Updated population pharmacokinetic (popPK) model for emapalumab using data from four prospective clinical trials in patients with hemophagocytic lymphohistiocytosis/macrophage activation syndrome (MAS)

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CONCLUSIONS

- In this updated popPK model, the pharmacokinetics (PK) of emapalumab in patients with primary hemophagocytic lymphohistiocytosis (pHLH) and MAS was described by a 2-compartment model, with fixed allometric exponents (0.75 on clearances and 1.0 on volumes of distribution)
- Maturation functions were introduced into the model as an age effect on emapalumab PK parameters, while total interferon-gamma (IFNγ) and bilirubin were found to mediate clearance, which was implemented using time-varying covariate effects for IFNγ, bilirubin, and age
- The covariate effect of baseline age was removed compared with a previous model,[1] while a significant difference in the drug distribution properties between patients with pHLH and MAS was identified and expressed as differences in the volume of the peripheral compartment
- This resulted in a newly added covariate effect for patients with MAS comprising a 78% larger volume of the peripheral compartment, although this effect did not translate into differences in emapalumab exposure
- Overall, patients with MAS appeared to have higher emapalumab exposure compared with patients with pHLH, although these differences could be attributed to the differences in age and body weight of participants in the respective studies, and higher baseline levels of IFNγ and bilirubin in patients with pHLH

INTRODUCTION

- Emapalumab, an anti-IFNγ antibody that binds and inactivates free and receptor-bound IFNγ, has demonstrated efficacy and safety in clinical trials in patients with pHLH and patients with MAS in Still's disease or systemic lupus erythematosus (SLE)[2–6]
- The differing underlying etiologies for pHLH, and MAS in Still's disease or SLE, mean that IFNγ levels can differ by orders of magnitude across the spectrum of patients treated with emapalumab[7]
- Once serum total (free and emapalumab-bound) IFNγ levels exceed a threshold of approximately 10^4 pg/mL, emapalumab can be subject to a target-mediated drug disposition-like mechanism, where the rate of emapalumab clearance increases exponentially[7]
- Combining PK observations from patients with pHLH and MAS administered emapalumab may facilitate development of a comprehensive popPK model across the full range of serum total IFNγ levels observed in patients with HLH/MAS
- A popPK model for emapalumab was previously developed using data from 58 patients treated with emapalumab (44 patients with pHLH; 14 patients with MAS in Still's disease) who participated in two clinical trials (and a long-term extension study)[1]

OBJECTIVE

- To further evaluate the PK of emapalumab in patients with pHLH, MAS in Still's disease and MAS in SLE by developing an updated popPK model using an expanded patient population

METHODS

- Data were pooled for 123 patients treated with emapalumab for pHLH (NI-0501-04 [NCT01818492], n=44, mean age 2.1 years[6]; NI-0501-09 [EudraCT 2017-003114-10], n=35, mean age 2.3 years[8]), MAS in Still's disease (NI-0501-06 [NCT03311854], n=14[2], mean age 10.4 years; NI-0501-14 Cohort 1 [NCT05001737], n=24, mean age 15.9 years [across both cohorts][3]), and MAS in SLE (NI-0501-14 Cohort 2 [NCT05001737], n=6[4]) who provided blood samples for PK analysis during prospective, open-label, single-arm clinical trials
- The suitability of the previous emapalumab popPK model[1] was assessed using a predictive performance check and updated, as required
- The model was evaluated using goodness-of-fit (GOF) diagnostics
- The adequacy of the final popPK model was investigated using a visual predictive check (VPC) method

RESULTS

- While the individual predictions of the previous popPK model closely aligned with the observed PK concentrations for the expanded dataset, there was substantial variability in the population-predicted versus observed emapalumab concentration plot
  - Therefore, all model parameters of the previous model were re-estimated using the expanded dataset
- Parameter estimates were generally similar between the previous model and the updated model derived from the expanded dataset
- Major differences were for the age effects only, which likely reflected data being incorporated from a younger population enrolled in the -09 study
- Removing the baseline age effect from the model was accepted because it did not significantly worsen model fit, but removing the baseline IFNγ effect did significantly worsen the model fit and was rejected
- Based on observations from the predictive performance check, a covariate effect of patient type (pHLH vs MAS) on peripheral volume was also tested and accepted after it was found to significantly improve the model
- The presence of anti-drug antibodies (prevalence, 2%) did not affect model fit
- The final model (**Table**) was found to adequately describe the observed emapalumab PK concentration profiles across all studies included in the analysis dataset and all investigated sub-populations
- All model parameters could be estimated with good precision and no substantial shrinkage was observed
- GOF plots indicated very good alignment with individual predictions (**Figure 1**)
- The VPC indicated that the model captured the mean and variability of the observed PK concentrations well (**Figure 2**)

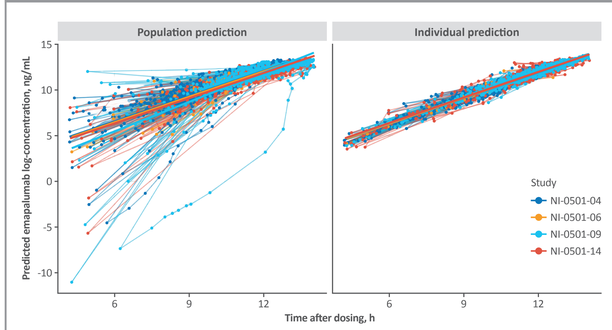
Table: Final emapalumab popPK model parameter estimates and precision

Parameter	Role	Estimate (95% CI)	RSE (%)
CL	Typical value, L/h	0.0108 (0.00934, 0.0123)	7.0
	IFNγ effect (intercept)	0.0421 (0.0218, 0.0624)	24.6
	IFNγ effect (exp)	0.502 (0.486, 0.519)	1.7
	CL,Q weight effect (exp)	0.75 (fixed)	
	CL,Q age effect (exp)	0.114 (0.0817, 0.147)	14.5
	CL, V1/2 bilirubin effect (exp)	0.127 (0.119, 0.136)	3.4
	Baseline IFNγ effect (exp)	0.0599 (0.0156, 0.104)	37.7
	BSV linear[a]	0.497 (0.424, 0.570)	7.5
	BSV non-linear[a]	1.58 (1.21, 1.96)	12.0
V1	Typical value, L	3.12 (2.80, 3.45)	5.3
	V1/2 weight effect (exp)	1 (fixed)	
	Age effect (exp)[b]	-0.0930 (-0.125, -0.0610)	17.5
	BSV[a]	0.256 (0.210, 0.302)	9.1
	COV (V1,V2)	0.535 (0.262, 0.809)	26.0
Q	Typical value, L/h[c]	0.0717 (0.0646, 0.0788)	5.1
V2	Typical value, L	3.10 (2.58, 3.62)	8.6
	MAS effect (ratio)[b]	1.78 (1.11, 2.44)	19.0
	BSV[a]	0.636 (0.535, 0.736)	8.0
RUV	Add (log)	0.315 (0.312, 0.317)	0.4

[a]Standard deviation/correlation as reported by NONMEM; [b]Bilirubin effect shared with CL (see CL row);
[c]Weight and age effects shared with CL (see CL row).

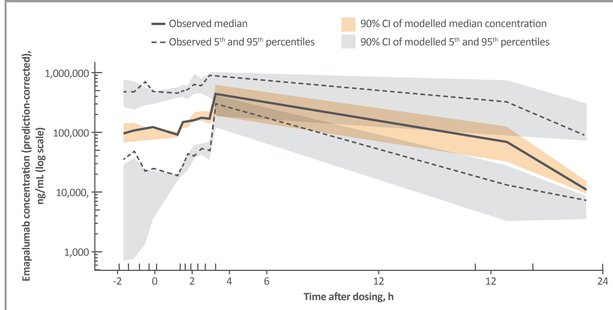
BSV, between-subject variability; CI, confidence interval; CL, clearance; COV, coefficient of variation; IFNγ, interferon-gamma; MAS, macrophage activation syndrome; popPK, population pharmacokinetic; Q, intercompartmental clearance; RSE, residual standard error; RUV, residual unexplained variability; V1, central compartment; V2, peripheral compartment.

Figure 1: GOF plots comparing observed versus population- and individual-predicted emapalumab concentrations for the final model



GOF, goodness-of-fit.

Figure 2: Prediction-corrected VPC for time after dosefor the final model (1000 simulations)



CI, confidence interval; VPC, visual predictive check.

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Disclosures
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