

A continuous-time Markov model (CTMM) for investigator's global assessment (IGA) score in moderate-to-severe atopic dermatitis treated with subcutaneous nemolizumab



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Aims

To characterize the time-course and exposure-response relationship of the investigator's global assessment (IGA) score in subjects with moderate-to-severe atopic dermatitis (AD) treated with subcutaneous nemolizumab.

Background

- Nemolizumab is a humanized monoclonal antibody directed against interleukin-31 receptor α and currently under development.
- IGA is an ordinal scale assessing the severity of AD, with higher scores denoting more severe disease status.

Methods

Data

- 3,818 IGA scores collected from 486 AD patients were available from two randomized placebo-controlled clinical studies:
 - a phase 2a safety and efficacy study, CIM003JG: N = 264 (261 with IGA data), dose range: 0.1-2 mg/kg Q4W or Q8W [1],
 - a phase 2b dose-range finding study, RD.03.SPR.114322: N = 225, dose groups: 20 mg loading dose (LD) + 10 mg, 60 mg LD + 30 mg or 90 mg Q4W [2].
- The 6-point IGA scale (range: 0-5) from CIM003JG was adapted into the 5-point IGA scale (range: 0-4) from RD.03.SPR.114322 by lumping scores of 4 and 5 into one category.
- The proportion of observed scores of 0 was small (1.8%). Therefore, scores of 0 and 1 were lumped together in the analysis.

Population PK Model

- One-compartment distribution model with linear elimination, first-order absorption with lag time, and dose effect on bioavailability.

IGA Model

- A previously developed continuous-time Markov model (CTMM) [3] was used as a starting point:
 - The probability of each score k (P_k) is assimilated to a compartment amount.
 - Ascending and descending transitions between compartments are modelled.
- Linear and non-linear drug effects driven by model-predicted daily concentrations (C_p) were evaluated on the rate constants of ascending (λ_{asc} : λ_{12} , λ_{23} , λ_{34}) and descending (λ_{desc} : λ_{21} , λ_{32} , λ_{43}) transitions.
- Placebo effects were evaluated on λ_{asc} and λ_{desc} .
- The effect of covariates (age, body weight, sex, and baseline IGA) was assessed on model parameters.
- A minimal CTMM approach was evaluated as an alternative [4].

Software

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

Results

- IGA data were best described by a 4-compartment CTMM including a stimulating drug effect (E_{desc}) common to all λ_{desc} (Fig.1, Table 1).
- A statistically significant linear placebo effect (T_{eff}) on all λ_{asc} was identified in study RD.03.SPR.114322, but not in study CIM003JG.
- Baseline IGA score of 4 or 5 was a significant covariate for all λ_{asc} .
- A simplified inter-individual variability structure using one term common to all λ_{asc} and one term common to all λ_{desc} improved numerical stability.
- Visual predictive checks (Fig. 2) showed an adequate model predictive performance for all scores and dose levels up to 24 weeks of treatment.

Conclusions

- The developed CTMM adequately described longitudinal IGA data in AD patients treated with a wide range of nemolizumab doses.
- The IGA model, in combination with models for the eczema area and severity index (EASI) and peak pruritus numeric rating scale (PP-NRS) [6], will be used to support the nemolizumab development program.

Results (cont'd)

Figure 1. Schematic representation and equations of the final model.

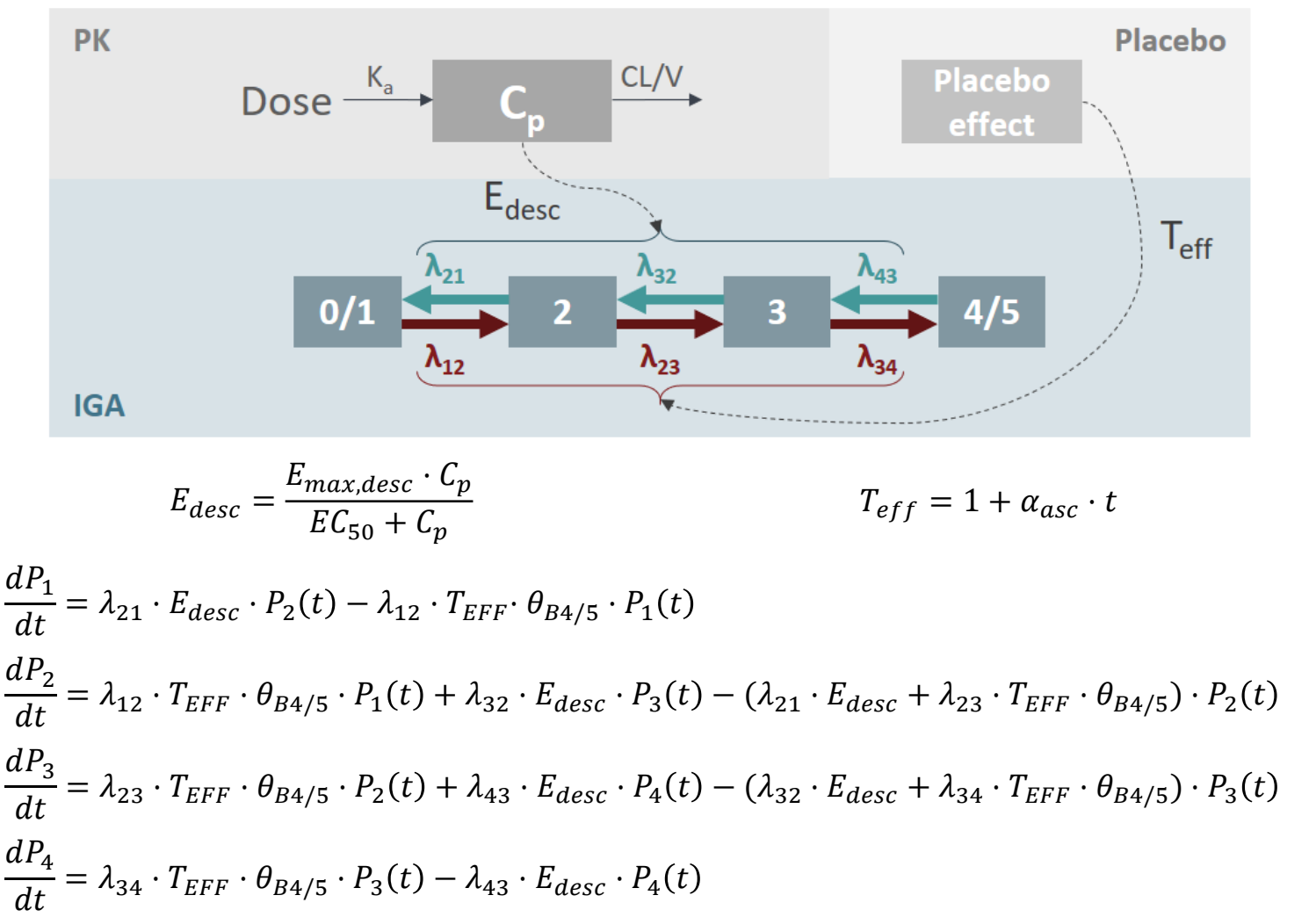
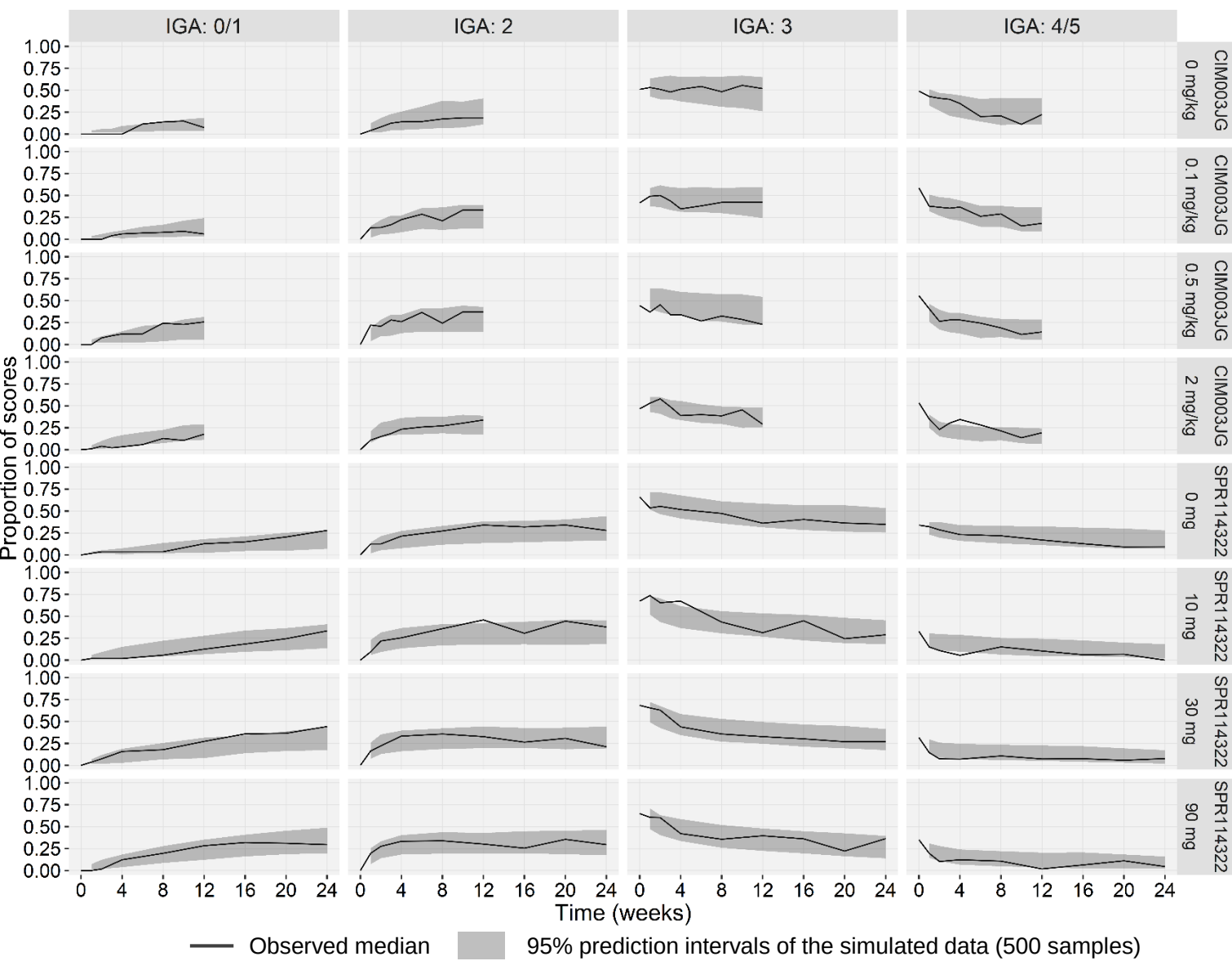


Table 1. Parameter estimates and their relative standard errors (%RSE^a).

Parameter	Estimate	IIV CV%	Parameter	Estimate	IIV CV%
λ_{12} (day ⁻¹)	0.0287 (27.0)	162 (11.6)	$E_{max,desc}$	2.46 (30.8)	-
λ_{21} (day ⁻¹)	0.00510 (20.6)	90.4 (8.81)	EC_{50} (µg/L)	2620 (64.4)	-
λ_{23} (day ⁻¹)	0.0178 (17.7)	162 (11.6)	$\alpha_{asc,SPR114322}$ (day ⁻¹)	-0.00366 (16.0)	-
λ_{32} (day ⁻¹)	0.0126 (15.8)	90.4 (8.81)	$\alpha_{asc,CIM003JG}$ (day ⁻¹)	0 (fixed)	-
λ_{34} (day ⁻¹)	0.00326 (26.2)	162 (11.6)	$\theta_{B4/5}$	4.66 (25.0)	-
λ_{43} (day ⁻¹)	0.0308 (15.8)	90.4 (8.81)			

IIV: inter-individual variability; CV: coefficient of variation; λ_{xy} : transition rate constant from x to y;
 $E_{max,desc}$: maximum stimulatory effect on λ_{desc} ; EC_{50} : concentration leading to half of $E_{max,desc}$; α_{asc} =slope of the placebo effect on λ_{asc} ; $\theta_{B4/5}$: fractional change in λ_{asc} for patients with baseline IGA of 4 or 5.
^a Relative standard errors obtained from NONMEM R variance-covariance matrix.

Figure 2. Visual predictive checks (VPCs) for the final model.



References

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