Effect of Siponimod on Disability Progression as Measured by the Ambulation Score, a Subscore of the Neurostatus-EDSS: Post hoc Analysis of the EXPAND Trial in SPMS

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Objective:

Assess siponimod's effect on the Ambulation Score (AS; representing the type of assistance used and walking distance measured) of the Neurostatus-Expanded Disability Status Scale (Neurostatus-EDSS) in secondary progressive multiple sclerosis (SPMS).

Background:

In the Phase 3 EXPAND study, siponimod reduced the Neurostatus-EDSS-measured risk of 3/6-month (M) confirmed disability progression versus placebo by 21%/26%, with more pronounced effects (31%/37%) in active SPMS (aSPMS). Characteristically, ambulation steadily declines in SPMS. In EXPAND, siponimod's effects on the timed-25-foot walk test were not significant, probably due to higher variability in this measure at higher EDSS scores. Here we evaluated the contribution of the AS to siponimod's effect on disability progression.

Design/Methods:

This post-hoc analysis included the overall population (OP); siponimod/placebo n=1099/546) and aSPMS/non-active (naSPMS) patients (siponimod, n=516/557; placebo, n=263/270). Outcomes included change from baseline in Neurostatus-EDSS/AS, time-to-first worsening on AS (3M/6M confirmed worsening [3M/6MCW]) by ≥1/≥2-points and categorical analysis (proportion of patients with 3M/6MCW or confirmed improvement [CI] by ≥1-point during the core study [median(range): 21(0.2–37.0)M]).

Results:

In the OP, the Neurostatus-EDSS, and more prominently, AS change from baseline, favored siponimod versus placebo at all visits (M6-M30); most pronounced at M18 (EDSS: 0.13 versus 0.23;p=0.003; AS: 0.50 versus 0.81;p=0.001). Siponimod significantly reduced the risk of 3MCW (≥1-point, HR=0.78,p=0.0046; ≥2-point, 0.71,p=0.0007) and 6MCW in AS (≥1 point, 0.74, p=0.0023. At M24, fewer patients worsened/more improved on siponimod versus placebo (Neurostatus-EDSS: 6MCW, 26.9% versus 35.7%; 6MCI, 11.1% versus 8.5%,p=0.03; AS: 6MCW, 33.4% versus 45.2%; 6MCI, 14.9% versus 10.6%,p=0.005). In aSPMS, pronounced effects were observed in 3MCW (≥1-point, HR=0.68,p=0.002; ≥2-point, 0.60,p=0.0005); 6MCW (≥1-point, HR=0.63,p=0.0007), with fewer patients worsening/more improving on siponimod and a trend for fewer patients worsening in naSPMS.

Conclusions:

These findings corroborate siponimod's efficacy on disability progression in SPMS. More pronounced effects on the Neurostatus-EDSS and AS were observed in aSPMS and when using more stringent endpoint definitions.