**PK-PD Analysis of PASI with Data at Boundary: BI 655066, an Anti-IL-23A mAb for the Treatment of Psoriasis**

BoljanOlajic1, James Rogers1, Jonathan French2, Mary Flack1

1Boehringer Ingelheim, Ridgefield, CT, USA; 2Methuen Research Group, Tarrytown, CT, USA

**Introduction**

PASI is the most prevalent immune-mediated skin disease, affecting 2% of the world population. It is found in North America and Europe.

In clinical trials, disease activity is measured using the PASO Area and Severity Index (PASI) for 6 or 8 regions, based on a combination of indexes: erythema, scaling, and thickness (Psoriasis). The PASI is a 0–72 scale.

A standardized mononuclear monoclonal antibody that inhibits the action of IL-23 and IL-17A is used for the formulation of anti-IL-23A mAbs.

PMX/Statistical Considerations

- PK/PD analyses of PASI data have addressed the link between the dynamics of psoriatic lesions and drug concentrations.1
- PASI scores are found with high variability around the mean and decreasing variability at the extremes similar to ADAM cog analysis.
- BI 655066 was not assayed in study 1311.2 and were assumed to be that of BI 655066, given the similar PK properties of the formulation as parameter accounting for potency difference between ustekinumab and BI 655066 was included.
- Individual-level estimates of BI 655066 PK were used to predict concentrations of BI 655066 in healthy volunteers.
- Ustekinumab PK were not assessed in study 1311.2 and were assumed to be those of BI 655066, given the similarity in PK properties of the formulation.
- For implementation of NONMEM, the use of NONMEM-related models was developed and implemented.

**Implementation in NONMEM**

Non-linear mixed effects (NLME) models were used. The dataset disposition is depicted in Table 1.

**Augmented Beta Distribution**

In general, one may define a 0-1 augmented Betas (x, x, x, x) distribution as with density:

\[ f(x; \alpha, \beta) = \frac{1}{B(\alpha, \beta)} (x^{\alpha-1} (1-x)^{\beta-1} \mathbb{1}_{(0,1)}(x)) \]

where \( B(\alpha, \beta) \) is the beta function. The cumulative distribution function is given by:

\[ F(x; \alpha, \beta) = \int_0^x \frac{1}{B(\alpha, \beta)} (t^{\alpha-1} (1-t)^{\beta-1}) \, dt \]

The augmented beta distribution can be expressed as a mixture of two beta distributions, each with a different baseline parameter, as follows:

\[ p(x) = \begin{cases} \alpha \beta x^{\alpha-1} (1-x)^{\beta-1} & \text{for } 0 < x < \lambda \\ (1-\alpha) \beta (1-x)^{\alpha-1} x^{\beta-1} & \text{for } \lambda < x < 1 \end{cases} \]

where \( \lambda \) is a threshold parameter. This distribution is often used in situations where data is censored or truncated.

**Results**

### Table 3. Impact of cutoff on PASI responses. Predictions of BI 655066 PASI 90 or PASI 100 responses time across time for a fixed effect regimen, using the current PK/PD model.

<table>
<thead>
<tr>
<th>Study 1311.2</th>
<th>BI 655066mAb 2mg/kg</th>
<th>PASI 90</th>
<th>PASI 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>60</td>
<td>69</td>
<td>52–76</td>
</tr>
<tr>
<td>60</td>
<td>47</td>
<td></td>
<td>42–60</td>
</tr>
<tr>
<td>90</td>
<td>29</td>
<td></td>
<td>70–90</td>
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<tr>
<td>120</td>
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<td>60–76</td>
</tr>
<tr>
<td>180</td>
<td>2</td>
<td></td>
<td>60–76</td>
</tr>
</tbody>
</table>

### References

1. An augmented beta regression model for poistive data with response of the boundary of the scale was developed and implemented. This approach reflects the reasonable expectation that conditions that make (non-zero) low-valued observations likely will make zero-valued observations unlikely.

2. Future work in this field could explore alternative mathematical formulations of the general assumption.

3. Also, other guidelines stating a particular target dose is not a positive可供的观察。

4. Figures 1–3 illustrate goodness of fit of the current model with predictions of change from baseline PASI and PASI 90 and PASI 100 response rates time across time as diagnostic of key clinical challenges.

5. The current model reflects high potency (IC50) of BI 655066 in the picomolar range and a high degree of maximal pharmacodynamic response (Emax) at pharmacological doses.

6. Table 3 includes all the concentrations of the concentration-PASI relationship data is currently investigated.