A Quantitative Systems Pharmacology Model Linking KIT Signaling to Mast Cell Degranulation and Depletion

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Introduction

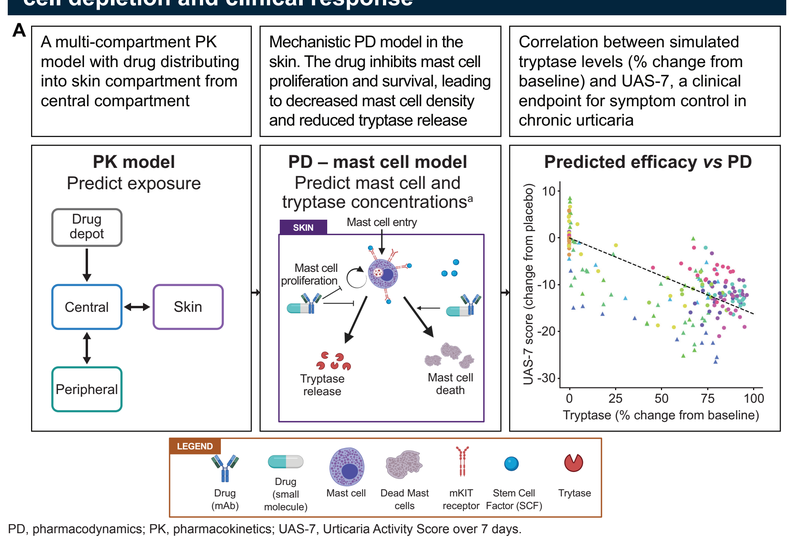
- Mast cells are central to the pathogenesis of allergic diseases such as chronic spontaneous and inducible urticarias, with symptoms driven by aberrant activation and mediator release from mast cells[1]
- The wild-type (WT) KIT receptor, which regulates mast cell survival, proliferation, and activation, has become a major therapeutic target in mast cell–driven diseases[2]
  - Recent advances have led to novel therapies targeting WT KIT, including monoclonal antibodies (mAbs; e.g., barzolvolimab[3], briquilimab[4]) and small molecule inhibitors (e.g., BLU-808 and THB-001)
- To support early, quantitative decision-making in drug development, we developed a quantitative systems pharmacology (QSP) model to characterize the impact of KIT inhibition on mast cell biology
- This model uses the biomarker serum tryptase to link KIT inhibition to downstream effects, including mast cell suppression and depletion
- By integrating pharmacokinetic (PK) and pharmacodynamic (PD) from *in vitro* studies, clinical trials, and literature, the QSP model enables comparison of different KIT inhibitors across modalities
- Ultimately, this QSP model serves as a translational tool for predicting on-target KIT effects on mast cells as well as informing clinical development strategies for mast cell–driven diseases

Methods

- Integrated *in vitro, in vivo,* and publicly available clinical and literature data were used to develop a QSP model of KIT inhibition (**Figure 1**)
- The model was calibrated using clinical data on mast cell dynamics and serum tryptase changes observed with KIT inhibitors, specifically the mAb barzolvolimab and the small molecule inhibitor THB-001 (**Figure 2**)

Methods (continued)

Figure 1. QSP model schematic: Mechanistic PK/PD model of mast cell depletion and clinical response



PD, pharmacodynamics; PK, pharmacokinetics; UAS-7, Urticaria Activity Score over 7 days.

B. Model structure

$$\text{RO-frac}(t) = \frac{\text{SCF-KIT-RO}(t)}{\text{SCF-KIT-RO}(0)}$$

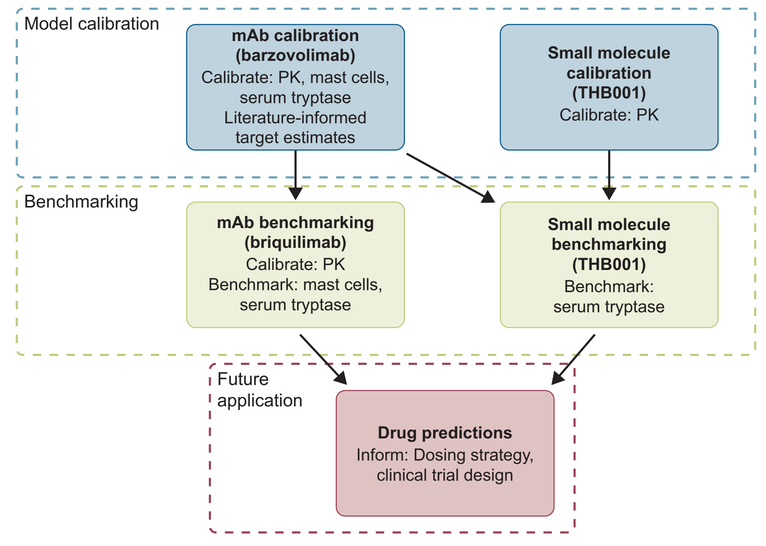
$$\frac{d\text{MC}}{dt} = k_{entry} + k_{prolif} \bullet \text{RO-frac}(t) \bullet \text{MC}(t) - (k_{death} + k_{\text{RO-inh death}} \bullet (1 - \text{RO-fract}(t))) \bullet \text{MC}(t)$$

$$\frac{d\text{Trp}}{dt} = k_{Trp} \bullet (w \bullet \text{RO-frac}(t) + (1 - w) \bullet \frac{\text{MC}(t)}{\text{MC}(0)}) - k_{deg,\ Trp} \bullet \text{Trp}(t)$$

k_{death}, death rate of MC; $k_{deg,\ Trp}$, degradation rate of tryptase; k_{entry}, rate of MC entry from progenitor pool; k_{prolif}, proliferation rate of MC; k_{Trp}, tryptase production rate; $k_{\text{RO-inh death}}$, death rate of MC due to loss of SCF-KIT survival signal; MC, mast cell count; RO-frac, fraction of SCF-KIT receptor occupancy at time t compared to baseline (time 0); Trp, tryptase concentration; w, weight of tryptase production by SCF-KIT RO signal.

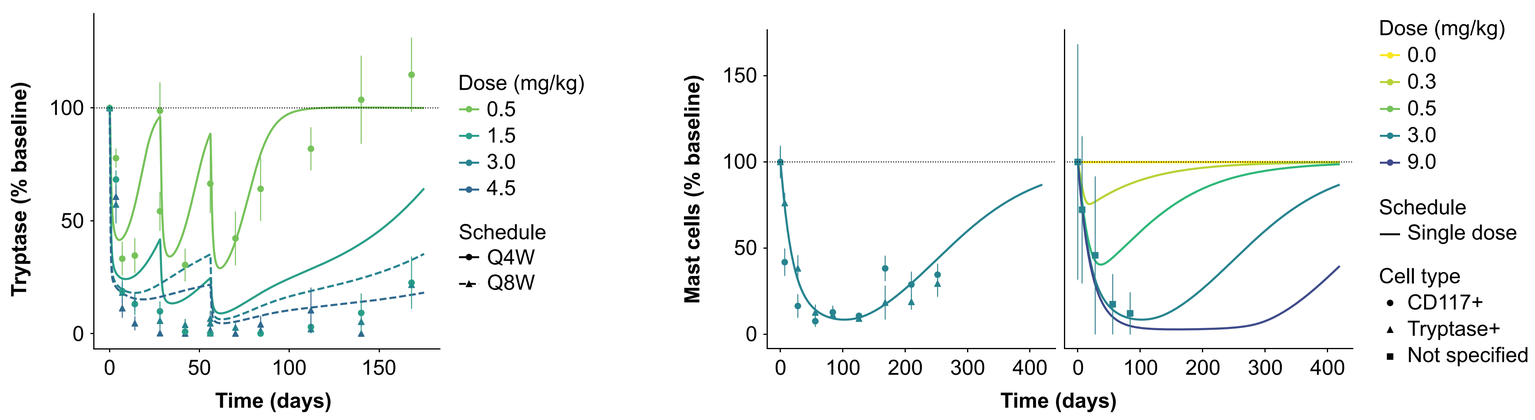
- The model predictions were validated against independent clinical data, including results from studies of the mAb briquilimab
- The validated model was used to estimate the optimal dose of a hypothetical compound based on its PK and potency characteristics, supporting informed decision-making in early drug development

Figure 2. Data integration and workflow



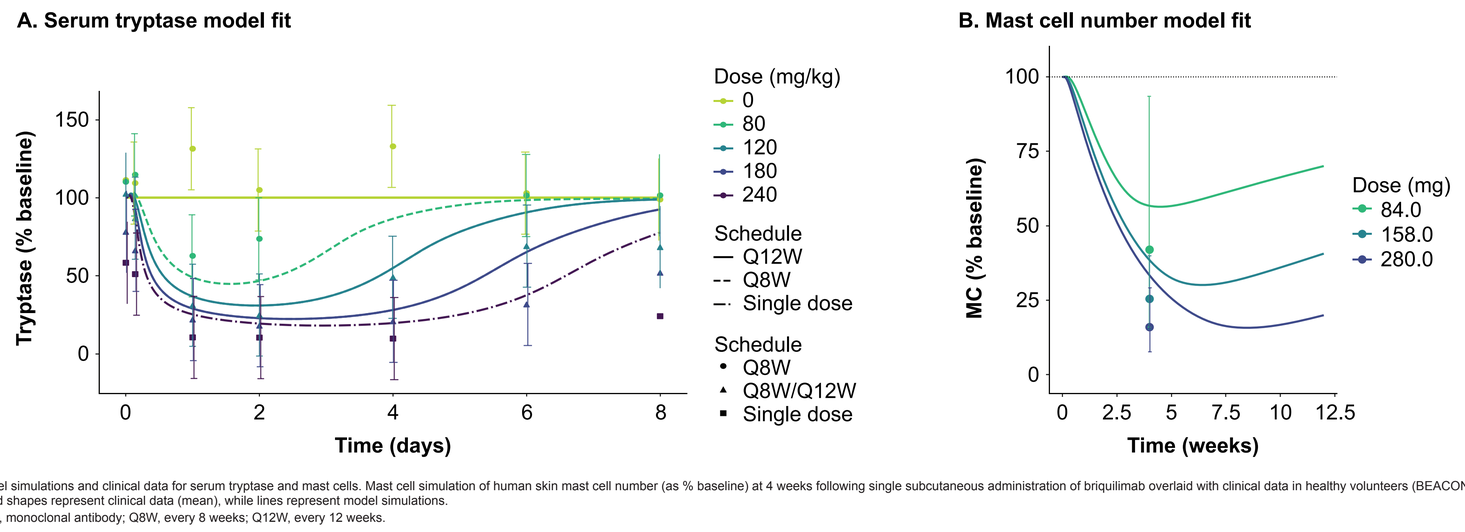
Results

Figure 3. QSP model calibration to the anti-KIT mAb barzolvolimab: Observed clinical data (shapes) *versus* model predictions (lines)



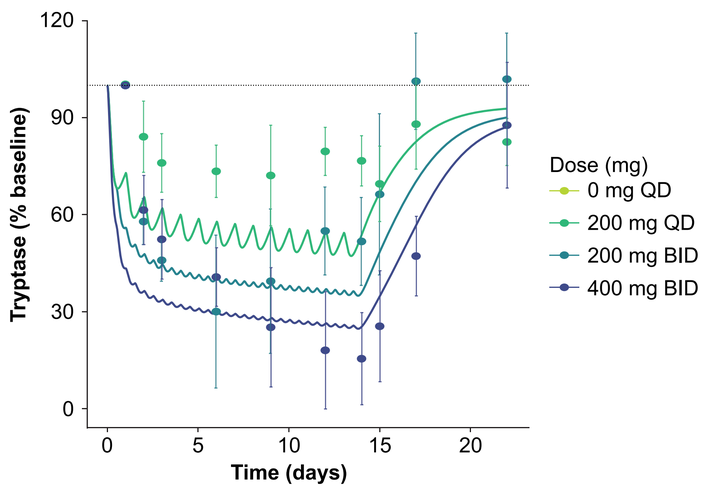
Model simulations and clinical data for serum tryptase and mast cells following barzolvolimab in healthy volunteers and patients with chronic spontaneous urticaria.[8,10] Filled shapes indicate observed clinical data, while lines represent model simulations.
CD117, cluster of differentiation 117; mAb, monoclonal antibody; Q4W, every 4 weeks; Q8W, every 8 weeks; QSP, quantitative systems pharmacology.

Figure 4. QSP model validation to the anti-KIT mAb briquilimab: Observed clinical data (shapes) *versus* model predictions (lines)



Model simulations and clinical data for serum tryptase and mast cells. Mast cell simulation of human skin mast cell number (as % baseline) at 4 weeks following single subcutaneous administration of briquilimab overlaid with clinical data in healthy volunteers (BEACON study[7]). Filled shapes represent clinical data (mean), while lines represent model simulations.
mAb, monoclonal antibody; Q8W, every 8 weeks; Q12W, every 12 weeks.

Figure 5. QSP model translation to the anti-KIT small molecule inhibitor THB-001: Serum tryptase model fit

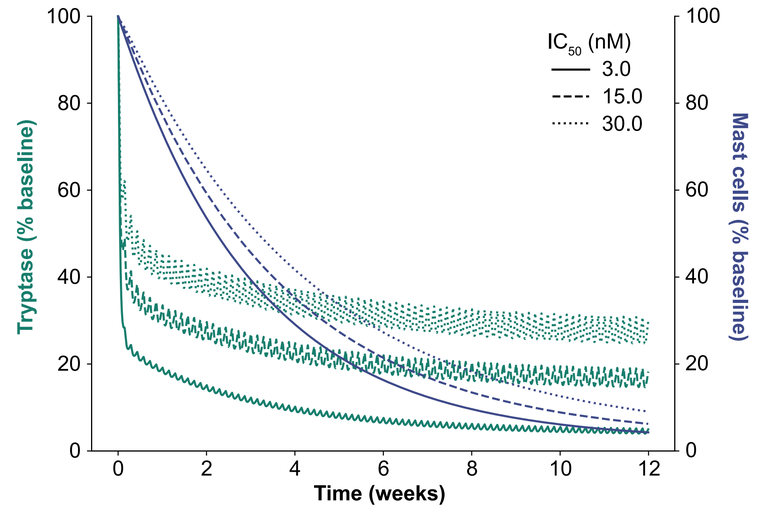


Model simulation and clinical pharmacokinetic data and serum tryptase levels following THB-001 (small molecule inhibitor) in healthy volunteers. Filled circles indicate observed clinical data, while lines represent model simulations. Clinical data were obtained from Sweeny et al., 2023.[6] Note that the overprediction of tryptase reduction at 200 mg QD is driven by overprediction of PK.

- The model successfully reproduced the available clinical data for PK and serum tryptase (all three compounds) and the mast cell depletion data which were only available for both mAbs
- After initial model calibration using barzolvolimab (**Figure 3**), the model predicted the reduction in serum tryptase (40% to 80%) and mast cell depletion (60% to 80%) for briquilimab based on its potency and PK characteristics (**Figure 4**)
- By substituting the mechanism of action (MoA) from mAb-mediated blocking of stem cell factor-KIT binding to small molecule inhibition via a half-maximal inhibitory concentration function, the model captured THB-001 responses without requiring modification of core biological parameters (**Figure 5**)
- Model predictions of serum tryptase were generated for a hypothetical small molecule KIT inhibitor, assuming different levels of KIT inhibition potency. The PK was assumed to be a two-compartment model (**Figure 6A**)
- Using a linear model fit of pooled clinical data from barzolvolimab and briquilimab, a strong negative correlation (coefficient of –0.1652, P<0.001) was observed between serum tryptase and Urticaria Activity Score over 7 days (UAS-7). This relationship was used to estimate UAS-7 from the predicted serum tryptase levels at each potency (**Figure 6B**)

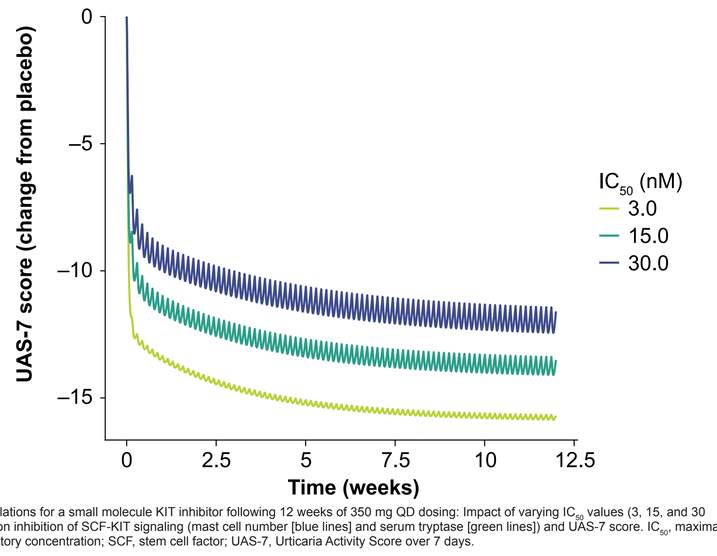
Figure 6. Effect of varying KIT inhibition potency on serum tryptase, for mast cells (A) and UAS-7 score (B)

A. Serum tryptase and mast cell simulations



Green lines represent tryptase, blue lines represent mast cells.

B. UAS-7 score simulations



Simulations for a small molecule KIT inhibitor following 12 weeks of 350 mg QD dosing: Impact of varying IC_{50} values (3, 15, and 30 nM) on inhibition of SCF-KIT signaling (mast cell number [blue lines] and serum tryptase [green lines]) and UAS-7 score. IC_{50}, maximal inhibitory concentration; SCF, stem cell factor; UAS-7, Urticaria Activity Score over 7 days.

Conclusions

- Wild-type KIT inhibitors are emerging as promising therapies for mast cell–driven diseases such as chronic spontaneous urticaria, demonstrating potent mast cell suppression and predictable hematopoietic effects
- To our knowledge, this is the first unified QSP framework that integrates diverse MoAs, links KIT inhibition to PD biomarkers, and enables comparison of efficacy across modalities
- The model provides a translational bridge between mechanistic biomarkers and symptom improvement (UAS-7), and enables informed decision-making during early clinical development

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Disclosures/conflicts of interest

Anitha Suram is an employee of Blueprint Medicines Corporation, a wholly owned subsidiary of Sanofi.

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