

TITLE:

Masitinib in primary progressive (PPMS) and non-active secondary progressive (nSPMS) multiple sclerosis: Results from phase 3 study AB07002

AUTHORS:

P. Vermersch¹, O. Hermine^{2,3}, ON BEHALF OF THE AB07002 STUDY GROUP

¹ Univ. Lille, INSERM UMR-S1172, CHU Lille, FHU Imminent, Lille, France;

² Imagine Institute, INSERM UMR 1163 and CNRS ERL 8254, Laboratory of Cellular and Molecular Mechanisms of Hematological Disorders and Therapeutic Implication, Hôpital Necker, Paris, France.

³ AB Science, Paris, France

ABSTRACT:**BACKGROUND:**

Masitinib (MAS) is a small molecule drug targeting KIT, LYN and CSF1R. Proof-of-concept that MAS slows progressive multiple sclerosis (MS) was previously demonstrated.

OBJECTIVE:

Assessment of oral MAS as a treatment for progressive MS. Study AB07002 (NCT01433497) evaluated 2 independent parallel groups; 4.5 mg/kg/d vs matched placebo (PBO), and titrated MAS dose of 6.0 mg/kg/d vs PBO.

METHODS:

Randomized (2:1), double-blinded, placebo-controlled, 2-parallel group trial. Eligible patients (pts) aged 18–75 years, with baseline Expanded Disability Status Scale (EDSS) 2.0–6.0, regardless of time-from-onset, and diagnosed with primary progressive (PPMS) or non-active secondary progressive (nSPMS) MS, were treated for 96 weeks. Primary endpoint was overall EDSS change from baseline using repeated measures (GEE model, timeframe W12–W96, measured every 12 weeks). Results are expressed as least-squares means difference (δ EDSS, positive value indicates worsening), with treatment-effect reported as between-group difference (Δ LSM, negative value favors MAS). A key sensitivity analysis was the 3-level ordinal EDSS model (± 1 or 0, repeated measures), which simultaneously measures improved, stable, or worsening outcomes over duration of treatment.

RESULTS:

MAS (4.5mg/kg/d) (n=199, median EDSS=5.5, mean age=49.3 \pm 9.6 years) showed significant benefit over PBO (n=101) with δ EDSS of 0.001 vs 0.098, respectively, and Δ LSM of -0.097(95%CI[-0.192,-0.002]);p=0.0256. This treatment-effect was numerically maintained for the subgroups of nSPMS (MAS n=120 vs 56) and PPMS (MAS n=79 vs 45) with Δ LSM of -0.104(95%CI[-0.198,-0.008]; p=0.032) and -0.128(95%CI [-0.285,0.0282];p=0.108), respectively. All EDSS sensitivity analyses were convergent with the primary outcome, including the conservative jump-to-reference approach with Δ LSM of -0.089 (95%CI[-0.173,-0.006];p=0.0367). Ordinal EDSS analysis showed a significant 39% relative probability of either reduction in EDSS progression or increase in EDSS improvement (hazard ratio (HR) 0.610 (95%CI[0.376,0.988];p=0.0446). Analysis of EDSS time-to-progression showed a significant reduced relative risk of 42% with MAS for first progression (HR 0.58, 95%CI[0.35,0.96];p=0.034), and a reduced relative risk of 37% with MAS for 12-week confirmed (HR 0.63, 95%CI[0.33,1.20];p=0.159). The proportion of pts presenting at least one adverse event (AE) was 94.5% for MAS (4.5 mg/kg/d) vs 87.1% for PBO. Safety was consistent with the known profile for MAS, common treatment-emergent AEs being diarrhea, nausea, rash, and hematological assessments. Efficacy results from the MAS high-dose parallel group (titrated 6.0 mg/kg/d) were inconclusive and no new safety signal was observed.

CONCLUSION:

MAS (4.5 mg/kg/d), a first-in-class TKI targeting the innate immune system via inhibition of mast cell and microglia/macrophage activity, may provide a new treatment option for PPMS and nSPMS