Use of informative prior distributions from mepolizumab data to support depemokimab PKPD model analysis

PKPD model for blood eosinophil count in eosinophilic indications

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Objective

To characterize the pharmacokinetic-pharmacodynamic (PKPD) relationship between depemokimab and blood eosinophil count, using informative prior distributions from a previous mepolizumab PKPD model.

Background

- Depemokimab is an anti-IL-5 monoclonal antibody that blocks IL-5 binding to its receptor and leading to a rapid reduction of the blood eosinophil count (BEC).
- Depemokimab showed enhanced affinity and extended half-life compared to first in class mepolizumab and it is currently in Phase 3 development in severe eosinophilic asthma, CRSwNP, EGPA and HES.
- A previous mepolizumab model, developed on combined data from various eosinophilic conditions, and a wide range of baseline BEC and treatment regimens, was available to support depemokimab PKPD analysis.

Results

- Depemokimab exposure relationship with BEC data in mild-moderate asthma was well characterized by a placebo linear model plus an indirect response model with an inhibitory E_{max} function on k_{in}.
- E_{max}, EC_{50} and HL_{onset} were estimated to 89.2% (RSE 1.1%), EC_{50} 151 ng/mL (RSE 14.4%), and 20.8 hours (RSE 7.4%), respectively, in line with previous mepolizumab and depemokimab knowledge[1,6].
- Supporting priors were included to estimate or predict a) changes in baseline BEC, E_{max} and EC_{50} in patients with different eosinophilic conditions, b) the effect of predicted baseline BEC on E_{max} and EC_{50}, c) the changes in baseline BEC in the Asian population, and d) the effect of body weight on E_{max}.
- The supporting prior of age effect on EC_{50}, based on mepolizumab data, was not included in the final model because the estimated effect of age on EC_{50} for depemokimab data was significantly different from the one estimated with mepolizumab data ($p<0.001$).
- Based on the mepolizumab prior implementation, HES patients were predicted to have higher baseline BEC and EGPA patients to have a higher EC_{50}, compared to other patient populations (Figure 1).
- The estimated effect of the model-predicted baseline BEC on E_{max} and EC_{50} was modest in the limited range of values present in the analysis population. However, based on the mepolizumab prior, high baseline BEC could substantially impact the exposure response (Figure 2).
- Prospective predictions need to be confirmed with additional depemokimab data.

Conclusions

- The depemokimab exposure-blood eosinophil count relationship was well characterized in mild-moderate asthma patients.
- Mepolizumab prior information efficiently supported prospective predictions of depemokimab exposure-response in other eosinophilic indications to be investigated.

Data and Methods

- Data from depemokimab first time in human (FTiH) study in mild-moderate asthma patients (NCT03287310): 727 BEC records from 48 patients[1].
- Depemokimab predicted plasma concentrations were first derived from a PK model developed on FTiH study data (not shown).
- The NWPRI prior subroutine in NONMEM was applied to support the estimation and prediction of covariate effects on a) baseline BEC, b) E_{max} and c) EC_{50}, using informative prior distributions from the wide-ranging mepolizumab analysis[2,3].
- The applicability of the supporting priors was evaluated using SCM+[3-5]. Supporting priors on parameters where depemokimab data was significantly different from the mepolizumab prior distribution were removed.

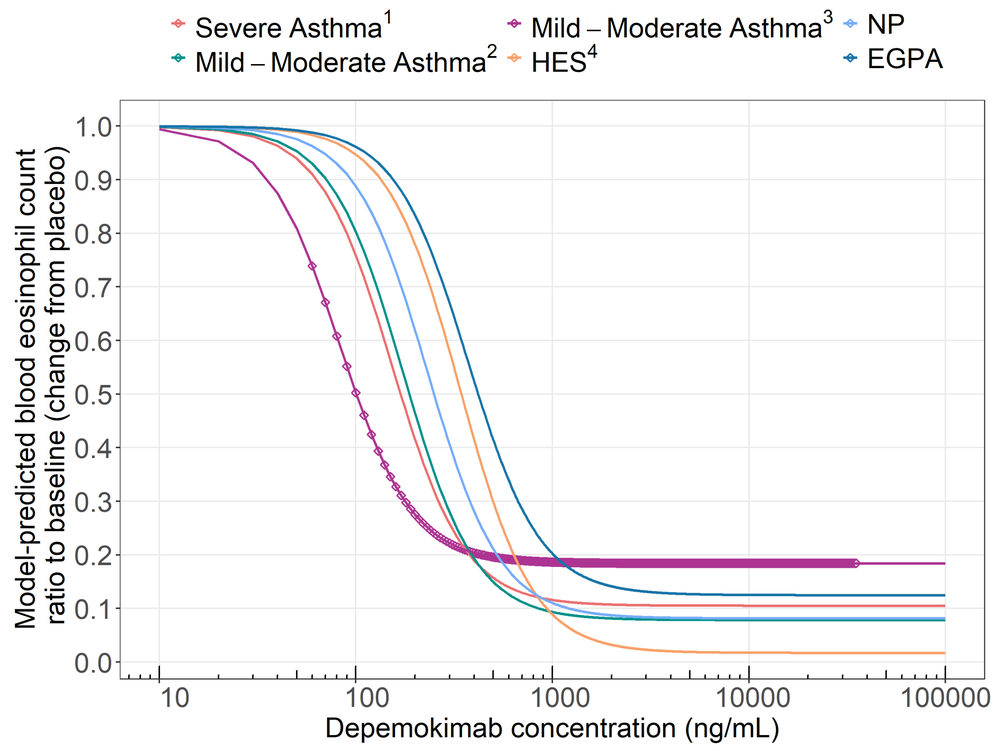

Figure 2. Exposure-response plot, where concentration is held constant, based on the final PKPD model and the typical baseline BEC for each patient population. Diamonds represent the range of model-predicted depemokimab concentrations for patients in the PKPD analysis data set.

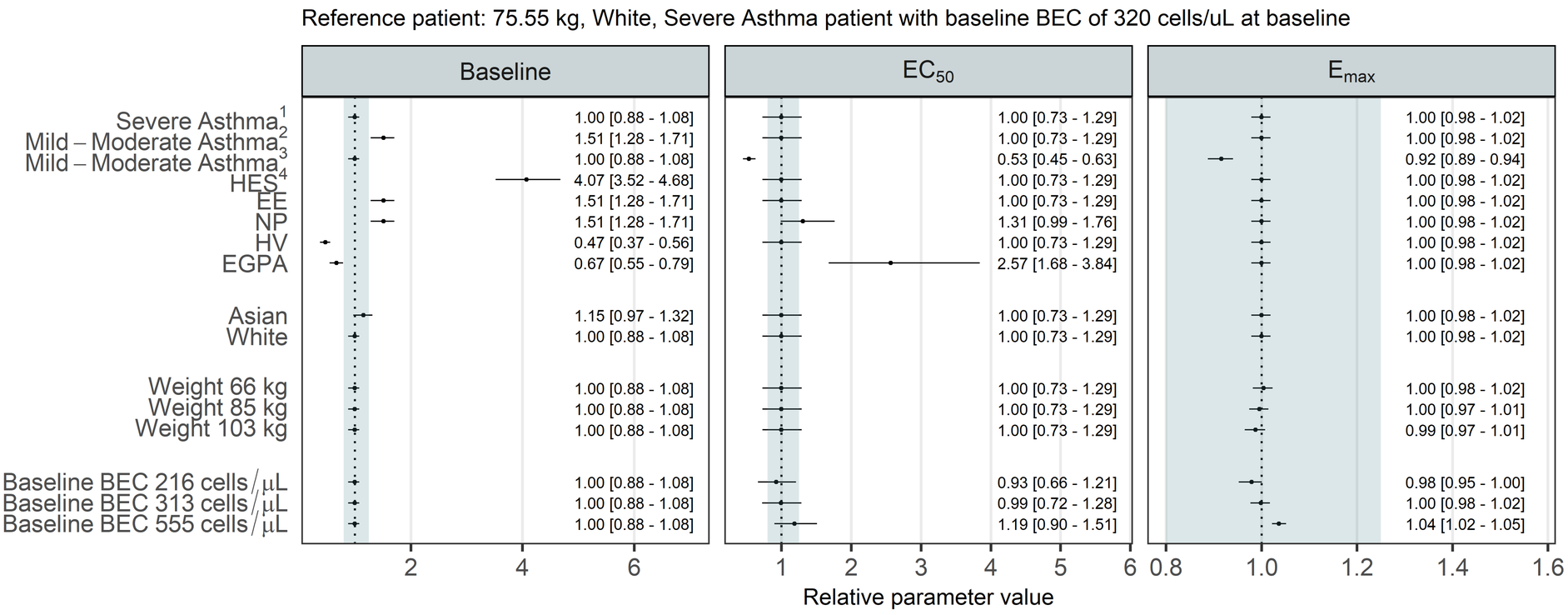

Figure 1. Forest plots illustrating the effects of covariates on PKPD parameters, conditioned on a typical reference subject, based on the final PKPD model. Other race categories in the data were grouped with White. Dots, error bars, and values, represent the median [90% CI] predicted relative change from the reference subject, based on 200 sampled parameter vectors from the variance-covariance matrix obtained from NONMEM. The dotted line and shaded area represent the parameter value for the reference patient and the 80%-125% margins relative to the reference subject, respectively.

[1]Severe Asthma with screening BEC ≥300 cells/µL;[2]Mild-Moderate Asthma with screening BEC ≥300 cells/µL;[3]Mild-Moderate Asthma with screening BEC ≥200 ells/µL/no BEC inclusion criteria;[4]HES with screening BEC ≥1000 cells/µL.

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Disclosures

CB, LT, CA and JR are Pharmetheus employees; JR is a Pharmetheus shareholder; CZ and SC are GSK employees and shareholders.

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Supplementary material

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Final PKPD model

- Placebo linear model with baseline and P_{slp} representing the proportional change over a year during treatment with placebo, plus a numerical (differential equation) solution describing an indirect response drug-effect on rate of formation, parameterized in terms of baseline, HL_{onset}, EC_{50}, E_{max} and HILL coefficient.
- Exponential IIV on baseline and RUV, and additive IIV on P_{slp} and logit-E_{max}
- Exponential RUV implemented as additive on the log-scale

Covariate analysis

- The SCM procedure with adaptive scope reduction (ASR), SCM+, was used for the evaluation of covariate-parameter relationships[1,2]. The forward selection and backward elimination p-values were, respectively, 0.01 and 0.001. Continuous covariate-parameter relationships were investigated as exponential models or linear models, on parameters without lower bound at zero, while categorical covariate-parameter relationships were implemented as a fractional difference to the most common category.
- Only one structural covariate-parameter relationship was evaluated. The effect of the predicted baseline BEC on the P_{slp} was not statistically significant (p>0.01), thus no covariate-parameter relationships were added to the model.

Model evaluation

- Model evaluation was based on the inspection of RSE, plausibility of the parameter estimates, graphical diagnostics, including VPCs, as well as changes in the OFV provided by NONMEM.

Model development with prior

- The PRIOR subroutine was used as an alternative to fixing parameters to a previous estimate or pooling mepolizumab and depemokimab data to facilitate the estimation of selected depemokimab PKPD parameters, that were believed to be shared for mepolizumab and depemokimab, and where sufficient information was not available in the analysis data set[3].
- The prior point estimates and covariance matrix in NONMEM from the reference mepolizumab PKPD model were used to generate the NONMEM prior values, using the NWPRI subroutine[3,4]. Prior values to fixed effects parameters were entered as a multivariate normal and their weight was informed by the covariance matrix. No prior information on the random effects parameters such as IIV and RUV were included in this analysis.
- Regarding fixed effects, the supporting prior covariates summarized in Table 1 were included to help the estimation or to allow for prospective predictions. Supporting priors on E_{max} and EC_{50} relative difference across patient populations were included in preparation for a model update with additional depemokimab data in various eosinophilic indications.

Evaluation of supporting priors

- The difference between depemokimab and mepolizumab populations in parameters implemented with priors was verified by testing a parameter of difference ($THETA_{new}$), estimated only on the new analysis data, on each of the model parameters implemented with prior, using SCM+ (Equation 1)[4-6].
- A significant improvement in OFV indicates that the parameter differs between depemokimab and mepolizumab population and thus, it is more appropriate to either remove the prior from the parameter or retain $THETA_{new}$ in the model.

Equation 1. Code implemented in SCM+.

$$Parameter\text{-}Covariate = THETA_{prior} * (1+THETA_{new}).$$

Table 1. Supporting prior covariates included in the depemokimab PKPD model development.

Supporting prior covariate	Justification	Purpose
• Mild-Moderate Asthma[1], EE or NP on Baseline • HES[2] on Baseline • EGPA on Baseline • HV on Baseline	Patient population not available in analysis data	Prediction
• Asian race on Baseline	Limited data available in analysis data	Prediction
• Mild-Moderate Asthma[3] on E_{max}	Indirect estimation of E_{max} for the reference patient population (severe asthma)	Estimation
• Predicted baseline BEC on E_{max} • Body weight on E_{max}	Limited range of covariate values in the analysis data	Estimation
• Mild-Moderate Asthma[3] on EC_{50}	Indirect estimation of $EC_{50}$for the reference patient population (severe asthma)	Estimation
• NP on EC_{50} • EGPA on EC_{50}	Patient population not available in analysis data	Prediction
• Predicted baseline BEC on EC_{50} • Age on EC_{50}	Limited range of covariate values in the analysis data	Estimation

Glossary

BEC	Blood eosinophil count	FTiH	First Time in Human	OFV	Objective function value
C_{trough}	Trough concentration	HES	Hypereosinophilic Syndrome	PK	Pharmacokinetic
CRSwNP	Chronic Rhinosinusitis with Nasal Polyposis	HL_{onset}	Half-life for drug on-/offset	PKPD	Pharmacokinetic-pharmacodynamic
E_{max}	Maximum effect	HV	Healthy volunteer	RSE	Relative standard error
EC_{50}	Concentration at half maximum effect	IIV	Inter-individual variability	RUV	Residual unexplained variability
EE	Eosinophilic Espohagitis	NP	Nasal Polyposis	SCM	Stepwise covariate model building procedure
EGPA	Eosinophilic Granulomatosis with Polyangiitis	NWPRI	Normal-inverse Wishart prior	VPC	Visual Predictive Check

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