Sensitivity analyses from the first phase 3 clinical study of masitinib (AB10015) in ALS demonstrate robustness of the positive primary analysis

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Masitinib (MAS) has previously reported positive phase 3 (AB10015) findings in ALS, signaling that it could provide an important new treatment option. Here we present results from various sensitivity analyses on the primary endpoint. The primary efficacy population of study AB10015 was predefined as patients (pts) receiving MAS 4.5 mg/kg/day with a ALSFRS-R progression rate from disease-onset to baseline (ΔFS) of <1.1 points/month. The primary endpoint, decline in ALSFRS-R from baseline to week-48 (ΔALSFRS-R), showed significant benefit for MAS (n=99) over placebo (n=102) with a between-group least-squares means difference (ΔLSM) of 3.39 (-9.24 vs -12.63); 95%CI 0.65–6.13, P=0.016. Missing data were imputed via last observation carried forward (LOCF) methodology for those pts discontinuing because of toxicity or lack of efficacy before week 48. In total, six predefined sensitivity analyses were conducted on the primary analysis, including two full analysis dataset (non-LOCF) imputation methods and four variations on LOCF via censoring on reason for discontinuation. All results from these sensitivity analyses were consistent with the significant outcome of the primary analysis, corroborating the robustness of this finding. Considering the most pessimistic full analysis dataset (imputation with penalty), which estimates progression for similarly clustered pts then imputes missing values using this average trend, ΔALSFRS-R for MAS (n=104) was -11.4 versus -14.4 for placebo (n=111); corresponding to a ΔLSM of 3.0 and significant 26% slowing in rate of decline (P=0.018). This result was further verified via tipping point analysis, a form of stress testing that assesses how large departures from the ‘Missing at Random’ assumption must be to overturn conclusions from the primary analysis. The tipping point was achieved with a penalty of 76% (i.e. as if 76% of discontinued MAS pts were equivalent to placebo). Because this is an improbable scenario, we can say that the analysis is robust. Additionally, a multiple imputation method was performed post-hoc using a monotone regression model (with initial conditioning by MCMC imputation). Results showed a significant slowing in decline of ALSFRS-R for MAS (n=105) versus placebo (n=113) by 21%, with ΔLSM of 2.8 (-11 vs -13.8); (P=0.0454). Taken together, these positive results from multiple/single imputation sensitivity analyses corroborate the robustness of study AB10015 primary endpoint data.

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STUDY AB10015 WAS THE FIRST SUCCESSFULLY COMPLETED PLACEBO CONTROLLED PHASE 3 TRIAL OF MASITINIB IN ALS

- Masitinib is an oral tyrosine kinase inhibitor that exerts a protective effect on both the CNS and PNS [1,2] (also ENCALS Pos).
- Multiple imputation (MI) is a well-recognized approach for addressing missing data.
- Primary efficacy outcome was declared to be significant in ALSFRS-R progression (ΔFS) of less than 1.1 points/month and treatment with masitinib at 4.5 mg/kg/day.
- The ΔFS-stratified design and cut-off used is supported by the literature [Gordon, 2006; Kimura, 2006; Kollewe, 2008; Labra, 2016].
- Masitinib demonstrated a clinically meaningful and significant benefit with acceptable safety in this prospectively declared population.

Sensitivity Analyses for Testing Robustness of Primary Outcome

- Interpretation of the primary analysis is complicated by use of last observation carried forward (LOCF) for missing data imputation as this method can generate bias.
- This concern was mitigated through sensitivity analyses, including predefined full analysis dataset (non-LOCF) imputation methods and variants on LOCF via censoring on reason for discontinuation.
- Additional validation was obtained through exploratory analyses based on methods widely recommended by industry guidelines and authorities [3–7].
- Of note also is that the discontinuation rate was similar between treatment-arms (34.2% versus 34.9%).

Predefined sensitivity analyses

- Rule 1 (primary analysis): Missing data was imputed via LOCF only when patients discontinued before week-48 for documented reasons of toxicity or lack of efficacy.
- Rules 2 to 5: As for rule 1 with additional reasons for withdrawal imputed via LOCF.
- Rule 6: Imputation done by clustering patients on a given prognostic factor, then using the average increment within groups (FDA recommended).
- Rule 7: As for rule 6 with the penalty of 50% applied for lack of efficacy.

Exploratory analyses

- Multiple imputation (MI) is a well-established widely recommended technique [3–7]
  - Fully Conditional Specification Regression Predictive Mean Matching (FCS REGPMM) method (non-montone regression).
  - Monotone regression model (with initial conditioning by MCMC imputation).
  - Jump to reference (different thresholds). Assumes any patient discontinuing treatment early would behave similarly to placebo patients post discontinuation.
  - Worst observation carried forward (WOCF) is a conservative method compared with LOCF and more appropriate due to the degenerative nature of the disease.
  - Tipping-point analysis assesses how severe departures from the MAR assumption must be in order to overturn conclusions from the primary analysis (serves as form of stress-testing). A high penalty (range 100–0) indicates greater robustness.
  - Tipping-point for the primary endpoint (rule 6) was achieved with a penalty of 76%.

The positive primary outcome from study AB10015 has now been corroborated by numerous (>10) industry recognized, health authority recommended, standard statistical techniques.