Poster 5392

Mechanistic drivers for potent pharmacodynamic activity of verekitug, a novel anti-TSLPR antibody

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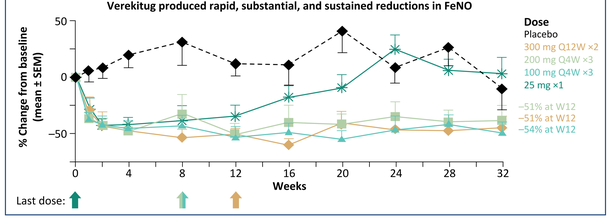
KEY FINDINGS

- Verekitug is a fully human unmodified IgG1 monoclonal antibody that binds thymic stromal lymphopoietin receptor (TSLPR) with sub-picomolar affinity
- Verekitug prevents thymic stromal lymphopoietin (TSLP) from binding TSLPR by occupying the ligand binding sites on TSLPR, preventing heterodimerization with interleukin 7 receptor alpha (IL-7Rα)
- Verekitug outcompetes TSLP in both binary and preformed heterodimeric complexes, effectively inhibiting downstream STAT5 signaling
- A semi-mechanistic pharmacokinetic/pharmacodynamic (PK/PD) model suggests that lower abundance and slower turnover of TSLPR vs TSLP drive the greater potency of verekitug as compared with tezepelumab observed in vitro and across clinical datasets[1–3]
- Phase 2 trials of verekitug in asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and chronic obstructive pulmonary disease (COPD) are underway to determine if this difference in potency translates into the ability to extend dosing to every 12 or 24 weeks with a potential for concomitant increased clinical efficacy

AIMS

- TSLP is a key upstream driver of airway inflammation in chronic respiratory diseases such as asthma, CRSwNP, and COPD
- Verekitug is a novel, fully human monoclonal antibody that binds to the TSLPR and blocks TSLP-mediated inflammation[1]
- In vitro and early clinical studies indicate that verekitug may provide greater PD effects than tezepelumab, including enhanced suppression of fractional exhaled nitric oxide (FeNO), a biomarker of airway inflammation and blood eosinophils (**Figure 1**)[2,3]
- Here, we aim to better understand the molecular and pharmacologic basis of the enhanced clinical potency of verekitug vs tezepelumab, an approved anti-TSLP antibody

Figure 1. Phase 1 clinical study data in patients with mild to moderate asthma



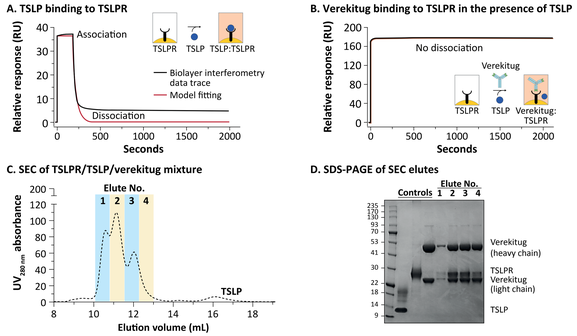
Percentage change in FeNO levels from baseline through 32 weeks. In cohorts receiving ≥ 100 mg, verekitug resulted in 51%–54% mean reduction from baseline at week 12.
FeNO, fractional exhaled nitric oxide; Q×W, every × weeks; SEM, standard error of the mean; W, week.

RESULTS

Verekitug inhibits the formation of TSLP and TSLPR complex, blocking the necessary priming step for heterodimeric complex formation with IL-7Rα

- TSLP binds to TSLPR with high affinity (K_D ~3-36 nM) and fast kinetics (K_a 8.66×10^6 M^{-1}s^{-1}, K_d 2.55×10^{-2} s^{-1}) (**Figure 2A**)
- Verekitug outcompetes TSLP binding to TSLPR due to higher affinity (K_D < 1 pM) and lack of measurable dissociation from TSLPR as evidenced by surface plasmon resonance (SPR) followed by complex integrity confirmation (**Figure 2B-D**)

Figure 2. SPR analysis of the ability of verekitug to bind to TSLPR in the presence of TSLP

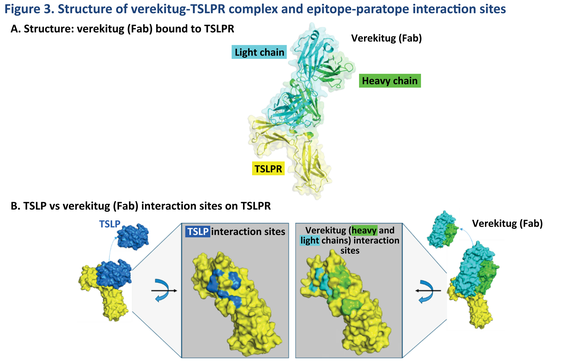


RU, relative units; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoresis; SEC, size-exclusion chromatography.

Verekitug interacts with most of the TSLP ligand binding sites on TSLPR, occupying ligand binding space and blocking TSLP/TSLPR interaction

- The crystal structure of verekitug (Fab) bound to the extracellular domain of TSLPR was obtained from a high-resolution (2.46 Å) x-ray diffraction pattern (**Figure 3A**)
- Verekitug interacts with most of the TSLP (PDB: 5j11) binding sites, and thus occupies the ligand binding pocket on TSLPR (**Figure 3B**)

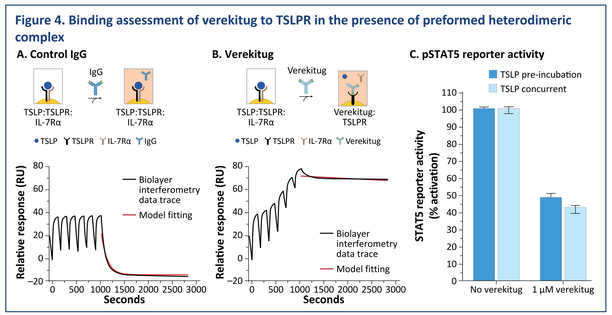
Figure 3. Structure of verekitug-TSLPR complex and epitope-paratope interaction sites



Verekitug outcompetes TSLP in the preformed heterodimeric complex and blocks STAT5-mediated TSLP/TSLPR signaling

- Single-cycle kinetics using a preformed complex of TSLPR, TSLP, and IL-7Rα was used to assess binding
- Verekitug specifically outcompetes TSLP in the preformed TSLP/TSLPR/IL-7Rα heterodimeric complex (**Figure 4A,B**)
- Verekitug blocks TSLP-mediated phosphorylation of STAT5 by outcompeting TSLP ligand 24 hours post treatment, even in cells pretreated with TSLP to induce receptor heterodimerization (**Figure 4C**)

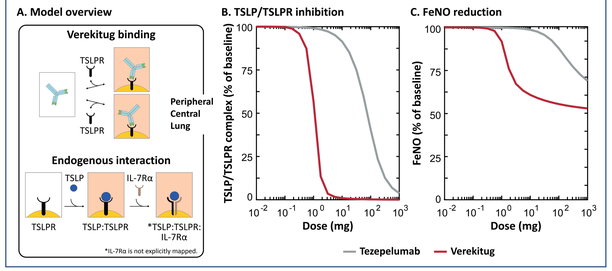
Figure 4. Binding assessment of verekitug to TSLPR in the presence of preformed heterodimeric complex



Semi-mechanistic PK/PD model predictions are consistent with clinical findings of more potent reduction in FeNO with verekitug vs published data for tezepelumab

- Models (**Figure 5A**) incorporated biological TSLP binding affinity to TSLPR, target (TSLP and TSLPR) concentrations, target turnover times, and drug-specific (eg, drug/target binding affinities and drug PK properties) parameters[1,4–6]
- Models were co-fit with the observed clinical PD data (inhibition of FeNO) for verekitug[3] and published data for tezepelumab[1]
- Consistent with observed clinical findings, dose-response simulations show that inhibiting TSLPR with verekitug results in more potent inhibition of TSLP/TSLPR complex formation and, consequently, a greater reduction in FeNO, as compared with neutralizing TSLP ligand with tezepelumab

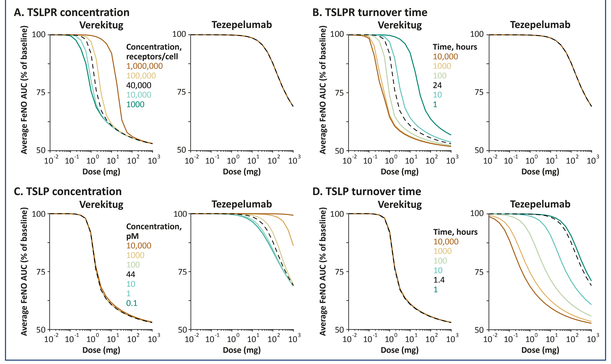
Figure 5. Semi-mechanistic PK/PD models predicting inhibition of TSLP/TSLPR complex and downstream PD suppression of FeNO



Greater reduction in FeNO with verekitug is likely driven by lower expression of TSLPR (steady-state concentration and turnover time) vs TSLP ligand

- FeNO reduction with verekitug is sensitive to TSLPR levels, a function of steady-state concentration, and protein turnover time (**Figure 6A,B**) and insensitive to TSLP levels (**Figure 6C,D**)
- FeNO reduction with tezepelumab is sensitive to TSLP levels (**Figure 6C,D**) and insensitive to TSLPR levels (**Figure 6A,B**)
- Relative target abundance (ie, lower levels of TSLPR vs TSLP) in the lung was identified as a key driver of the observed differences in potency with respect to FeNO reduction

Figure 6. Model-based sensitivity analysis comparing dose-response simulations



CONCLUSIONS

- Verekitug (K_D < 1 pM) outcompetes TSLP binding to TSLPR in a preformed heterodimeric complex
- Verekitug binds to the majority of TSLP binding sites on TSLPR, blocking TSLP interaction with the binding pocket of the TSLPR
- A semi-mechanistic PK/PD model indicates that lower abundance and slower turnover of TSLPR vs TSLP drive the greater potency of verekitug vs tezepelumab observed in vitro and across clinical datasets[1–3]
- These findings provide a mechanistic explanation for the observed greater potency of targeting TSLPR with verekitug as compared with the ligand
- Clinical efficacy and safety of verekitug are being studied in four phase 2 trials for treatment of severe asthma,[7,8] CRSwNP,[9] and COPD[10] in dosing intervals of up to 24 weeks

ACKNOWLEDGMENTS

Under the direction of the authors, medical writing assistance was provided by Luciana Gardner, MSc, of Parexel International, and supported by Upstream Bio, Inc.

FUNDING AND DISCLOSURES

This study was funded by Upstream Bio, Inc., Waltham, MA, USA. FC, AK, SS, and AD are employees of and receive compensation from Upstream Bio, Inc. AD has leadership or fiduciary roles with Upstream Bio, Inc.

REFERENCES

1. Numazaki M, et al. *J Pharmacol Exp Ther*. 2022;380:26–33. **2.** Corren J, et al. *N Engl J Med*. 2017;377: 936–946. **3.** Deykin A, et al. *Eur Res J*. 2024;64(suppl 68):OA3651. **4.** Ly N, et al. *J Clin Pharmacol*. 2021;61:901–912. **5.** Sundnes O, et al. *Mol Med*. 2021;27:29. **6.** Henriques CM, et al. *Blood*. 2010;115: 3269–3277. **7.** ClinicalTrials.gov. NCT06196879. **8.** ClinicalTrials.gov. NCT06966479. **9.** ClinicalTrials.gov. NCT06164704. **10.** ClinicalTrials.gov. NCT06981078.

Presented at the European Respiratory Society (ERS) Congress 2025; September 27–October 1; Amsterdam, the Netherlands