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

**BACKGROUND**
- Tildrakizumab is a humanized, IgG1κ 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)2.
- 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 cells3,4.
- Specific blocking of IL-23, through the p19 subunit, has demonstrated important clinical improvement in the treatment of psoriasis1,4.

**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).

**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 (unavailable)) were statistically significant, but their effect size was small.
- Multivariate and univariate 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**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Mean</th>
<th>CV(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance</td>
<td>0.32 L/day</td>
<td>38</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>10.8 L</td>
<td>24</td>
</tr>
<tr>
<td>Absorption t1/2</td>
<td>1.5 days</td>
<td>18</td>
</tr>
<tr>
<td>Elimination t1/2</td>
<td>23.4 days</td>
<td>23</td>
</tr>
<tr>
<td>Absorption lag time</td>
<td>0.05 days (1.2 h)</td>
<td></td>
</tr>
<tr>
<td>Cmax (100 mg dose)</td>
<td>8.1 μg/mL</td>
<td>34</td>
</tr>
<tr>
<td>Cmax (200 mg dose)</td>
<td>612 μg/dL</td>
<td>40</td>
</tr>
<tr>
<td>Cmax (200 mg dose)</td>
<td>16.3 μg/dL</td>
<td>33</td>
</tr>
<tr>
<td>Tmax</td>
<td>6.2 days</td>
<td>46</td>
</tr>
</tbody>
</table>

- Steady state was achieved by 16 weeks with the clinical regimen, with a 1.1-fold accumulation in Cmax.
- 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 on body weight on AUCc was illustrated in Figure 1.

**Figure 1. Tildrakizumab AUCc, Stratified by Weight (cutoff: 90 kg)**

**Table 1. Studies Included in Population PK Analysis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Tildrakizumab Doses</th>
<th>Total N/ Evaluable</th>
<th>Observations/ Evaluative Observations</th>
<th>BLQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>P057761 (Phase 1)</td>
<td>50 mg 200 mg</td>
<td>34/31</td>
<td>352/340</td>
<td>23</td>
</tr>
<tr>
<td>P063064 (Phase 1)</td>
<td>50 mg 200 mg 400 mg</td>
<td>53/53</td>
<td>648/648</td>
<td>54</td>
</tr>
<tr>
<td>PN 0561 (Phase 1)</td>
<td>200 mg</td>
<td>19/19</td>
<td>311/309</td>
<td>20</td>
</tr>
<tr>
<td>P054908 (Phase 2b)</td>
<td>5 mg 25 mg 100 mg 200 mg</td>
<td>354/349</td>
<td>5690/4679</td>
<td>352</td>
</tr>
<tr>
<td>resURFACE 1 11 (Phase 3)</td>
<td>100 mg 200 mg</td>
<td>763/763</td>
<td>6434/6329</td>
<td>1253</td>
</tr>
<tr>
<td>resURFACE 2 11 (Phase 3)</td>
<td>100 mg 200 mg</td>
<td>883/883</td>
<td>5056/5016</td>
<td>1608</td>
</tr>
</tbody>
</table>

- The model was developed in NONMEM 7.3/PaN 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 (PaN) 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.

**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 scenarios.
- No marked differences in efficacy (PSAI 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 AUCc (100-mg Dose Administered Every 12 Weeks)**

![Figure 2. Univariate Impact of Covariates on MK-3222 AUCc (100-mg Dose Administered Every 12 Weeks)](image)

**PK Effects on Clinical Response**
- Clinical comparability was defined by the absence of marked differences in efficacy (PSAI 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**