COMBAT-ALS – A PHASE IIB/III TRIAL OF MN-166 (IBUDILAST) IN ALS: TRIAL UPDATE

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Introduction

- MN-166 (Ibudilast), an orally available, centrally active small molecule, inhibits macrophage migration inhibitory factor, cyclic AMP phosphodiesterase (PDE) 3,4,10, and 11, and toll-like receptor 4.
- Relevant properties of MN-166 include glial attenuation, penetration of the blood-brain barrier, acceptable safety profile, and efficacy in oral administration.
- A promising neuroprotective agent for the treatment of neurodegenerative disease, including amyotrophic lateral sclerosis (ALS), has shown to slow down disease progression.

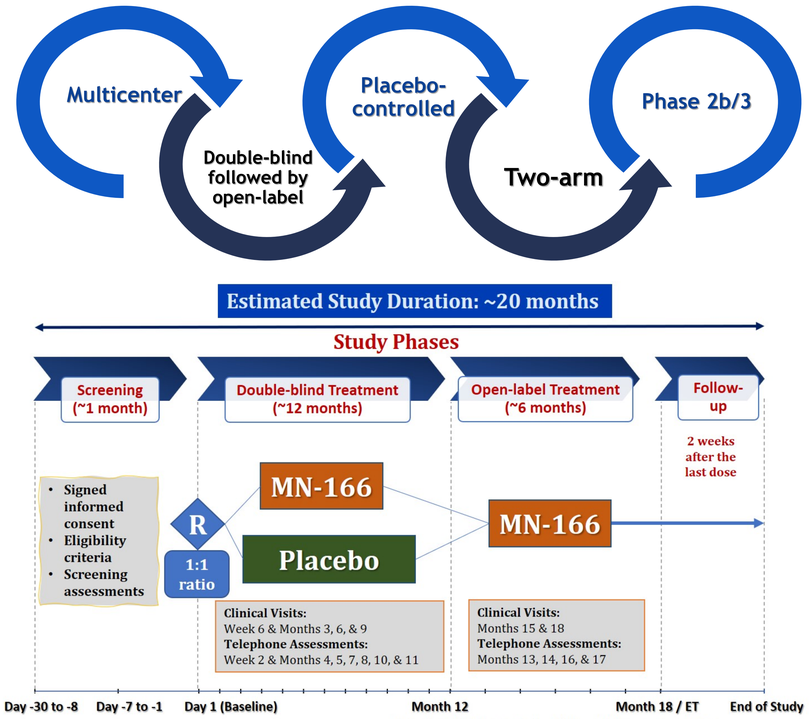
Study Rationale

- Ibudilast enhanced clearance of disease-linked TDP-43 and SOD1 protein aggregates, thus acting as an autophagy enhancer [1].
- A completed Phase 1b/2a trial suggested MN-166 slows disease progression more effectively than riluzole alone in certain subgroups of ALS participants and observed higher rates of stability or improvement in ALS functional activity in participants treated with MN-166.

Objectives

Primary	
1. Efficacy of MN-166 vs placebo on participant's functional activity measured by ALSFRS-R score and survival in people living with ALS	1. A change from baseline in ALSFRS-R score at Month 12 (or last measurement before death in case of censoring) & survival time.
Secondary	
1. Efficacy of MN-166 vs placebo on muscle strength (measured by hand-held dynamometry), quality of life (measured by ALSAQ-5), and functional activity (measured by ALSFRS-R).	1. Mean change at Month 12 from baseline in terms of muscle strength, QoL, and functional activity. 2. Responder analysis (%) defined as participants whose ALSFRS-R score was stable or improved over the 12-month Treatment Phase. 3. Time to survival as defined by death or permanent (>22/24 h) dependency on ventilator or tracheostomy.
2. Safety and tolerability of MN-166.	2. Adverse events (incl. clinical labs)
3. Characterization of the pharmacokinetics (PK) of MN-166 using population PK modeling.	3. Relationship between MN-166 plasma levels and ALSFRS-R and AEs.

Study Design



DB: Double-blind; ET: Early Termination; OLE: Open-label Extension; R: randomization.

	Treatment Group	Dosage	Duration
Double-blind Treatment Phase	MN-166	60 mg/day (30 mg BID)	Day 1 - 14
		Up to 100 mg/day (50 mg BID)	Day 15 - EOT
	Placebo (MN-166 matching)	3 capsules BID	Day 1 - 14
		5 capsules BID	Day 15 - EOT

Participants will be given the option to continue to the OLE phase for 6 months. If they do not wish to enter the OLE phase, this will be the end of the treatment, but they will be followed approximately 2 weeks later after the Month 12 visit.

OLE Treatment Phase	MN-166	60 mg/day (30 mg BID)	Day 1 - 14
		Up to 100 mg/day (50 mg BID)	Day 15 - EOS

Abbreviations: BID=twice daily; EOS=End of Study; EOT=End of Treatment; OLE=Open-label Extension.

Eligibility Criteria

Inclusion:

- ✓ Age 18 to 80 years, inclusive.
- ✓ Diagnosis of familial or sporadic ALS (the El Escorial-Revised, 2000).
- ✓ ALS onset of ≤18 months from first clinical signs of weakness before screening.
- ✓ Documented ALS history of location of disease onset (i.e., bulbar/limb onset).
- ✓ A total ALSFRS-R score of at least 35 overall at screening.
- ✓ Last documented pulmonary function test result must be ≥70% predicted.

Exclusion:

- x Psychiatric disorder or dementia that would preclude evaluation of symptoms.
- x Medical condition (other than ALS).
- x Use of tracheostomy or >22/24-hour ventilatory support.

Results

Number of Sites: ~20 sites in the USA and Canada
Planned Sample size: 230 participants
Enrolled Participants: 59 (actively recruiting)
First Participant In: 17 July 2020

Demographic and Baseline Parameters at Screening		N=59
Age (years)	Mean (range)	61.7 (30 - 79 years)
Sex, n (%)	Male	35 (59.32%)
	Female	24 (40.67%)
Race, n (%)	Caucasian/White	53 (89.83%)
	Black or African American	2 (3.39%)
	Asian	3 (5.08%)
	Other	1 (1.7%)
Ethnicity, n (%)	Not Hispanic or Latino	59 (100.0%)
Mean ALSFRS-R score	ALSFRS-R (baseline)	40.03
Site of Onset, n (%)		n=58
	Upper Limb	20 (34.5%)
	Lower Limb	17 (29.3%)
	Bulbar	16 (27.6%)
	Limb (nonspecific)	4 (6.9%)
	Other	1 (1.7%)

Abbreviations: N=total number of participants; n=number of participants meeting specified criteria.

Discussion

Of 230 participants planned to be enrolled in the study, 59 were enrolled as of now. Recruitment of participants was slow due to Covid-19 pandemic; however, the study sites are now actively recruiting.

At Screening, more than half of the participants are males and Caucasian. A greater percentage of participants had upper or lower limb onset for ALS, followed by bulbar onset.

Please also refer to the COMBAT-ALS webinar for more details on MN-166 [2], patient support system (MedACT), and social media sites supporting the trial.

Acknowledgments

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REFERENCES
1. Chen Y, Wang H, Ying Z, Gao Q. Biochem Biophys Res Communications. 2020;526(1):231-238.
2. https://medicinova.com/medicinova-webinar/