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ANTICOAGULANT PRIMARY PROPHYLAXIS

MECHANISTIC POPULATION PHARMACOKINETIC/PHARMACODYNAMIC AND TIME-TO-EVENT MODELING SUPPORT SUSTAINED FACTOR XI INHIBITION AND SUPERIOR POST-OPERATIVE VENOUS THROMBOEMBOLISM PREVENTION WITH REGN7508^{CAT}

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Introduction. Although Factor XI (FXI) inhibition offers a novel anticoagulant approach, quantitative linkage between FXI suppression, pharmacodynamic (PD) biomarkers, and clinical efficacy is limited. Mechanistic modeling can bridge this gap and support translation from healthy volunteers (HVs) to patient populations.

Aim. Integrate HV and post-operative venous thromboembolism (VTE) prevention data using a joint population pharmacokinetic (PK)/PD and time-to-event (TTE) framework, and evaluate the relationship between REGN7508^{CAT}-mediated FXI inhibition and VTE risk reduction.

Materials and Methods. Data from a first-in-human HV study (NCT05603195) and a Phase 2 post-operative VTE prevention study (NCT06454630) were analyzed with a unified target-mediated drug disposition-based population PK/PD model describing REGN7508^{CAT} exposure, FXI activity suppression, and aPTT prolongation. TTE analyses for adjudicated deep vein thrombosis (DVT) were conducted during a prespecified 12-day post-operative assessment period using Kaplan–Meier estimation, log-rank testing, Cox proportional hazards modeling, and restricted mean survival time (RMST). Participants without confirmed DVT were censored at Day 12 or right censored at last confirmed DVT-free assessment, consistent with the imaging-based endpoint definition.

Results. The joint model successfully linked REGN7508^{CAT} exposure to FXI inhibition and aPTT response in HVs and post-operative participants. A single intravenous REGN7508^{CAT} 250 mg dose resulted in rapid, sustained FXI suppression (>99%) and a 3-fold increase in median aPTT prolongation from baseline, with >95% of participants maintaining a 2.5-fold increase for ~≥2 weeks. In the VTE study, REGN7508^{CAT} improved DVT prevention relative to enoxaparin, with Kaplan–Meier curves separating in the post-operative period. TTE analyses showed a significant treatment effect favoring REGN7508^{CAT}, supported by RMST estimates over the 12-day assessment period. These findings support a clinically meaningful reduction in post-operative VTE risk.

Conclusions. Joint mechanistic PK/PD and TTE modeling demonstrated that sustained FXI inhibition with REGN7508^{CAT} results in improved post-operative VTE prevention versus standard-of-care anticoagulation. These results support REGN7508^{CAT} dose selection, validate mechanistic–clinical linkage, and provide a quantitative framework to evaluate thrombosis prevention and treatment in other populations, including patients with cancer.

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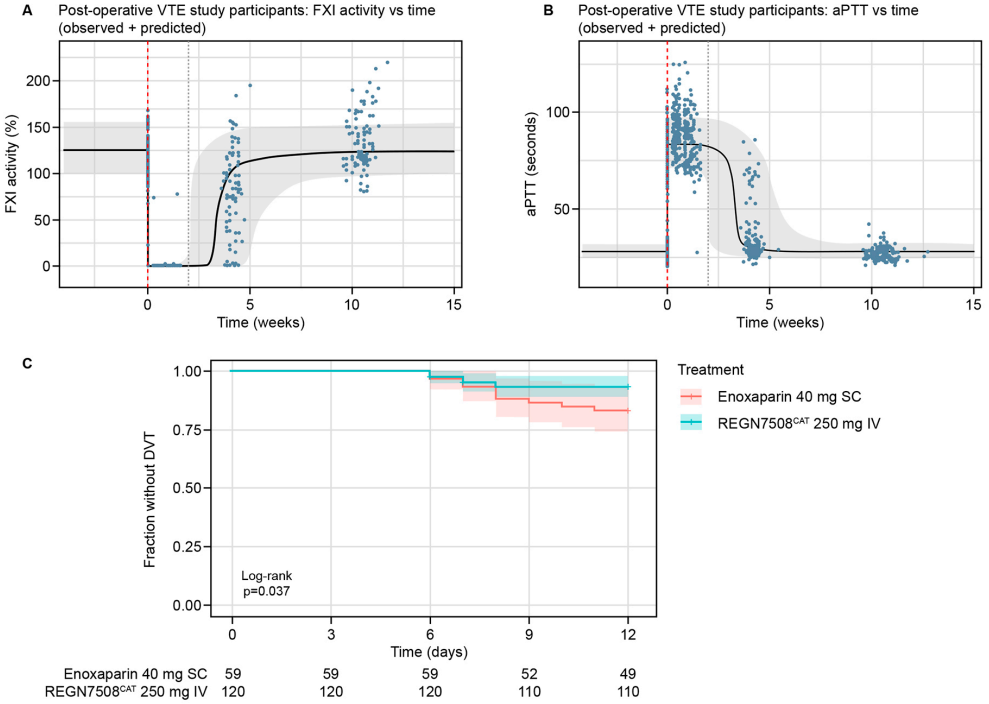
Figure. Sustained FXI suppression following administration of REGN7508^{CAT} is associated with delayed post-operative VTE events compared with administration of enoxaparin



Observed and model-predicted (A) FXI activity and (B) aPTT, over time in post-operative VTE study participants following administration of single-dose REGN7508^{CAT}. Solid lines denote median model predictions; shaded regions represent 90% prediction intervals; points denote observed data. FXI suppression was sustained across the post-operative risk window. Red dashed vertical lines mark the time of dosing, and black dotted lines indicate the 2-week post-dose coverage period.
(C) Kaplan–Meier estimates of DVT-free survival comparing REGN7508^{CAT} and enoxaparin over 12 days post-surgery, demonstrating delayed VTE events with REGN7508^{CAT} versus enoxaparin (log-rank p=0.037). RMST analysis over 12 days demonstrated an absolute difference of 0.33 days favoring REGN7508^{CAT} versus enoxaparin, consistent with sustained FXI inhibition during the post-operative risk period.

aPTT, activated partial thromboplastin time; DVT, deep vein thrombosis; FXI, factor XI; IV, intravenous; SC, subcutaneous; VTE, venous thromboembolism.