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Bounded integer model-based analysis of psoriasis area and severity index in patients with moderate-to-severe plaque psoriasis receiving BI 730357 treatment

Qing Xi Ooi[1], Anders Kristoffersson[1], Julia Korell[2], Mary Flack[2], Elodie L. Plan[1], Benjamin Weber[2]

[1]Pharmetheus, Uppsala, Sweden; [2]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA

Objectives

To provide support for drug development decisions linked to the key questions:

- Which psoriasis area and severity index (PASI) outcome can be expected in the target patient population for the investigated BI 730357 (a RORγ inhibitor) dosage regimens?
- Could higher efficacy be anticipated if drug exposure is increased?

Background

The PASI scale is used to evaluate treatments for plaque psoriasis.[1,2] The assessment covers the extent of skin area affected and the severity of erythema, thickness, and scaling. The PASI score is of a composite nature and ranges 0-72. Challenges with composite scores modeling concern the boundaries of the data and parsimony of the model. The bounded integer model[3] is expected to lead to precise and realistic simulations.

Methods

Clinical Data: A phase II study in patients with moderate-to-severe plaque psoriasis (1407-0030), receiving 25-400 mg once (QD) or twice (BID) daily, under fasted or fed conditions, was included. Additional PK data were provided from three phase I studies (1407-0002, 1407-0032, 1407-0033) in healthy volunteers (HV), following single (oral or intravenous) or repeated (oral) doses.

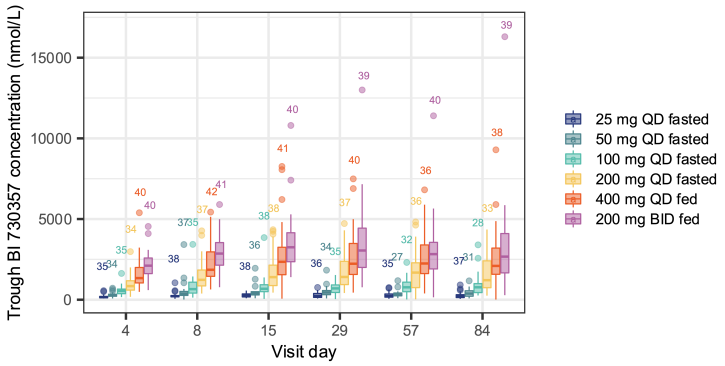

Figure 1. *Observed trough plasma concentrations by visit for patients with moderate-to-severe plaque psoriasis in study 1407-0030 colored by dosage regimen*

PK Model: Multiple absorption and disposition models were explored.

PKPD Model: A bounded integer model implemented with improved numerical stability[4] was used as a basis. The model consisted of the latent function and the scaling parameter for each subject. Different PK metrics, predicted using the individual PK parameters approach, were tested to drive the I_{max} model to describe the drug effect. An indirect response model was tested to describe the delay in the onset of the drug effect.

Exposure-Response Simulations: Administration of BI 730357 200 mg QD, 400 mg QD, and 200 mg BID under fed conditions were simulated. Each of the 300 simulated data sets contained 500 patients per dosage regimen. The individual vectors of covariates, sampled by non-parametric bootstrap, and the point estimates of the parameters were used.

Conclusions

- Robust predictions of the impact of BI 730357 dosing regimens on the PASI outcome were obtained, along with precise simulations of full exposure-response profile to address the key questions.
- Our analyses demonstrated how application of a bounded integer model resulted in accurate description of composite score data, and ultimately contributed to model-informed drug development.

Results

Clinical Data: 244 patients (Figure 1) and 109 HV yielded 7,686 BI 730357 concentrations. With the same dose, patients generally had higher exposure than HV. Increasing the dose from 200 mg QD led to sub-proportional increase in exposure.

PK Model: 2 compartments, 1st-order elimination, and dual, sequential 0 and 1st-order absorption after a brief lag, and 0-order absorption after a long lag, were selected. Bioavailability was dose-dependent and lower in patients, who also had lower clearance, like subjects with higher AST or CRP.

PKPD Model: Indirect response, with I_{max} driven by individual predicted average concentration at steady state ($C_{av,ss}$), and largest for patients with no prior biologic use, was characterized, along with a placebo response centered around 0.

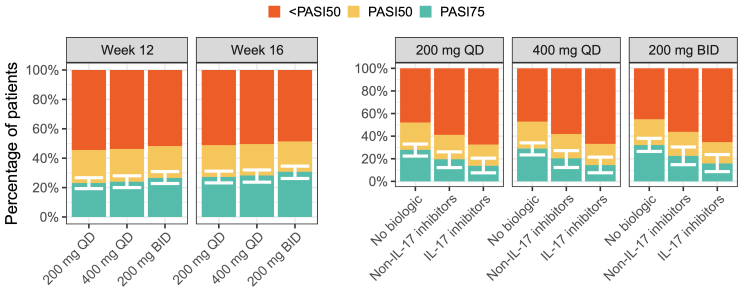

Figure 2. *Simulated (with 95% confidence interval) percentage of patients with moderate-to-severe plaque psoriasis attaining <PASI50, PASI50, and PASI75 at 12 and 16 weeks after first dose by dosage regimen and by dosage regimen and prior biologic use at 12 weeks after first dose*

Exposure-Response Simulations: ~25% of patients attained PASI75 at week 12, similar between the explored dosing regimens (Figure 2). ~50% relative change from baseline PASI score at week 12 was reached at $C_{av,ss}$ of about 2,000 nmol/L, higher simulated concentrations were linked to minor improvements (Figure 3).

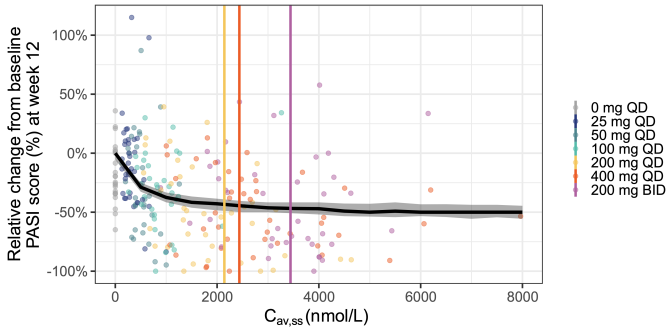

Figure 3. *Simulated (lines, including 95% confidence interval) and observed (dots) BI 730357 exposure-PASI response relationship at 12 weeks after first dose*

References

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Contact

elodie.plan@pharmetheus.com
www.pharmetheus.com

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