Poster XXXX

In silico system pharmacology modeling provides insights into a mechanism for greater potency of TSLP/TSLPR pathway inhibition with verekitug, a novel antibody antagonist of the TSLP receptor, as compared with tezepelumab

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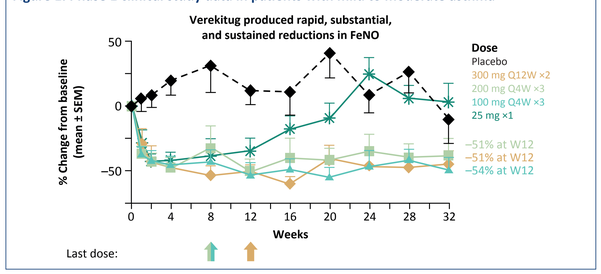
KEY FINDINGS

- Verekitug is a novel, fully human IgG1 monoclonal antibody targeting the thymic stromal lymphopoietin receptor (TSLPR)
- Verekitug demonstrates greater potency compared with tezepelumab in vitro and greater reductions in fractional exhaled nitric oxide (FeNO; up to 54%) in patients with asthma compared with published studies with tezepelumab
- A semi-mechanistic pharmacokinetic/pharmacodynamic (PK/PD) model identifies lower TSLPR levels over time (ie, lower abundance and slower turnover time) compared with thymic stromal lymphopoietin (TSLP) ligand as potential drivers of the greater potency of verekitug
- Phase 2 trials of verekitug in asthma, chronic obstructive pulmonary disease (COPD), and chronic rhinosinusitis with nasal polyps (CRSwNP) are underway to determine if this difference in potency translates into ability to extend dosing to every 12 or 24 weeks with a potential for concomitant increased clinical efficacy

BACKGROUND

- Verekitug, a novel high-affinity fully human monoclonal antibody antagonist of TSLPR, is in development as a potential therapy for severe asthma, CRSwNP, and chronic COPD
- Preclinical (in vitro) data with verekitug indicated a 4- to 5-fold increased potency as compared with tezepelumab, which targets the TSLP ligand[1]
- In a phase 1 multi-ascending dose clinical study in patients with mild to moderate asthma,[2] verekitug achieved up to ~54% reduction in FeNO, a relevant downstream PD marker, representing a greater impact on FeNO than that reported with tezepelumab[3] (**Figure 1**)
- This study uses a systems pharmacology modeling approach to provide a mechanism-based understanding for the observed greater potency of verekitug compared with tezepelumab

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



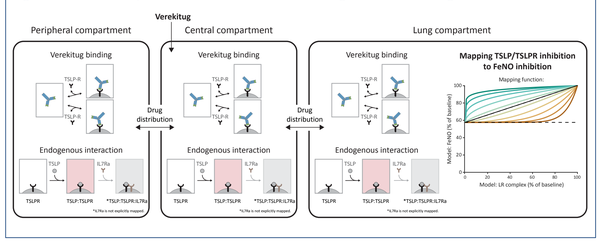
Percentage change in FeNO levels from baseline through 32 weeks. In cohorts receiving ≥ 100 mg, verekitug resulted in 51%–54% mean reduction from baseline at week 12.
FeNO, fractional exhaled nitric oxide; Q×W, every × weeks; W, week.

METHODS

Semi-mechanistic PK/PD models were built to predict inhibition of TSLP/TSLPR complex and downstream PD suppression of FeNO

- Both the verekitug (**Figure 2**) and tezepelumab models incorporated the same biological parameters, including TSLP binding affinity to TSLPR, target (TSLP and TSLPR) concentrations, and target turnover time. In addition, drug-specific parameters (eg, drug/target binding affinities and drug PK properties) were incorporated in the model
- Models were then co-fit with the observed clinical PD data (inhibition of FeNO) with verekitug[3] and published data with tezepelumab[4]
- Model-derived simulations allowed comparison between verekitug and tezepelumab potency as assessed by their ability to inhibit
  - TSLP/TSLPR complex formation, and
  - Subsequent downstream inhibition of FeNO

Figure 2. Three-compartmental PK and PD model diagram for verekitug



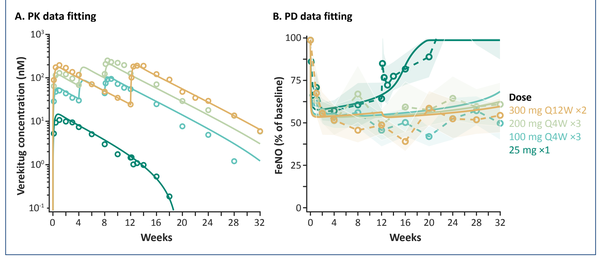
This model was parameterized using literature and experimental data and calibrated against the available human clinical PD data. The calibrated model was then utilized to predict reductions in TSLP/TSLPR complex levels, and thereby suppression of downstream PD (FeNO) effects.
FeNO, fractional exhaled nitric oxide; IL7Ra, interleukin 7 receptor alpha; LR, ligand receptor; PD, pharmacodynamic; PK, pharmacokinetic; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor.

RESULTS

PK/PD models provide projections consistent with the observed clinical data with verekitug

- Model simulations provide a good fit with the observed clinical PK and PD (FeNO) profile for verekitug (**Figure 3**)
- A similar model parameterization approach provided a good fit with tezepelumab published data for the PK profile[3] and FeNO reductions[5] (not shown)

Figure 3. Model calibration to verekitug clinical data from phase 1 MAD clinical study



Verekitug PK and PD models were parameterized using literature data and calibrated against human clinical data. **A.** Observed verekitug serum concentrations (open circles) are overlaid with the model-projected PK profiles (solid lines). **B.** Observed clinical PD effects of reduction in FeNO levels with verekitug (open circles) superimposed with model*projected changes in FeNO levels (solid lines) with the SEM (shaded area).
FeNO, fractional exhaled nitric oxide; MAD, multi-ascending dose; PD, pharmacodynamic; PK, pharmacokinetic; Q×W, every × weeks; SEM, standard error of the mean.

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DISCLOSURES

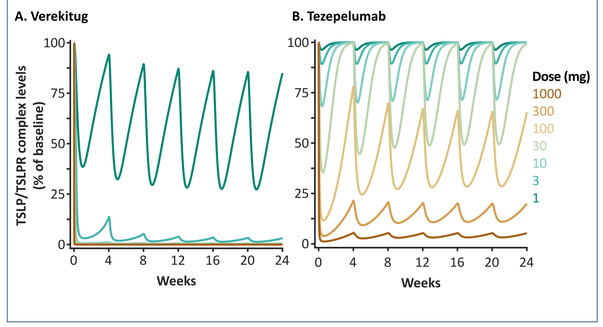
AK, SS, and AD are employees of Upstream Bio, Inc. EP and BM are co-founders of Residual Dynamics, LLC, and performed the analyses in connection with this study. AD has a leadership or fiduciary role with Upstream Bio, Inc. AK and SS have received stock options from Upstream Bio, Inc.

RESULTS

Model simulations predict sustained reductions in TSLP/TSLPR complex levels with verekitug as compared with tezepelumab

- At simulated doses of ≥ 10 mg, verekitug completely inhibits TSLP/TSLPR complex formation (**Figure 4A**)
- In comparison, tezepelumab is unable to completely inhibit the TSLP/TSLPR complex even at the highest dose of 1000 mg, as observed by fluctuations in complex levels (**Figure 4B**)

Figure 4. TSLP/TSLPR complex inhibition

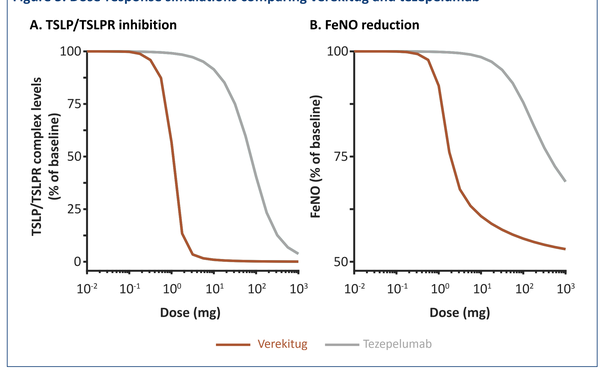


Model simulations across doses range from 1 mg to 1000 mg Q4W. Lines represent model-derived simulations for TSLP/TSLPR complex levels in lungs for **A.** verekitug and **B.** tezepelumab.
TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor.

Dose-response model predictions are consistent with clinical findings of more potent reduction in FeNO with verekitug as compared with tezepelumab

- Consistent with observed clinical findings, dose-response simulations across an expanded dose range 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**)

Figure 5. Dose-response simulations comparing verekitug and tezepelumab



Lines represent model-predicted percent change from baseline for **A.** TSLP/TSLPR complex levels (average area under the curve) and **B.** FeNO reductions (average area under the curve) across a range of dosing regimens from 0.01 to 1000 mg every 4 weeks.
TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor.

FUNDING

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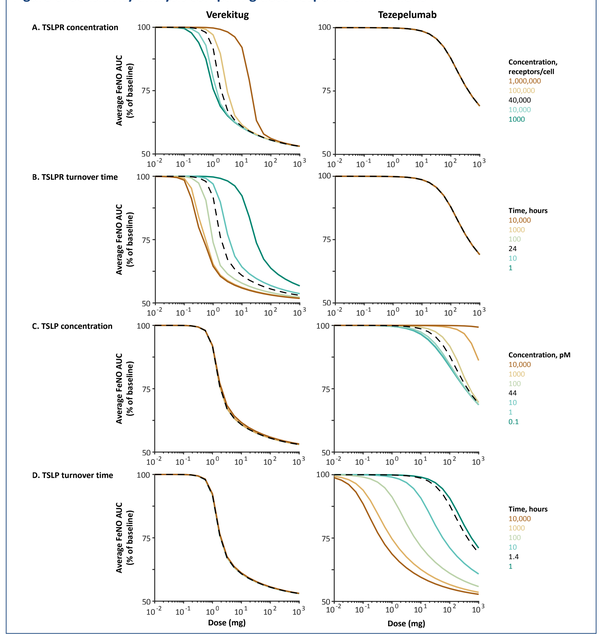
1. Numazaki M, et al. *J Pharmacol Exp Ther.* 2022;380:26–33. **2.** Deykin A, et al. Poster presented at the European Respiratory Society (ERS) Congress 2024; September 7–11; Vienna, Austria. **3.** Ly N, et al. *J Clin Pharmacol.* 2021;61:901–912. **4.** Sundnes O, et al. *Mol Med.* 2021;27:29. **5.** Corren J, et al. *N Engl J Med.* 2017;377:936–946. **6.** Henriques CM, et al. *Blood.* 2010;115:3269–3277. **7.** ClinicalTrials.gov NCT06196879. Accessed May 7, 2025. **8.** ClinicalTrials.gov NCT06164704. Accessed May 7, 2025.

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

- FeNO reduction with verekitug is sensitive to TSLPR levels, a function of steady-state concentration, and protein turnover time (**Figure 6A,B**)
  - Notably, FeNO reduction with verekitug is not sensitive to TSLP levels (**Figure 6C,D**)
- Conversely, FeNO reduction with tezepelumab is sensitive to TSLP levels (**Figure 6C,D**) and insensitive to TSLPR levels (**Figure 6A,B**)
- This sensitivity analysis identifies relative target abundance (ie, lower levels of TSLPR compared with TSLP) in the lung as a key driver of the observed differences in FeNO response

Figure 6. Sensitivity analysis comparing dose-response simulations



Model-predicted effects of **A.** TSLPR concentration, **B.** TSLPR turnover time, **C.** TSLP concentration, and **D.** TSLP turnover time on FeNO reductions with verekitug and tezepelumab. Sensitivity analysis was conducted by investigating changes in verekitug and tezepelumab responses at varying parameter values (colored lines) compared with the nominal parameter values (black lines) derived by model fitting and/or published literature.[4,6]
AUC, area under the curve; FeNO, fractional exhaled nitric oxide; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor.

CONCLUSIONS

- This semi-mechanistic PK/PD modeling indicates that the greater potency in FeNO reduction observed with verekitug compared with published data for tezepelumab is potentially driven by lower TSLPR and higher TSLP ligand abundance over time
- In contrast with tezepelumab, the PD effect following verekitug administration is minimally impacted by the relatively high abundance of TSLP ligand
- These findings provide a mechanistic explanation for the observed greater potency of targeting TSLPR with verekitug as compared with the ligand
- Whether this difference in potency translates into augmented clinical efficacy with verekitug is currently under investigation in ongoing phase 2 clinical trials[7,8]

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