Phosphodiesterase Type 4 Inhibitor Protocol

Objectives

1. Report relationship of randomized DB-delayed-start/placebo-controlled ibudilast treatment combined with OLE treatment on clinical endpoint-responsiveness [ALSFRS-R total/sub/item scores, manual muscle strength measurements in limb/oro-facial muscles, vital capacity, maximal-inspiratory pressure, maximal-voluntary ventilation, bulbar/limb timed-functional-tests, quality-of-life measures, survival] at end of DB OLE / WO epochs continuing into PWO epoch in Per-Protocol completers (PP) compared with nonPP-completers (nPP) [ECPP=35;EC-nPP=16;ANC-PP=12;ANC-nPP=7].

2. Compare a priori statistical plan responder analysis of ≤ 2 units drop in ALSFRS-R in DB epoch with post hoc analysis of novel composite endpoint consisting of [a ≤ 12 unit drop in ALSFRS-R; b ≤ 1 MMT unit drop in neck and/or leg strength during DB and OLE epochs on post washout (WO) survival].

3. Showed improved survival (P=0.0025) in the 30 months post treatment.

4. Subjects who showed no progression on 6 or 12 months ibudilast treatment.

Methods

- MN-166-ALS-1201 Adaptive Design Protocol
- NCT02238626 Protocol Outcome Measures
- ALSFRS-R Responders
- ALSFRS-R Score
- EC/PP population
- Protocol completers (PP)
- Placebo

Conclusions

In this phase 1b/2a clinical trial, a novel composite endpoint defined as less than 12 units (< 1 unit per month) decrease in ALSFRS-R total score and/or not losing 1 MMT unit in neck and leg muscles in the DB and OLE epochs (12 months) was analyzed. 11/34 ALS subjects randomized to ibudilast compared with 2/17 subjects randomized to placebo showed improved survival (P=0.0117) showed no progression.

Subjects who showed no progression on 6 or 12 months ibudilast showed improved survival (P=0.0010) in the 30 months post ibudilast treatment.

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Ibudilast, effective in two ALS-gene-based models, has a known human safety profile that permits assessment of its effectiveness targeting multiple disease pathways at early–distal-axonopathy/late–microglial-activation ALS stages. Ibudilast delays development of brain atrophy in progressive MS.