Assessment of phase 1 pharmacokinetic-pharmacodynamic predictions, based on phase 3 clinical trials results - Depemokimab pharmacokinetics and response in blood eosinophil count reduction for patients with asthma and chronic rhinosinusitis with nasal polyps

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Objective

To compare the predictions from a model developed with phase 1 data to the phase 3 results.

Background

Depemokimab is the first ultra-long-acting biological drug engineered with enhanced interleukin-5 binding affinity, high potency, and an extended half-life, enabling dosing every 6 months and sustained suppression of type 2 inflammation.

In previous analyses[1], model development and model predictions of the relationship between depemokimab pharmacokinetic (PK) and blood eosinophil count (BEC) reduction, as biomarker of type 2 inflammation, were based on a phase 1 (Ph1) first time in human (FTIH) single ascending dose (SAD) study in asthma patient with increased baseline BEC≥200 cells/µL. Recently, depemokimab phase 3 (Ph3) studies in (severe) asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) have been completed[2,3]; the PK-BEC relationship has then been updated.

Data and methods

The model developed on FTIH data, called *Ph1 model* in the following, integrated prior knowledge from mepolizumab, for which a PK-BEC model was established using data in multiple type 2 inflammatory conditions, including asthma and CRSwNP, and thereby allowed for predictions of the depemokimab PK-BEC in these patient populations, for which depemokimab was not yet investigated.

The model including the phase 3 results, called *Ph3 model* in the following, was developed with pooled depemokimab data from three phase 1 studies (two in healthy volunteers [PK only] and the above FTIH) and four phase 3 studies (two studies in patients with severe asthma and two studies in patients with CRSwNP).

The PKPD relationship between PK and BEC consisted of an indirect-response model, linked to individual predicted depemokimab concentration, with an inhibitory sigmoidal Emax model, supplemented by a placebo linear effect.

Predictions of the exposure-response (ER) curves were generated to illustrate the steady-state relations for different patient populations. This was done a priori, based on the FTIH SAD study[1] and later repeated post hoc to evaluate the phase 3 outcome, after completion of the studies.

Model predictions of Week 52; **a)** absolute BEC, and **b)** ratio of BEC to baseline change from placebo (RTBw52), were evaluated in four different scenarios (**Table 1**).

Table 1. Scenarios of the different use of the data and models

Scenario	Characteristics
A priori	Ph1 model adjusted by patient characteristics from mepolizumab trials
Ph1 covariate-adjusted	Ph1 model adjusted with patient characteristics (median covariate values) from the Ph3 trials
Ph3 estimation	Ph3 model estimated on the pooled data including the Ph1 and Ph3 trials
Ph3 observation	Ph3 observations* from the two studies in patients with severe asthma and the two studies in patients with CRSwNP

* RTBw52 calculated as the median of the ratios to baseline at Week 52 for treated subjects divided by the median of the ratios to baseline at Week 52 for placebo subjects.

Conclusions

This analysis demonstrates that the use of model-informed drug development principles can be applied to generate prospective predictions that support dose selection.

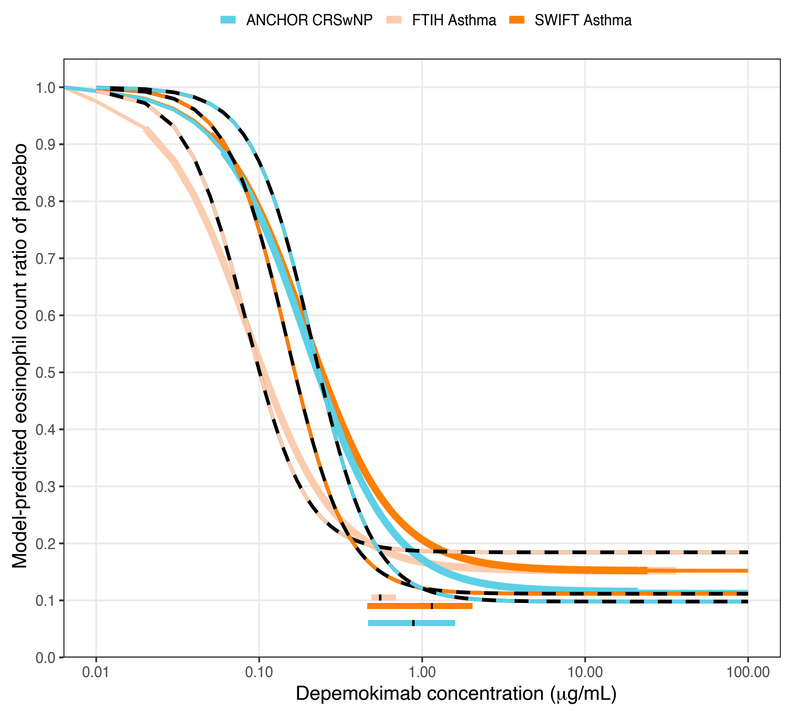
The phase 1 model provided accurate predictions for the target absolute BEC (<100 cells/µL) at W52 and for the target RTBw52 (<0.2, i.e. 80% reduction) in both asthma and CRSwNP patient populations.

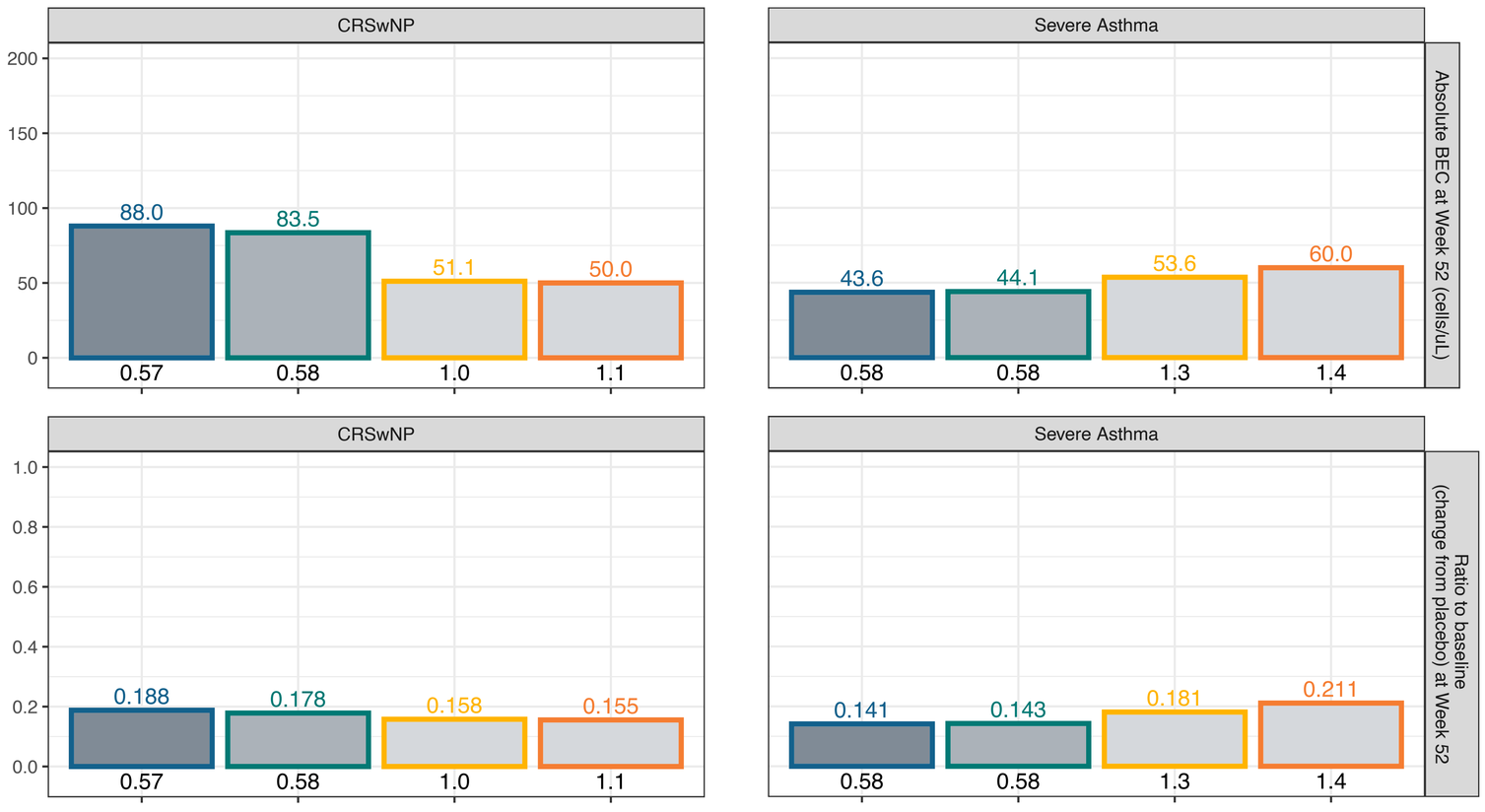
Results

The ER curves were well predicted for patients with CRSwNP, and small changes in estimates were seen for the Ph3 asthma patients **(Figure 1)**, and overall, with notably less steep ER curves. The differences in EC50 values between asthma indications in the mepolizumab trials were confirmed in the depemokimab trials.

↳ FTIH patients had a 56% lower EC50 than patients belonging to phase 3 studies (Ph1 prediction was 46% lower EC50).

Figure 1. Predictions of the exposure-response curves. The solid and dashed curves represent the Ph1 and Ph3 model predictions, respectively. Ph1 a priori prediction used the median covariates from the prior mepolizumab program. The colored, horizontal bands and the vertical black line represent, respectively, the predicted 2.5th, 97.5th percentiles and median depemokimab trough concentration at Week 26, following 100 mg subcutaneous dose administration.





A priori and *Ph1 covariate-adjusted* predictions (**Figure 2**) showed good agreement due to the similarities in patients' characteristics across the mepolizumab and depemokimab trials (e.g. baseline BEC) for the severe asthma and CRSwNP patient populations.

When compared to the *Ph3 estimation* (as well as the actual *Ph3 observation*), the Ph1 model slightly underpredicted the response in patients with CRSwNP and slightly overpredicted the response in patients with asthma (**Figure 2**).

↳ Potential causes include higher than predicted trough concentrations (below the bar plot in **Figure 2**) and potentially other differences between the depemokimab Ph1 and Ph3 trials, including differences in population, study conduct, or bioanalytical assay.

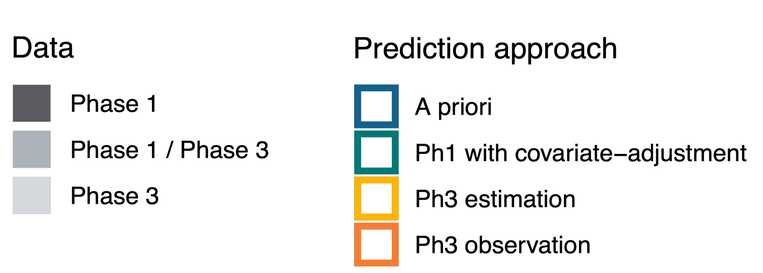


Figure 2. Model-predictions at Week 52 of absolute blood eosinophil count and ratio to baseline (change from placebo). Numbers below each bar plot represent the median predicted depemokimab concentration at Week 52 in µg/mL, given each scenario. Numbers on top of each bar represent for 'A priori' and 'Ph1 with covariate-adjustment' scenarios predictions for a typical subject at Week 52, and for the other scenarios the median of the predictions for all subjects at Week 52.

References

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