

Modeling bounded scales for evaluation of treatment response to subcutaneous nemolizumab in moderate to severe atopic dermatitis

Petra Jauslin^{1*}, Anna Largajolli^{1*}, Emilie Schindler¹, Tomohisa Saito², Luca Loprete³, Nathalie Wagner³, Vincent Duval¹

¹ Certara Strategic Consulting, ² Chugai Pharmaceutical Co., Ltd, ³ Nestlé Skin Health, Galderma Research and Development. *Equal contribution

Aims

To characterize the PK-PD relationships between serum concentrations of nemolizumab and the following clinical outcome variables: eczema area and severity index (EASI) and weekly average peak pruritus numeric rating scale (PP-NRS)

Background

- Nemolizumab is a humanized monoclonal antibody directed against interleukin-31 receptor α and currently under development.
- EASI is a tool to measure the extent (area) and severity of atopic dermatitis (score range 0-72).
- PP-NRS is a scale for patient-reported itch severity (score range 0-10).

Methods

Data

- 3'620 EASI scores from 525 subjects and 4'578 weekly PP-NRS scores from 225 subjects were analyzed.
- EASI scores were available from the following randomized placebo-controlled clinical studies in patients with atopic dermatitis (AD):
 - CIM001JP: a phase 1 single ascending dose study
N = 36, dose range: 0.3-3 mg/kg [1]
 - CIM003JG: a phase 2a safety and efficacy study
N = 264, dose range: 0.1-2 mg/kg Q4W or Q8W [2]
 - RD.03.SPR.114322: a phase 2b dose-range finding study
N = 225, dose groups: 20 mg loading dose (LD) + 10 mg, 60 mg LD + 30 mg or 90 mg Q4W [3]
- PP-NRS scores were only available from the phase 2b study RD.03.SPR.114322.

Population PK Model

- One-compartment distribution model with linear elimination, first-order absorption with lag time and dose effect on bioavailability.
- Covariate effects of serum albumin on CL and body weight on CL and V were identified.

PD Models

- The indirect response model for pruritus visual analogue scale published by Saito et al [4] was used as a starting point.
- Logistic functions were used to transform the amount in the indirect response model compartment from $[0, +\infty]$ to the bounded scales of EASI $[0, 72]$ or PP-NRS $[0, 10]$.
- The drug effect was described with an inhibiting effect on the zero-order rate constant for production of response (R_{in}) in both cases. Linear and non-linear link functions and placebo effects were evaluated.

Software

All models were developed in NONMEM 7.3 [5] aided by PsN.

Results

- For both PD endpoints, an inhibiting I_{max} model was chosen as most appropriate link function between concentration and R_{in} (Fig 1, Table 1).
- A constant placebo effect was introduced as additive to the drug effect in both models. For EASI, this placebo effect was study-specific (larger placebo effect in the Phase 2b study than in the earlier trials).
- For EASI, IC_{50} was difficult to estimate with sufficient precision. IC_{50} was therefore replaced by the parameter S_0 , computed as I_{max}/IC_{50} , as suggested by Schoemaker et al [6].
- For PP-NRS, the baseline score was estimated; for EASI, the observed baseline was included as a covariate acknowledging residual variability [7].

References

- [1] Nemoto O, et al. Br J Dermatol. 2016;174(2):296-304
[2] Ruzicka T, et al. N Engl J Med. 2017;376(8):826-834
[3] <https://clinicaltrials.gov/ct2/show/NCT03100344>
[4] Saito et al. J Clin Pharmacol. 2017;57(12):1564-1572
[5] Beal et al. NONMEM 7.3.0 users guides (1989-2013)
[6] Schoemaker RC et al. J Pharmacokinet Biopharm. 1998;26(5):581-93
[7] Dansirikul C et al. J Pharmacokinet Pharmacodyn. 2008;35(3):269-83
[8] Schindler et al. PAGE (2019) Abstract 9178

Conclusions

- The developed turnover models provide a good description of the EASI and PP-NRS data in AD patients treated with a wide range of nemolizumab doses (Figures 2 and 3).
- These models, together with a continuous-time Markov model for an additional PD endpoint (investigator's global assessment [IGA] score) [8] will be used to further support the nemolizumab development program.

Results (cont'd)

Figure 1. Schematic representation and equations of the final model

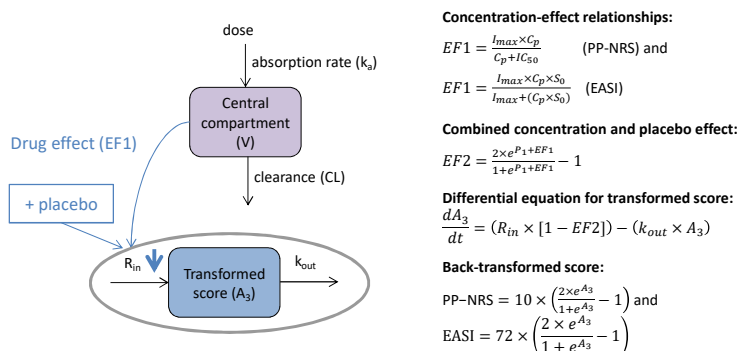


Table 1. Parameter estimates and their relative standard errors (%RSE)

Parameter	EASI		PP-NRS	
	Estimate	IIV CV%	Estimate	IIV CV%
PP-NRS ₀	-	-	2.42 (2.65)	35.1 (4.11)
k _{out} (day ⁻¹)	0.0664 (8.80)	89.2 (16.8)	0.0654 (8.76)	114 (7.60)
P ₁	0.727 (12.1)	102 (10.8)	1.18 (14.0)	126 (8.00)
IC ₅₀ (μg/L)	-	-	856 (19.4)	-
I _{max}	2.76 (17.1)	-	1.31 (13.9)	127 (11.8)
S ₀ (L/ng)	0.0950 (29.1)	292 (24.8)	-	-
Study effect on P ₁	1.82 (12.5)	-	-	-
Additive RUV	0.0259 (19)	-	0.105 (0.930)	-
Proportional RUV	0.331 (4.26)	-	0.181 (0.774)	-

A₃: logit-transformed score; CL: clearance; C_p: drug concentration; CV: coefficient of variation; EF1: drug effect; EF2: drug and placebo effect; IC₅₀: concentration leading to half of the maximum effect; IIV: inter-individual variability; I_{max}: maximum inhibitory effect; k_o: absorption rate constant; k_{out}: first-order rate constant for loss of response; P₁: placebo parameter; PP-NRS₀: baseline weekly average PP-NRS (on transformed scale); R_{in}: zero-order rate constant for production of response; RSE: relative standard error; RUV: residual unexplained variability; S₀: initial slope of the concentration-response curve; V: distribution volume

Figure 2. Visual predictive check (VPC) for the final EASI model

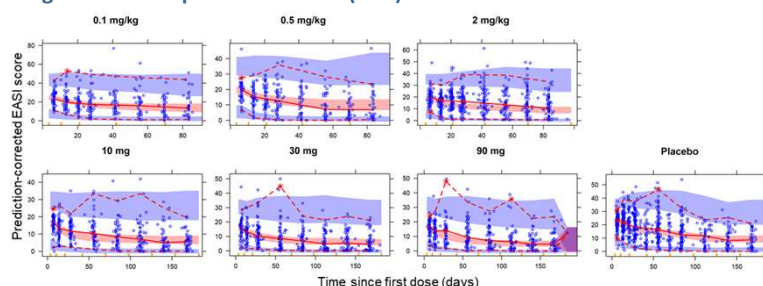
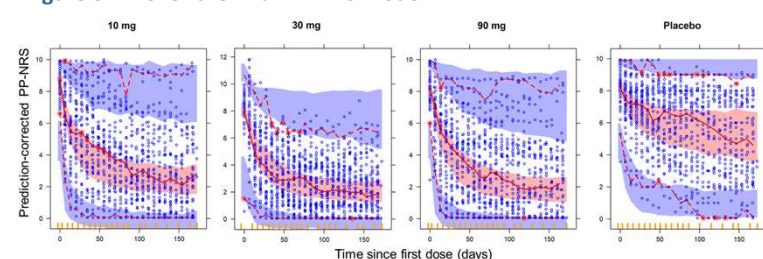


Figure 3. VPC for the final PP-NRS model



Median (solid line) and 2.5th and 97.5th percentiles for EASI / 5th and 95th percentiles for PP-NRS (dashed lines) of the observed data are compared to the 95% prediction intervals (shaded areas) for the respective percentiles of the simulated data (500 samples).