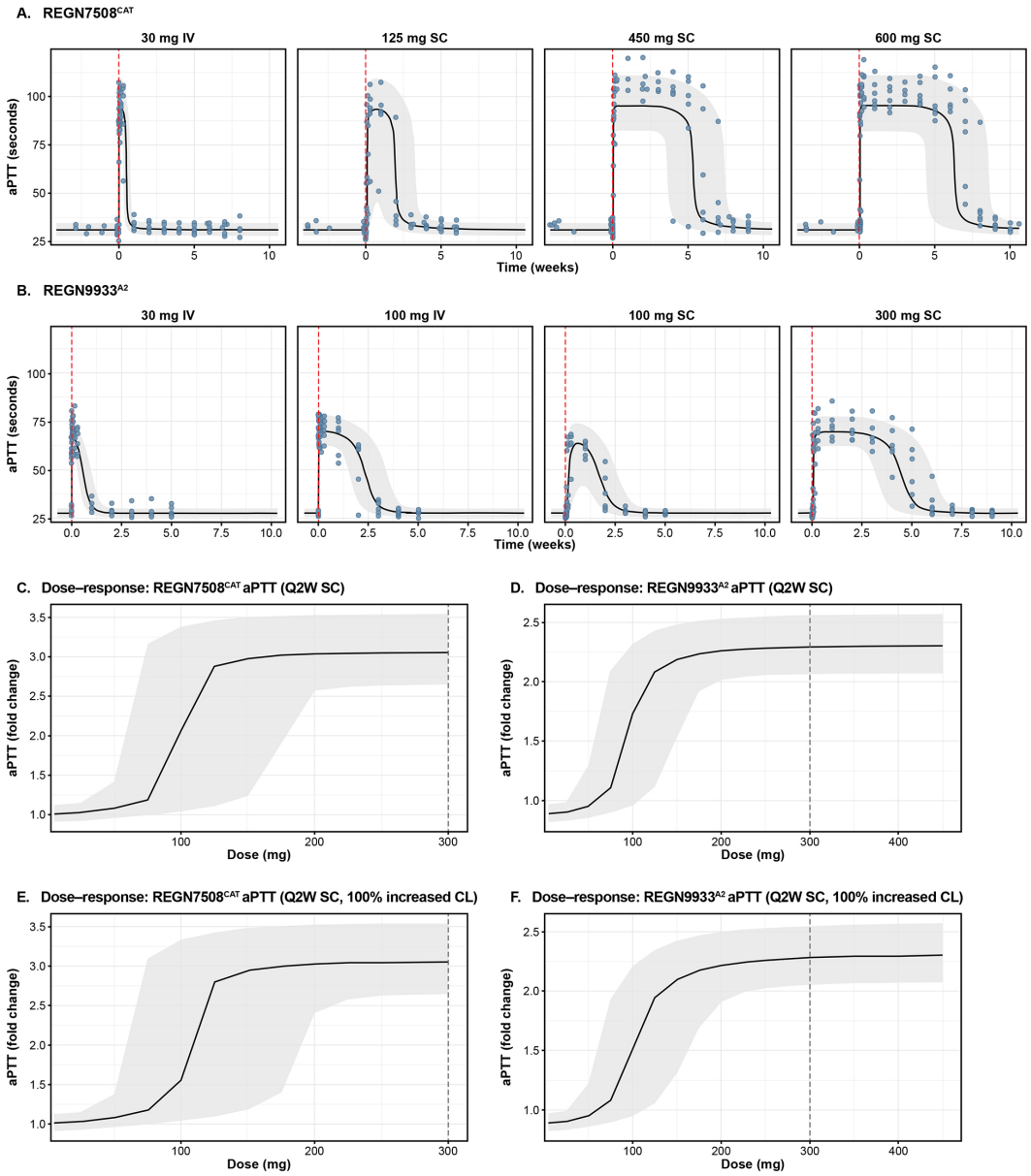
Aim. To develop a PK/PD framework for FXI inhibition by REGN7508^{CAT} and REGN9933^{A2} Abs in healthy volunteers (HVs), quantify sources of interindividual variability, and support translational dose and regimen selection.

Materials and Methods. Data from first-in-human HV studies (6:2 active:placebo) of REGN7508^{CAT} (NCT05603195) and REGN9933^{A2} (NCT05102136) subcutaneous or intravenous (IV) administration were integrated using target-mediated drug disposition (TMDD) models in MonolixSuite 2024R1. Models described total and functional drug concentrations, total FXI concentrations, and activated partial thromboplastin time (aPTT) prolongation. Allometric bodyweight scaling was applied to PK. Covariate effects were screened using the COnditional Sampling use for Stepwise Approach based on Correlation tests (COSSAC). Simulations and visualization were performed in Simulx and R 4.2.2.

Results. The TMDD models captured nonlinear PK/PD effects following REGN7508^{CAT} and REGN9933^{A2} administration. Dose-dependent aPTT prolongation with sustained PD plateaus was consistent with target saturation and epitope binding. Compared with small-molecule FXI inhibition reported in the literature, Ab-based FXI inhibition demonstrated longer PD coverage, rapid IV onset, and reduced sensitivity to peak-trough fluctuations. Under two-fold clearance stress, simulated Q2W dosing maintained continuous FXI suppression and aPTT response over the full dosing interval in >95% of HVs. In contrast, previously reported HV data for Q4W FXI Ab regimens suggest incomplete maintenance of FXI suppression over the full dosing interval.

Conclusions. Mechanistic TMDD modeling demonstrates that Ab-based FXI inhibition provides durable, robust anticoagulant coverage relative to small-molecule approaches. Within the Ab class, dose and regimen selection are critical for maintaining continuous PD coverage. Q2W regimens for REGN7508^{CAT} and REGN9933^{A2} maintained full dosing-interval FXI suppression under clearance stress, supporting translational dose and regimen selection across physiological conditions.

Figure. Observed versus predicted aPTT following single-dose administration of REGN7508^{CAT} and REGN9933^{A2} in HVs (A, B), and simulated dose–aPTT response comparison between HV model parameters and disease state parameters (100% increased clearance for REGN7508^{CAT} and REGN9933^{A2}) (C, D, E, F)



Panel A shows observed (points) and predicted (solid lines; median, with 90% prediction intervals, shaded) aPTT versus time for selected REGN7508^{CAT} IV and SC doses (30 mg IV, 125 mg SC, 450 mg SC, 600 mg SC).
Panel B shows corresponding results for REGN9933^{A2} (30 mg IV, 100 mg IV, 100 mg SC, 300 mg SC). The model captured the dose-dependent aPTT prolongation and time course of PD response across both molecules.
Red dashed vertical lines indicate the time of dose administration.
Panels C and D show simulated aPTT fold change from baseline versus dose for REGN7508^{CAT} and REGN9933^{A2} using HV model parameters at steady state (Q2W SC).
Panels E and F show the impact of 100% increased CL on the predicted dose–response profiles. Shaded areas represent 90% prediction intervals. Both models predict a plateau in aPTT response beyond 250–300 mg, indicating near-maximal FXI suppression, with only modest rightward shifts in the dose–response curves under increased CL conditions.

aPTT, activated partial thromboplastin time; CL, clearance; FXI, factor XI; HV, healthy volunteer; IV, intravenous; PD, pharmacodynamic; Q2W, once every 2 weeks; SC, subcutaneous.