Population Pharmacokinetic Modeling of Tildrakizumab (MK-3222), an Anti-interleukin-23-p19 Monoclonal Antibody, in Healthy Volunteers and Subjects With Psoriasis

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BACKGROUND

- Tildrakizumab is a humanized, IgG1/κ anti-IL-23 p19 monoclonal antibody that demonstrated efficacy in subjects with chronic plaque psoriasis in two phase 3 studies during 64- and 52-week base periods (reSURFACE 1 and reSURFACE 2, respectively)[1]
- IL-23 has been identified as a key regulatory cytokine in the pathology of psoriasis responsible for stimulation of differentiation, proliferation, and survival of Th17 cells[2-3]
- Specific blocking of IL-23, through the p19 subunit, has demonstrated important clinical improvement in the treatment of psoriasis[1,4]

OBJECTIVES

- In this analysis, we characterize the population pharmacokinetics (popPK) of tildrakizumab and identify covariates influencing its exposure

METHODS

- A popPK model was developed using 6 studies conducted in 2,098 evaluable healthy volunteers and subjects with psoriasis, with a total of 17,321 evaluable observations (**Table 1**)

Table 1. Studies Included in Population PK Analysis

Study	Tildrakizumab Doses	Total N/ N Evaluable	Observations/ Evaluable Observations	BLQ
P05776[5] (Phase 1)	50 mg 200 mg	34/31	352/340	23
P06306[6] (Phase 1)	50 mg 200 mg 400 mg	53/53	648/648	54
PN 009[7] (Phase 1)	200 mg	19/19	311/309	20
P05495[8] (Phase 2b)	5 mg 25 mg 100 mg 200 mg	354/349	5690/4679	352
reSURFACE 1[1] (Phase 3)	100 mg 200 mg	763/763	6434/6329	1253
reSURFACE 2[1] (Phase 3)	100 mg 200 mg	883/883	5056/5016	1608

- The model was developed in NONMEM 7.3/PsN 4.2.0.
- Covariates of interest included body weight, formulation type, gender, age, race, serum albumin, ethnicity, creatinine clearance, Japanese origin, previous biologics therapy, subject disease status, and concomitant corticosteroid treatment.
- The covariate model was built using SCM (PsN) with forward addition (α=0.01) followed by backward elimination (α=0.001).
- The model was qualified for robustness and predictive performance with a non-parametric bootstrap and a prediction-corrected visual predictive check, respectively.
- The impact of covariates and need for dose adjustment was assessed by conducting univariate and multivariate covariate simulations.

RESULTS

- Tildrakizumab PK was described by a 1-compartment model with first-order absorption and elimination, and inter-individual variability on clearance, volume of distribution, and absorption rate constant.
- Similar to other therapeutic monoclonal antibodies, tildrakizumab PK was characterized by low clearance and limited volume of distribution.
- The base model contained the structural covariates patient status (healthy volunteer vs subject with psoriasis) and body weight. A satisfactory fit could not be obtained without these.
- Most other covariates [except previous treatment with biologics (non-significant) and concomitant steroid treatment (unevaluable)] were statistically significant, but their effect size was small.
- Univariate and multivariate simulations showed that the effects of all identified covariates on tildrakizumab steady-state AUC were within the established clinical comparability bounds, ie, would be expected to result in no important change in tildrakizumab efficacy or safety.

Final Model

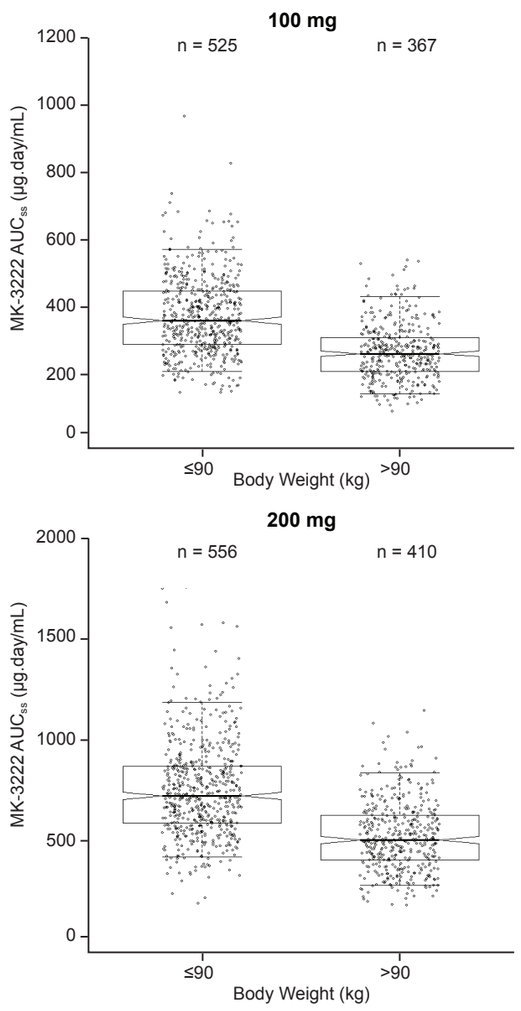
- Geometric mean clearance (%CV), distribution volume, absorption and elimination half-life, and absorption lag time are shown in **Table 2**.

Table 2. Final PK Parameters

Parameters	Geometric Mean	CV(%)
Clearance	0.32 L/day	38
Volume of distribution	10.8 L	24
Absorption $t_{1/2}$	1.5 days	18
Elimination $t_{1/2}$	23.4 days	23
Absorption lag time	0.05 days (1.2 h)	
AUC_{ss} (100 mg dose)	305 µg*day/mL	41
C_{max} (100 mg dose)	8.1 µg/mL	34
AUC_{ss} (200 mg dose)	612 µg*day/mL	40
C_{max} (200 mg dose)	16.3 µg/mL	33
t_{max}	6.2 days	46

- Steady state was achieved by 16 weeks with the clinical regimen, with 1.1-fold accumulation in C_{max}.
- Body weight had a clinically significant effect on clearance and volume of distribution; extremes of body weight (range: 40.6–222.2 kg) were positively correlated to a -53% to +163% change in clearance and to a -43% to +107% change in distribution volume compared to a subject with median body weight.
- The effect of body weight on AUC_{ss} is illustrated in **Figure 1**.

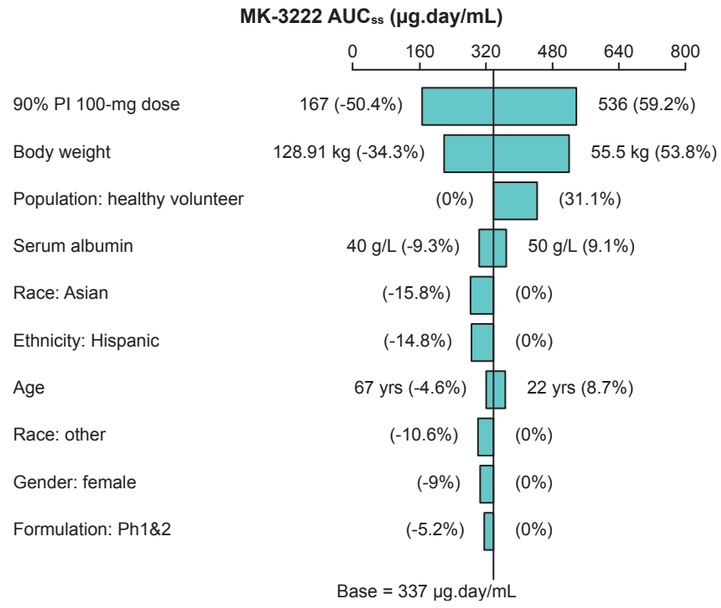
Figure 1. Tildrakizumab AUC_{ss} Stratified by Weight (cutoff: 90 kg)



Covariate Simulations

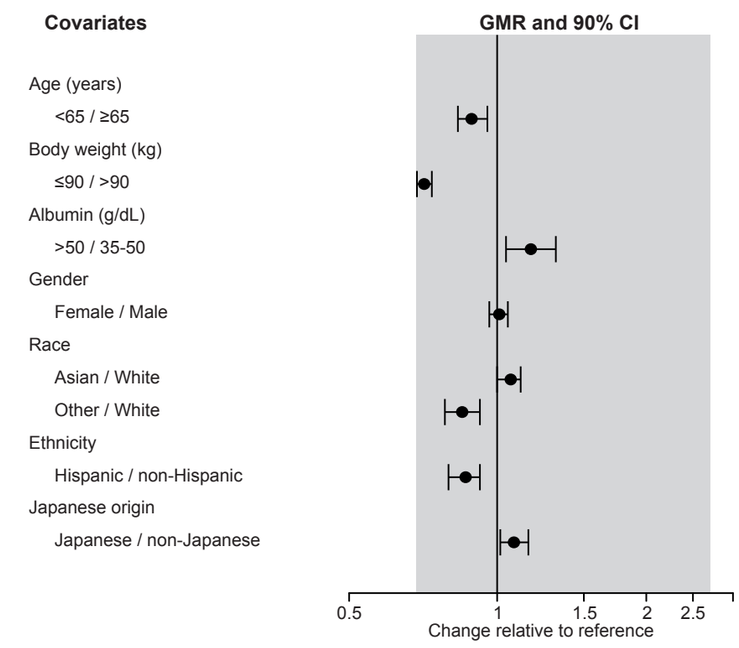
- Body weight and subject status (healthy volunteer vs subject with psoriasis) were the most influential covariates (**Figure 2**).
- Subject status (as well as formulation) is not relevant in clinical practice.
- No marked differences in efficacy (PASI response) and safety (AEs) are expected for different body weight brackets or any other evaluated subgroup (clinical comparability bounds indicated by gray square; **Figure 3**).

Figure 2. Univariate Impact of Covariates on MK-3222 AUCss (100-mg Dose Administered Every 12 Weeks)



Reference patient: White, male, non-Hispanic, psoriasis patient, Ph3 formulation, body weight= 85 kg, age=45 years, albumin=45g/L.

Figure 3. Multivariate Impact of Covariates on the AUC_{ss} of MK-3222 (100-mg Dose Administered Every 12 Weeks)



PK Effects on Clinical Response

- Clinical comparability was defined by the absence of marked differences in efficacy (PASI response) and safety (AEs) across all quartiles of exposures in both the 100mg and 200mg dose group; thus, clinical comparability bounds were defined by the median exposure of the extreme quartiles (indicated by gray square; **Figure 3**)
- All covariate effects (intrinsic and extrinsic factors, including body weight) resulted in exposures contained within the clinical comparability bounds (**Figure 3**).

CONCLUSIONS

- The pharmacokinetics of tildrakizumab is similar to that of a typical monoclonal antibody.
- Based on PK data only, there is no need for dosage adjustment for these intrinsic and extrinsic factors, although body weight had an effect on exposure.

References

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