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BRIEF REPORT

Population Pharmacokinetics of the Anti-Interferon-Gamma Monoclonal Antibody Emapalumab: An Updated Analysis

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ABSTRACT

Introduction: Emapalumab is a fully human monoclonal antibody that targets free and receptor-bound interferon-gamma (IFNγ), neutralizing its biological activity. IFNγ levels differ by orders of magnitude between patients with primary hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS; a form of secondary HLH) in systemic juvenile idiopathic arthritis (sJIA). Therefore, this study aimed to develop a population pharmacokinetic model for emapalumab across a patient population with a wide range of total (free and emapalumab-bound) IFNγ levels using observations from patients with primary HLH or MAS in sJIA in clinical trials.

Methods: Pharmacokinetic data were pooled (n = 58; 2709 observations) from studies enrolling patients administered emapalumab for primary HLH or MAS in sJIA. Patients with primary HLH were administered emapalumab 1 mg/kg (potentially increasing to 3, 6, and up to 10 mg/kg based on clinical response) every 3 days. Patients with MAS in sJIA were administered emapalumab 6 mg/kg, followed by 3 mg/kg every 3 days until day 15 and twice weekly until day 28. An earlier population PK model was re-parameterized using this data.

Results: The final model for emapalumab comprised a 2-compartment model with first-order elimination. Emapalumab clearance remains constant when the total IFNγ concentration (free and emapalumab-bound) is $< \sim$ 10,000 pg/ml but increases proportionally to total IFNγ concentration above this threshold. Emapalumab clearance was estimated to be 0.00218, 0.00308, 0.00623 and 0.01718 l/h at total serum IFNγ concentrations of 10^3, 10^4, 10^5 and 10^6 pg/ml, respectively, with corresponding terminal half-lives of 19.2, 13.8, 7.18 and 3.12 days for a 1-year-old patient weighing 10 kg with primary HLH. The median terminal half-life for emapalumab in patients with MAS in sJIA was estimated to be 24.0 (range, 6.13–32.4) days, which is similar to observations in healthy volunteers.

Conclusions: Emapalumab pharmacokinetics in patients with primary HLH and MAS in sJIA were described by a two-compartment model with fixed allometric exponents and an age-related effect. Differences in total IFNγ levels between patients with primary HLH and MAS may affect emapalumab pharmacokinetics, suggesting that each indication may require different dosing to rapidly control hyperinflammation.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40744-024-00669-y.

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Trial registration: Clinicaltrials.gov identifiers: NCT01818492, NCT03311854 and NCT02069899.

PLAIN LANGUAGE SUMMARY

Patients with a rare condition called hemophagocytic lymphohistiocytosis (HLH) produce excessive amounts of a molecule called interferon-gamma. Excessive interferon-gamma causes extreme (or hyper) inflammation, which can be fatal. A drug called emapalumab can be used to block the action of interferon-gamma. However, we need to understand how the concentration of emapalumab in the blood changes over time to ensure that the correct dose is administered when attempting to control interferon-gamma-driven hyperinflammation in patients with HLH. Because HLH is a rare condition, data from a small number of patients were used to create a mathematical model that predicts emapalumab concentrations in the blood at various times after it is administered. Importantly, the amount of interferon-gamma observed in patients with different types of HLH is highly variable, which can alter how quickly emapalumab is removed from the blood. The higher interferon-gamma levels go above a certain threshold, the faster emapalumab is removed. In particular, interferon-gamma levels generally only exceed this threshold in patients with a familial or genetic form of HLH (primary HLH). Interferon-gamma levels in patients with a type of HLH called macrophage activation syndrome, which can occur in patients with systemic juvenile idiopathic arthritis (sJIA), do not usually cross the threshold associated with faster removal of emapalumab. This means that higher dosing may be required for patients with primary HLH compared with patients who have macrophage activation syndrome in sJIA to expedite control of hyperinflammation because of differences in the rate at which emapalumab is removed from the blood.

Keywords: Adult-onset Still's disease; Emapalumab; Hemophagocytic lymphohistiocytosis; Hyperinflammation; Interferon-gamma; Modeling; Pharmacokinetics; Systemic juvenile idiopathic arthritis

Key Summary Points

Why carry out this study?

Emapalumab is a fully human monoclonal antibody that targets free and receptor-bound interferon-gamma (IFNγ), neutralizing its biological activity and subduing IFNγ-driven hyperinflammation in patients with primary hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS) in systemic juvenile idiopathic arthritis (sJIA)

Total (free and emapalumab-bound) IFNγ levels differ by orders of magnitude between patients with primary HLH and MAS in sJIA

This study aimed to develop a population pharmacokinetic (popPK) model for emapalumab across a patient population with a wide range of total IFNγ levels using observations from patients with primary HLH or MAS in sJIA in clinical trials

What was learned from the study?

Emapalumab pharmacokinetics in patients with primary HLH and MAS were described by a two-compartment model with fixed allometric exponents and an age-related effect

Increased clearance associated with a target-mediated drug disposition-like mechanism is incorporated into the popPK model for emapalumab in patients with primary HLH, but not MAS

Differences in total IFNγ levels between patients with primary HLH and MAS may affect emapalumab pharmacokinetics, suggesting that each indication may require different dosing to rapidly control hyperinflammation

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare, aggressive, and potentially fatal syndrome characterized by excessive, uncontrolled immune activation and systemic hyperinflammation [1–3]. Primary HLH is associated with genetic defects and can only be cured by hematopoietic stem cell transplant (HSCT) [1, 4–8], whereas secondary forms of HLH can be triggered by different underlying conditions such as infection, malignancy, autoimmune/autoinflammatory disease, or immunochemotherapy [1, 4–7, 9]. For example, macrophage activation syndrome (MAS), a life-threatening form of secondary HLH, is most commonly associated with the autoinflammatory condition systemic juvenile idiopathic arthritis (sJIA)/adult-onset Still's disease, with approximately 10% of patients with sJIA presenting clinically with MAS, while ~ 30% are believed to experience subclinical MAS [9, 10].

Interferon-gamma (IFNγ) contributes to macrophage activation in patients with HLH by priming the production of pro-inflammatory cytokines, which can result in a hyperinflammatory positive feedback loop [8, 11, 12]. Emapalumab is a fully human monoclonal antibody that targets free and receptor-bound IFNγ, neutralizing its biological activity and subduing IFNγ-driven hyperinflammation [13–15]. The efficacy and safety of emapalumab has been demonstrated in patients with both primary HLH and MAS in sJIA [14, 15].

Prior population pharmacokinetic (popPK) modeling of serum emapalumab concentrations in patients with primary HLH indicated that emapalumab can be subject to a target-mediated drug disposition (TMDD)-like mechanism, where the rate of emapalumab clearance begins to accelerate once serum total (free and emapalumab-bound) IFNγ levels exceed a threshold of approximately 10^4 pg/ml [13]. However, substantial variability in pharmacokinetic (PK) parameters meant that data derived from patients administered emapalumab during clinical trials needed to be supplemented with additional PK data collected from patients with HLH administered emapalumab on compassionate grounds outside of clinical trials to develop a robust, stable popPK model for emapalumab [13].

The differing underlying pathologies for primary versus secondary HLH [3] mean that IFNγ levels can be orders of magnitude higher in patients with primary HLH compared with patients with MAS in sJIA or healthy volunteers. Therefore, combining PK observations from patients with primary HLH and MAS administered emapalumab may provide data in the context of a broader range of serum total IFNγ levels, supporting the development of a robust, broadly applicable popPK model for emapalumab in patients with IFNγ-driven hyperinflammation (i.e., creating a unified popPK model for patients with primary HLH or MAS).

This study aimed to develop an updated, robust popPK model using data from patients with primary HLH or MAS in sJIA administered emapalumab during clinical trials, without relying on supplemental data derived from patients administered emapalumab for compassionate reasons outside of a formal clinical trial environment.

METHODS

Study Design

Pharmacokinetic data were pooled (n = 58; 2709 observations) from three studies: (1) an open-label, single-arm, phase 2/3 clinical trial of 45 patients who received emapalumab for primary HLH (NCT01818492); (2) a pilot, open-label, single-arm, phase 2 study of 14 patients who received emapalumab for MAS in sJIA (NCT03311854); (3) a 1-year, long-term, follow-up study of patients from both studies (NCT02069899).

All studies were conducted in accordance with the principles set forth in the Declaration of Helsinki, the Guidelines of the ICH on Good Clinical Practice (GCP) (CPMP/ICH/135/95), European Union Directive 95/46/EC, and other applicable regulatory requirements. Independent ethical committee review and approval were obtained prior to initiating the studies and

all patients (or their legal guardians) provided written informed consent prior to enrollment.

Patients with primary HLH were administered emapalumab 1 mg/kg via intravenous infusion over 1 h, while subsequent doses could be increased to 3, 6, and up to 10 mg/kg on the basis of clinical response [14], whereas patients with MAS in sJIA were administered an initial intravenous infusion of emapalumab 6 mg/kg, followed by 3 mg/kg every 3 days until day 15 and twice weekly until day 28 over 1 h [15]. Emapalumab could continue to be administered during the long-term follow-up study to patients with primary HLH to control hyperinflammation until HSCT was performed [14]. Emapalumab treatment ceased at Day 28 in patients with MAS in sJIA, except for one participant who continued treatment until Day 39 [15].

Blood samples for PK analysis were collected before and between 15 and 30 min after completing each emapalumab infusion. Additional samples were collected approximately 24 and 48 h after the first infusion and 48 h after the second emapalumab infusion. For patients undergoing follow-up who were no longer receiving emapalumab infusions, samples for PK assessment were collected in accordance with the clinical study visit schedule until serum emapalumab concentrations were no longer detectable. One patient with primary HLH was excluded from the analysis after being identified as an outlier because population predictions were much higher than observed concentrations. PK samples were analyzed for free emapalumab, which was quantified in serum samples using a sandwich immunoassay (Gyrolab, Gyros Protein Technologies, Uppsala, Sweden), which was validated according to international standards (e.g., the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] [16]). The lower limit of quantification for emapalumab was 62.5 ng/ml.

Model Development

The starting point for this model was a previously developed popPK model from patients with HLH administered emapalumab [13]. This comprised a two-compartment disposition model with allometric scaling of body weight [13]. A power function was also added to account for clearance being dependent on the observed serum total IFNγ concentration (free and emapalumab-bound) [13]. The parameters of this model have been reported previously [13].

In this analysis, exploratory individual plasma concentration-time profiles were plotted for each study on a linear-logarithmic scale. Univariate and multivariate covariate distributions were visualized to identify possible outliers and to explore the correlation structure, and if two or more covariates were highly correlated, then the most clinically/biologically and practically relevant covariates were tested and the others discarded.

A two-compartment structural model with linear elimination, as previously proposed, was investigated [13]. Allometric exponents were fixed at + 0.75 and + 1 for clearances and volumes of distribution, respectively, based on a request from the European Medicines Agency because these allometric exponents could not be estimated from the data sets themselves. The impact of HSCT and a diagnosis of MAS, which was associated with much lower levels of IFNγ compared with primary HLH, on non-linear clearance (CLNL) was also checked and incorporated in the base model [15].

The following covariates were tested in the model for their association with PK parameters: age, race, and sex; body weight; renal function (creatinine clearance); liver function (alanine aminotransferase and total bilirubin); total IFNγ levels; and primary HLH versus MAS. Creatinine clearance was calculated using the Schwartz formula for participants aged ≤ 18 years old [17] and the Cockcroft-Gault formula for participants > 18 years old [18].

A forward addition/backward deletion procedure was applied to the base model using the analysis dataset (see Supplementary Table 1). Forward covariate selection was performed using a p-value of $p < 0.01$ ($\chi^2_{p=0.01}$, $\nu_{=1} = 6.63$) as the selection criterion. Subsequently, backwards deletion was performed using a p-value of

$p < 0.001$ ($\chi^2_{p=0.001, \nu=1} = 10.83$) as the selection criterion.

Goodness-of-fit plots were generated and interpreted in the context of epsilon shrinkage, where shrinkage < 20% was considered to represent a reliable plot. Shrinkage was computed in accordance with the methods of Karlsson and Savic [19]. Visual predictive checks (VPC) were also performed on the final model parameter estimates. Plasma concentrations of emapalumab were simulated 1000 times using the dose and covariate data, as well as the same sampling schedule, from participants whose data were used in the model development dataset. Given the differences between studies and administered dose, a prediction correction was applied on observed and simulated emapalumab concentrations as a function of time of total IFNγ concentrations to standardize the data set, allowing all data to be presented on a single VPC [20]. Stratified VPCs were also generated as a function of dose level and study.

Software

SAS software version 9.4 was used to prepare the analysis dataset. PopPK analysis was performed using NONMEM version 7.5.0 and the first-order conditional estimate method with interaction. NONMEM runs and VPCs were executed using PsN version 5.0.0.

R software version 4.1.1 was used for exploratory analysis and to evaluate goodness of fit. Simulations were performed using Campsis package version 1.2.0, an R package developed internally by Calvagone SAS (Liergues, France).

RESULTS

Data from 58 participants were included in this analysis (see Table 1 for baseline characteristics). The base model was adapted from the previous model developed using data from patients with HLH administered emapalumab (Fig. 1) [13] to include the impact of HSCT on total IFNγ levels after 28 days and for the much lower total IFNγ levels in patients with MAS not reaching the threshold for TMDD [15] (Table 2). The precision of the fixed-effects estimates was very good, as indicated by the low relative standard error. There was also good agreement between observations and individual predictions, although a slight underprediction was observed in patients with MAS at lower serum emapalumab concentrations. However, the distribution of residuals showed no trend with time or prediction, demonstrating the absence of systematic model misspecification. Epsilon shrinkage was 2.5%, also indicating no sign of over-parameterization.

Covariate analyses indicated that total clearance (CL) and intercompartmental clearance (Q) increased with age, while the volume of the central compartment (V1) decreased with age. Linear clearance (CLL) and the volumes of V1 and the peripheral compartment (V2) also increased with increasing levels of total bilirubin.

The final PK model for emapalumab comprised a two-compartment model with first-order elimination (Table 3). The precision of the fixed-effects estimates was good; only CLNL and the effects of age on PK parameters had a residual standard error > 20%, and allometric scaling was implemented on clearance and volume of distribution parameters. A power function was added to account for CL being dependent on the observed total IFNγ concentration, although this was not necessary for patients with MAS or patients with primary HLH who had undergone HSCT 28 or more days earlier. The effects of age on CL, Q, and V1 and total bilirubin on CLL, V1, and V2 were also incorporated into the model. Interindividual variation was quantified on CL, V1, and V2 and residual error accounted for as additive on the log scale.

There was good agreement between observations and individual predictions, with the distribution of residuals showing no trend with time or prediction, indicating an absence of systematic model misspecification. Epsilon shrinkage was 2.5%, also indicating no sign of over-parameterization (Supplementary Figs. 1, 2, 3).

A prediction-corrected VPC stratified by study indicated that the simulated and observed concentrations of emapalumab were in

Table 1 Baseline characteristics of participants in the analysis dataset

	Patients with primary HLH (*N* = 44)[a]	Patients with MAS (*N* = 14)	Total (*N* = 58)
Age, years, median (range)	1.0 (0.0–13.9)	11.5 (2.1–25.4)	1.7 (0.0–25.4)
Sex, male, *n* (%)	21 (47.7)	4 (28.6)	25 (43.1)
Body weight, kg, median (range)	9.6 (3.0–53.0)	45.5 (12.0–68.8)	11.7 (3.0–68.8)
Race, *n* (%)			
White	27 (61.4)	11 (78.6)	38 (65.5)
Asian	10 (22.7)	2 (14.3)	12 (20.7)
Black	4 (9.1)	0 (0)	4 (6.9)
Other	3 (6.8)	0 (0)	3 (5.2)
Unknown	0 (0)	1 (7.1)	1 (1.7)
Total IFNγ at Day 3, pg/ml			
Mean (CV%)	20,201.6 (296.8)	4618.9 (139.8)	16,440.3 (320.0)
Median (range)	1885.7 (50.0–375,054.5)	2583.8 (50.0–24,038.2)	1992.1 (50.0–375,054.5)
CrCl, ml/min, median (range)	47.0 (6.9–280.8)[a]	140.7 (54.2–259.5)	56.6 (6.9–280.8)
ALT, IU/l, median (range)	116.0 (8.0–1020)	301.5 (70.0–1492)	146.5 (8.0–1492)
Total bilirubin, µmol/l, median (range)	12.8 (1.7–424.1)	12.8 (4.6–76.1)	12.8 (1.7–424.1)

[a]Data missing for three participants

ALT alanine aminotransferase, *CrCl* creatinine clearance, *CV%* percent coefficient of variation, *HLH* hemophagocytic lymphohistiocytosis, *IFNγ* interferon-gamma, *MAS* macrophage activation syndrome, *IU* international units

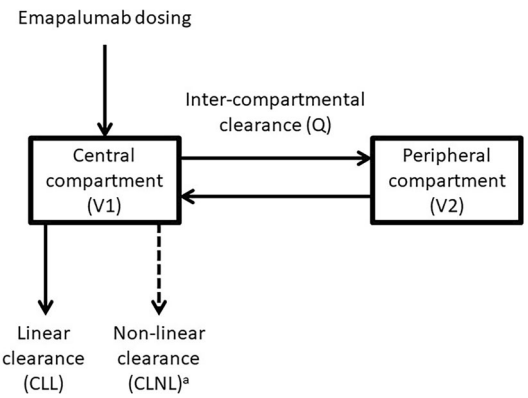

Fig. 1 Schematic of base and final PK models. [a]Only in patients with primary HLH who have not undergone HSCT within 28 days. *HLH* hemophagocytic lymphohistiocytosis, *HSCT* hematopoietic stem cell transplant, *PK* pharmacokinetic

agreement for both studies (Fig. 2). A prediction-corrected VPC as a function of total IFNγ level also demonstrated no bias in the simulations across total IFNγ levels (Fig. 3).

Emapalumab clearance remains constant when the total IFNγ concentration is $< \sim$ 10,000 pg/ml but increases proportionally to total IFNγ concentration above this threshold (Fig. 4). At total serum IFNγ concentrations of 10^3, 10^4, 10^5, and 10^6 pg/ml, emapalumab CL was estimated to be 0.00218, 0.00308, 0.00623, and 0.01718 l/h, respectively, with corresponding terminal half-lives of 19.2, 13.8, 7.18, and 3.12 days for a 1-year-old patient weighing 10 kg with primary HLH (reference patient parameters for the purposes of providing a standardized estimate of CL and half-life). The

Table 2 Parameter estimates for the base PK model

Parameter	Estimate (RSE%)	Shrinkage, %
Fixed effects parameters		
CLL, l/h/70 kg	0.00876 (7.93)	
CLNL, l/h/70 kg	0.0748 (25.1)	
V1, l/70 kg	4.07 (3.92)	
Q, l/h/70 kg	0.0814 (20.0)	
V2, l/70 kg	4.21 (10.9)	
CLNL_IFNγ	0.562 (15.6)	
CLs_BW	+ 0.75 (fixed)	
Vs_BW	+ 1 (fixed)	
CLNL_MAS	− 1 (fixed)	
CLNL_HSCT_28D	− 1 (fixed)	
Random effects parameters		
IIV_CL, CV%	42.0 (18.9)	1.8
IIV_V1, CV%	25.4 (27.1)	8.0
Corr V1,V2	0.74 (26.2)	
IIV_V2, CV%	86.2 (25.1)	4.4
Residual variability		
RUV_add	0.313 (4.29)	

CLL linear clearance independent of total interferon-gamma, *CLNL* non-linear clearance dependent of total interferon-gamma, *CLNL_HSCT_28D* effect of hematopoietic stem cell transplant, 28 days after transplant, on non-linear clearance (fixed to -1, meaning CLNL set to zero), *CLNL_IFNγ* effect of total interferon-gamma on non-linear clearance, *CLNL_MAS* effect of patients with macrophage activation syndrome on non-linear clearance (fixed to − 1, meaning CLNL set to zero), *CLs_BW* allometric scaling exponent for clearances and intercompartmental clearance, *Corr* correlation (for individual parameters), *CV%* percent coefficient of variation, *IIV_P* inter-individual variability assigned to parameter P, *PK* pharmacokinetic, *Q* inter-compartmental clearance, *RSE* residual standard error, *RUV_add* additive component of residual unexplained variability (on the log scale), *V1* volume of the central compartment, *V2* volume of the peripheral compartment, *Vs_BW* allometric scaling exponent for the central and peripheral compartments

median terminal half-life for emapalumab in patients with MAS in sJIA was estimated to be 24.0 (range, 6.13–32.4) days based on individual post hoc analyses and is expected to be consistent across the MAS in the sJIA patient population because of serum IFNγ concentrations generally remaining below the estimated threshold for TMDD (10^4 pg/ml).

DISCUSSION

The PK of emapalumab in patients with primary HLH or MAS in sJIA can be successfully described using a two-compartment popPK model. No differences in the PK parameters of emapalumab were observed between patients with primary HLH or MAS, and the updated model was generally consistent with the previous model developed using data from patients with primary HLH alone, despite fixing the allometric effect of body weight on CL at a lower level [13]. Furthermore, the PK model was not substantially altered when data from patients with HLH administered emapalumab for compassionate use were substituted with data from patients with MAS collected during a clinical trial, confirming the robustness of the model [13].

Increased clearance related to a TMDD-like mechanism is relatively common in patients with primary HLH, whose serum IFNγ levels routinely exceed the threshold of ~10,000 pg/ml, but is much less common, and relatively transient by comparison, in patients with MAS in sJIA [13, 15]. Thus, TMDD is only incorporated into the model for patients with primary HLH. In the absence of TMDD, the PK of emapalumab in patients with MAS was similar to that predicted for healthy volunteers, providing further evidence that emapalumab is associated with a low volume of distribution and slow CL, as expected for a monoclonal antibody [13]. However, it is not possible to rule out IFNγ levels in patients with MAS exceeding the threshold for TMDD, which could increase the rate of emapalumab CL under some circumstances [15].

The practical implications of this popPK model largely relate to predicting the need for dose escalation in patients with primary HLH.

Table 3 Parameter estimates from the final PK model

Parameter	Estimate (RSE%)	Shrinkage, %
Fixed effects parameters		
CLL, l/h/70 kg	0.0143 (11.2)	
CLNL, l/h/70 kg	0.121 (25.1)	
V1, l/70 kg	3.08 (10.2)	
Q, l/h/70 kg	0.105 (14.4)	
V2, l/70 kg	4.28 (10.4)	
CLNL_IFNγ	0.542 (14.9)	
CLs_BW	+ 0.75 (fixed)	
Vs_BW	+ 1 (fixed)	
CLNL_MAS	− 1 (fixed)	
CLNL_HSCT_28D	− 1 (fixed)	
CLs_AGE	0.187 (20.2)	
V1_AGE	− 0.104 (36.2)	
CLs_V1_TBIL	0.162 (14.8)	
Random effects parameters		
IIV_CL, CV%	37.3 (18.8)	2.0
IIV_V1, CV%	20.9 (32.6)	12.7
Corr V1,V2	0.567 (28.9)	
IIV_V2, CV%	81.2 (23.1)	5.4
Residual variability		
RUV_add	0.301 (4.29)	

CLL linear clearance independent of total interferon-gamma, *CLNL* non-linear clearance dependent of total interferon-gamma, *CLNL_HSCT_28D* effect of hematopoietic stem cell transplant, 28 days after transplant, on non-linear clearance (fixed to − 1, meaning CLNL set to zero), *CLNL_IFNγ* effect of total interferon-gamma on non-linear clearance, *CLNL_MAS* effect of patients with macrophage activation syndrome on non-linear clearance (fixed to − 1, meaning CLNL set to zero), *CLs_AGE* effect of age on clearances and intercompartmental clearance, *CLs_BW* allometric scaling exponent for clearances and intercompartmental clearance, *CL_V1_TBIL* effect of total bilirubin on clearances and central and peripheral compartment volume, *Corr* correlation (for individual parameters), *CV*% percent coefficient of variation, *IIV_P* inter-individual variability assigned to parameter P, *PK* pharmacokinetic, *Q* inter-compartmental clearance, *RSE* residual standard error, *RUV_add* additive component of residual unexplained variability (on the log scale), *V1* volume of the central compartment, *V1_AGE* effect of age on central compartment volume, *V2* volume of the peripheral compartment, *Vs_BW* allometric scaling exponent for the central and peripheral compartments

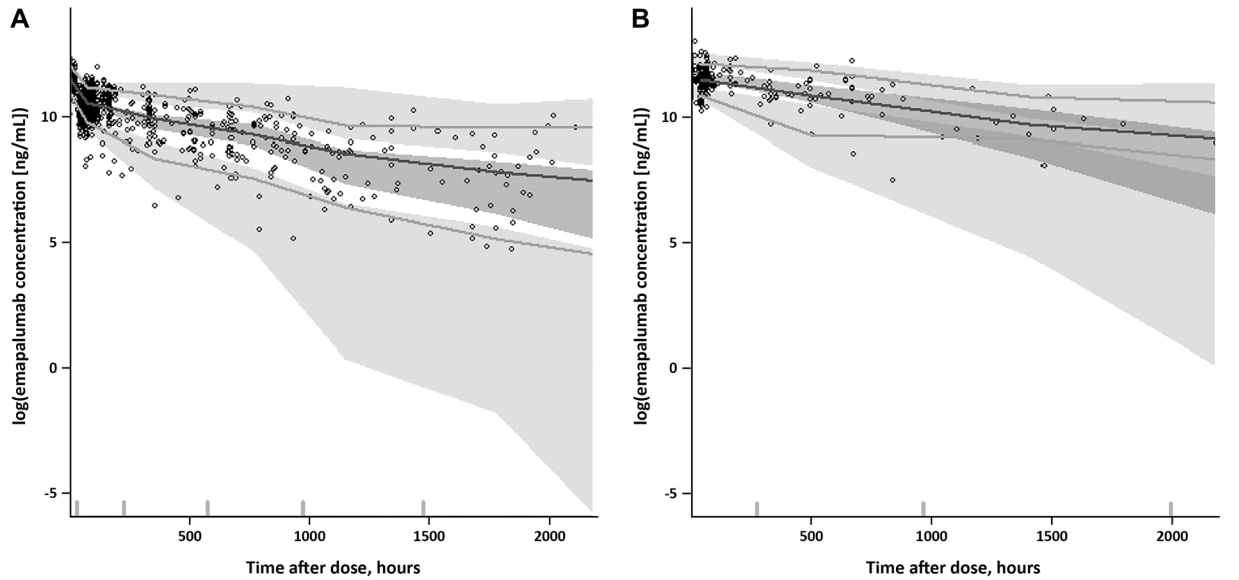

Fig. 2 Prediction-corrected VPC from the final model comparing observed and simulated log concentrations as a function of time after dose in (**A**) patients with primary HLH and (**B**) MAS up to 3 months after dosing. *HLH* hemophagocytic lymphohistiocytosis, *MAS* macrophage activation syndrome, *VPC* visual predictive check

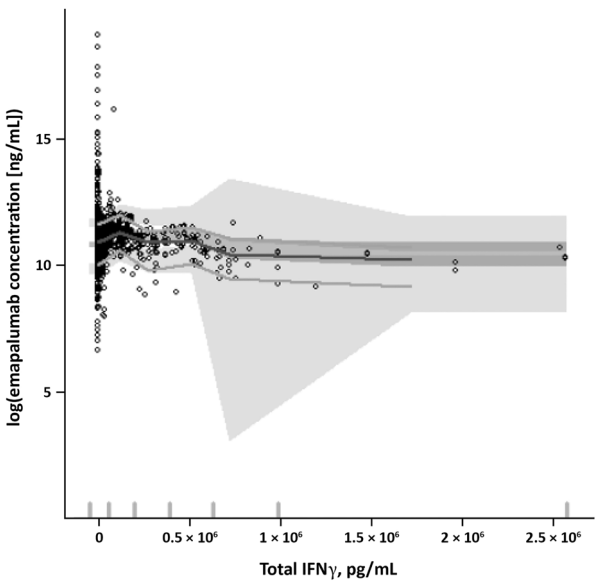

Fig. 3 Prediction-corrected VPC from the final model comparing observed and simulated log-concentrations as a function of total IFNγ level. INFγ, interferon-gamma; *VPC* visual predictive check

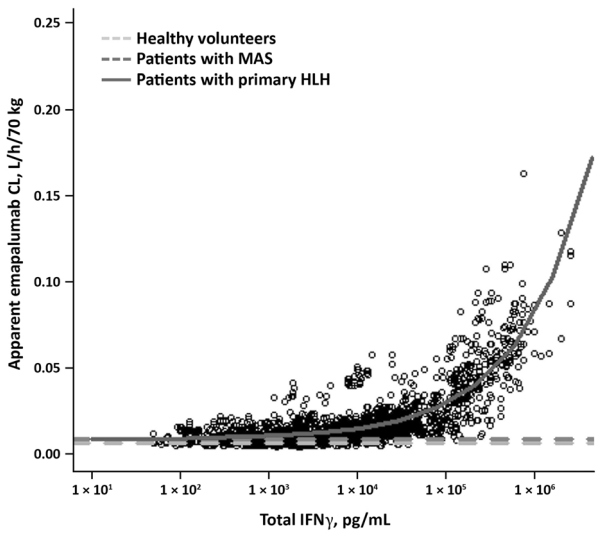

Fig. 4 Estimated apparent CL versus total IFNγ concentrations in patients with primary HLH or MAS. Dots are individual predicted clearances in patients. *CL* total clearance, *HLH* hemophagocytic lymphohistiocytosis, *IFNγ* interferon-gamma, *MAS* macrophage activation syndrome

Emapalumab may be rapidly cleared in patients with primary HLH, necessitating increased dosing and/or dose frequency to expedite control of hyperinflammation. On the other hand, increased exposure and the extended half-life of emapalumab in patients with MAS

do not appear to increase the risk of adverse events, particularly infections [15, 21].

This analysis also highlights the importance of separating allometric scaling (adjusting fixed parameters based on age) from maturation factors (all changes in physiology associated with growth and development). Model development was limited by the fixed allometric scaling of clearance and compartmental volumes in response to regulatory requirements. Accordingly, to overcome the crude prediction of age-related changes in body weight applied through allometric scaling, an additional age-related increase in CL and decrease in V1 for patients administered emapalumab were identified through covariate analyses and incorporated into the final model. However, while statistically significant, the magnitude of age-related changes in CL and V1 parameters is low and unlikely to result in clinically relevant differences in serum emapalumab concentrations across age ranges.

CONCLUSION

In conclusion, emapalumab PK in patients with primary HLH and MAS was described by a two-compartment model, with fixed allometric exponents (+ 0.75 on clearances and + 1 on volumes of distribution) and an age-related effect. A loading dose of emapalumab that exceeds the 1 mg/kg dose administered in the phase 2/3 study of patients with primary HLH may need to be considered to account for TMDD, while patients with MAS in sJIA may benefit from a rapid onset of action and negligible TMDD when administered an initial dose of emapalumab 6 mg/kg.

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Data Availability. The datasets analyzed during the current study are available from the corresponding author on reasonable request. Sobi is committed to responsible and ethical sharing of data on the participant level and summary data for medicines and indications approved by the European Medicines Agency and/or Food and Drug Administration, while protecting individual participant integrity and compliance with applicable legislation. Data access will be granted in response to qualified research requests. All requests are evaluated by a cross-functional panel of experts within Sobi and a decision on sharing will be based on the scientific merit and feasibility of the research proposal, maintenance of personal integrity and commitment to publication of the results. To request access to study data, a data sharing

request form (available on www.sobi.com) should be sent to medical.info@sobi.com. Further information on Sobi's data sharing policy and process for requesting access can be found at: https://www.sobi.com/en/policies.

Declarations

Conflict of Interest. Patrick Brossard is an employee of Sobi. Christian Laveille is a paid consultant to Sobi.

Ethics Approval. All studies were conducted in accordance with the principles set forth in the Declaration of Helsinki, the Guidelines of the ICH on Good Clinical Practice (GCP) (CPMP/ICH/135/95), European Union Directive 95/46/EC and other applicable regulatory requirements. Independent ethical committee review and approval was obtained prior to initiating the studies and all patients (or their legal guardians) provided written informed consent prior to enrollment.

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