

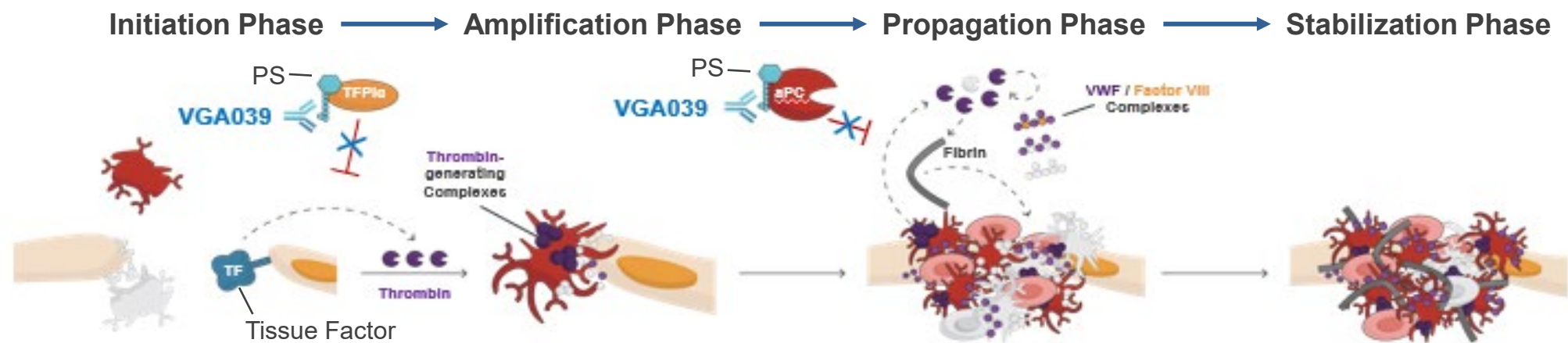
# Pharmacokinetic and Pharmacodynamic Characterization of VGA039 (Latacibart), a Protein S-targeting Monoclonal Antibody, Supports Subcutaneous Every-4-Week Dosing for Routine Prophylaxis in Phase 3 VWD Trial

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## Introduction

- VGA039 (latacibart) is a fully human IgG4 monoclonal antibody which targets Protein S (PS), and functions by dual actions, on the initiation of coagulation by modulating tissue factor pathway inhibitor alpha pathway and on the propagation of coagulation by modulating the activated Protein C (aPC) pathway, to the effect of promoting platelet accumulation and enhance fibrin deposition to restore hemostasis and reduce bleeding<sup>1</sup>



- Herein, we characterize the pharmacokinetic (PK) and pharmacodynamic (PD) data from human multi-dose studies performed in healthy volunteer (HV) and von Willebrand disease (VWD) participants to inform dose regimen selection for the Phase 3 VWD trial (NCT07115004)<sup>2,3,4</sup>

## Objective

- Characterize the PK/PD of latacibart to identify target exposure ranges that support safe, efficacious, and sustained hemostatic activity
- Model and identify a selected dose regimen for a Phase 3 trial in subjects with VWD

## Methods

- Dose-dependent plasma latacibart concentrations were determined following multiple subcutaneous (SC) doses of latacibart in VWD participants (with dose optimization across cohorts)
- PD analyses included the following assays on plasma samples from treated subjects:
  - Total PS levels to assess sustained modulation of target antigen concentration
  - Ex-vivo thrombin generation (TG) assay to assess changes in hemostatic potential (reversal of aPC-mediated thrombin inhibition)
  - Prothrombin F1+2 (F1+2) levels to evaluate in vivo activity (thrombin production)
  - D-dimer levels to indirectly measure cross-linked fibrin deposition
- A population PK (popPK) model was developed using the totality of PK data from single-ascending dose (SAD) data from Parts 1 (HV) and 2 (VWD) of the multi-modular VGA039-CP001 study (NCT05776069<sup>2</sup>), validated using multiple-dose (MD) Part 3 data, and then simulations of dosing regimens in the Phase 3 target population was performed to identify the VGA039-CP002 Phase 3 weight-banded dose selection

## References

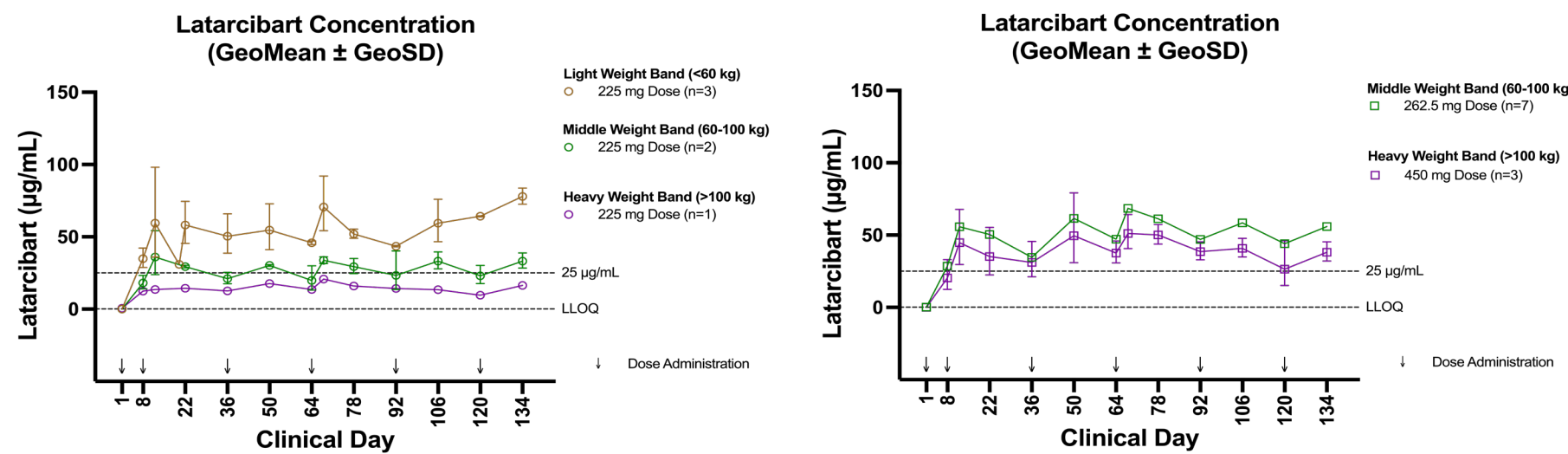
- Sakurai, Y. et al. A protein S-targeting monoclonal antibody, VGA039, improves both primary and secondary hemostatic activity of von Willebrand disease patient blood in an ex vivo vascularized hemostasis-on-a-chip. *Blood*. 2025;146(Suppl 1):305.
- ClinicalTrials.gov Identifier: NCT05776069 (VIVID-3, Phase 1/2 study module).
- Wheeler, A.P. et al. Subcutaneous, every-four-week maintenance dosing of a novel protein S antibody is well-tolerated and substantially reduces bleeding rates: Results from a phase 1/2 multidose study of VGA039 in patients with von Willebrand disease. *Blood*. 2025;146(Suppl 1):308.
- Koch, V. et al. Diagnostic performance of D-dimer in predicting venous thromboembolism and acute aortic dissection. *Eur Heart J Acute Cardiovasc Care*. 2021;10(5):559-566.
- ClinicalTrials.gov Identifier: NCT07115004 (VIVID-6, Phase 3 study).

## PK and PD Results Support Flat Weight-Banded Dosing

### PK with Multi-dosing of Latacibart in VWD Subjects

Cohort 1 Flat Dosage 225 mg SC → Cohort 2 Weight-Banded Flat Dosage

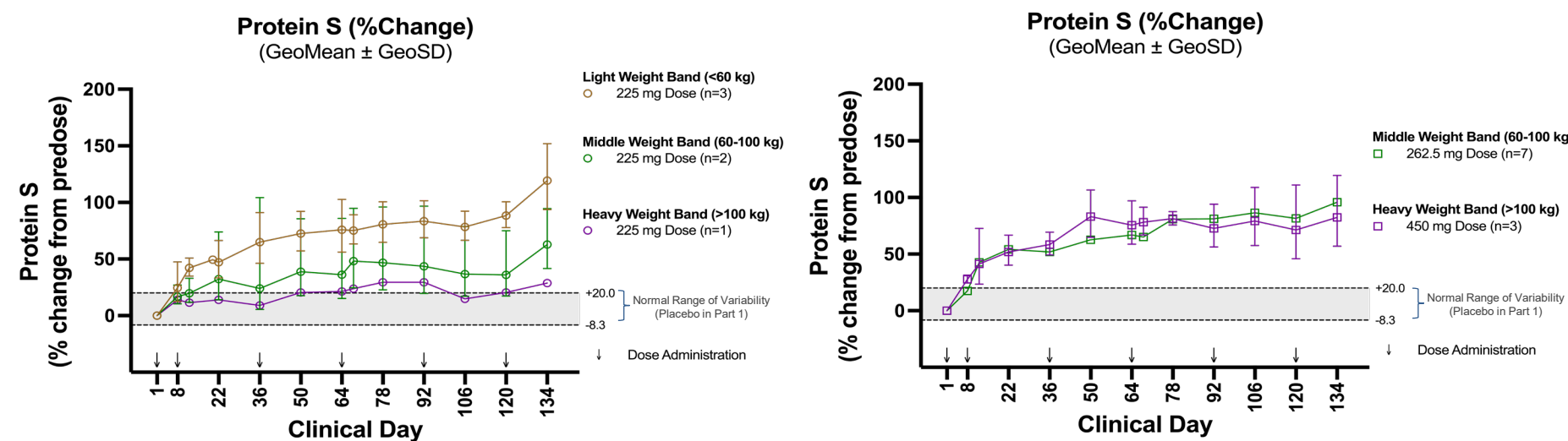
#### Plasma Latacibart (PK)



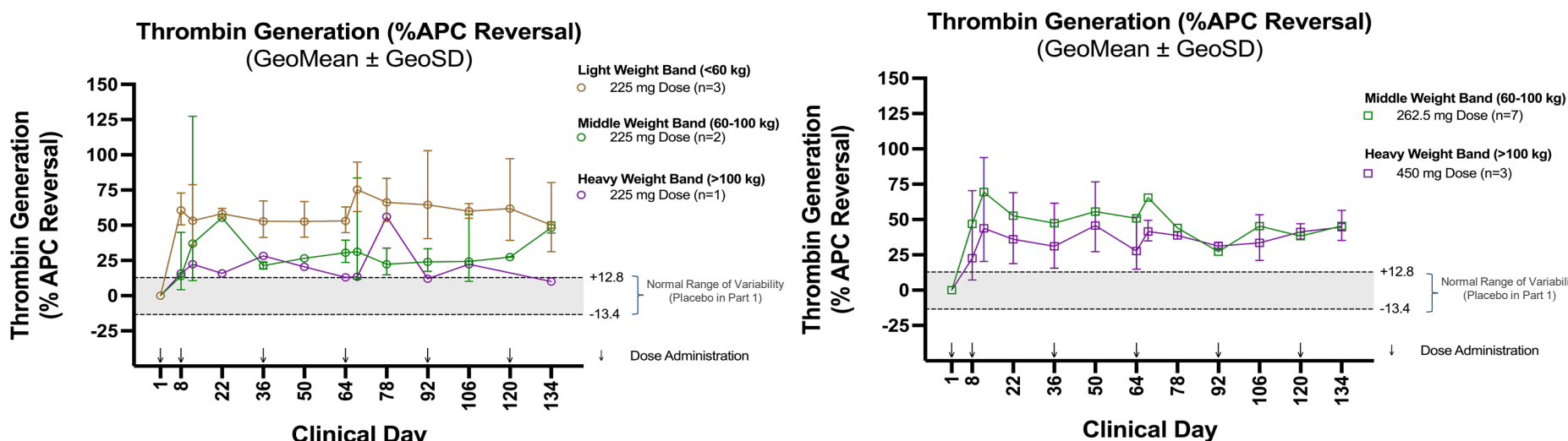
### Dose Optimization for PD+ Activity in VWD Subjects

Cohort 1 Flat Dosage 225 mg SC → Cohort 2 Weight-Banded Flat Dosage

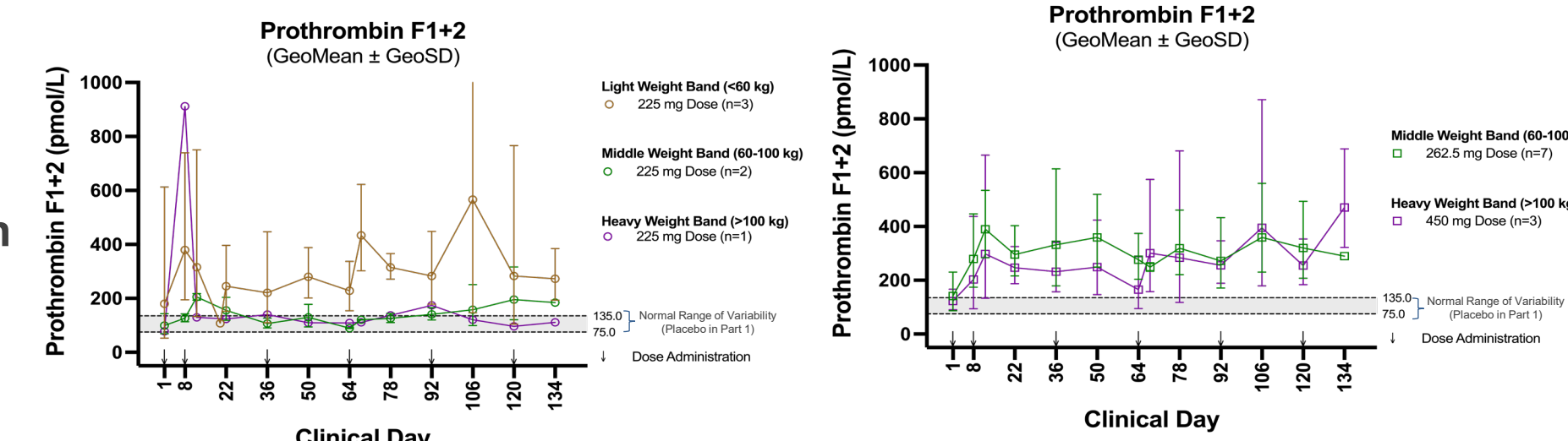
#### Plasma Protein S



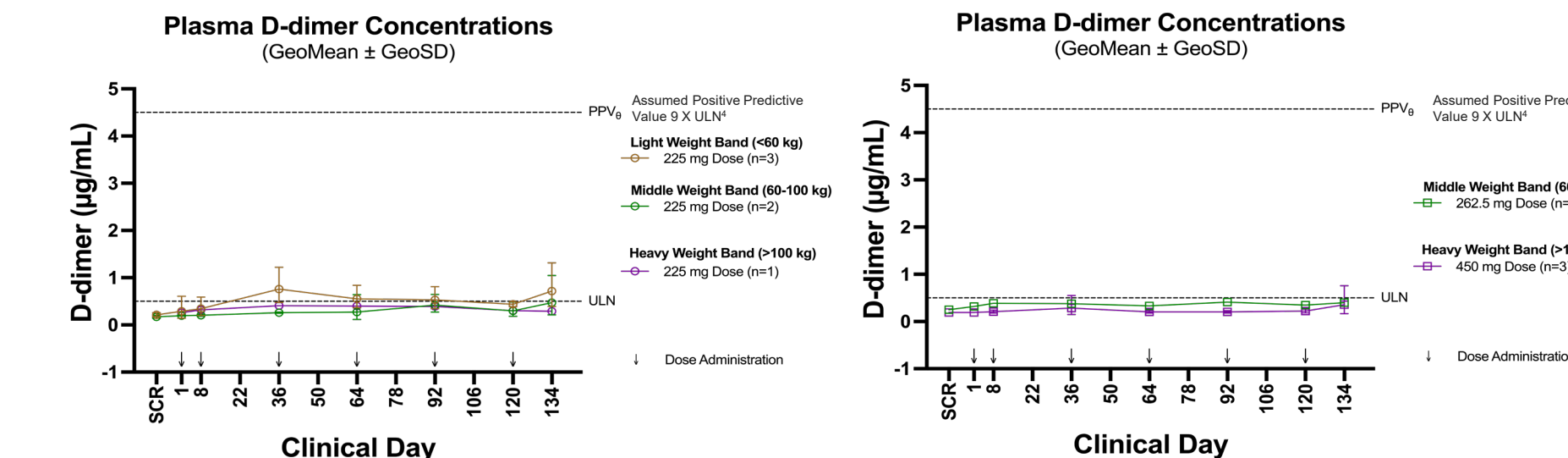
#### Thrombin Generation



#### Plasma Prothrombin F1+2



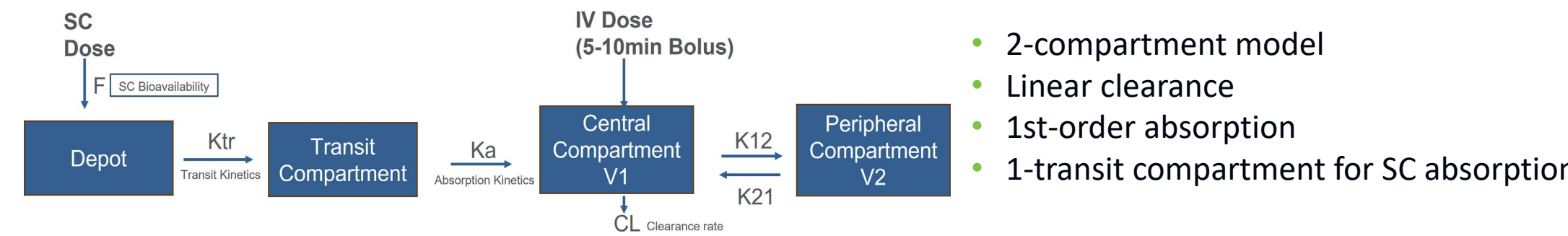
#### Plasma D-dimers



## PK and PK-PD Data Informed Phase 3 Dose Selection

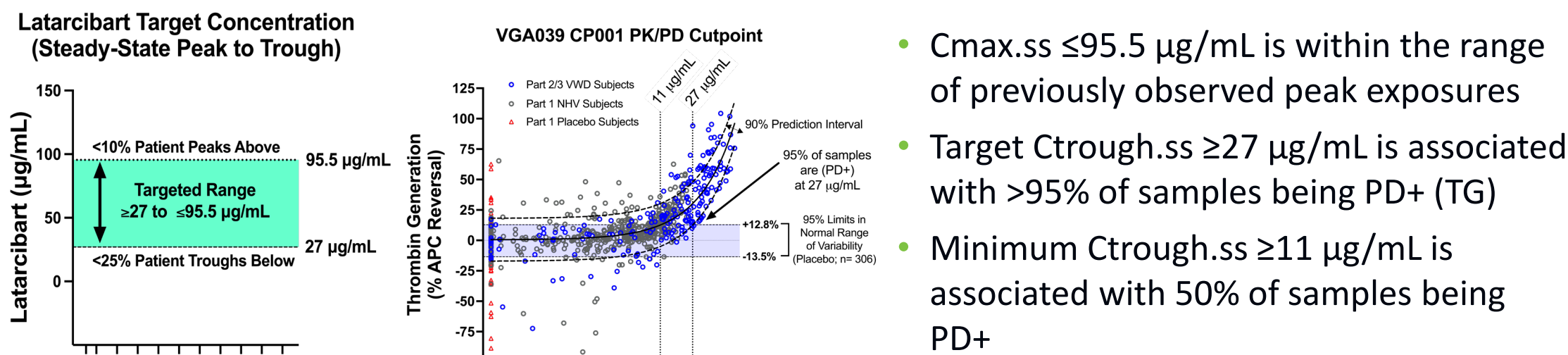
### Building a PopPK Model

- PK data from single ascending dose studies with latacibart displayed a ~28-day terminal half-life supporting every-4-week (Q4W) SC dosing, and data were used to develop a robust PopPK model



- Body weight was identified as a significant covariate, further supporting weight-banded flat dosing
- Loading dose on Day 1 followed by Q4W dosing on Day 8 achieved target exposures within ~1 week

### Modeling Dose for Maintaining Steady-State Trough-Peak Exposures to be PD+ and Within Range of Prior Safe Exposures (27–95.5 µg/mL)



- Cmax.ss ≤95.5 µg/mL is within the range of previously observed peak exposures
- Target Ctrough.ss ≥27 µg/mL is associated with >95% of samples being PD+ (TG)
- Minimum Ctrough.ss ≥11 µg/mL is associated with 50% of samples being PD+

### Simulated weight-banded dosing where:

- >90% of subjects are predicted to have a Cmax.ss ≤95.5 µg/mL (Prior exposures range)
- >75% of subjects are predicted to have a Ctroughs.ss ≥27 µg/mL (Target PD+ range)
- >99% of subjects are predicted to have a Ctroughs.ss ≥11 µg/mL (Minimum PD+ range)

## Conclusions

- Latacibart exhibits a favorable PK profile that supports SC Q4W (monthly) dosing
- Weight-adjusted dosing during Phase 2 dose optimization showed improvement across all measurements of PD activity—Protein S target modulation, ex-vivo TG potential, and in-vivo TG (F1+2)—with minimal signs of excess fibrin deposition (limited D-dimer elevations) and no safety issues
- These PK/PD findings establish and confirm weight-banded flat dosing and the popPK model used to select the Phase 3 dose and regimen for latacibart as a routine prophylactic therapy being investigated in the ongoing Phase 3 VWD trial<sup>4</sup>

### Phase 3 Weight-Banded Dosing Regimen

- 225 mg (1.5 mL) SC Q4W: subjects weighing 40 to <60 kg
- 300 mg (2.0 mL) SC Q4W: subjects weighing 60 to <100 kg
- 450 mg (3.0 mL) SC Q4W: subjects weighing ≥100 kg