Dose-Response and Exposure-Response Modeling of Alpha 1 Proteinase Inhibitor (A1-PI) in Patients with A1-PI Deficiency Based on RAPID and RAPID Extension Trials

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Background/Aim:

1. Alpha 1 antitrypsin deficiency (AATD) is a hereditary genetic disorder affecting 1-4% of the population.
2. AATD is characterized by decreased circulating levels of alpha 1 proteinase inhibitor (A1-PI), which regulates the activity of neutrophil elastase (NE).
3. In A1-PI deficient patients, NE degrades lung tissue and can lead to chronic obstructive pulmonary disease (COPD).

Methods:

1. Median (post-treatment) trough A1-PI concentrations were obtained from patients enrolled in RAPID and RAPID Extension Trials.
2. The dose-exposure analysis included all randomized patients with at least one post-baseline recorded A1-PI concentration (Table 1).

Results:

1. The dose-exposure model was used to predict A1-PI concentrations as a function of covariates:
   - Baseline weight and A1-PI had a small effect on post-baseline A1-PI levels.
   - Baseline weight had practically no effect on post-baseline A1-PI levels above the protective threshold (11 µM) were of the PMT24 genotype.
2. The exposure-response analysis was based on A1-PI concentrations (Table 2) and included the model:
   - Final parameters for the exposure-response model are shown in Table 3.

Exposure-response analysis

- Final parameters for the exposure-response model are shown in Table 3.
- The model includes the covariates weight and baseline A1-PI, and was expanded to incorporate the effect of baseline A1-PI on ‘natural’ decline rate.

Table 1: Simplex exams for analysis of data sets

<table>
<thead>
<tr>
<th>Analysis Set</th>
<th>Described in RAPID</th>
<th>Described in RAPID Extension and RAPID Extension Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>All available data</td>
<td>87 88</td>
<td>64 76</td>
</tr>
<tr>
<td>Dose-exposure analysis data set</td>
<td>81 88</td>
<td>64 74</td>
</tr>
<tr>
<td>Exposure-response analysis data set</td>
<td>70 88</td>
<td>61 73</td>
</tr>
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</table>

- Dose-exposure was assessed using time-aggregated A1-PI concentrations modeled as a function of dose.
  - Two distinct aggregate dose measures were computed for each subject, corresponding to the two phases of the study.
- Exposure-response analysis included all subjects in the dose-exposure model who had at least one CT lung density measurement (Table 1).
- Exposure-response was assessed using a disease progression model with the ability to accommodate the two-phase structure of combined RAPID/RAPID Extension trials and utilized CT lung density measurements (TLC) as the clinical endpoint.
- The effects of the following baseline covariates were assessed in each model:
  - Dose-exposure: weight (kg), age (y), and gender.
  - Exposure-response: lung function (FVC, FEV1, PtFeNO, and FEV1/FVC) at screening, baseline, month 12, month 24, and year 4.

Conclusions:

- A1-PI exposure was consistent across a range of body weights, providing weight-based dosing of A1-PI with at least 2.2 g/L improvement from RAPID for the 4-year analysis.
- Over 4 years an estimated 61% of A1-PI treated patients achieved the threshold of 0.5 g/L improvement in lung density decline rate, compared to 32% of placebo-treated patients (Figure 4).
- There was an increasing disparity between placebo and A1-PI therapy with increasing reduction in lung density decline rate (Figure 4).
- A threshold value of 0.5 g/L was used to evaluate the effect of covariates on slope change (Table 4).