Mechanistic drivers for potent pharmacodynamic activity of verekitug, a novel anti-human thymic stromal lymphopoietin receptor (TSLPR) antibody

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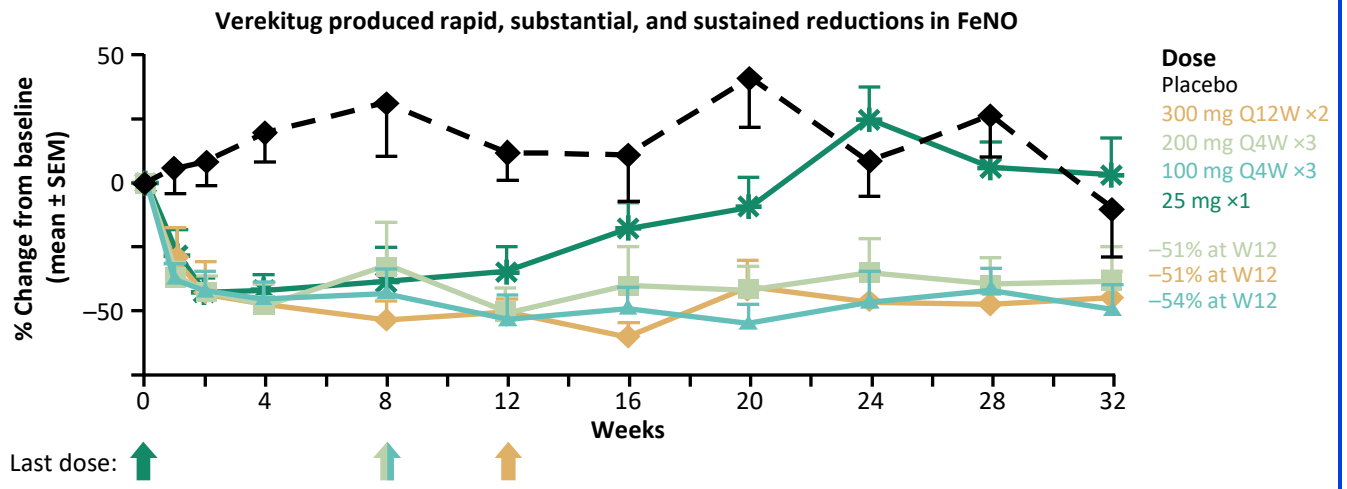
Verekitug, targeting TSLPR, can substantially reduce biomarkers of airway inflammation

- 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 FeNO, a biomarker of airway inflammation and blood eosinophils[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

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

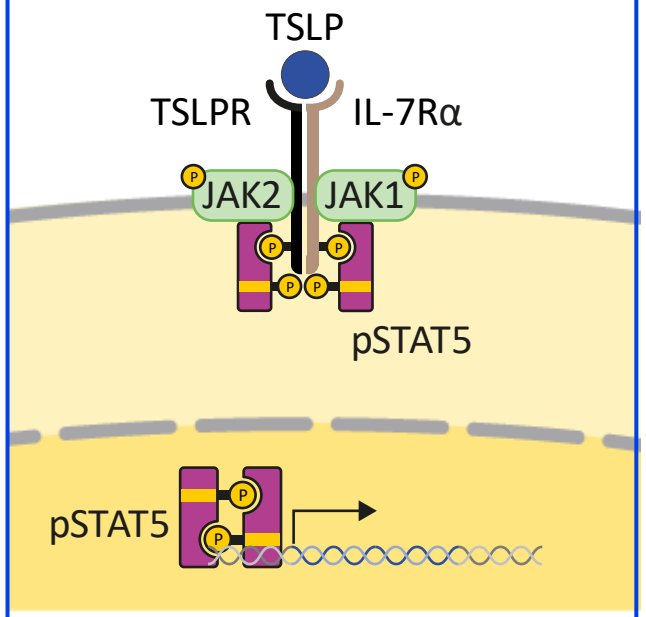


COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; FeNO, fractional exhaled nitric oxide; QxW, every x weeks; PD, pharmacodynamic; SEM, standard error of the mean; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor; W, week.

Verekitug binds to TSLPR with a sub-picomolar affinity and inhibits the formation of TSLP-TSLPR complex

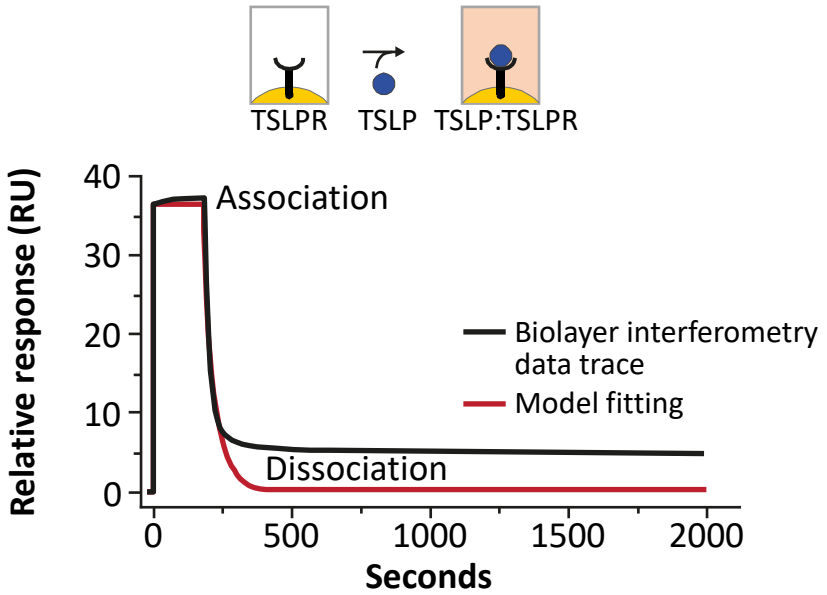
Blocks the necessary priming step for heterodimeric complex formation with IL-7Rα

Mechanism of TSLP-induced signaling[4]



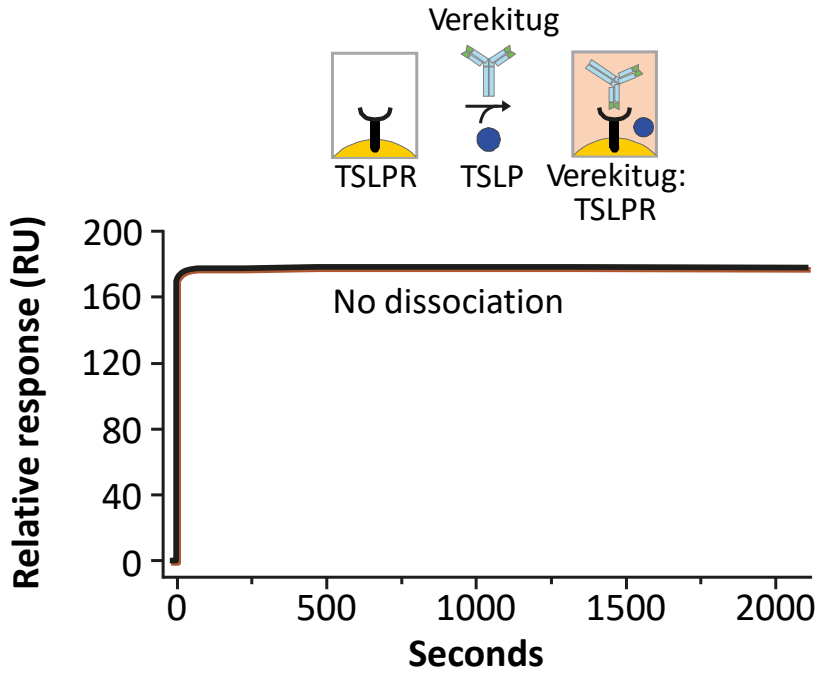
1. TSLP binds TSLPR
2. TSLP recruits IL-7Rα
3. TSLPR-TSLP-IL-7Rα complex formed
4. pSTAT5 signaling

TSLP binding to TSLPR



K_D ~3-36 nM

Verekitug binding to TSLPR in the presence of TSLP

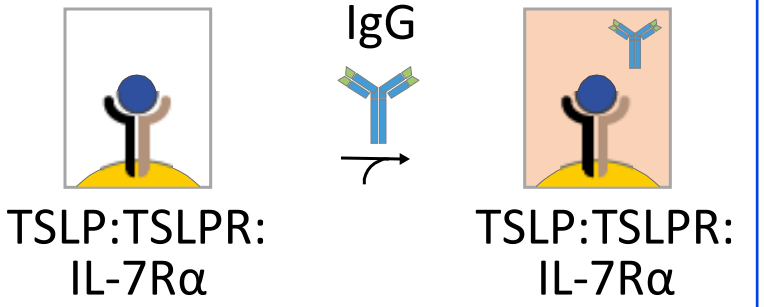


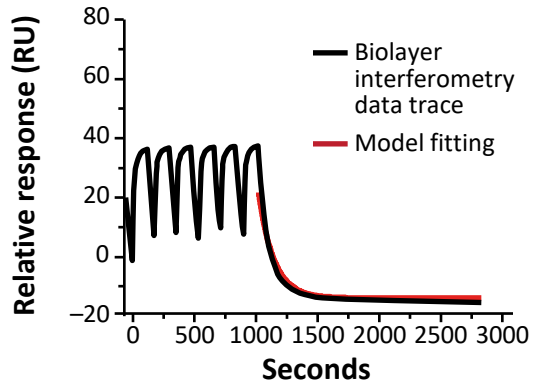
K_D <1 pM

Left figure reproduced in part from Ebina-Shibuya E, Leonard WJ. *Nat Rev Immunol*. 2022;23:24–37.
IL-7Rα; interleukin 7 receptor, subunit α; RU, relative units.

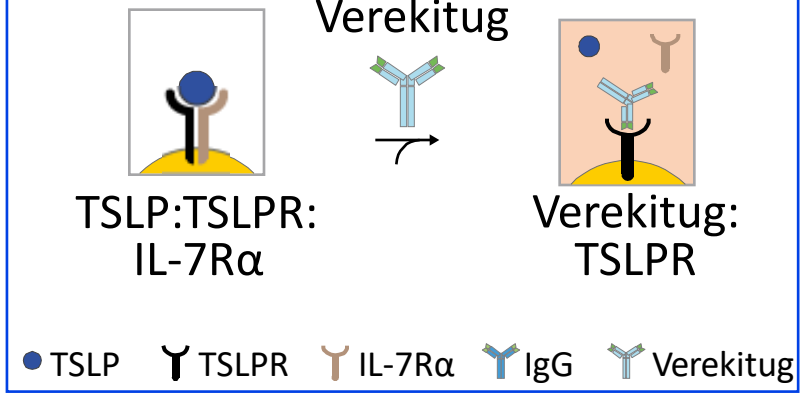
Verekitug outcompetes TSLP in the preformed heterodimeric complex and blocks STAT5-mediated TSLP/TSLPR signaling

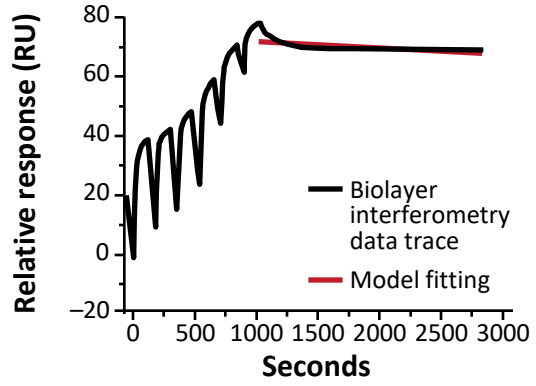
Control IgG does not inhibit receptor complex formation



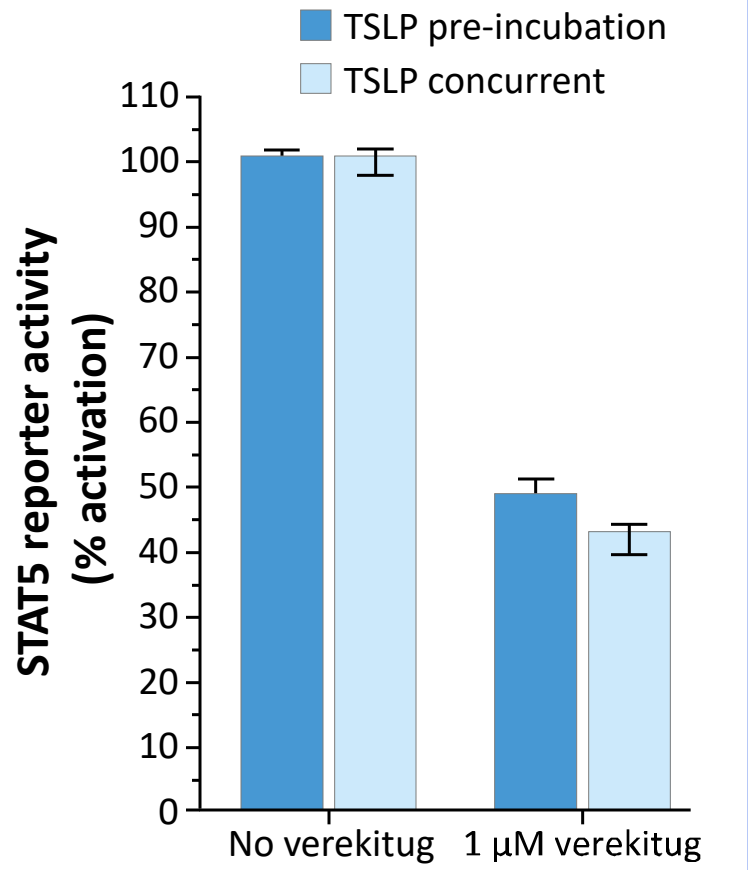


Verekitug outcompetes TSLP in binding to TSLPR and inhibits complex formation



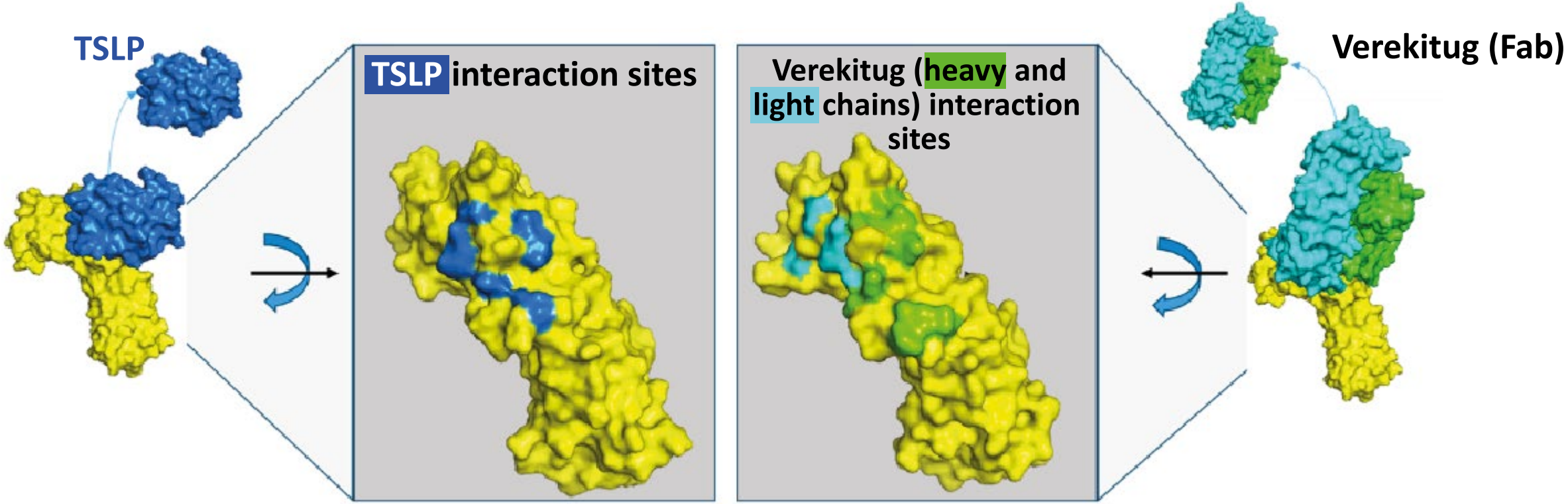


Verekitug blocks pSTAT5 mediated signaling even when cells were pre-incubated with TSLP



IgG; immunoglobulin G; pSTAT5; phosphorylated signal transducer and activator of transcription 5; RU, resonance units.

Verekitug blocks TSLP/TSLPR interaction by occupying majority of the TSLP ligand binding sites



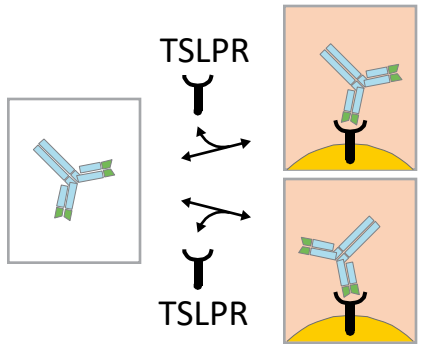
Fab, fragment antigen-binding region.

Superior potency of verekitug over tezepelumab may stem from targeting receptor with lower abundance and slower turnover

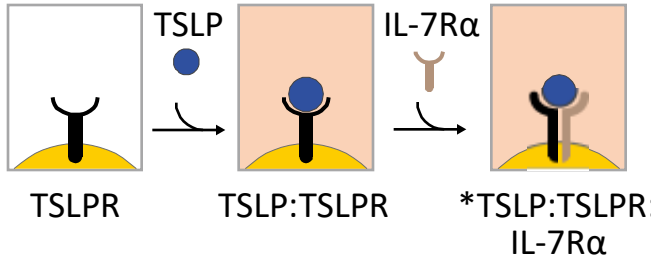
Semi-mechanistic PK/PD modeling co-fit with phase 1 clinical data

Model overview[5–7]

Verekitug binding

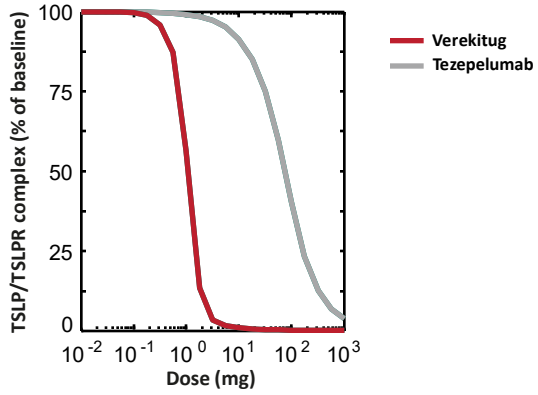


Endogenous interaction

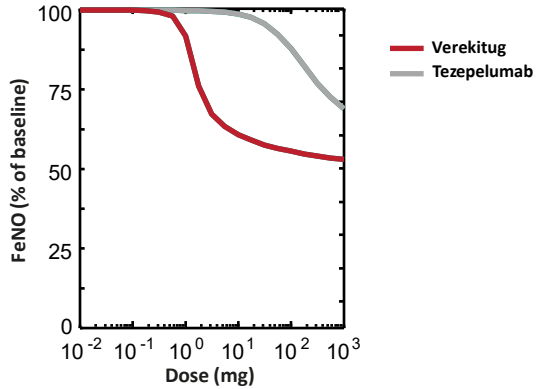


*IL-7Rα is not explicitly mapped.

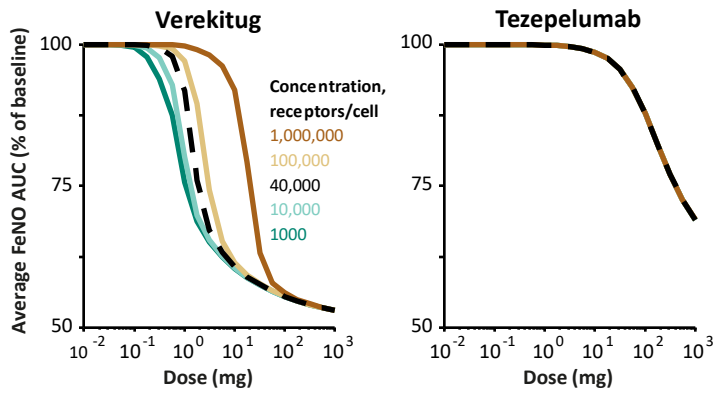
TSLP/TSLPR inhibition



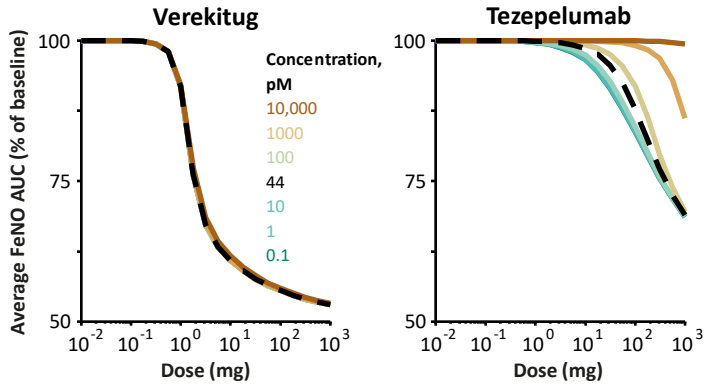
FeNO reduction



TSLPR concentration



TSLP concentration



AUC, area under curve; PK, pharmacokinetic.

Conclusions

- Verekitug (K_D < 1 pM) outcompetes TSLP binding to TSLPR in a preformed heterodimeric complex
- Verekitug binds and occludes 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 is being studied in four phase 2 trials for treatment of severe asthma,[8,9] CRSwNP,[10] and COPD[11] in dosing intervals of up to 24 weeks

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. Verstraete K, et al. *Nat Commun*. 2017;8:14937.
5. Ly N, et al. *J Clin Pharmacol.* 2021;61:901–912.
6. Sundnes O, et al. *Mol Med*. 2021;27:29.
7. Henriques CM, et al. *Blood*. 2010;115:3269–3277.
8. ClinicalTrials.gov NCT06196879.
9. ClinicalTrials.gov NCT06966479.
10. ClinicalTrials.gov NCT06164704.
11. ClinicalTrials.gov NCT06981078.