Masitinib (MAS) has previously reported positive phase 3 findings in ALS. Here we present post-hoc analyses that explored whether patient (pt) susceptibility to MAS is influenced by baseline disease severity, as measured by the individual component scores of ALSFRS-R. Study AB10015 used a prospectively stratified design based on ALSFRS-R progression rate calculated from disease-onset to baseline ($\Delta$FS). A dichotomizing cutoff at 1.1 points/month distinguished between Normal Progressor (NP, $\Delta$FS<1.1) and Fast Progressor (FP, $\Delta$FS≥1.1) pts. The assumption here is that heterogeneity in ALS disease aggressiveness reflects differing disease mechanisms, leading to divergent treatment susceptibility. This approach therefore defines a more homogeneous primary efficacy population (i.e. NP pts receiving oral MAS 4.5 mg/kg/day), while concurrently permitting evaluation of the more heterogeneous population (i.e. ‘NP plus FP’ pts receiving MAS 4.5 mg/kg/day). The primary outcome endpoint, decline in ALSFRS-R from baseline to week-48 ($\Delta$ALSFRS-R), showed benefit for MAS (n=99) over placebo (PBO) (n=102) with a between-group least-squares means difference ($\Delta$LSM) of 3.39 (-9.24 vs -12.63), corresponding to a significant and clinically meaningful slowing in functional decline of 27% (P=0.016). Conversely, significance on $\Delta$ALSFRS-R was not reached for the ‘NP plus FP’ cohort (secondary analysis), with a $\Delta$LSM of 2.09 in favor of MAS (P=0.12). Post-hoc analysis showed that initiation of MAS treatment at a less severe stage of disease produced greater treatment-effect for both $\Delta$FS-stratified cohorts in terms of $\Delta$ALSFRS-R (as well as secondary endpoints of FVC, ALSAQ-40, and survival-to-event analysis). Notably, this minor adjustment in pt selection criteria revealed a significant benefit for MAS in the ‘NP plus FP’ cohort. For pts with a baseline score of ≥1 on each ALSFRS-R item, $\Delta$ALSFRS-R was -9.8 for MAS (n=92) vs -13.1 for PBO (n=105); a $\Delta$LSM of 3.3 and 25% slower rate of decline (P=0.0266). For pts with ≥2 on each ALSFRS-R item, $\Delta$ALSFRS-R was -6.7 for MAS (n=48) vs -11.5 for PBO (n=57); a $\Delta$LSM of 4.8 and 42% slower rate of decline (P=0.0152). Finally, for pts with ≥3 on each ALSFRS-R item, $\Delta$ALSFRS-R was -4.3 for MAS (n=20) vs -15.1 for PBO (n=27); a $\Delta$LSM of 10.8 and 72% slower rate of decline (P=0.0064). Results indicate greater benefit is possible when initiating MAS at a less severe stage of disease, with a significant treatment-effect seen regardless of post-onset $\Delta$FS.
**INITIATION OF MASITINIB AT A LESS SEVERE STAGE OF DISEASE PRODUCES GREATER TREATMENT-EFFECT: SUBGROUP ANALYSES FROM STUDY AB10015**

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**SUMMARY OF MASITINIB STUDY AB10015**

**DESIGN**

Prospectively stratified design based on ALSFRS-R progression (ΔFS)

- Defines homogenous target population for primary analysis (patient enrichment criteria).
- This approach and defined cut-off supported by the literature [Gordon, 2006; Kimura, 2006; Kollewe, 2008; Labra, 2016].
- Study enrichment leads to lower sample size / increased power for the trial.
- Concurrently permits evaluation (secondary) of the broader population.
- Rationale: heterogeneity in ALS disease aggressiveness reflects differing disease mechanisms, with possible divergent treatment-effect.
- Double blind, randomized 1:1:1, oral, 48 week treatment
- Masitinib 4.5 mg/kg/day + riluzole (high-dose cohort) vs. Placebo + riluzole
- Masitinib 3.0 mg/kg/day + riluzole (low-dose cohort) vs. Placebo + riluzole

- Main inclusion criteria:
  - Lab-supported probable, probable, or definite ALS; sporadic or familial
  - Disease duration <36 months, FVC ≥60%, stable riluzole dosing

- Two distinct patient populations
  - 'Normal Progressors': progression rate <1.1 points/month
  - 'Fast Progressors': progression rate ≥1.1 points/month

- Four distinct efficacy datasets
  - Primary efficacy population predefined as the 'Normal Progressor' cohort receiving 4.5 mg (high-dose) masitinib

- Efficacy analysis endpoints:
  - Primary – Decline in ALSFRS-R from baseline to week-48
  - Secondary included – Survival-to-event analysis (a surrogate measure for overall survival) defined as the time interval (months) for an ALSFRS-R deterioration of 9 points from baseline or death.

**EXPLORATORY ANALYSES SHOWED GREATER BENEFIT IS POSSIBLE WHEN INITIATING MASITINIB AT A LESS SEVERE STAGE OF DISEASE**

- Post-hoc analyses explored whether treatment-effect was influenced by baseline disease severity, as measured by ALSFRS-R individual item scores.
- Exclusion of patients with zero-point ALSFRS-R items scores (i.e. very severely affected) is a credible clinical scenario in which treatment is initiated prior to severe symptom onset and better matches clinical practice.
- Logical trial design feature, considering that any ALSFRS-R component scoring zero at baseline cannot register any slowing of disease (i.e. insensitive to masitinib treatment-effect).
- Results showed that initiation of masitinib at a less severe stage of disease produced greater treatment-effect for both ΔFS-stratified high-dose cohorts.
- Notably, this minor adjustment in patient selection criteria revealed a significant benefit for masitinib over placebo in the broader ('Normal and Fast Progressor') masitinib 4.5 mg/kg/day cohort.
- Fast Progressors well-represented and balanced in the ALSFRS-R item ≥1 cohort (M4.5 12 pts vs. PBO = 11 pts).
- Positive treatment-effect demonstrated for decline in ALSFRS-R (primary endpoint) and several secondary endpoints such as survival-to-event analysis, FVC, and ALSAQ-40.
- Sensitivity analyses based on full analysis dataset (non-LOCF) imputation methods were also positive with similar results.

- Results of subgroup analysis exploring effect of baseline disease severity, as measured by the individual component scores of ALSFRS-R, where a higher threshold indicates less severe disease.

- **ALSFRS-R analysis in ‘Normal & Fast Progressor’ (4.5 mg/kg/d) cohort**

```
<table>
<thead>
<tr>
<th>Severity</th>
<th>n</th>
<th>LSM</th>
<th>∆LSM [95%CI]</th>
<th>Effect</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe, Moderate</td>
<td>15</td>
<td>0.9</td>
<td>-7.7 [11.1]</td>
<td>18%</td>
<td>0.0115</td>
</tr>
<tr>
<td>Mild</td>
<td>10</td>
<td>1.1</td>
<td>-5.0 [8.0]</td>
<td>14%</td>
<td>0.016</td>
</tr>
</tbody>
</table>
```

**KEY RESULTS FROM HIGH-DOSE COHORT**

Masitinib (4.5 mg/kg/day) demonstrated a significant benefit in ALS patients with a ΔFS of <1.1 points/month (primary analysis population)

```
<table>
<thead>
<tr>
<th>n</th>
<th>LSM</th>
<th>∆LSM [95%CI]</th>
<th>Effect</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRO</td>
<td>102</td>
<td>-12.6</td>
<td>3.4 [0.7; 6.1]</td>
<td>27%</td>
</tr>
<tr>
<td>M4-5</td>
<td>99</td>
<td>-11.2</td>
<td>3.2 [0.6; 5.7]</td>
<td>27%</td>
</tr>
<tr>
<td>PRO</td>
<td>113</td>
<td>-16.0</td>
<td>4.8 [1.8; 7.8]</td>
<td>29%</td>
</tr>
<tr>
<td>M4-5</td>
<td>105</td>
<td>-20.4</td>
<td>4.2 [1.5; 6.9]</td>
<td>29%</td>
</tr>
</tbody>
</table>
```

However, significance was not reached in the more heterogeneous, population (secondary analysis) of the ‘Normal and Fast Progressor’ masitinib (4.5 mg/kg/day) cohort

```
<table>
<thead>
<tr>
<th>n</th>
<th>LSM</th>
<th>∆LSM [95%CI]</th>
<th>Effect</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRO</td>
<td>119</td>
<td>-13.0</td>
<td>2.9 [0.5; 4.7]</td>
<td>16%</td>
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<tr>
<td>M4-5</td>
<td>120</td>
<td>-11.9</td>
<td>2.8 [0.5; 4.5]</td>
<td>16%</td>
</tr>
<tr>
<td>PRO</td>
<td>132</td>
<td>-14.0</td>
<td>2.9 [1.1; 4.8]</td>
<td>21%</td>
</tr>
<tr>
<td>M4-5</td>
<td>128</td>
<td>-17.0</td>
<td>3.0 [1.2; 4.8]</td>
<td>21%</td>
</tr>
</tbody>
</table>
```

These findings have revealed a relevant design consideration for future clinical studies of masitinib in ALS.

Together with patient selection based on ΔFS, such clinical trial enrichment strategies are important for efficient study design in ALS.
