PT019

Updated population pharmacokinetic/pharmacodynamic analysis of emapalumab in patients with macrophage activation syndrome (MAS) associated with Still's disease and systemic lupus erythematosus (SLE)

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CONCLUSIONS

- Population pharmacokinetics (PK)/pharmacodynamic (PD) modelling indicates that emapalumab rapidly suppresses production of chemokine C-X-C motif ligand 9 (CXCL9; a specific marker of interferon-gamma [IFNγ] activity), soluble CD25 (sCD25; a marker of T cell activity) and ferritin (a marker of hyperinflammation) in MAS associated with both Still's disease and SLE

INTRODUCTION

- MAS is a rare, life-threatening complication of rheumatic diseases that is characterised by IFNγ-driven hyperinflammation[1]
- Emapalumab, a fully human anti-IFNγ monoclonal antibody, binds and neutralises free and receptor-bound IFNγ and is approved by the US Food and Drug Administration for adult and paediatric patients with haemophagocytic lymphohistiocytosis/MAS in known or suspected Still's disease, including systemic juvenile idiopathic arthritis, with an inadequate response or intolerance to glucocorticoids, or with recurrent MAS[2]
  - Data from a clinical trial also supports the efficacy and safety of emapalumab in patients with MAS in SLE[3]

OBJECTIVE

- To update a previously developed population PK/PD model that described the PD effect of emapalumab in patients with MAS in Still's disease using an expanded data set from patients with MAS in Still's disease and MAS in SLE

METHODS

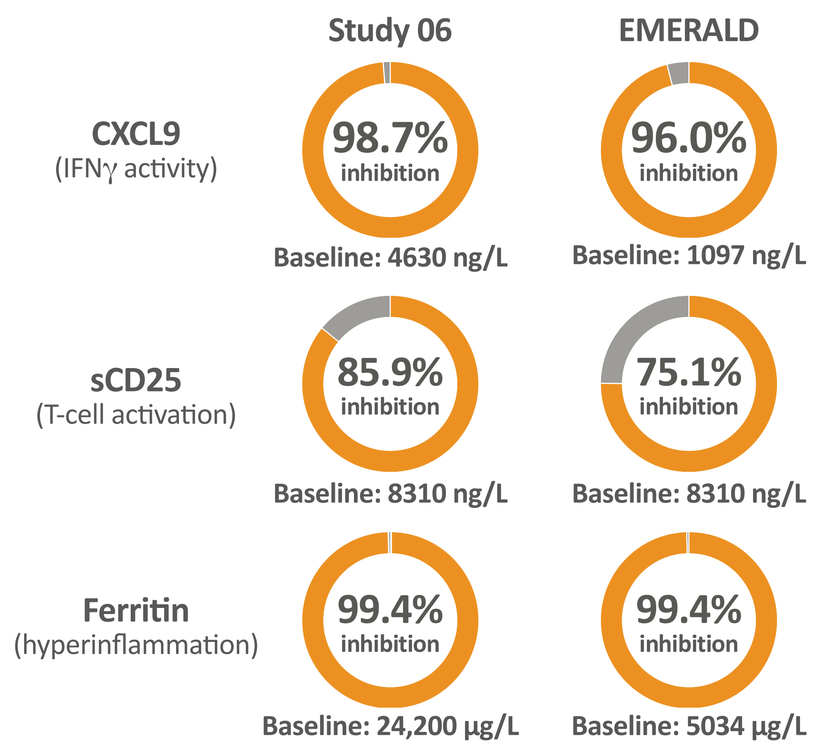
- A previously established population PK/PD model using data from patients with MAS in Still's disease treated with emapalumab (NI-0501-06 [Study 06; NCT03311854])[4] was updated using additional data from a study of emapalumab in patients with MAS in Still's disease and SLE (NI-0501-14 [EMERALD; NCT05001737])[5]
- Individual PK parameters from the updated population PK model were fixed in the PK/PD models
- The PD effects of emapalumab on serum CXCL9, sCD25 and ferritin concentrations were implemented as inhibition of the respective synthesis rates using maximum inhibition (I_{max}) models
- These PD parameters and their treatment-induced changes were characterised by turnover models
- Parameters were assumed to be in steady-state at baseline with exposure-induced inhibition after treatment start

FINAL MODEL DEVELOPMENT

- The final PK/PD model comprised a two-compartment PK model linked with three turnover models for CXCL9, sCD25 and ferritin concentrations (**Table**)
- The model had correlation parameters between baseline CXCL9 levels, I_{max} of CXCL9 and I_{max} of ferritin, as well as between baseline and I_{max} of sCD25 concentrations implemented

RESULTS

Figure: PD effect of emapalumab in Study 06 and EMERALD[a]



[a]6 mg/kg on Day 0, followed by 3 mg/kg every 3 days, then twice weekly until Day 28.[3,6]
CXCL9, chemokine C-X-C motif ligand 9; IFNγ, interferon-gamma; PD, pharmacodynamic; sCD25, soluble CD25.

- Emapalumab rapidly suppressed CXCL9, sCD25 and ferritin production (**Figure**)
- No continuous exposure–response relationship was identified; near complete inhibition was observed immediately after treatment start
- Standard errors of all parameters obtained by a bootstrap procedure were <50% of their respective bootstrap means, indicating good parameter precision
- Goodness-of-fit plots and visual predictive checks indicated good alignment between model predictions and observed concentrations for all PD markers

Table: Final emapalumab population PK/PD model parameter estimates and variability

PD marker		Role	Estimate (95% CI)	RSE (%)
CXCL9	Baseline	Typical value, ng/L EMERALD study effect (ratio) BSV non-linear[a] Correlation with baseline ferritin[a]	4630 (-3400, 12,700) 0.237 (-0.500, 0.973) 1.40 (-0.395, 3.19) 0.456 (-0.371, 1.28)	88.4 158.7 65.5 92.5
	Degradation rate	Typical value, day^{-1} BSV non-linear[a]	0.250 (-0.0217, 0.522) 0.779 (0.0913, 1.47)	55.4 45.0
	I_{max}	Typical value, % EMERALD study effect (additive) BSV (logit)[a]	98.7 (96.8, 101) -1.15 (-2.76, 0.457) 1.51 (0.193, 2.82)	1.0 71.3 44.5
	RUV	Proportion, %	47.9 (43.2, 52.6)	5.0
sCD25	Baseline	Typical value, ng/L BSV non-linear[a] Correlation with I_{max}[a]	8310 (3580, 13,000) 0.927 (-0.395, 2.25) 0.770 (0.261, 1.28)	29.1 72.8 33.7
	Degradation rate	Typical value, day^{-1} EMERALD study effect (ratio) BSV non-linear[a]	0.122 (-0.00404, 0.248) 0.656 (0.0692, 1.24) 0.594 (0.0999, 1.09)	52.7 45.6 42.4
	I_{max}	Typical value, % EMERALD study effect (additive) BSV (logit)[a]	85.9 (62.1, 110) -0.701 (-2.09, 0.684) 1.47 (-0.0696, 3.01)	14.1 100.8 53.4
	RUV	Proportion, %	31.9 (29.3, 34.6)	4.2
Ferritin	Baseline	Typical value, µg/L EMERALD study effect (ratio) BSV non-linear[a] Correlation with I_{max}[a]	24,200 (-21,000, 69,400) 0.208 (-0.251, 0.666) 1.34 (0.446, 2.24) 0.563 (-0.225, 1.35)	95.3 112.7 34.1 71.4
	Degradation rate	Typical value, day^{-1} EMERALD study effect (ratio) BSV non-linear[a]	0.173 (-0.00185, 0.349) 0.753 (-0.204, 1.71) 0.731 (0.395, 1.07)	51.6 64.8 23.4
	I_{max}	Typical value, % BSV (logit)[a]	99.4 (99.3, 99.5) 1.92 (0.545, 3.29)	0.1 36.5
	RUV	Proportion, %	43.2 (38.1, 48.4)	6.1

[a]Standard deviation/correlation as reported by NONMEM.
BSV, between-subject variability; CI, confidence interval; CXCL9, chemokine C-X-C motif ligand 9; I_{max}, maximum inhibition; PD, pharmacodynamic; PK, pharmacokinetic; RSE, relative standard error; RUV, residual unexplained variability; sCD25, soluble CD25.

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Disclosures
P. Brossard is an employee of Sobi.
A. Facius is a consultant to Sobi.
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