COMBAT-ALS Phase 2b/3 Trial of MN-166 (Ibudilast) in ALS: Study Design and Trial Update (NCT04057898)

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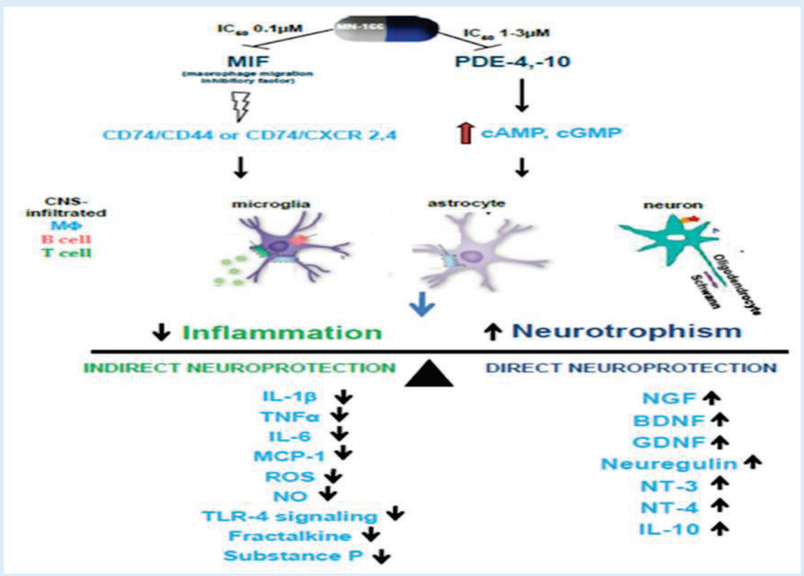
Introduction

MN-166 is an orally available small molecule that penetrates the CNS well. It inhibits the pro inflammatory cytokine macrophage migration inhibitory factor (MIF) and PDE 3, 4, and 10 with demonstrated neuroprotective action and glial cell attenuation in multiple in-vitro/in-vivo studies.



MN-166 (ibudilast) Mechanism of Action

Preclinical studies have suggested that ibudilast may also act by inducing autophagy via mammalian target of rapamycin complex 1 (mTORC1)–transcription factor EB signaling in vitro, resulting in clearance of SOD1 and TAR DNA-binding protein 43 (TDP-43) aggregates. (Chen et al 2020). MN-166 has been exposed to > 900 subjects with favorable safety profile.

Background

The first clinical trial targeted ALS was Phase 1b/2, a single-center, randomized double-blind (6 months), placebo-controlled trial followed by OLE (6 months). (NCT 02238626). This study showed no overall change in disease progression between placebo and MN-166 groups, but more patients receiving MN-166 remained stable or improved ALSFRS-R, ALSAQ-5 and average muscle strength in the post-hoc analysis.

Responder Analysis in MN-166-ALS-1201

Parameter	Responder category	Placebo (n=16)	MN-166 (n=33)
ALSFRS-R Total score	Stable or improved	2/16 (12.5%)	7/33 (21.2%)
ALSAQ-5		4/16 (25%)	17/33 (51.5%)
MMT		4/16 (25%)	11/33 (33.3%)

ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale – revised
ALSAQ-5: Amyotrophic Lateral Sclerosis Assessment Questionnaire-5, MMT: Manual muscle testing.
Oskarsson et al 2022 (originally from B. Brooks)

Study Objectives

Primary objective

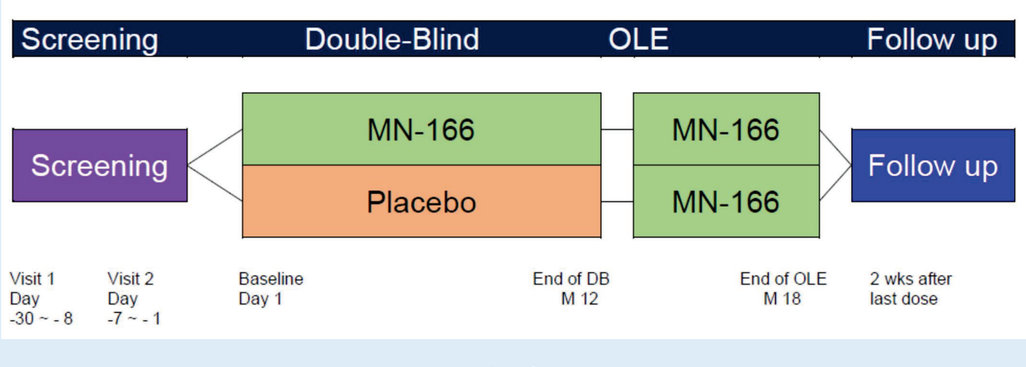
- To evaluate the efficacy of MN-166 (ibudilast) on ALSFRS-R score and survival in ALS patients.

Major Secondary objectives are

- To evaluate the efficacy on muscle strength measured by hand-held dynamometry (HHD)
- To evaluate the efficacy of MN-166 on quality of life measured by ALSAQ-5
- To evaluate the efficacy of safety and tolerability

Study Design / Method

This is a Phase 2b/3, multicenter, randomized, double-blind (12 months) placebo-controlled study followed by open-label extension phase (6 months) in ALS patients on riluzole. Patients who meet entry-criteria are randomly assigned 1 of treatment groups, MN-166 or placebo.



Study Design

Major Inclusion Criteria

- Male or female subjects ages 18 to 80 years, inclusive;
- Diagnosis of familial or sporadic ALS as defined by the El Escorial-Revised (2000) research diagnostic criteria for ALS [clinically definite, clinically probable, probable-laboratory-supported];
- ALS onset of ≤ 18 months from first clinical symptoms of weakness prior to screening;
- If currently using edaravone, subject should have completed the first 14 days of their initial treatment cycle prior to initiating study drug;
- A total ALSFRS-R score of at least 35 overall at screening and:
  - a. No more than one of the 12 ALSFRS-R individual component items has a score of 1 or less at screening;
  - For limb onset subjects, ALSFRS-R score of ≥ 3 on item #1 (speech), #2 (salivation) and #3 (swallowing);
- ALSFRS-R progression rate from onset of first symptom of weakness to the ALSFRS-R score at Screening of ≥ 0.3 points and ≤ 1 point per month calculated as: a. ALSFRS-R score at onset of first symptom of weakness (assume 48) minus ALSFRS-R score at Screening divided by number of months since onset of first symptom of weakness.
- Documented pulmonary function test (PFT) result within the last 6 months (i.e., slow vital capacity or forced vital capacity) must be ≥70% of predicted

Study Status

Currently we are enrolling in US and Canada at 17 sites. Referrals are requested.
As of 18 Oct 2024, a total of 210 subjects were enrolled and 179 participants have been randomized.

Conclusion & Future Plan

COMBAT-ALS is predicted to complete enrollment in 2025 with results from the blinded phase of the study in 2026.

U.S. patients who complete the COMBAT-ALS study OLE phase and wish to continue MN-166 treatment or patient is who do not meet inclusion criteria for COMBAT- ALS study are eligible to participate in the NINDS funded Scalable Expanded Access with Analysis of Neurofilament and Other Biomarkers for Ibudilast in ALS (SEA-NOBI-ALS) program.

This multi-sites study plans to offer 6 months of MN-166 treatment to 200 patients under an Expanded Access Protocol (EAP). The EAP will also collect blood for long read genetic sequencing, sample banking and novel biomarker discovery.

Ref: Oskarsson B, Maragakis N, Bedlack RS, Goyal N, Meyer JA, Genge A, Bodkin C, Maiser S, Staff N, Zinman L, Olney N, Turnbull J, Brooks BR, Klonowski E, Makhay M, Yasui S, Matsuda K. MN-166 (ibudilast) in amyotrophic lateral sclerosis in a Phase IIb/III study: COMBAT-ALS study design. *Neurodegener Dis Manag*. 2021 Dec;11(6):431-443. doi: 10.2217/nmt-2021-0042. Epub 2021 Nov 24. PMID: 34816762.