

A Categorical Time Course PKPD Model Describing the Effect of Ixekizumab on Improvement from Baseline in Psoriasis Area and Severity Index (PASI) score in Patients with Moderate-to-Severe Plaque Psoriasis

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ABSTRACT

Objectives: The Psoriasis Area and Severity Index (PASI) score is a clinical tool for evaluating the severity and extent of psoriasis and the score ranges from 0 (no disease) to 72 (most severe disease). Ixekizumab is a monoclonal antibody that selectively binds and neutralizes interleukin 17A and has shown high levels of efficacy in the treatment of psoriasis [1]. The aim of this work is to describe and quantify the effect of ixekizumab on the PASI percent improvement from baseline scores (PASI 50/75/90/100) over time in patients with moderate-to-severe plaque psoriasis using a longitudinal PKPD model.

Methods: Data up to Week 32 from a Phase 2 study (N=141 patients), and data up to Week 60 from a Phase 3 study (N=1296) were included in the analysis. Phase 2: Ixekizumab was administered subcutaneously (SC) at doses from 10 to 150 mg at weeks 0, 2, 4, 8, 12, and 16. Phase 3: Ixekizumab 80mg SC was dosed every 2 or 4 weeks (Q2W or Q4W) during an induction period (up to Week 12). A starting dose of 160 mg was administered at Week 0. Responders to ixekizumab at Week 12 were randomly assigned to 80 mg Q4W, Q12W, or placebo, while nonresponders (ixekizumab and placebo) received 80mg Q4W. Responders to placebo remained on placebo or until relapse when they were switched to 80mg Q4W. Sequential PKPD modeling was conducted using NONMEM 7.3. Posthoc ixekizumab concentrations and area under the curve (AUC) estimates from a population PK model were used as the exposure inputs to an indirect latent variable response PKPD model.

Results: The developed model is able to simultaneously describe PASI 50/75/90/100 over time. The drug effect was best described by two different components: (i) an $E_{\max}$ model on the Type III indirect latent variable response model, with $EC_{50}=1.47\mu\text{g/mL}$; (ii) a direct effect of AUC on the logit model for cumulative probabilities (proportional odds model) defined as $E_{\max D} \times \log(\text{AUC}(t)+1)$ where $E_{\max D}=0.419$. The placebo effect was included as a direct effect on the logit model with a sigmoidal time function, described with parameters, $PL_{50}=1.67$ weeks and $PL_{\max}=4.23$. The PKPD model described the data well when evaluated using the treatment adaptive simulations which mimicked the complexity of the Phase 3 adaptive study design.

Conclusions: The developed latent variable indirect response PKPD model well described the time course of PASI percent improvement in patients with moderate-to-severe plaque psoriasis.

BACKGROUND & OBJECTIVES

- Ixekizumab (Taltz®) is a humanized immunoglobulin G subclass 4 monoclonal antibody that selectively binds and neutralizes interleukin (IL) 17A (also known as IL-17) [1]. Specific inhibition of IL-17 represents a targeted approach to the management of psoriasis.
- Ixekizumab was recently approved in the US and EU for the treatment of patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
- The approved dose is 160 mg starting dose, 80 mg every 2 weeks (Q2W) at weeks 2, 4, 6, 8, 10, 12 and every 4 weeks (Q4W) thereafter.
- The objective of this analysis is to describe and quantify the effect of ixekizumab on the PASI percent improvement from baseline scores over time in patients with moderate-to-severe plaque psoriasis using a longitudinal PKPD model.
 - Percentage of improvement from baseline ≥ 50 (PASI50), ≥ 75 (PASI75), ≥ 90 (PASI90) and $=100$ (PASI100).

METHODS

Study Design:

- Phase 2** (N=141): Ixekizumab was administered subcutaneously (SC) at doses of 10 to 150mg at weeks 0, 2, 4, 8, 12, and 16.
- Phase 3** (N=1296): Ixekizumab 80mg SC was dosed Q2W or Q4W during an induction period (weeks 0 to 12); and Q4W or every 12 weeks (Q12W) during a maintenance period (weeks 12 to 60). A starting dose of 160 mg was administered at Week 0. Responders to ixekizumab at Week 12 were randomly assigned to 80 mg Q4W, Q12W, or placebo, while non responders (ixekizumab and placebo) received 80mg Q4W. Responders to placebo remained on placebo or until relapse when they were switched to 80mg Q4W.

Data analysis:

A categorical time course PKPD model was developed to simultaneously describe PASI50/60/75/90/100. Since PASI50/60/75/90/100 indicate different levels of disease improvement using the same scale, they can be combined into one unique ordered categorical dependent variable: **DV = 5**, for PASI100; **DV = 4**, for PASI90 but not PASI100; **DV = 3**, for PASI75 but not PASI90; **DV = 2**, for PASI60 but not PASI75; **DV = 1**, for PASI50 but not PASI75; **DV = 0**, if not achieving PASI50.

Stepwise covariate modeling (SCM) was implemented using Perl-Speaks NONMEM (PsN) for covariate selection. Eleven covariates were evaluated: treatment-emergent antidrug antibodies, antibody titer, palmoplantar psoriasis involvement, previous systemic treatment with a non-biologic agent, previous treatment with methotrexate, previous systemic treatment with a biologic agent, number of previous treatments (≥ 3), baseline PASI score, baseline C-reactive protein, body mass index, and baseline body weight. The final backward model from the SCM process was further evaluated in a step-wise manner taking into account factors such as parameter precision, model stability and magnitude of effect of the covariate on the clinical endpoints to obtain the final model.

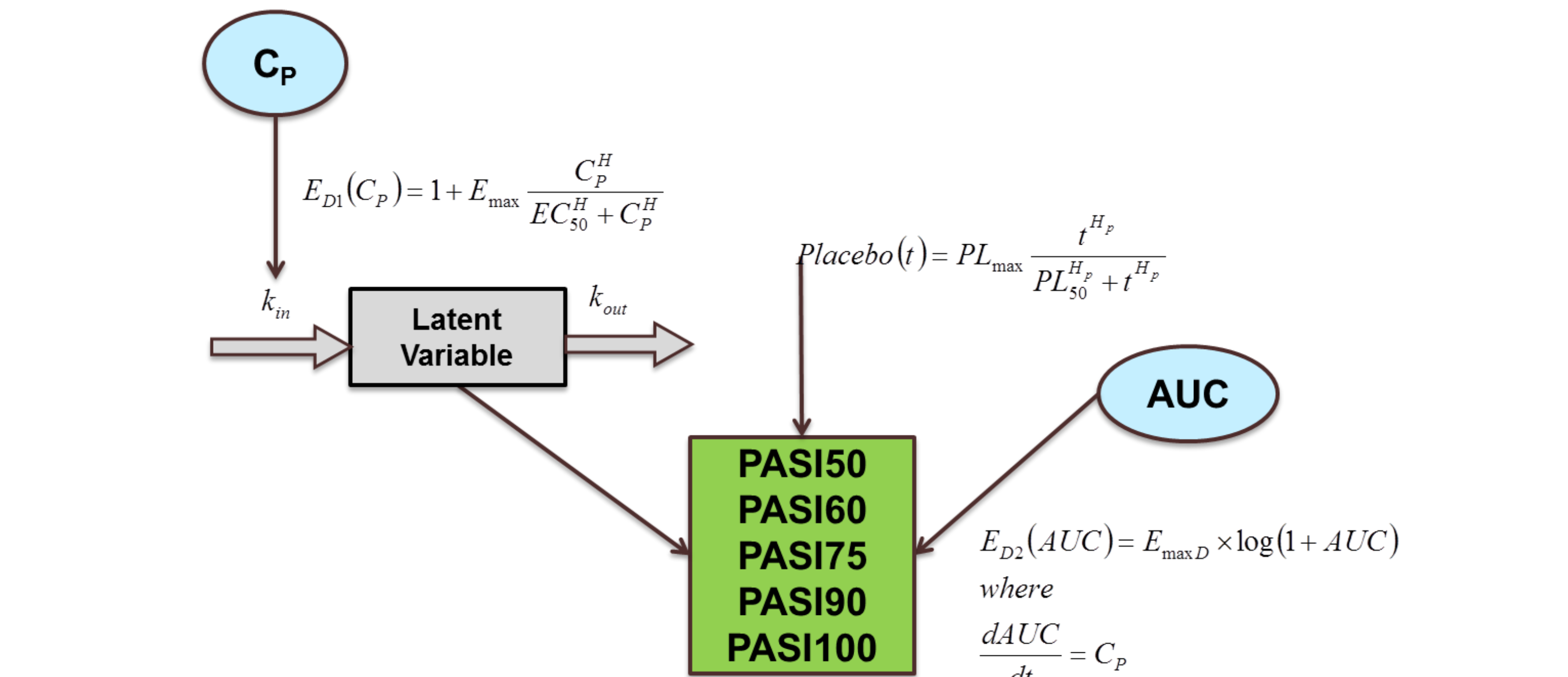
Selection criterion between models was mainly based on the objective function value (OFV) and visual predicted checks (VPCs) (100 studies simulated). Precision of parameter estimates were computed from the analysis of 500 nonparametric bootstrap datasets (sampling with replacement) performed using PsN.

Model evaluation:

The Phase 3 study had a complex design, where patient's dosing regimens were re-assigned during the maintenance period, based on patient response to the Static Physicians Global Assessment (sPGA). In order to evaluate the model using VPCs, the study simulation must mimic the original study design, allowing for the change of treatments based on efficacy (response / remission / relapse). Here, PASI improvement is the efficacy dependent variable, therefore PASI surrogates must be used for $sPGA \leq 1$ and $sPGA \geq 3$:

- Responders:** $sPGA \leq 1$ is best correlated with **PASI75**
 $sPGA \leq 1 \rightarrow 98\%$ of patients were also PASI75.
- Relapse:** $sPGA \geq 3$ is best correlated with **PASI60**
 $sPGA \geq 3 \rightarrow 86\%$ of the patients were <PASI60.

Figure 1: Selected Longitudinal Categorical Model for PASI Endpoints



The drug effect was best described by two different components: (i) $E_{D1}(C_P)$: an $E_{\max}$ model increasing k_{in} ; (ii) $E_{D2}(AUC)$: a direct effect of AUC on the logit model for cumulative probabilities. The placebo effect was included as a direct effect on the logit model with a sigmoidal time function.

RESULTS

- The developed model is able to simultaneously describe PASI 50/60/75/90/100 over time (Figure 1).
- The final model parameters including covariate effects are shown in Table 1. All parameters were estimated with good precision.
- Figure 2 shows the VPC for the clinical trial. The model is able to well describe all the treatment groups.
- A simulation of the approved dosing regimen is shown in Figure 3 and demonstrates that the model predictions agree well with the observed data.
- Three covariates were retained in the final PKPD model: (1) Palmoplantar psoriasis involvement (PSIL1) on EC_{50} ; (2) Previous treatment with a biologic therapy (PTX4) on EC_{50} ; (3) Body weight on B1.
- The effect of each covariate on response was evaluated individually through simulation (Figure 4).

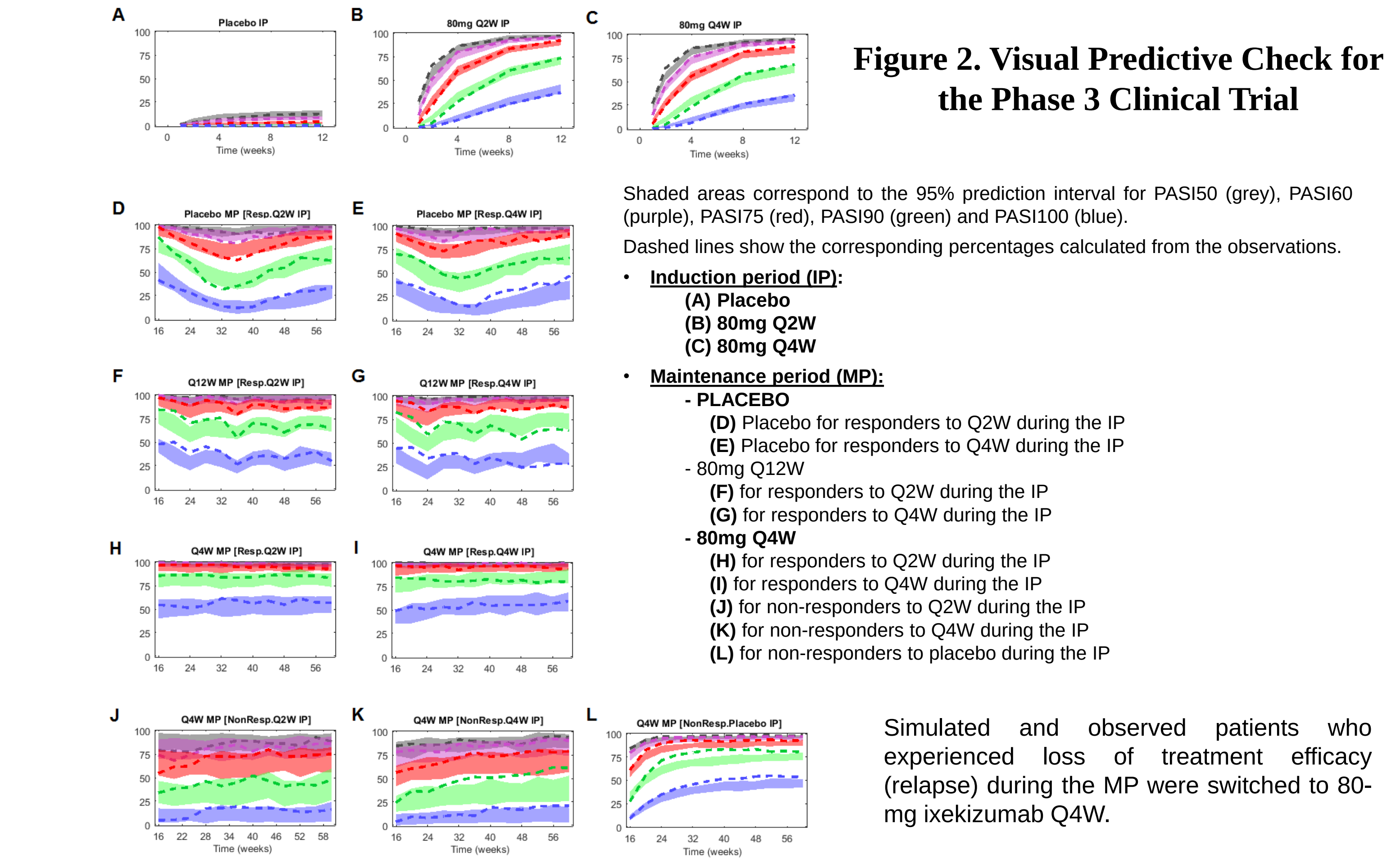


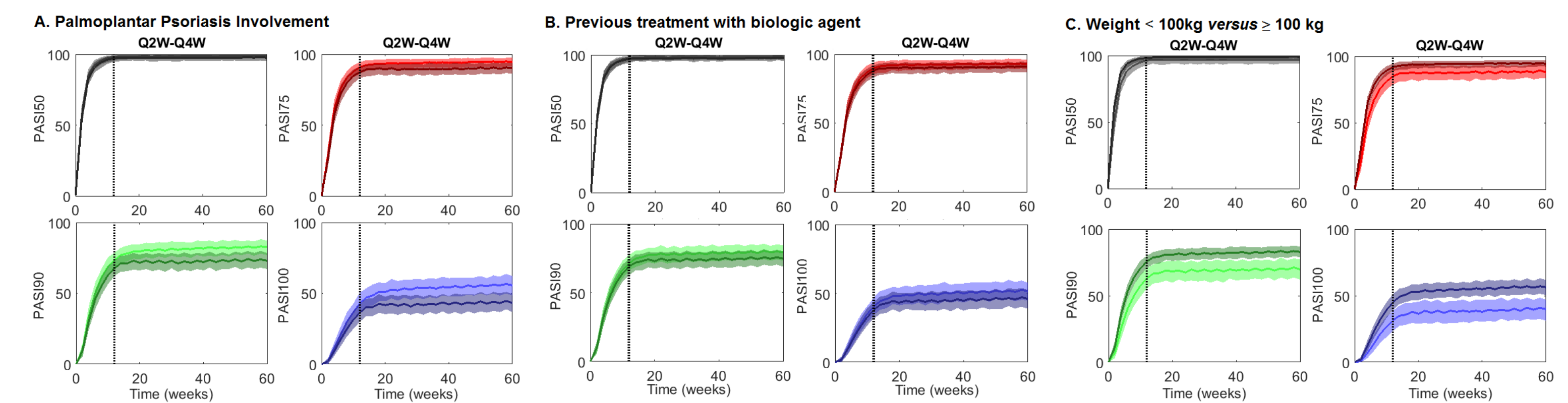
Table I. Final Model Estimates

Parameters	Estimates (RSE%)	Bootstrap analysis 50 th (5 th -95 th)
B1	-7.49 (5)	-7.51 [-8.17 -6.97]
B2	0.85 (4)	0.85 [0.8 0.92]
B3	1.37 (3)	1.38 [1.31 1.45]
B4	2.05 (2)	2.05 [1.98 2.13]
B5	2.4 (2)	2.4 [2.32 2.49]
PL ₅₀	1.64 (8)	1.65 [1.43 1.87]
PL _{MAX}	4.23 (10)	4.23 [3.68 4.98]
H _p	2.23 (9)	2.24 [1.96 2.59]
k _{in}	0.15 (5)	0.15 [0.14 0.16]
EC ₅₀	0.843 (32)	0.870 [0.50 1.47]
E _{MAX}	6.11 (5)	6.16 [5.74 6.67]
E _{MAXD}	0.41 (6)	0.41 [0.37 0.46]
Weight on B1	-0.02 (17)	-0.02 [-0.02 -0.01]
PSIL1 on EC ₅₀	1.41 (32)	1.38 [0.68 2.16]
PTX4 on EC ₅₀	0.75 (47)	0.7 [0.27 1.44]
ISV Prob. Function	229 (5)	230 [219 240]

Relative Standard Error (RSE) was calculated as $100 \times \text{std} / \text{mean}$ from the bootstrap analysis
InterSubject Variability (ISV) is reported in percentage as $100 \times \text{sqrt}(\text{variance})$

- B1, B2, B3, B4 and B5 correspond to the baseline values used for the calculation of the logits for Y₂₁, Y₂₂, Y₂₃, Y₂₄ and Y₂₅ respectively
- PL₅₀ is the time (weeks) needed for reaching half-maximal placebo response PL_{MAX}; H_p is hill exponent that describes sigmoidal steepness of such effect
- k_{in} is the zero order input rate for the latent variable, EC₅₀ (μg/mL) is the half-maximal effective concentration and E_{max} the maximum drug effect. Note that the hill exponent (H) for the E_{max} model was fixed to 1.
- E_{maxD} is the effect parameter based on the log transformed AUC

Figure 4. Model Simulations of Individual Covariate Effects on Predicted PASI Responses



- Dashed areas correspond to the 95% simulation interval. Solid lines correspond to the simulated median.
- (A) Palmoplantar psoriasis involvement (darker color)
- (B) Previous treatment with biologic agent (darker color)
- (C) Weight < 100kg (darker color)

CONCLUSIONS

- The relationship between ixekizumab drug levels and efficacy (PASI) response in patients with moderate-to-severe plaque psoriasis was well described using the selected longitudinal model.
- Latent variable indirect response model was used for drug effect
 - The drug effect was best described by an $E_{\max}$ model.
 - The response increases with the drug accumulated exposure (AUC).
- The simulation of the approved dosing regimen of a 160 mg starting dose, 80 mg Q2W at weeks 2, 4, 6, 8, 10 and 12, then 80mg Q4W thereafter, showed high levels of response by week 12, that were maintained through the week 60 evaluation period. There was good agreement between model-predicted and observed responses.
- Covariates retained in the final PKPD model were not considered to be clinically relevant therefore, the approved dosing regimen for all patients is a 160 mg starting dose, 80 mg Q2W at weeks 2, 4, 6, 8, 10 and 12, then 80mg Q4W thereafter.

Reference:

[1] Griffiths CE, et al. Lancet. 2015 Aug 8;386(9993):541-51.