Mechanistic target-mediated population PK/PD modelling of REGN7508^{Cat} across healthy volunteers and orthopaedic surgery populations with translational evaluation in patients with PICCs

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BACKGROUND

- REGN7508^{Cat} is a high-affinity human monoclonal antibody targeting the catalytic domain of factor XI (FXI)
  - A Phase 1 trial[1] evaluated the safety, tolerability and pharmacokinetic (PK)/pharmacodynamic (PD) profile of REGN7508^{Cat}
  - REGN7508^{Cat} reduced the risk of post-operative (post-op) venous thromboembolism (VTE) versus enoxaparin in a Phase 2 trial in participants who underwent total knee arthroplasty[2,3]
- Mechanistic population PK/PD modelling can quantify exposure–target–response relationships and support translation across clinical populations, including patients with altered coagulation biology and/or comorbidities, such as cancer

OBJECTIVES

- To develop and evaluate a joint structural target-mediated drug disposition (TMDD) population PK/PD model describing REGN7508^{Cat} PK, FXI turnover, FXI activity suppression and activated partial thromboplastin time (aPTT) response across healthy volunteers (HVs) and post-orthopaedic surgery (VTE)-prevention participants
- To assess translational consistency of the model in patients with peripherally inserted central catheters (PICCs), including individuals with and without active cancer
- To evaluate a dosing regimen for chronic dosing in PICC patients

METHODS

Data sources

- Data from a first-in-human HV study (NCT05603195)[1] and a Phase 2 post-orthopaedic surgery VTE-prevention study (NCT06454630)[2] (**Figure 1**) were analysed using non-linear mixed-effects modelling (Monolix 2024R1) and simulations were performed in Simulx/RsSimulx (R 4.2.2)
- In an exploratory translational assessment, preliminary PD data from the ongoing Phase 2 ROXI-CATH PICC study (NCT06299111)[5] were overlaid with model-based predictions for the post-op population to evaluate consistency of FXI suppression and aPTT response across populations; the aPTT was refit to ROXI-CATH PICC study data

Structural model

- A modified full TMDD structural model[4] was implemented (**Figure 2**), incorporating:
  - Two-compartment free antibody disposition
  - Target (FXI) synthesis (K_{SYN}) and degradation (K_{DEG})
  - Drug–target binding (K_{ON}, K_{OFF})
  - Formation and clearance of drug–target complexes
  - Parallel first-order systemic clearance and saturable target-mediated elimination

Model development

- Estimation was performed sequentially: PK parameters were estimated first, followed by estimation of FXI activity parameters with PK parameters fixed, and lastly, aPTT parameters with PK and FXI activity parameters fixed
- Measurements were total drug (composed of free antibody, single arm–bound antibody, and two arm–bound antibody), functional drug (composed of free antibody and single arm–bound antibody only), total FXI (both free and bound FXI), FXI:C activity (FXI activity with a limit of quantification of 1%), and aPTT in seconds
- FXI activity was described as a function of functional drug, and aPTT was linked to FXI activity through a direct response relationship relative to baseline
- Between-subject variability was included for key PK parameters, FXI activity and aPTT-related parameters, with allometric scaling on body weight for clearance and volume
- Covariate selection followed a COnditional Sampling use for Stepwise Approach based on Correlation (COSSAC) procedure, as implemented in Monolix

Model evaluation

- Model qualification included goodness-of-fit diagnostics, prediction-corrected visual predictive checks, parameter precision assessment and evaluation of structural plausibility

RESULTS

Model evaluation

- The model quantitatively linked REGN7508^{Cat} exposure to FXI inhibition and aPTT response in HVs and post-op participants, reproducing non-linear PK and the observed PD time course across dose levels (HVs) and the single-dose post-op regimen
- In model validation, goodness-of-fit plots demonstrated close agreement between observed and predicted values across all doses and routes (**Figure S1**)

Model-based simulations

- In post-op participants receiving REGN7508^{Cat} 250 mg IV, simulations predicted rapid and near-maximal FXI suppression with corresponding aPTT prolongation early post-dose (**Figure 3**)
- The model predicted that most participants (95%) would maintain a 2.5-fold increase in aPTT through approximately Day 12, with gradual recovery thereafter; FXI levels and aPTT prolongation were projected to be less than maximal, while remaining meaningfully suppressed (aPTT ~2-fold higher) relative to baseline by Day 12–14
- Across populations, FXI activity suppression and aPTT fold-change trajectories were consistent with robust target engagement over the intended early post-op window
- Population differences were best explained by shifts in FXI turnover (elevated K_{SYN} and K_{DEG}) and modestly lower aPTT baseline/maximum-effect parameters in post-op participants, while linear free-antibody clearance was similar between populations, supporting disease- and surgery-related modulation of target biology rather than altered systemic antibody disposition as the primary driver of PK/PD differences

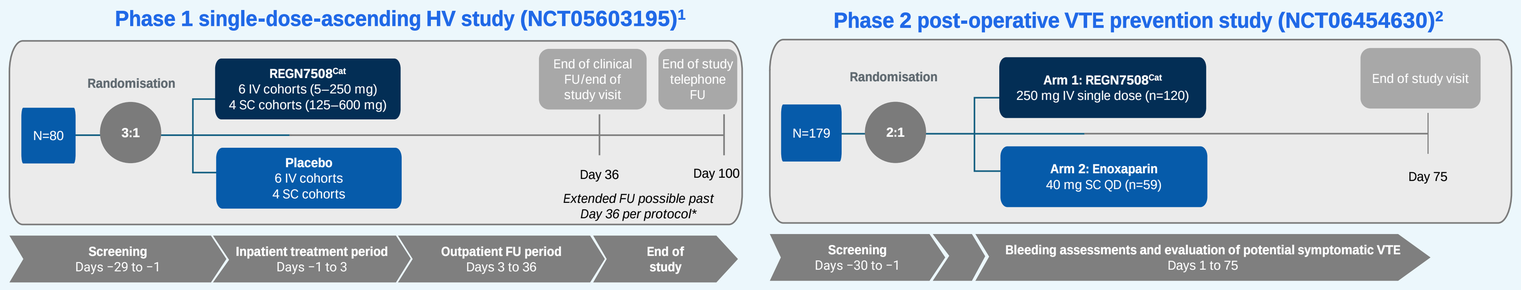
Exploratory translational assessment

- Exploratory overlay of preliminary ROXI-CATH PICC patient PD data were generally consistent with the model-predicted FXI suppression and aPTT trajectories from the post-op population (**Figure 4**), supporting structural robustness of the mechanistic framework across populations, including patients with active cancer
  - aPTT maximum effect (E_{max}) was the only parameter refit to capture the lower fold change from baseline
- These findings support a common model-informed framework for interpreting PICC data and projecting chronic dosing to ensure maximal target engagement throughout the treatment period

CONCLUSIONS

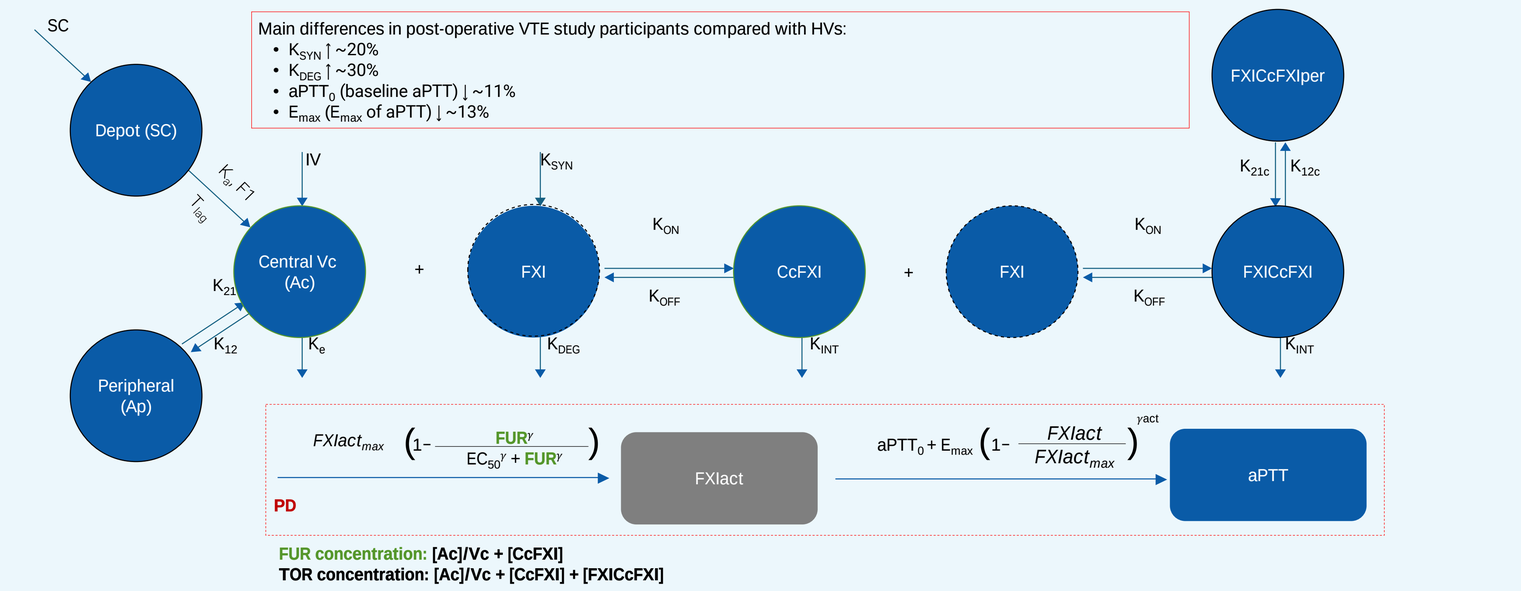
- **A mechanistic TMDD population PK/PD model quantitatively characterised REGN7508^{Cat} non-linear disposition, FXI turnover dynamics and downstream aPTT response in HVs and post-op VTE-prevention participants**
- **In post-op participants receiving REGN7508^{Cat} 250 mg IV, model-based simulations supported rapid near-maximal PD through approximately Day 12, followed by gradual recovery**
- **Population differences were driven primarily by FXI turnover dynamics rather than changes in systemic antibody clearance in the post-op setting**
- **Evaluation in PICC study participants supported cross-population applicability of the mechanistic framework and its use for model-informed dose selection, cross-indication extrapolation and evaluation of disease-related modulation of FXI biology in FXI-mediated thrombotic indications**
- **These findings support a common model-informed framework for interpreting PICC data and projecting chronic dosing to ensure maximal target engagement throughout the treatment period**

FIGURE 1. Study designs



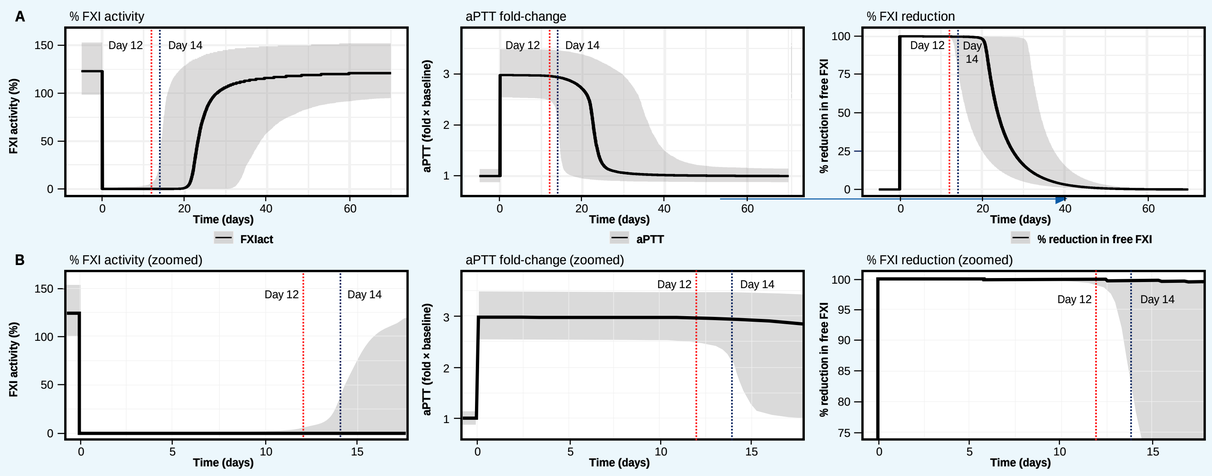
*Day 36 is the primary end of the FU/end of study visit; extended FU could be triggered by aPTT values per protocol.
aPTT, activated partial thromboplastin time; FU, follow-up; HV, healthy volunteer; IV, intravenous; QD, once daily; SC, subcutaneous; VTE, venous thromboembolism.

FIGURE 2. Structural model



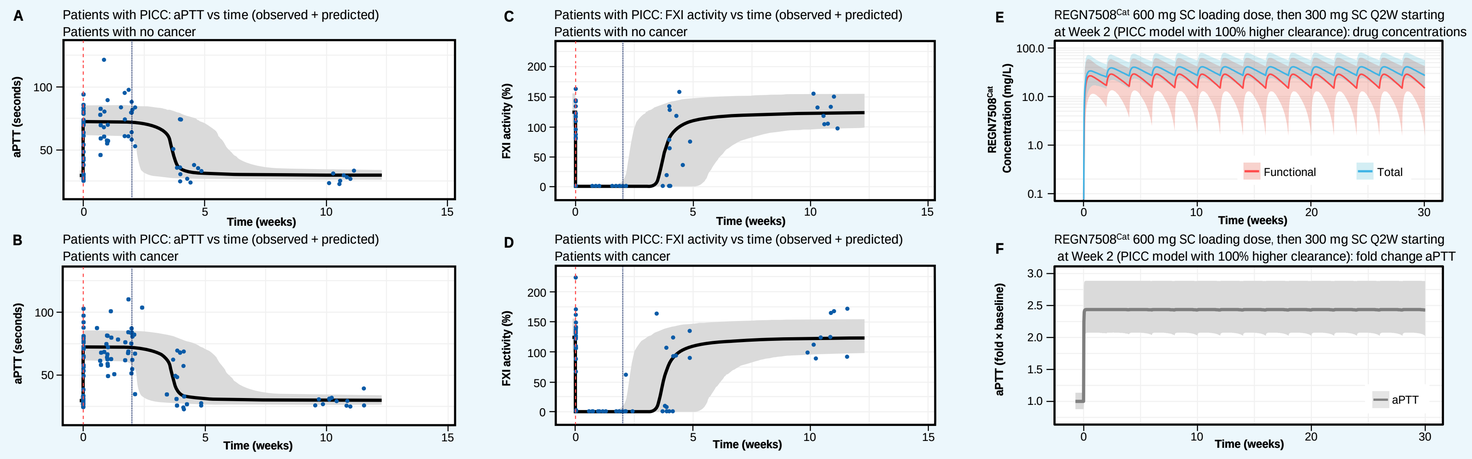
γ, hill coefficient; γact, γ activity; Ac, amount in the central compartment; Ap, amount in the peripheral compartment; aPTT, activated partial thromboplastin time; $aPTT_0$, aPTT at baseline; CcFXI, concentration of the complex bound by one arm only to a subunit of FXI in the vascular space; EC_{50}, half-maximal effective concentration; E_{max}, maximal effect; FUR, functional drug; FXI, factor XI; FXIact, factor XI activity; $FXIact_{max}$, maximum factor XI activity; FXICcFXI, concentration of the complex and two subunits of FXI, one bound to each antibody arm in the vascular space; FXICcFXIper, concentration of complex and two subunits of FXI, one bound to each antibody arm in the peripheral space; HV, healthy volunteer; IV, intravenous; K_{12}/K_{21} and K_{12c}/K_{21c}, denote bidirectional intercompartmental distribution rate constants for free antibody and fully-bound antibody complex, respectively; K_a, absorption rate constant from the SC depot to the central department; K_{DEG}, rate of clearance of FXI from the plasma; K_e, linear elimination rate; K_{INT}, internalisation rate of REGN7508^{Cat}–FXI complex; K_{OFF}, dissociation rate constant for REGN7508^{Cat} binding to the catalytic domain of the FXI subunit; K_{ON}, association rate constant of REGN7508^{Cat} binding to catalytic domain of the FXI subunit; K_{SYN}, rate of FXI synthesis; SC, subcutaneous; T_{lag}, lag time; TOR, total drug; Vc, volume of the central compartment; VTE, venous thromboembolism.

FIGURE 3. Model-based simulations predicted near-complete target engagement through Day 12



Zoomed panels highlight the Day 0–18 post-dose interval relevant to post-op VTE prophylaxis; vertical dashed red lines denote Day 12 (prespecified efficacy assessment period) and blue lines denote Day 14 (reference time point shown).
Solid line: median; shaded band: 90% prediction interval. % FXI reduction indicates free FXI suppression and % FXI activity indicates functional assay readout.
aPTT, activated partial thromboplastin time; FXI, factor XI.

FIGURE 4. PICC patient PD data



Shaded regions represent 90% prediction intervals, solid lines denote model predictions, blue points denote observed data, red dashed vertical lines mark the time of dosing, and black dotted lines indicate the 2-week post-dose coverage period.
LOQ for drug concentration (panel E) was 0.041 mg/L, which is below the scale of the y-axis being shown. For % FXI activity, the LOQ is 1%. aPTT does not have an LOQ established.
aPTT, activated partial thromboplastin time; FXI, factor XI; LOQ, limit of quantification; PICC, peripherally inserted central catheter; Q2W, every 2 weeks; SC, subcutaneous.

Scan the QR code for supplementary materials

Poster

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ACKNOWLEDGEMENTS

This study was supported by Regeneron Pharmaceuticals, Inc. Medical writing assistance was provided by Anna Nagy, MSc, of Oberon, a division of OPEN Health Communications, funded by Regeneron Pharmaceuticals, Inc., according to Good Publication Practice guidelines. The authors would also like to recognise John Davis, PhD, for his contributions to the research.

DISCLOSURES

Oleg Milberg, Hisham Abdallah, Lutz O. Harnisch, Robert Dingman, Karoline A. Meagher, Poulabi Banerjee, Michael E. Burczynski, Ethan Marin, Aaron P. Kithcart, and David E. Gutstein are employees of and shareholders in Regeneron Pharmaceuticals, Inc. Rachel Kudgus Lokken is an employee of Allucent and a consultant for Regeneron Pharmaceuticals, Inc.

Presented at the Population Approach Group Europe (PAGE) Meeting, Dubrovnik, Croatia, 2–5 June 2026. Presenting author: Oleg Milberg; medical.information@regeneron.com