PROTOCOL NO. MN-166-ALS-1201

A SINGLE-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, SIX MONTH CLINICAL TRIAL FOLLOWED BY AN OPEN-LABEL EXTENSION TO EVALUATE THE SAFETY, TOLERABILITY AND CLINICAL ENDPOINT RESPONSIVENESS OF IBUDILAST (MN-166) IN SUBJECTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)

STEP-IBU-ALS-DB-OLE-1

IND Number:	118318
Study Phase:	1b/2a
Sponsor:	Kazuko Matsuda, MD PhD MPH Chief Medical Officer MediciNova, Inc. 4275 Executive Square La Jolla, CA 92037
Investigational Product Name:	MN-166 (ibudilast)
Indication:	Amyotrophic Lateral Sclerosis (ALS)
Principal Investigator:	Benjamin Rix Brooks, MD Director Carolinas Neuromuscular/ALS-MDA Center Carolinas HealthCare System Neurosciences Institute Adjunct Professor of Neurology University of North Carolina School of Medicine 1010 Edgehill Road North Charlotte, NC 28207

ORIGINAL VERSION OF PROTOCOL	14 JULY 2014
AMENDMENT 1	20 FEBRUARY 2015
AMENDMENT 2	27 FEBRUARY 2015
AMENDMENT 3	08 JULY 2015
AMENDMENT 4	31 MAY 2016

INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: MN-166-ALS-1201

I have read the foregoing protocol and agree to conduct the study as described herein.

By signing the protocol, the Investigator agrees to keep all information provided by MediciNova, Inc. in strict confidence and to request the same from his/her staff and the Institutional Review Board. Study documents provided by MediciNova, Inc. will be stored appropriately to ensure their confidentiality. The Investigator should not disclose such information to others without authorization, except to the extent necessary to conduct the study.

Signature: _____ Date: 31 MAY 2016

Investigator Name (Print): Benjamin Rix Brooks MD

PROTOCOL SIGNATURE PAGE

Protocol Number: MN-166-ALS-1201

Carolina Neuromuscular/ALS-MDA Center Carolinas Healthcare System Neuroscience Institute:

Signature: _____ Date: 31 MAY 2016

Investigator Name (Print): BENJAMIN RIX BROOKS MD

MediciNova:

Signature: _____ Date: 31 May 2016

Name: Kazuko Matsuda, MD PhD MPH

1. SYNOPSIS

Name of Sponsor: MediciNova, Inc.

Name of Investigational Product: MN-166 (ibudilast)

Protocol No: MN-166-ALS-1201

Title of Study: A Single-Center, Randomized, Double-Blind, Placebo-Controlled, Six Month Clinical Trial Followed by an Open-Label Extension to Evaluate the **S**afety, **T**olerability and Clinical **E**nd**P**oint Responsiveness of Ibudilast (MN-166) in Subjects with Amyotrophic Lateral Sclerosis (ALS)
STEP-IBU-ALS-DB-OLE 1

Principal Investigator: Benjamin Rix Brooks, MD

Study Center: Carolina Neuromuscular/ALS-MDA Center, Carolinas Healthcare System Neurosciences Institute

Duration of Study Treatment: MN-166 group: 6 months; Placebo group: 12 months (6 months placebo followed by 6 months MN-166)	**Phase of Development:** 1b/2a

Study Objectives

Primary Objective

The primary objective is to evaluate the safety and tolerability of MN-166 60 mg/d versus placebo when administered for 6 months with riluzole in subjects with amyotrophic lateral sclerosis.

Secondary Objectives

The secondary objective is to evaluate the clinical endpoint responsiveness of MN-166 60 mg/d versus placebo when administered with riluzole in subjects with amyotrophic lateral sclerosis as measured by the following assessments:

- Functional activity as assessed by the Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRS-R)
- Respiratory function as measured by slow vital capacity (SVC), Maximum Inspiratory Pressure (MIP) also known as Negative Inspiratory Force (NIF), Forced Expiratory Volume in 1 second (FEV_1) measured under SVC protocol and Maximal Voluntary Ventilation (MVV)
- Muscle strength measured by manual muscle testing (MMT) and instrumented hand grip dynamometry
- Non-invasive ventilation (NIV) utilization measured by clinically indicated prescription for NIV intervention and time to clinically indicated prescription for NIV intervention in each group (for early ALS subjects only)

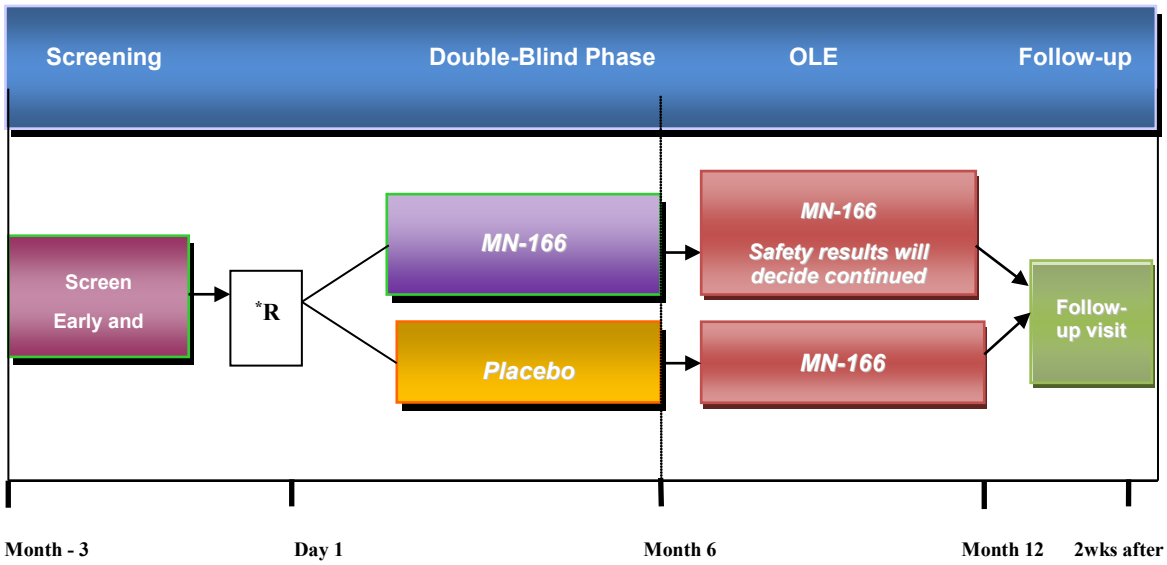
Tertiary Objectives

- To evaluate quality of life as assessed by the Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-5)
- To evaluate Clinical Global Impression of Change (CGIC) as assessed by ALS subjects, caregivers and physician anchored to most recent standard of care visit prior to screening visit
- To evaluate serum creatinine as a biomarker for disease progression
- To evaluate the pharmacokinetics of MN-166 when administered as an adjunct to riluzole

STUDY DESIGN

This is a single center, randomized, double-blind, placebo-controlled, 6-month study designed to evaluate the safety, tolerability and clinical endpoint responsiveness of MN-166 (60 mg/d) when administered as an adjunct to riluzole (50 mg bid) in subjects with ALS. This study will consist of two treatment arms, MN-166 and matching placebo. Randomization will occur in a 2:1 ratio (MN- 166: placebo). To be eligible, subjects must have a diagnosis of sporadic or familial ALS with onset of ≤5 years ("early ALS") from first clinical weakness prior to screening or with onset of ≤10 years ("advanced ALS") from first clinical weakness prior to screening for ALS patients on non-invasive ventilator support. All subjects must be on a stable dose of riluzole for at least 1 month prior to study drug treatment. All subjects will receive optimized standard of care at an ALS Multidisciplinary Clinic affiliated with an academic medical center in addition to study medication. A total of approximately 120 male and female subjects from 18 to 80 years old, inclusive will be enrolled. Eligible subjects will be stratified by ALS stage. Sixty subjects will be enrolled into the "early ALS" group and 60 subjects will be enrolled into the "advanced ALS" group. Subjects will be randomized in a 2:1 ratio for active drug and placebo (80 subjects in the MN-166 group; 40 subjects in the placebo group). Upon completion of the Double-blind Phase, subjects randomized to the placebo arm will continue for an additional 6 months and will receive open-label MN-166. The safety and tolerability of MN-166 will be evaluated by an unblinded Independent Safety Monitor during an interim safety monitoring assessment after approximately 20-30 subjects have been followed for approximately 3 months. The safety data will also be reviewed at Month 6 and if there are no safety or tolerability concerns in the MN-166 treated group, a decision will be made to extend participation to the MN-166 treated group into the Open-label Extension (OLE) Phase. Otherwise, only the placebo-treated patients will participate in the OLE Phase. Subjects will be informed of the treatment that they have received during the double-blind phase after the last subject has completed the open-label extension or at a time defined by the principal investigator in consultation with MediciNova.

Study Design



*R = randomize

MN-166= ibudilast

The study will consist of a Screening Phase (up to 3 months prior to baseline) followed by a double-blind Treatment Phase (6 months) and an Open-label Extension (OLE) Phase for the Placebo treatment arm (6 months). A follow-up visit will take place within 2 weeks after the last dose of study drug.

Screening Phase (up to 3 months prior to Day 1)

During the Screening Phase, ALS patients who are potential subjects will be advised concerning the clinical trial through open announcement and, if interested, will be approached for study participation and provided an informed consent form. On Day -7, subjects will return to the clinic, and if there are no additional questions, subjects will sign the informed consent form. The following screening assessments will be performed: review of inclusion/exclusion criteria: medical history including review of prior and current medications, physical and neurological examination, height, body weight, and vital signs [temperature, pulse rate, respiratory rate, blood pressure, oxygen saturation (room air)] and an electrocardiogram [ECG]. Clinical laboratory testing consisting of [1] comprehensive metabolic panel (CMP) including GGT, [2] CK, [3] complete blood count, [4] urinalysis (without microscopic analysis) and [5] serum pregnancy test will be collected. An EMG report to support diagnosis together with World Federation of Neurology El Escorial Diagnostic Criteria (Airlie House version) Level of Diagnosis [Clinically Definite, Clinically Probable, Probable -Laboratory-Supported] will be documented and an ALSFRS-Revised questionnaire, ALSAQ-5 questionnaire and CGIC questionnaire will be administered.

During the Screening Phase, subjects who are not currently taking riluzole will be started on riluzole 50 mg qd for the first 7 days and then 50 mg bid for the next 3 weeks prior to entry into the clinical trial.

Double-Blind Treatment Phase (6 months)

On Day 1, subjects will return to the clinic, eligibility criteria confirmed, and will be randomized to MN-166 versus matching-placebo in a 2:1 ratio, respectively. Subjects randomized to MN-166 will

begin on MN-166 30 mg/d for 14 days followed by MN-166 60 mg/d for the remainder of the Double-blind Phase. Subjects who cannot tolerate 60 mg/d will have their dose decreased to 30 mg/d. After 7 days, if no tolerability issues arise, the dose can be increased to 60 mg/d. If the 60 mg/d dose is still not tolerable, subjects may remain on 30 mg/d for the remainder of the study. If necessary, an alternative dosing regimen may be implemented (e.g., 10 mg tid for the 30 mg/d dose and 20 mg tid for the 60 mg dose. Subjects who cannot tolerate 30 mg will be discontinued from the study. For each subject who discontinues from the study due to not tolerating the 30mg daily dose, there will be a replacement subject entered.

Subjects who are currently taking riluzole will continue on the same dose (100 mg/d) during the study. Subjects who are not currently taking riluzole will be started on riluzole 50 mg qd for the first 7 days and then 50 mg bid for the next 3 weeks prior to entry into the study. Subjects will remain on riluzole throughout the study.

During the double-blind Treatment Phase, subjects will return to the clinic at Months 3 and 6 and will be telephoned by a study staff member at Months 1, 2, 4, and 5 to collect information about adverse events and concomitant medications.

At the end of the Double-blind Phase, subjects randomized to the MN-166 group will complete the study and return for the Follow-up visit if continued participation is not extended. Subjects randomized to the placebo group will continue to the Open-label extension (OLE) Phase.

Open-Label Extension (OLE) Phase for Placebo-Treated Group (6 months)

Upon completion of the Double-blind Treatment Phase, subjects who were taking placebo, will participate in the open-label extension (OLE) phase for 6 months. Subjects who were randomized to the placebo group will be administered MN-166 30 mg/d for the first 14 days and then 60 mg/d for the remainder of the OLE Phase. Subjects who cannot tolerate 60 mg/d will have their dose decreased to 30 mg/d. After 7 days, if no tolerability issues arise, the dose can be increased to 60 mg/d. Subjects who are not able to tolerate MN-166 30 mg/d as judged by the Investigator will be discontinued from the OLE and will not be replaced. Subjects who are currently taking riluzole will continue on the same dose (100 mg/d) during the study.

Follow-up Phase

All subjects (subjects who complete the Double-blind Phase and subjects who complete the Open-label Phase) or prematurely discontinue will return for a follow-up visit approximately 2 weeks after the last dose of study drug to assess adverse event status and to document concomitant medications.

Number of Subjects (Planned):

The number of subjects planned for the Double-Blind Phase is approximately 120 (60 subjects with early ALS, 60 subjects with advanced ALS, 80 subjects will be randomized to the MN-166 group; 40 subjects will be randomized to the placebo group).

The number of subjects planned for the Open-label Extension is approximately 40 placebo subjects from the Double-blind Phase). If no safety or tolerability issues are identified during the Double-blind Phase in the MN-166 treated group**,** based on the safety review of approximately 30 patients at the 3-month time point, this group of approximately 80 subjects will be extended continued participation into the Open-label Extension Phase.

Study Entry Criteria:

Inclusion Criteria:

- Written informed consent is obtained and willing and able to comply with the protocol in the opinion of the Investigator;
- 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];
- Diagnosis of ALS with onset of less than or equal to 5 years from first clinical weakness
- Slow vital capacity ≥ 60% of predicted (Knudsen 1983) within 1 month prior to Treatment Day 1;
- Currently on a stable dose of riluzole for at least 30 days prior to initiation of study drug. Subjects not currently taking riluzole will be started on 50 mg qd for the first 7 days followed by 50 mg bid for the following 21 days prior to screening. Patients may be screened during this time period but not started on study drug until they are on a stable dose of riluzole;
- All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (i.e., bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing). Females of childbearing potential must use an effective method of contraception (e.g., total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation;
- Females must not be lactating or pregnant at Screening or Baseline (as documented by a negative beta-human chorionic gonadotropin [ß-hCG] (or human chorionic gonadotropin [hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug;
- Males should practice contraception as follows: condom use and contraception by female partner;
- Able to swallow study medication capsules;
- Subject is willing and able to comply with the protocol assessments and visits, in the opinion of the study nurse/coordinator and the Investigator;
- Has no known allergies to the study drug or its excipients;
- Has received 23-valent pneumococcal vaccine within 4 years prior to starting clinical trial.

Exclusion Criteria:

- Use of tracheostomy, tracheostomy invasive mechanical ventilation [TIMV], or non-invasive pressure - [P-NIV] or volume – [V-NIV] cycled ventilation within the last 3 months prior to screening;
- Greater than 3% predicted loss in post-diagnosis vital capacity per month or a greater than 1-unit loss in post diagnosis ALSFRS-R total score per month [exclusive of loss due to

beginning use of assistive devices];

- Confirmed hepatic insufficiency or abnormal liver function (AST and/or ALT greater than 3 times the upper limit of the normal range);
- Renal insufficiency as defined by a serum creatinine greater than 1.5 times the ULN;
- Currently has a clinically significant psychiatric disorder or dementia which would preclude evaluation of symptoms;
- Has a clinically significant medical condition (other than ALS) including the following: neurological, metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, urological disorder, or central nervous system infection that would pose a risk to the subject if they were to participate in the study or that might confound the results of the study;
- History of malignancy < 5 years prior to signing the informed consent, except for adequately treated basal cell or squamous cell skin cancer or *in situ* cervical cancer;
- ECG finding of QTcB prolongation > 450 ms for males and > 470 ms for females at screening;
- History of HIV (human immunodeficiency virus), clinically significant chronic hepatitis, or other active infection;
- Subject has a history of stomach or intestinal surgery or any other condition that could interfere with or is judged by the Investigator to interfere with absorption, distribution, metabolism, or excretion of study drug;
- Subject has a history of alcohol or substance abuse (DSM-IV-TR criteria) within 3 months prior to screening or alcohol or substance dependence (DSM-IV-TR criteria) within 12 months prior to screening;
- Subject has poor peripheral venous access that will limit the ability to draw blood as judged by the Investigator;
- Currently participating, or has participated in, a study with an investigational or marketed compound or device within 3 months prior to signing the informed consent;
- Unable to cooperate with any study procedures, unlikely to adhere to the study procedures and keep appointments, in the opinion of the Investigator.

Advanced ALS group will follow the same inclusion/exclusion as the early ALS subjects with the exception of the following:

Inclusion criteria:

- Diagnosis of ALS with onset of ≤10 years from first clinical weakness;
- On Non-invasive ventilator with Non-invasive pressure [P-NIV] or volume [V-NIV] cycled ventilation stable use for ≥ 4 hours daily for 1 month prior to Treatment Day 1;
- Slow vital capacity ≥ 20% of predicted (Knudsen 1983) within 1 month prior to Treatment Day 1;
- Able to swallow study medication capsules or have gastrostomy tube access for delivery of contents of medication capsule.

Exclusion criteria:

- Use of tracheostomy, tracheostomy invasive mechanical ventilation [TIMV];
- No rate of progression exclusion.

Investigational Product, Dosage and Mode of Administration: MN-166 10 mg capsules administered orally. Daily dose will be administered as either MN-166 30 mg (3 x 10 mg) qd in AM during the titration period or bid in AM and PM. Study drug dosing may be varied based on individual tolerability (e.g., 10 mg tid instead of 30 mg qd or 20 mg tid instead of 30 mg bid).

Duration of Treatment: Screening Phase: up to 3 months; Double-blind Phase: 6 months; Open-label Phase 6 months (for placebo subjects only); Follow-up Phase: 2 weeks after last dose.

Reference Therapy, Dosage, and Mode of Administration: Matching placebo

Criteria for Evaluation

Safety Assessments

Safety will be assessed by monitoring and recording all treatment-emergent adverse events (TEAEs) including serious adverse events (SAEs) and discontinuations due to TEAEs. and Additional assessments will include regular monitoring of hematology, blood chemistry, and urine values, regular measurement of vital signs, ECGs, medical history, physical and neurological examinations.

Clinical Endpoint Responsiveness Assessments

Clinical Endpoint Responsiveness will be assessed by change in 1) ALSFRS-R, 2) muscle strength by manual muscle testing, 3) instrumented hand grip, 4) slow vital capacity (SVC), 5) maximum inspiratory pressure (MIP)/negative inspiratory force (NIF), 6)Forced Expiratory Volume in One Second (FEV_1) measured under SVC protocol 7) maximal voluntary ventilation (MVV) and 8) non-invasive ventilation (NIV) utilization (for early ALS subjects only).

The ALSFRS-R is a well-established scale to measure the functional status of patients with ALS. It is based on 12 items, each of which is rated on a 0–4 point scale. The rate of total functional disability thus ranges from 0 (maximum disability) to 48 (normal) points. The components of the scale group into four factors that encompass gross motor tasks, fine motor tasks, bulbar functions and respiratory function (Cedarbaum et al 1997, Gordon et al 2007, Kaufmann et al 2007).

The manual muscle test (MMT) is a scored neurologic examination derived from the Medical Research Council scale (Great Lakes ALS Study Group 2003, Miller 1999, Gordon 2013). The scale is numerical, with scores between 0 and 5 per muscle, based on the examination of 42 muscles. The final MMT score per subject is the mean of the scores of all 42 muscles at screening/baseline, Month 3 and Month 6.

Instrumented hand grip will be measured with a dynamometer (Brinkmann et al 1997, Sanjak et al 2001). The best of two hand grips will be represented as Kg hand grip strength per hand and percent predicted at screening/baseline and Months 3 and 6.

Slow vital capacity (SVC) is an index of respiratory function measured by a spirometry test to indicate potential respiratory compromise in ALS patients (Chhabra 1998, Sanjak 2010). The subject will be asked to inspire fully and then slowly expire all the air in their lungs. SVC will be assessed at screening/baseline, Months 3 and Month 6.

Maximum Inspiratory Pressure (MIP) or Negative Inspiratory Force (NIF) is a measure of diaphragm strength (Mendoza 2007, Roth 2010). MIP/NIF will be assessed at screening/baseline, Month 3 and Month 6.

Forced Expiration Volume in 1 second [FEV_1] is usually measured under conditions of slow vital capacity (Camargo 2008, Cooper 1993). FEV_1 will be captured under the protocol of slow vital

capacity at screening/baseline, Month 3 and Month 6.

Maximal Voluntary Ventilation (MVV) is a measure of respiratory stamina that will be assessed at screening/baseline, Month 3 and Month 6 (Berto 2007)

Non-invasive Ventilation Utilization will be measured by occurrence of prescription for NIV and time to occurrence of prescription for NIV (for early ALS patients only).

ALSAQ-5 (Amyotrophic Lateral Sclerosis Assessment Questionnaire-5) (Golab-Janowska 2010; Jenkinson 2003, 2007)

CGIC (Clinical Global Impression of Change) (Brooks 1996; Guy 1976)

| – 3 much worse | – 2 moderately worse | – 1 minimally worse | 0 no change
| +1 minimally better | +2 moderately better | +3 much better

Pharmacokinetics: Plasma samples for analysis of MN-166 will be collected at specified timepoints throughout the study.

Analysis Sets

Safety Analysis Set: The group of randomized subjects who received at least 1 dose of study drug and had at least one postdose safety assessment.

Full Analysis Set (FAS): The group of randomized subjects who received at least 14 days of study drug and had at least one post-dose efficacy measurement.

Statistical Methods

Safety will be assessed based on the frequency of treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, and ECG results. Evaluation of safety will be performed on the Safety Analysis Set. Assessments that will be evaluated include TEAEs, clinical laboratory results, vital signs, and 12-lead ECGs. Treatment-emergent AEs will be summarized by presenting the incidence of TEAEs and the overall incidence. The incidence of out-of-normal-range laboratory safety tests variables will be summarized along with change from baseline in laboratory safety test variables and vital sign measurements. Descriptive summary statistics of the laboratory, vital signs, and ECG parameters will also be evaluated.

The secondary endpoints focused on clinical responsiveness endpoints are:

- Change from baseline in functional status (ALSFRS-R);
- Change from baseline in muscle strength as measured by a manual muscle test;
- Change from baseline in instrumented hand grip strength;
- Change from baseline in respiratory function as measured by Slow Vital Capacity (SVC);
- Change from baseline in respiratory function as measured by Maximum Inspiratory Pressure / Negative Inspiratory Force (MIP/NIF);
- Change from baseline in respiratory function as measured by Forced Expiration Volume in 1 second [FEV_1] under conditions of slow vital capacity;
- Change from baseline in respiratory function as measured by Maximal Voluntary Ventilation [MVV];
- Change from baseline in Amyotrophic Lateral Sclerosis Assessment Questionnaire-5 (ALSAQ-5);
- Change from baseline in Clinical Global Impression of Change (CGIC).

All clinical responsiveness endpoints will be analyzed using analysis of covariance (ANCOVA) models with treatment group as a factor and the baseline value of the corresponding endpoint as a covariate. All efficacy analyses will be carried out using two-sided tests at the alpha=0.05 level of significance.

Pharmacokinetics

PK parameters for MN-166 concentrations and its metabolite will be calculated.

Sample Size Justification

No prior data are available on which to base assumptions for sample size/power considerations. The results of this pilot study will be used to design future studies, and the sample size of approximately 120 subjects is deemed to be appropriate for this purpose.

Safety Monitoring

Safety monitoring will be performed after approximately 20-30 subjects have been followed for 3 months and a safety analysis of the MN-166 treated subjects will be done at 6 months of treatment by an unblinded Independent Safety Monitor to assess whether these subjects will continue treatment in the OLE.

Table 1: Schedule of Assessments

Phase	Screening		Double-Blind Treatment					Open-Label Extension for Placebo Group only				Follow-up	ET[e]
	Day -90 to Day -8	Day -7	Day 1 Baseline	Month 1/ Month 2 (±7days)	Month 3 (±7days)	Month 4/ Month 5 (±7days)	Month 6[d] (±7days)	Month 7/ Month 8 (±7days)	Month 9 (±7days)	Month 10/ Month 11 (±7days)	Month 12 (±7days)	End of Study	
Visit Type				TEL	Clinic	TEL	Clinic	TEL	Clinic	TEL	Clinic		
Study Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Informed consent	X[a]	X[b]											
Inclusion/exclusion criteria review		X	X										
Medical history		X											
Medication history		X											
Physical/Neurological Examination		X			X		X		X		X	X	X
Body height		X											
Body weight		X			X		X		X		X		
Vital signs (sitting)		X	X		X		X		X			X	X
12-lead ECG		X	X*		X		X*		X		X		
Comprehensive Metabolic Panel including GGT		X			X		X		X		X		
Serum creatine kinase		X			X		X		X		X		
Serum pregnancy test		X											
Urine pregnancy test					X		X		X		X		
SVC/MIP/FEV_1/MVV		X			X		X		X		X		X[f]
Muscle strength		X			X		X		X		X		X[f]
ALSFRS-R		X			X		X		X		X		X[f]
ALSAQ-5		X					X				X		X[f]
CGIC		X			X		X		X		X		X[f]
Plasma PK MN-166					X		X		X		X		X
Randomization			X										
Adverse event review			X	X	X	X	X	X	X	X	X	X	X
Concomitant med review			X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensing			X		X		X[c]		X				
Dispense/Review Patient Diary/Collect			X		X		X		X		X	X	X
Study Drug Accountability					X		X		X		X	X	X

a. A copy of the informed consent form (ICF) will be given to the patient for review.
b. Signing of the ICF will occur on Day -7.
c. End of Double-blind Phase and start of open-label study for Placebo-treated subjects only.
d. Month 6 safety analysis will determine whether subjects who received MN-166 in the Double-blind Phase will continue to receive 6 additional months of treatment in the OLE Phase.
e. ET early termination: Assessments to be done for Double-blind and OLE early termination. Other assessments/procedures to be done at PI discretion, if necessary.
f. Assessments do not need to be performed if prior assessments were within one month of this early termination visit.
g. TEL: Telephone follow up by study staff via telephone, Email or TEXT message
* 12-lead ECG 3-4 hour after first dose of study drug for only subjects on Nuedexta

2. TABLE OF CONTENTS

List of Figures and Tables

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2 Abbreviations and Terms

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALS	amyotrophic lateral sclerosis
ALSAQ-5	Amyotrophic Lateral Sclerosis Assessment Questionnaire-5
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale-revised
ALT (SGPT)	alanine aminotransferase
ANCOVA	analysis of covariance
AST (SGOT)	aspartate aminotransferase
AV	atrioventricular
AUC	Area under the curve
β-hCG	beta-subunit of human chorionic gonadotropin
bid	twice daily
BP	blood pressure
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of Change
CIRB	Central Institutional Review Board
CK	creatine kinase
C_{max}	maximum plasma concentration
CMP	comprehensive metabolic panel
CNS	central nervous system
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
CYP	cytochrome
DDI	drug-drug interaction

Abbreviation	Term
DHD	dihydrodiol
dL	deciliter
DM	diabetes mellitus
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition-Text Revision
ECG	electrocardiogram
EMG	electromyography
ET	Early Termination
EW	early withdrawal
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HV	healthy volunteer
IBU	ibudilast
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ISF	Investigator Site File
ISM	Independent Safety Monitor
L	liter
MMT	Manual Muscle Test
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MIF	macrophage migration inhibitory factor

Abbreviation	Term
MIP	maximum inspiratory pressure
MVV	Maximal Voluntary Ventilation
NIF	negative inspiratory force
NIV	non-invasive ventilation
NSAID	Non-steroidal anti-inflammatory drug
OLE	Open-label extension
PET	positron emission tomography
PDE	phosphodiesterase
PI	Principal Investigator
PK	pharmacokinetics
PO	per oral
qd	once-daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
SA	sinoatrial
SAE	serious adverse event
SAP	statistical analysis plan
SI	sub investigator
SVC	slow vital capacity
SOD	superoxide dismutase
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
tid	three times daily
TMF	trial master file
TRAE	treatment-related adverse event
ULN	upper limit of normal
WBC	white blood cells
WHO-DD	World Health Organization Drug Dictionary

4. BACKGROUND AND RATIONALE

4.1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive, degenerative neurological disorder. In its classic form, ALS affects motor neurons at two or more levels of the motor neuron network supplying multiple regions of the body. It affects lower motor neurons (LMN) that reside in the anterior horn of the spinal cord and in the brain stem, corticospinal upper motor neurons (UMN) that reside in the precentral gyrus, and, frequently, prefrontal motor neurons that are involved in planning or orchestrating the work of the upper and lower motor neurons. The most common symptoms of ALS are muscle weakness, atrophy, loss of motor control, weakness, fatigue, and dysarthria. As the disease progresses, symptoms may include shortness of breath, difficulty breathing, dysphagia, and paralysis. Approximately 5600 people in the United States are diagnosed with ALS each year. The annual incidence is 2-3 per 100,000 population. It is estimated that as many as 18,000 Americans may have ALS at any given time. ALS is a fatal disease. Median survival is 3 years from clinical onset of weakness. However, longer survival is not rare. About 15% of patients with ALS live 5 years after diagnosis, and about 5% survive for more than 10 years (Carmel 2014).

Rationale for the use of MN-166 for the treatment of ALS is based on animal model studies and ALS patient studies which indicate that activated glia plays a major role in the progression of this disease. Exact pathophysiology of motor neuron degeneration in ALS is unknown, however, there is growing evidence that glial activation and inflammatory processes may play a key role in the pathogenesis of ALS. Microglia, macroglia and neuroinflammation are implicated in many CNS disorders. Evidence implicating activation of microglia in motor neuron disease was seen in studies on mutant SOD1 (mSOD1) transgenic mice, the predominant animal model of ALS. These studies showed that microglial activation occurred in the earliest stages of motor neuron degeneration, even before symptoms of weakness (Alexianu et al 2001; Hall et al 1998). In human studies, strong microglia activation and proliferation have been described in the primary motor cortex, brainstem motor nuclei and ventral horns of the spinal cord: all areas with motor neuron loss. (Ince et al 1996; Kawamata et al 1992) Furthermore, a positron emission tomographic (PET) scan study showed that microglial activation strongly correlated with clinical signs of upper motor neuron loss in sporadic ALS (Turner et al 2004) and a recent PET scan study in ALS patients showed microglial activation found in primary motor, supplementary motor and temporal cortex (Corcia et al 2012).

MN-166 (ibudilast) is a small molecule macrophage migration inhibitory factor (MIF)- and phosphodiesterase (PDE)-4,10-inhibitor drug candidate with demonstrated neuroprotective action in vitro and in vivo. MIF knockout or antibody-neutralization studies have provided neuroprotection validation in certain MS and other neurological animal models. Ibudilast has additionally shown attenuation of glial cell activation in multiple in vitro and in vivo model systems which may represent a novel pharmacotherapeutic approach in ALS treatment.

Ibudilast is an anti-inflammatory/neuroprotective agent that has been in use for over 20 years in Japan and other Asian countries for the treatment of asthma and cerebrovascular disorders (post-stroke dizziness). Ibudilast is marketed as Ketas® in delayed-release capsule (innovator, Kyorin Pharmaceuticals) or Pinatos® (generic by Teva/Taisho Pharmaceuticals). While ibudilast has not yet been approved for any conditions outside of Asia, clinical development for neurological conditions, including multiple sclerosis, neuropathic pain, and certain drug addictions, has been undertaken by Avigen, Inc. (as AV411) and MediciNova, Inc. (as MN-166). (Ledeboer et al 2007a, 2007b; Rolan et al 2009; Barkhof et al 2010). These entities merged at the end of 2009 such that all ibudilast assets could be integrated with continued development as MN-166 with MediciNova, Inc. (La Jolla, CA).

Ibudilast distributes well to the CNS and it is a selective inhibitor of certain cyclic nucleotide phosphodiesterases (Gibson et al 2006) and the pro-inflammatory cytokine, macrophage migration inhibitory factor (MIF) (Cho et al 2010). At clinically-relevant plasma or CNS concentrations, ibudilast selectively inhibits macrophage migration inhibitory factor (MIF) and, secondarily, PDEs 3, 4 and 10. MIF inhibition or knockout has been linked to attenuated disease progression in animal models of multiple sclerosis (Powell et al 2005; Kithcart et al 2010) and attenuates neuronal death and promotes recovery in mouse spinal cord injury (Nishio et al 2009). Another MIF knockout study revealed its role in neurodegeneration in an experimental stroke model (Inacio et al 2011). PDE inhibition has likewise shown some neuroprotective actions (Chen et al 2007; Nakamizo et al 2003).

Ibudilast has been recognized to have glial attenuating activity in vitro and in vivo. In activated glia cells in vitro, ibudilast suppresses the production of proinflammatory cytokines and increases the production of anti-inflammatory cytokine and various neurotrophic factors. (Suzumura et al 1999; Kawanokuchi et al 2004; Mizuno et al 2004). Ibudilast also protects hippocampal neurons (Tominaga et al 1996) and oligodendrocytes against excitotoxicity (Yoshioka et al 1998, 2000) and astrocytes against apoptosis (Takuma et al 2001). In an animal model of cerebral ischemia, ibudilast reduces white matter lesions and microglial activation (Wakita et al 2003). MediciNova scientists, in collaboration with Dr. Linda Watkins and researchers at the University of Colorado, have determined that MN-166 reduces glial activation and attenuates allodynia in several validated animal models of peripheral and central neuropathic pain (Ledeboer et al 2007a; Ellis et al 2010).

In addition, Ibudilast suppresses the expression of matrix metalloproteinase-9 (MMP-9) (Lee et al 2012; Yagi et al 2010): MMP-9 potentially plays an important role in the pathogenesis of ALS and when knocked down in animal models, leads to slower progression of the disease (Kaplan, et al 2014).

4.2. Rationale to include advanced ALS patients

We are amending the current MN-166-ALS-1201 protocol to include ALS patients with advanced disease as being defined by requiring non-invasive ventilation due to respiratory motor neuron involvement.

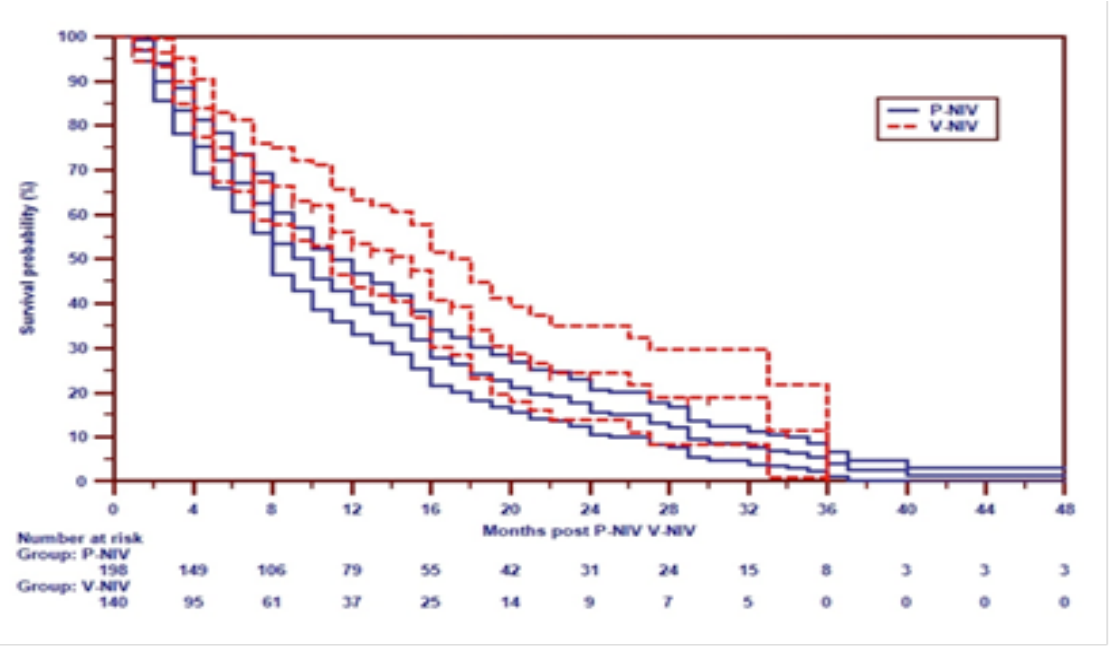
This decision is based on our initial safety report (Brooks et al 2015) that indicated safety for three months of ibudilast in a cohort of ALS patients in the United States and the finding coincident with the report, that there was a decreased mean rate of vital capacity decrease over 3 months in all patients in this clinical trial compared with previously published studies and our own internal observation. We will evaluate whether MN-166 (ibudilast) may be beneficial for patients in the advanced stages of ALS defined by having respiratory involvement requiring non-invasive ventilation.

Recent animal studies have shown that hypoxia-induced spinal inflammation inhibits respiratory motor neuron plasticity via p38 MAPK activation suggesting that at this advanced stage of ALS there may be a benefit of ibudilast for the reasons outlined above (Huxtable et al 2015; Huxtable et al 2013; Vinit et al 2011; Zhan et al 2015).

Clinical observational studies conducted at the Carolinas Neuromuscular /ALS-MDA Center have indicated that 198 patients have received pressure [P-NIV] – and 142 patients received volume-cycled [V-NIV] –non-invasive ventilation.

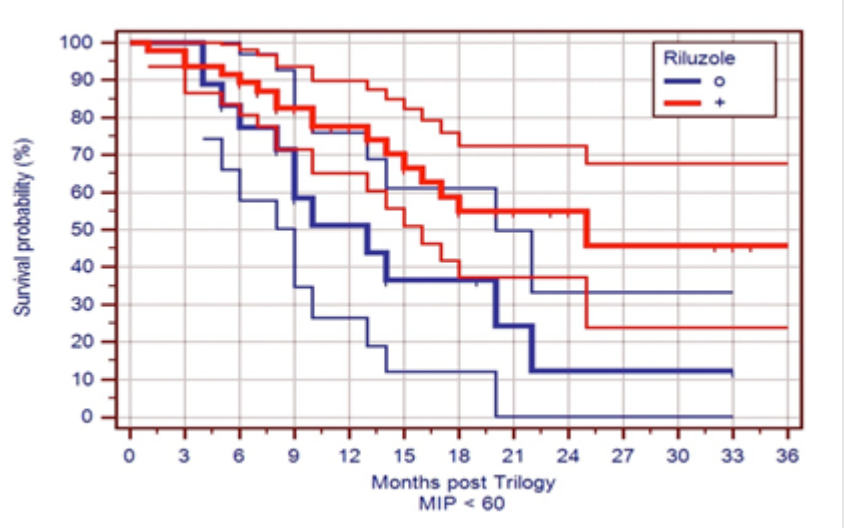
Survival was significantly [p = 0.0261] improved with a decreased hazard ratio = 0.748 (95%CI = 0.580 - 0.965) in patients with V-NIV [50% survival = 15 months (95%CI = 11-18)] compared with P-NIV [50% survival = 9 months (95%CI = 8-11)].

Figure 1 Survival in V-NIV vs. P-NIV



Another observational study at the Carolinas Neuromuscular /ALS-MDA Center has shown that ALS patients with V-NIV and maximal inspiratory pressure < 60 cm H20 have a better survival if they are on riluzole. Survival post V-NIV Trilogy is significantly enhanced in ALS patients taking Riluzole when MIP is < 60 cm H2O.

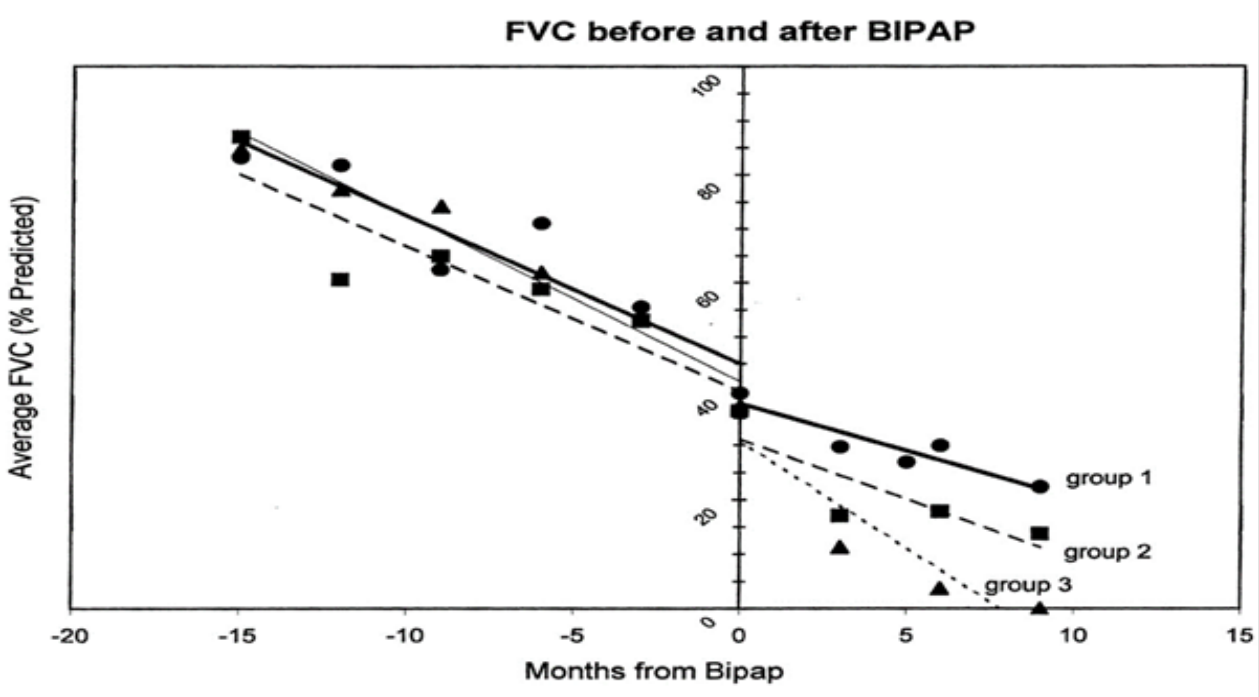
Figure 2 Survival post V-NIV Trilogy



Mean survival on Riluzole is 22.3 months (95% CI = 18.5 - 26.1 months) compared with 14.7 months (95%CI = 9.8 - 19.6 months) [P = 0.019]

Vital capacity declines prior to introduction to pressure [P-NIV] – and volume-cycled [V-NIV] – cycled non-invasive ventilation. Following introduction of P-NIV in the form of BiPAP the rate of vital capacity loss is reduced almost in half depending on the degree of compliance with use of assisted ventilation.

Figure 3 FVC Before and After BIPAP [From Kleopa et al, 1999]



In the medical literature we have collated studies that confirm the rate of loss of vital capacity in patients before the initiation of NIV and when on NIV. In the Kleopa clinical study (Kleopa et al 1999) patients who use BiPAP for greater than four hours daily demonstrate a small decline in rate of vital capacity loss [group 1] [- 3.5 + 5.3 (standard deviation)] which is significantly less than in those patients who do not use the BiPAP at all [group 3] [- 8.3 + 5.0]. Patients who use the BiPAP for less than four hours daily are intermediate [- 5.9 + 4.8]. In this clinical study the results are significant only between the patients who use the BiPAP for more than four hours daily and those who do not use the BiPAP at all.

More recent studies show smaller rates of vital capacity decline [VC % Predicted / month] than in the past for those patients monitored prior to use of non-invasive ventilation in the amalgamated Pro-Act Database consisting of a set of patients who participated in ALS clinical trials (Atassi et al 2014), in clinic-based populations (Baumann et al 2010; Vender et al 2007), small clinical trial populations (Tandan et al 1996; de Carvalho et al 2015).

The comparability of the rates of decline in vital capacity early in the course of ALS across centers and across different population groups [clinic-based participants, clinical trial eligible participants] provides support for this as an outcome measure in clinical trials and other observational studies.

At the Carolinas Neuromuscular / ALS-MDA Center, we see a comparable vital capacity decline [VC % Predicted / month] in our patients early [- 2.8 + 13.2] prior to the need for non-invasive ventilation defined on the basis of vital capacity, maximum inspiratory pressure or other indicators. We also confirm a decline in rate of loss of vital capacity when are patients are first put on NIV [- 1.2 + 20.5]. In addition, for the subgroup of patients who are participating in MN-166-ALS-1201, we see a comparable decrease to that achieved with non-invasive ventilation [- 1.3 + 7.7].

We plan to evaluate the feasibility, tolerability, safety and clinical endpoint responsiveness of ibudilast treatment in ALS patients requiring non-invasive ventilation in this protocol. For clinical endpoint responsiveness analysis, in addition to the rate of vital capacity as well as MIP decline, we will monitor use of NIV daily, Trilogy pressures will be required daily and the rate of increase in use of NIV and transition to other treatments such as mouthpiece ventilation during the day and tracheostomy invasive mechanical ventilation will be documented.

4.3. Prior Clinical Experience

4.3.1. Clinical Study Overview

To date, 8 clinical studies have been completed in Central Eastern Europe (CEE), Australia and US and 4 clinical trials are ongoing in the US. A total of 461 subjects have been known to be exposed to ibudilast (MN-166/AV411) in clinical trials. A summary of completed and ongoing MediciNova (and Avigen) and collaborative Investigator-initiated trials is as follows:

Table 3 Summary Table of Completed and Ongoing Clinical Trials

Type of Study	Study Protocol Number	Study Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
1	AV411-009	To assess safety, tolerability and PK	R (3:1), DB, PC	On Day 1 subjects received a single dose of AV411 30 mg, or placebo. On Day 2 subjects received no study medication and on Day 3 subjects commenced dosing with AV411 30 mg or placebo bid for 14 d; PO	18 (14 active, 4 pbo)	Healthy Volunteers	2 wk	Completed
1	AV411-016	To assess safety, tolerability and PK	R (3:1), DB, PC, single escalating dose	30 mg, 50 mg, 70 mg, 80 mg, and 100 mg or placebo; PO	60 (45 active, 15 pbo)	Healthy Volunteers	Single dose except 80 mg group who received dose in both fed and fasted state	Completed

Type of Study	Study Protocol Number	Study Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
1b	AV411-026	To assess safety, tolerability and PK	R (3:1), DB, PC, MD	On Days 1 through 6, subjects received MN-166 (or matching placebo) as follows: 20 mg bid x 2 d, then 30 mg bid x 2 d, and then 40 mg bid x 2 d. On Days 7 through 14, subjects were administered AV411 50 mg bid or matching placebo; PO	24 (18 active, 6 pbo)- 12 HV; 12 DM	Healthy Volunteers & Diabetes Mellitus (Type 1 and 2) Subjects	2 wk	Completed
1b/2a	AV411-010	To assess safety, tolerability, PK and preliminary efficacy	R, DB, PC; 7-day single-blind run-in phase (placebo and active dose) followed by 14day treatment phase in 2 cohorts	Treatment Phase: Cohort 1: randomized 1:1:1 to 40 mg, 60 mg or pbo. Cohort 2: randomized 2:1 (active:pbo) to 60 mg/ 80 mg or pbo.	34 (34 active in Run-in phase 24 active/10 pbo in Treatment phase)	Diab. Periph. Neuropath. Pain (DPN) subjects	Single and multiple dosing 2 wk	Completed
1b/2a	AV411-OWA (Investigator IND 102,942)	To assess safety, tolerability and preliminary efficacy to reduce opioid withdrawal syndrome and prolong the analgesic effect of oxycodone	R (1:1:1), DB, PC	20 mg BID x 14 days, 40 mg BID x 14 days, pbo; PO	44 (22 active/22 pbo)	Heroin addicts	Multiple dose 2 wk	Completed
2	MN166-CL-001	To assess safety, tolerability and efficacy	R, DB, PC followed by an OLE	10 mg tid, 20 mg tid,	297 (194 active/103 pbo)	Multiple Sclerosis	Core 12 months; extension 12	Completed

Type of Study	Study Protocol Number	Study Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
				Pbo for 12 mo, then MN-166 for 12 mo; PO			months	
1b	UCLA Meth. (Investigator IND 108,996)	To assess safety, tolerability, PK and methamphetamine interaction	R, DB, PC, Within-subject CO	20 mg bid, 50 mg bid x 7 d, pbo; PO	11	Methamphetamine addicts	2 wk	Completed
2a/2	IBU-002 (Investigator-sponsored)	To determine the effect of ibudilast in patients with medication over use headaches.	R, DB ,PC	40 mg bid, placebo; PO	34 (15 active/19 pbo)	Medication Overuse Headache	8 wk	Completed
2a	AV411 SA (Columbia / NYSPI)	To evaluate the ability of AV411 to alter the reinforcing, analgesic, subjective, physiological effects of oxycodone	R, PC, CO	50 mg bid, placebo; PO	Planned 24	Opioid and heroin dependent users	3 wk	Ongoing
2	UCLA-Meth-Ph2	To determine whether MN-166 reduces MA use more than placebo	R, DB, PC	50mg bid, placebo, PO	Planned: 140	Methamphetamine addicts	12 wk	Ongoing

Type of Study	Study Protocol Number	Study Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
2	UCLA Alcohol Addiction	To assess safety, tolerability and preliminary efficacy of MN-166 in alcohol addiction participants	R, DB, PC, CO	50mg bid, placebo, PO	Planned: 24	Alcohol addiction	7 d session x 2	Ongoing
2	SPRINT-MS	To evaluate safety, tolerability and activity of MN-166	R, DB, PC	Up to 100 mg/d	Planned: 250 (125 MN-166; 125 placebo) Enrolled: 66	Progressive Multiple sclerosis	96 wk	Ongoing

In the completed studies, the safety of ibudilast from 30 to 80 mg/day has been evaluated in single and multiple doses for up to 8 weeks in healthy volunteers and diabetes mellitus Type 1 & 2 patients, chronic pain patients (diabetic neuropathy and complex regional pain syndrome), opioid-addicted subjects and in chronic medication overuse headache (MOH) pain. The dosage of 100 mg/day has been evaluated in single and multiple doses for up to 8 days in healthy volunteers (HV), diabetes mellitus (DM) Type 1 & 2 patients and in methamphetamine-dependents subjects. In the methamphetamine dependents study (UCLA-Meth-Ph1b), subjects received MN-166 40 mg/day for 1 week followed by 100 mg/day for 1 week.

Safety Results Multiple Sclerosis Study (24 Months)-30 to 60 mg/day

A Phase 2 clinical trial evaluating the safety and efficacy of MN-166 in multiple sclerosis subjects was completed. The study was a 12-month randomized, double-blind, placebo-controlled study followed by a 12-month open-label extension (OLE) study. A total of 297 subjects were randomized to MN-166 30 mg/d, 60 mg/d or matching placebo. During the 12-month double-blind core period, the adverse events most frequently reported (>5%) occurred in the SOCs of Infections and Infestations (36%), Nervous System Disorders (19%), Gastrointestinal Disorders (15%), Psychiatric Disorders (13%), General Disorders and Administration Site Conditions (9%), and Musculoskeletal and Connective Tissue Disorders (7%). No significant differences in TEAEs by SOC were observed between treatment groups. There was a slight dose-related increase in the percent of subjects with gastrointestinal AEs; 8%, 12%, and 15% for the placebo, 30 mg/day, and 60 mg/day treatment groups, respectively.

During the core period, more treatment-related TEAEs were experienced by subjects in the 60 mg/day group (26) compared to the 30 mg/day (18) or placebo group (12). The most common treatment-related AEs were headache (n=3) and nausea (n=2) in the 30 mg/d group; nausea (n=4), headache (n=3), vomiting (n=2) and dizziness (n=2) in the 60 mg/d group; and upper respiratory infection (n=5) and headache (n=2) in the placebo group.

During the open-label extension period, five additional treatment-related adverse events (TRAEs) occurred. These TRAEs were night cramps (1subject in 60 mg/d cohort), hepatotoxity (1 subject in 60 mg/d cohort), depression (1 subject in 60 mg/d cohort), and pruritus (2 subjects in placebo to 60 mg/d cohort).

Over the entire 24-month study, the most frequently occurring AEs (≥ 5% of subjects) were nasopharyngitis (20%), headache (14%), urinary tract infection (9%), pharyngitis (6%) and nausea (5%). Gastrointestinal AEs occurred in a percentage of subjects: 10%, 12%, 17%, and 18% for placebo to 30 mg/day, placebo to 60 mg/day, 30 mg/day, and 60 mg/day treatment groups, respectively. There was a slight increase in gastrointestinal AEs in the percent of subjects who received MN-166 treatment for 24 months.

Over the entire 24-month study, a total of 21 SAEs were reported by 20 subjects. SAEs were reported by 12 subjects in the core period and 9 SAEs were reported by 7 subjects during the extension period. More subjects in the 60 mg/day dose group (10/99=10.1%) experienced an SAE compared to other active group. Four subjects in placebo group (4/103= 3.8%) experienced SAEs during core period while on placebo, 1 subject in placebo

to 60 mg/d cohort (1/48=2.1%) experienced an SAE during the OLE period while on 60 mg/d dosage and 4 subjects in the 30 mg/d cohort (4/95=4.2%) experienced an SAE. The SAEs were as follows: acetabulum fracture, duodenal ulcer perforation, calculus ureteric, and menorrhagia in the placebo group; inguinal hernia, epilepsy, peptic ulcer perforation, fibula fracture and menorrhagia in the 30 mg/d group; and bladder diverticulum, epilepsy, intervertebral disc protrusion, pneumonia haemophilus, uterine cancer, gastrointestinal malignant neoplasms, retinal detachment, hip surgery, depression, acute pancreatitis, ankle fracture and congenital anomaly resulting in death (partner pregnancy) in the 60 mg/d group. All of these SAEs were considered by the Investigator to be unlikely related or not related to study drug. Eight of the SAEs were considered by the Investigator to be severe or life threatening. Subject SE-001-009, who was diagnosed with gastrointestinal malignant neoplasms, died due to this SAE approximately 1 year after he withdrew from the study due to this SAE.

A total of nine subjects discontinued from the study due to a TEAE. Two of these subjects experienced a TEAE that were considered to be related to study drug; hepatic steatosis (severe) and hepatotoxicity (moderate) treated with 30 mg/d group and 60 mg/d group, respectively. None of the other TEAEs (duodenal ulcer perforation, osteoarthritis, tachycardia, epilepsy, uterine cancer, gastrointestinal neoplasm, acute pancreatitis) that resulted in study discontinuation were considered to be related to study medication by investigator.

The pharmacokinetics of MN-166 have been closely monitored in most of the studies and the PK has generally been shown to be dose-proportional both within and between studies. Based on prior trials, steady state plasma C_{max} and $AUC_{0\text{-}24h}$ levels at the highest dose (50 mg bid; 100 mg/d) are anticipated to be approximately 116 ng/ml (C_{max}) and 1613 ng*hr/ml ($AUC_{0\text{-}24h}$) (study AV411-026 HV group). All of the trials listed in the table except for the first two have included all concurrent concomitant medications with ibudilast dosing at 80 or 100 mg/d. While pharmacokinetic drug-drug interactions have not been carefully assessed (or are in progress), there are no clear pharmacologic or safety interactions noted to date.

5. TRIAL OBJECTIVES AND PURPOSE

This is a single center, randomized, double-blind, placebo-controlled study followed by an open-label extension phase (for the placebo-treated group only). This study is designed to evaluate the safety, tolerability and efficacy of MN-166 (60 mg/d) when administered as an adjunct to riluzole (50 mg bid) in subjects with ALS.

5.1. Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of MN-166 60 mg/d versus placebo when administered with riluzole in subjects with amyotrophic lateral sclerosis.

5.2. Secondary Objectives

The secondary objective is to evaluate the clinical endpoint responsiveness of MN-166 60 mg/d versus placebo when administered with riluzole in subjects with amyotrophic lateral sclerosis as measured by the following assessments:

- Functional activity as assessed by the Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRS-R)
- Respiratory function as measured by slow vital capacity (SVC), Maximum Inspiratory Pressure (MIP also known as Negative Inspiratory Force (NIF), Forced Expiratory Volume in 1 second (FEV_1) measured under SVC protocol and Maximal Voluntary Ventilation (MVV).
- Muscle strength measured by manual muscle testing (MMT) and instrumented hand grip dynamometry
- Non-invasive ventilation (NIV) utilization measured by clinically indicated prescription for NIV intervention and time to clinically indicated prescription for NIV intervention in each group (for early ALS subjects only)

5.3. Tertiary Objectives

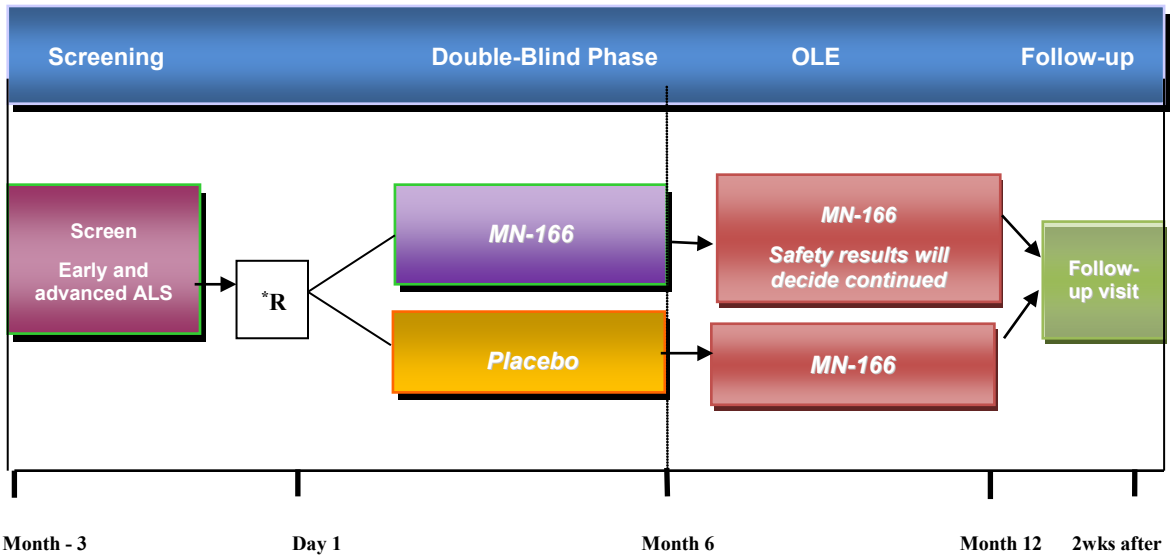
- To evaluate quality of life as assessed by the Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-5)
- To evaluate Clinical Global Impression of Change (CGIC) as assessed by ALS subjects, caregivers and physician anchored to most recent standard of care visit prior to screening visit
- To evaluate serum creatinine as a biomarker for disease progression
- To evaluate the pharmacokinetics of MN-166 when administered as an adjunct to riluzole

6. OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

This is a single center, randomized, double-blind, placebo-controlled, 6-month study designed to evaluate the safety, tolerability and clinical endpoint responsiveness of MN-166 (60 mg/d) when administered as an adjunct to riluzole (50 mg bid) in subjects with ALS. This study will consist of two treatment arms, MN-166 and matching placebo. Randomization will occur in a 2:1 ratio (MN- 166: placebo). To be eligible, subjects must have a diagnosis of sporadic or familial ALS with onset of ≤ 5 years ("early ALS") from first clinical weakness prior to screening or with onset of ≤ 10 years ("advanced ALS") from first clinical weakness prior to screening for ALS patients on non-invasive ventilator support. All subjects and must be on a stable dose of riluzole for at least 1 month prior to study drug treatment. All subjects will receive optimized standard of care at an ALS Multidisciplinary Clinic affiliated with an academic medical center in addition to study medication. A total of approximately 120 male and female subjects from 18 to 80 years old, inclusive will be enrolled. Eligible subjects will be stratified by ALS stage. Sixty subjects will be enrolled into the "early ALS" group and 60 subjects will be enrolled into the "advanced ALS" group. Subjects will be randomized in a 2 : 1 ration for active drug and placebo (80 subjects in the MN-166 group; 40 subjects in the placebo group). Upon completion of the Double-blind Phase, subjects randomized to the placebo arm will continue for an additional 6 months and will receive open-label MN-166. The safety and tolerability of MN-166 will be evaluated by an unblinded Independent Safety Monitor during an interim safety monitoring assessment after approximately 20-30 subjects have been followed for approximately 3 months. The safety data will also be reviewed at Month 6 and if there are no safety or tolerability concerns in the MN-166 treated group, a decision will be made to extend participation to the MN-166 treated group into the Open-label Extension (OLE) Phase. Otherwise, only the placebo-treated patients will participate in the OLE Phase. Subjects will be informed of the treatment that they have received during the double-blind phase after the last subject has completed the open-label extension or at the time defined by the principal investigator in consultation with MediciNova.

After approximately 20-30 subjects have been enrolled for 3 months, an unblinded independent Safety Monitor (ISM) will review the safety data by treatment group to determine whether there are any safety concerns. If any unexpected safety issues arise, the sponsor and PI will be notified and a decision to continue the study will be made. If there are no safety concerns, subjects will continue on MN-166 (ibudilast) during the open label extension study. The safety data will also be reviewed at Month 6 and if there are no safety or tolerability concerns in the MN-166 treated group, a decision will be made to extend participation to the MN-166 treated group in to the Open-label Extension (OLE) Phase.
The study phases are described below and displayed in Figure 1 and the Schedule of Assessments is displayed in Table 1.

Figure 4 Study Schema



*R = randomize

MN-166 = ibudilast

6.1. Screening Phase (up to 3 months prior to Day 1)

During the Screening Phase, subjects will be approached for study participation and an informed consent form will be given to the patient. On Day -7, subjects will return to the office, and if there are no additional questions, subjects will sign the informed consent form. The following screening assessments will be performed: review of inclusion/exclusion criteria: medical history including review of prior and current medications, physical and neurologic examination, height, body weight, and vital signs (sitting). An EMG report will be documented and an ALSFRS-revised questionnaire will be administered. Safety labs (chemistry, hematology, urinalysis, and serum pregnancy test) and 12- lead ECG. Slow vital capacity and a manual muscle strength test will be conducted; an ALSAQ-5 and CGIC questionnaire will be administered.

Subjects who are not currently taking riluzole will be started on riluzole 50 mg qd for the first 7 days and then 50 mg bid for the next 3 weeks prior to entry into the study.

Detailed information on permitted and excluded concomitant medications is provided in Section 8.2 and Section 8.3 of the protocol.

6.1.1. Diagnosis at Screening

Subjects must have a diagnosis of familial or sporadic ALS as defined by the El Escorial-Revised research diagnostic criteria for ALS (clinically definite, clinically probable, probable-laboratory supported).

6.1.2. Double-Blind Treatment Phase (6 months)

Subjects who complete all of the screening assessments and continue to meet eligibility criteria will be randomized. Subjects will return to the clinic on Treatment Day 1 and will be randomized to 1 of 2 treatment arms. They will then receive their first dose of study medication. Subjects will be administered 30 mg/d (30 mg qd) for the first 14 days. Subjects will be instructed to take study medication with food or within an hour of eating to improve gastrointestinal tolerability. On Day 15, subjects will be instructed to begin taking 60 mg/d (30 mg bid) for the remainder of the study. Subjects who cannot tolerate 60 mg/d will have their dose decreased to 30 mg/d. After 7 days, if no tolerability issues arise, the dose can be increased to 60 mg/d. A different dosing regimen may be implemented (e.g., 10 mg tid for the 30 mg/d dose; 20 mg tid for the 60 mg/d dose) to improve tolerability. Subjects who are not able to tolerate 30 mg/d as judged by the Investigator will be discontinued from the study. Subjects who discontinue from the study because they cannot tolerate 30 mg/day may be replaced. Subject replacement for other reasons is not permitted.

Subjects will continue on the same dose (100 mg/d) of riluzole throughout the study.

Subjects will return to the clinic at Month 3 and Month 6 and will be followed by telephone at Months 1, 2, 4, and 5.

Subjects who received placebo during the Double-blind Phase and completed the 6-month Double-blind Phase will continue to the OLE Phase.

Safety monitoring will be performed after approximately 20-30 subjects have been followed for 3 months and a safety analysis of the MN-166 treated subjects will be done at 6 months of treatment by an unblinded Independent Safety Monitor to assess whether these subjects will also continue treatment in the OLE.

6.1.3. Open-Label Extension Phase for Placebo-Treated Group (6 months)

Upon completion of the double-blind treatment phase, subjects who had been randomized to the placebo-treated group will participate in the open-label extension phase for 6 months. Subjects will be administered MN-166 30 mg/d for the first 14 days and then 60 mg/d for the remainder of the OLE phase. Subject who cannot tolerate 60 mg/d will have their dose decreased to 30 mg/d. After 7 days, if no tolerability issues arise, the dose can be increased to 60 mg/d. Subjects who are not able to tolerate MN-166 30 mg/d as judged by the Investigator will be discontinued from the study. A different dosing regimen may be

implemented (e.g., for the 30 mg/d dose, 10 mg tid; for the 60 mg/d dose, 20 mg tid) to improve tolerability. Subjects who are not able to tolerate 30 mg/d as judged by the Investigator will be discontinued from the study.

Subjects will continue on the same dose (100 mg/d) of riluzole throughout the OLE Phase.

6.1.4. Follow-up Phase

All subjects who complete the study (double-blind and open-label) or prematurely discontinue will return for a safety visit 14 days after their last dose to assess the subject's general health status and to document adverse events and concomitant medications.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Clinical Trial Population

The population for this trial will include approximately 120 male and female subjects ≥ 18 to 80 years old, inclusive with a diagnosis of ALS stratified by early ALS and advanced ALS.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

7.2. Inclusion/Exclusion Criteria

7.2.1. Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Written informed consent is obtained and willing and able to comply with the protocol in the opinion of the Investigator;
2. Male or female subjects ages ≥ 18 to 80 years, inclusive;
3. 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];
4. Diagnosis of ALS with onset of ≤ 5 years from first clinical weakness;
5. Slow vital capacity ≥ 60% of predicted (Knudsen 1983) within 1 month prior to Treatment Day 1;
6. Currently on a stable dose of riluzole for at least 30 days prior to initiation of study drug. Subjects not currently taking riluzole will be started on 50 mg qd for the first 7 days followed by 50 mg bid for the following 21 days prior to screening. Patients may be screened during this time period but not started on study drug until they are on a stable dose of riluzole;
7. All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing). Females of childbearing potential must use an effective method of contraception (e.g., total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation;

8. Females must not be lactating or pregnant at Screening or Baseline (as documented by a negative beta-human chorionic gonadotropin [ß-hCG] (or human chorionic gonadotropin [hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug;

9. Males should practice contraception as follows: condom use and contraception by female partner;

10. Able to swallow study medication capsules;

11. Subject is willing and able to comply with the protocol assessments and visits, in the opinion of the study nurse/coordinator and the Investigator;

12. Has no known allergies to the study drug or its excipients;

13. Has received 23-valent pneumococcal vaccination within 4 years prior to starting clinical trial.

7.2.2. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Use of tracheostomy, tracheostomy invasive mechanical ventilation [TIMV], or non-invasive pressure - [P-NIV] or volume – [V-NIV] cycled ventilation within the last 3 months prior to screening;
2. Greater than 3% predicted loss in post-diagnosis vital capacity per month or a greater than 1-unit loss in post diagnosis ALSFRS-R total score per month [exclusive of loss due to beginning use of assistive devices];
3. Confirmed hepatic insufficiency or abnormal liver function (ALP greater than 1.5 times of upper normal limit, AST and/or ALT greater than 3 times the upper limit of the normal range);
4. Renal insufficiency as defined by a serum creatinine greater than 1.5 times the ULN;
5. Currently has a clinically significant psychiatric disorder or dementia which would preclude evaluation of symptoms;
6. Has a clinically significant medical condition (other than ALS) including the following: neurological, metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, urological disorder, or central nervous system infection that would pose a risk to the subject if they were to participate in the study or that might confound the results of the study;
7. History of malignancy < 5 years prior to signing the informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer;

8. ECG finding of QTcB prolongation > 450 ms for males and > 470 ms for females at screening;
9. History of HIV (human immunodeficiency virus), clinically significant chronic hepatitis, or other active infection;
10. Subject has a history of stomach or intestinal surgery or any other condition that could interfere with or is judged by the Investigator to interfere with absorption, distribution, metabolism, or excretion of study drug;
11. Subject has a history of alcohol or substance abuse (DSM-IV-TR criteria) within 3 months prior to screening or alcohol or substance dependence (DSM-IV-TR criteria) within 12 months prior to screening;
12. Subject has poor peripheral venous access that will limit the ability to draw blood as judged by the Investigator;
13. Currently participating, or has participated in, a study with an investigational or marketed compound or device within 3 months prior to signing the informed consent;
14. Unable to cooperate with any study procedures, unlikely to adhere to the study procedures and keep appointments, in the opinion of the Investigator.

Advanced ALS group will follow the same inclusion/exclusion as the early ALS subjects with the exception of the following:

Inclusion criteria:

- Diagnosis of ALS with onset of ≤ 10 years from first clinical weakness;
- On Non-invasive ventilator with Non-invasive pressure [PNIV] or volume [V-NIV] cycled ventilation stable use for ≥ 4 hours daily for 1 month prior to Treatment Day;
- Slow vital capacity ≥ 20% of predicted (Knudsen 1983) within 1 month prior to Treatment Day 1;
- Able to swallow study medication capsules or have gastrostomy tube access for delivery of contents of medication capsule.

Exclusion criteria:

- Use of tracheostomy, tracheostomy invasive mechanical ventilation [TIMV];
- No rate of progression exclusion.

7.3. Subject Withdrawal/Discontinuation Criteria

Subjects may request to be withdrawn from the study at any time for any reason.

The Investigator may interrupt the treatment of any subject whose health or well-being may be compromised by continuation in the study. The following instances require subjects to be withdrawn from the study:

- Subject fails to adequately comply with the dosing, evaluations, or other requirements of the study at the discretion of Investigator;
- Subjects who have adverse events that require discontinuation of study medication;
- Subjects who, in the opinion of the Investigator, should be discontinued for their well-being;
- Subjects who are no longer able to understand task instructions or to perform tests adequately;
- Subject becomes pregnant during the study. See section 11.7 for reporting requirements and follow-up of the pregnancy.

If a subject withdraws or is removed from the study for any reason, the reason and date of discontinuation of study medication should be recorded in the appropriate section of the Case Report Form (CRF). At the time of study discontinuation, every effort should be made to ensure all Early Termination (ET) procedures and evaluations are performed.

The study sponsors reserve the right to discontinue the study at any time for medical or administrative reasons.

7.3.1. Follow-up Procedures Upon Discontinuation/Withdrawal

An early termination CRF page should be completed for every subject who received study medication whether or not the subject completed the study. The reason for discontinuation should be indicated on the CRF. Any AEs that are present at the time of discontinuation/ withdrawal should be followed in accordance with the safety requirements outlined in Section 11.

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

MN-166 will be provided in 10 mg capsules in polyethylene bottles and will be stored at room temperature. Study drug should be taken with food.

8.2. Concomitant Medications

Concomitant medications required for the treatment of symptoms and signs of amyotrophic lateral sclerosis are permitted except as excluded below.

Concomitant medications for treatment of adverse events may be allowed. Subjects will be instructed to contact a member of the study staff prior to taking any medication.

8.3. Prohibited Medications

The following medications are **prohibited** prior to and during study participation:

- Systemic corticosteroid treatment within 3 months prior to screening (inhaled or topical steroids are allowed);
    - A single course of systemic corticosteroid treatment will be allowed and a course of steroids along with antibiotics to treat intercurrent sinobronchitis will be allowed
- Current use of intermittent systemic corticosteroids (i.e., monthly or bimonthly intravenous methylprednisolone);
- Oral immunosuppressants (e.g. azathioprine, methotrexate, cyclosporine (topical and ophthalmic cyclosporine are allowed), teriflunomide (Aubagio®) within 6 months of screening;
- Mitoxantrone or natalizumab within 6 months of screening;
- Fingolimod or dimethyl fumarate [Tecfidera®] within 3 months of screening;
- Rituximab or other B-cell therapy within12 months of screening;
- Current use of glatiramer acetate and IFNβ-1 (any formulation);
- Intravenous or Subcutaneous Immunoglobulin (IVIg/SCIg).

The following medications are **prohibited** during study participation:

- cimetidine, cyclosporine (topical and ophthalmic cyclosporine are allowed), dronedarone, lopinavir, probenecid, quinidine (Nuedexta is allowed), ranolazine, rifampin, ritonavir, or tipranavir

8.4. Treatment Compliance

Compliance will be monitored closely at each visit. Subjects will be instructed to bring all unused study medication with them to each visit. Compliance will be assessed by counting capsules and dividing the actual number of doses taken (per capsule count) by the number of doses the subject should have taken within a visit period and multiplying by 100. All subjects will be reminded of the importance of strict compliance with taking study medication for the effectiveness of treatment and for the successful outcome of the study. Subjects who miss more than 25% of scheduled doses over the course of the study or take more than 125% of the scheduled doses will be considered noncompliant and may be discontinued from the study per investigator's judgment.

8.5. Randomization and Blinding

During the Double-blind Treatment Phase, subjects and all personnel involved with the conduct and interpretation of the study, including the investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor and accessible only to authorized persons (e.g., unblinded safety monitor) until the time of unblinding. Randomization procedures will be addressed in the statistical analysis plan.

To ensure that treatment allocation remains concealed to both staff and participants, the following measures will be taken:

- Active drug and placebo will be identical in appearance;
- Drug supplies to investigational pharmacy will be coded;
- The randomization list will be held by Dickson Advanced Analytics (DA^2) to ensure that treatment allocation is concealed from the investigator's team and the participant, whilst providing provisions for emergency unblinding.

Details of the randomization process will be available in the Investigator Site File (ISF). The identities of the Dickson Advanced Analytics (DA^2) whose randomization roles in the trial require them to have access to treatment allocation codes will be recorded in the trial master file (TMF).

The randomization system will be web-based and require a personal log-in and password. Only those individuals who have attended the site-initiation visit, are trained and are in the delegation-log can carry out this process.

Once a consented patient meets criteria for clinical trial entry as a subject has been randomized they will be given a card to indicate they are on the trial with the emergency contact numbers for medical advice. Patients will be instructed to show this card to any healthcare professional involved in their care who is not involved in the trial. Any trial participant who withdraws from the study will not be replaced.

Subjects will be informed of the treatment that they have received during the double-blind phase after the last subject has completed the open-label extension or at the time defined by the principal investigator in consultation with MediciNova.

8.5.1. Emergency Unblinding Procedures

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

Unblinding may take place in situations where the safe management of the patient's medical condition necessitates knowledge of the study medication by the person(s) responsible for the patient's care. Where possible, members of the local research team should remain unblinded.

If unblinding is required, the local PI/other medical staff should contact the sponsor at 858-373-1500 via telephone or safetymonitors@medicinova.com via email.

The person requesting the unblinding will provide details including the protocol number and trial name, name of the requester, reason for unblinding, patient name, participant number and timeline to receive the unblinded information. If knowledge of the treatment allocation is required in order to treat the patient, the code break number will be given to the local PI/other medical staff requesting to unblind the patient. In this way, the treatment will be unblinded at the local site but not to sponsor.

The local PI/medical staff will deal with the medical emergency (upon receipt of the treatment allocation revealed by the code break number). Details of the code break will be documented on the code break form and filed at the local site.

Code breaks will also be documented at the end of the study in the statistical report.

8.6. Dosing Guidelines

8.6.1. Treatment Phase

Study drug will be administered as MN-166 30 mg/d (3 capsules) for the first 14 days then titrated to 60 mg/d (6 capsules) for the remainder of the study. Study drug should be taken with food or within an hour of eating to improve gastrointestinal tolerability. Subject who cannot tolerate 60 mg/d will have their dose decreased to 30 mg/d. After 7 days, if no tolerability issues arise, the dose can be increased to 60 mg/d. If the 60 mg/d dose is still not tolerable, subjects may remain on 30 mg/d for the remainder of the study. If necessary, an alternative dosing regimen may be implemented (e.g., 10 mg tid for the 30 mg/d dose

and 20 mg tid for the 60 mg dose. Subjects who cannot tolerate 30 mg/d will be discontinued from the study.

On Day 1, subjects will be given a paper diary to record the number of capsules they take each day. Subjects will be instructed to bring the diary to each visit.

If a subject forgets to take their study drug dose, subjects will be encouraged to take their medication as soon as possible. If subjects missed to take study drug for more than 12 hours, subjects will be instructed to skip the dose and take the next dose at their regularly scheduled time.

If a subject is not tolerating the study drug or experiences an adverse event that is severe in intensity, the subject will be instructed to contact a member of the study team prior to taking their next dose of study drug so that they can be closely monitored.

8.6.2. Dose Interruptions

Laboratory tests should be repeated within two weeks after any of the following laboratory values are met:

- AST or ALT or ALP or T.bil >3x upper limit of normal (ULN);
- GGT $\geq$ 4 x ULN;
- Cre > 1.5 x ULN;
- White blood count <2500/mm^3;
- Platelet count <75,000/ mm^3.

If, after repeat testing, the laboratory value is still outside the above limits, then the subject should stop study medication. While dosing is withheld, subjects will continue tests and assessments according to the schedule defined in the protocol (and may also undergo additional assessments to evaluate the laboratory abnormality as per the Investigator's standard practice). In addition, subjects must have the abnormal laboratory result rechecked at least every 2 weeks (rechecks will be run at the local laboratory) until resolution or stabilization of the laboratory value.

After laboratory values return within normal limits, resumption of blinded study treatment is to be considered on a case by case basis and must be discussed with the Independent Safety Monitor.

8.6.3. Subsequent Additional Laboratory Abnormalities

Subjects who subsequently develop the same abnormal laboratory value at any other time must permanently discontinue dosing with study treatment (i.e., only one dosing interruption is allowed for the same lab abnormality). However, subjects who subsequently experience a different laboratory abnormality can have study treatment withheld again for a different laboratory abnormality. However, only two dosing interruptions are allowed for each subject. Any subject who experiences a third abnormal laboratory tests as defined in the section above (Section 8.6.2) must permanently discontinue study treatment.

8.7. Written Informed Consent

Each subject is required to provide written informed consent prior to undergoing any study procedures. A copy of the signed and dated informed consent (in a language in which the subject is fluent) is required to be given to the subject. If a subject withdraws consent, data collected up to the time of discontinuation will be used to evaluate study results.

8.8. Assessments

The Schedule of Assessments is presented in Table 1.

Each visit during the Treatment Phase and Open-label Extension will have a window of ± 5 days.

Clinical laboratory evaluations will be performed by Carolinas Laboratory Network Diagnostic Services. All clinical and laboratory evaluations, procedures related to inclusion/exclusion criteria, or performed during treatment must be reviewed, initialed and dated by the Principal Investigator or appropriate designee listed on Form FDA 1572.

8.8.1. Study Assessments by Visit

The following is a summary of assessments by study visit:

8.8.1.1. Screening

Study Visit 1 (Day - 90 to Day -8)

At any point during this time, subject may be approached for participation in the study. An informed consent form (ICF) will be given to the subject and the subject will be instructed to read the ICF and ask the study staff any questions they may have. The subject can either sign the ICF then or defer signing until they return for Study Visit 2.

Study Visit 2 (Day -7)

Signing of informed consent (if not signed during Visit 1) the following assessments will be performed during Study Visit 2:

- Inclusion/Exclusion review
- Medical history
- Medication history (include all medication taken for ALS and all current medication within 1 month prior to screening)
- Physical/neurological examination
- Height/body weight
- Vital signs (sitting) [Temperature, pulse rate, respiratory rate, blood pressure]

- 12-lead ECG
- Laboratory: Comprehensive Metabolic Panel (CMP) including GGT, Complete Blood Count (CBC), Urinalysis without microscopic examination
- Serum β-hCG (in pre-menopausal females)
- Serum CK
- Slow Vital capacity (SVC), Maximum Inspiratory Pressure (MIP/NIF), Forced Expiratory Volume in 1 second (FEV_1) measured with SVC protocol, Maximal Voluntary Ventilation (MVV)
- Muscle strength by manual muscle testing and instrumented hand grip dynamometry
- ALSFRS-R
- ALSAQ-5
- CGIC

8.8.1.2. Double-Blind Treatment Phase

The following assessments will be performed at Day 1 (Baseline):

- Inclusion/Exclusion review
- Vital signs (sitting) [Temperature, pulse rate, respiratory rate, blood pressure]
- Randomization
- Study drug dispensing
- Adverse Event review
- Concomitant medication review
- 12-lead ECG* (3-4 hours after first dose)
- Dispense paper diary to record medication compliance

Once the assessments have been completed, the subject will be instructed to take 3 capsules per day with a meal or the subject may take the capsules in the clinic with food.

*for patients on Nuedexta

Month 3 and Month 6

The following evaluations will be conducted at Month 3 and Month 6:

- Physical/neurological exam
- Body weight
- Vital signs (sitting) [Temperature, pulse rate, respiratory rate, blood pressure]

- 12-lead ECG*
- Laboratory: Complete Metabolic Panel (CMP) including GGT, Complete Blood Count (CBC), Urinalysis without microscopic examination
- Urine β-hCG (in pre-menopausal females)
- Serum CK

Slow Vital capacity (SVC), Maximum Inspiratory Pressure (MIP/NIF), Forced Expiratory Volume in 1 second (FEV_1) measured with SVC protocol, Maximal Voluntary Ventilation (MVV)

- Muscle strength by manual muscle testing and instrumented hand grip dynamometry
- ALSFRS-R
- ALSAQ-5 (at Month 6 only)
- CGIC
- Plasma PK sample
- Study drug dispensing
- Review patient diary
- Study drug accountability
- Adverse Event review
- Concomitant medication review

Month 6 Clinic Visit is the start day (Day 1) of the Open-Label Extension (OLE) phase. All subjects will take MN-166 in OLE if there are no safety or tolerability issues. Otherwise, only the placebo-treated patients will participate in the OLE Phase.

*For the patients on Nuedexta, 12-lead ECG at Month 6 visit should be done 3-4 hours after first dose of Ibudilast

8.8.1.3. Open-Label Extension Phase

The following assessments will be conducted at Month 9 and Month 12:

- Physical/neurological exam
- Body weight
- Vital signs (sitting) [Temperature, pulse rate, respiratory rate, blood pressure]
- 12-lead ECG
- Laboratory: Comprehensive Metabolic Panel (CMP) including GGT, Complete Blood Count (CBC), Urinalysis without microscopic examination

- Urine β-hCG (in pre-menopausal females)
- Serum CK
- Slow Vital capacity (SVC), Maximum Inspiratory Pressure (MIP/NIF), Forced Expiratory Volume in 1 second (FEV_1) measured with SVC protocol, Maximal Voluntary Ventilation (MVV)
- Muscle strength by manual muscle testing and instrumented hand grip dynamometry
- ALSFRS-R
- ALSAQ-5 (at Month 12 only)
- CGIC
- Plasma PK sample
- Study drug dispensing (at Month 9 only)
- Study drug accountability
- Adverse Event review
- Concomitant medication review

8.8.1.4. Follow-up Visit (2 weeks after last dose of study drug)

Subjects who complete the study and subjects who discontinue prematurely will complete a follow-up visit.

The following assessments will be conducted:

- Physical/neurological exam
- Vital signs (sitting) [Temperature, pulse rate, respiratory rate, blood pressure]
- Adverse Event review
- Concomitant medication review
- Study drug accountability

8.8.1.5. Early Termination visit

Subjects who prematurely discontinue from the study will have the following assessments performed:

- Physical/neurological exam

- Vital signs (sitting) [Temperature, pulse rate, respiratory rate, blood pressure]
- Slow Vital capacity (SVC), Maximum Inspiratory Pressure (MIP/NIF), Forced Expiratory Volume in 1 second (FEV_1) measured with SVC protocol, Maximal Voluntary Ventilation (MVV)
- Muscle strength by manual muscle testing and instrumented hand grip dynamometry*
- ALSFRS-R*
- ALSAQ-5 (at Month 12 only)*
- CGIC*
- Plasma PK sample
- Adverse event review
- Concomitant medication review
- Study drug accountability

Additional procedures and assessments may be done at PI's discretion, if necessary.

*Assessments do not need to be performed if prior assessments were within one month of this early termination visit.

8.8.1.6. Laboratory Re-test visit

Subjects who have an abnormal lab finding will return for a laboratory re-test visit and will have the following assessments performed, as needed:

- Laboratory: Comprehensive Metabolic Panel (CMP) including GGT, CK, Complete Blood Count (CBC), Urinalysis without microscopic examination as indicated.

Adverse events and concomitant medication will also be documented.

8.8.1.7. Telephone Follow-ups

Subjects will be contacted by telephone between office visits at Months 1, 2, 4, and 5 for double-blind phase and Months 7, 8, 10, and 11 for the open-label-phase by a member of the study staff to inquire about adverse events or changes in concomitant medications.

In the event that subjects have difficulty communicating via telephone, (i.e. due to respiratory distress), alternative ways of communication with study staff (i.e., email, text

message or patients' care-giver communications, etc.) will be acceptable with prior consent from the MediciNova, Inc. medical monitor.

8.8.1.8. Follow-up by local neurologist

If, during the course of subject participation, remotely-located subjects find it difficult to travel to the study site for the clinic visits (e.g., physical deterioration or other physical hardship etc.), evaluation by the subject's local neurologist may be accepted with prior consent from the MediciNova, Inc. medical monitor.

8.8.2. Additional Safety Assessment with patients on Dextromethorphan-20mg and Quinidine-10mg (Nuedexta) in MN-166-ALS-1201 Clinical Trial

8.8.2.1. Patients already on Nuedexta prior to participating MN-166-ALS-1201 Trial

If patient is already on Nuedexta, then patient should undergo additional electrocardiogram (ECG) evaluation at 3-4 hours after receiving Study Medication on Day 1 and Month 6 visit (first day of Open-Label–Extension phase) Review of the QTc results should occur prior to continuing patient on Study Medication and Nuedexta. If there is an increase in QTc to above 450 ms in males and above 470 ms in females, but less than 500 ms for both groups, the patient may continue on both medications, receiving ECG evaluations every three months per protocol. If there is an increase in QTc above 500 ms, then investigator should repeat ECG within 24 hours before allowing the patient to continue on both medications. If the repeat QTc is above 500 ms, the patient will have to discontinue Study Medication in order to be treated with Nuedexta.

8.8.2.2. Patients starting Nuedexta after beginning Study Medication in MN-166-ALS-1201 Trial

If patient is already on Study Medication and it is deemed medically necessary to start Nuedexta, then patient should undergo additional electrocardiogram (ECG) evaluation 3-4 hours after receiving Nuedexta the first time and again at Month 6 visit (first day of Open-Label-Extension phase). Review of the QTc results should occur prior to continuing patient on Nuedexta and the Study Medication. If there is an increase in QTc to above 450 ms in males and above 470 ms in females, but less than 500 ms, the patient may continue on both medications, receiving ECG evaluations every three months per protocol. If there is an increase in QTc above 500 ms, then investigator should repeat ECG within the next 24 hours before allowing the patient to continue on both medications. If the repeat QTc is above 500 ms, the patient will have to discontinue Study Medication in order to be treated with Nuedexta.

8.8.3. Procedures/Assessment Details

8.8.3.1. Informed Consent

The Principal Investigator or a qualified designee (e.g., a licensed, qualified medical practitioner such as a physician's assistant or a nurse practitioner) listed on Form FDA 1572 will explain the study to the subject, answer all of the subject's questions, and obtain written informed consent before performing any study-related procedure. Informed Consent should be conducted in accordance with local requirements. Subjects should be able to verbally describe the benefits and risks associated with this study and what other treatment alternatives are available (as described in the consent form). Only subjects who provide informed consent, as assessed and documented by the Investigator, will be enrolled.

8.8.3.2. Medical History

A medical history obtained by the PI or qualified designee as listed on the Form FDA 1572.

8.8.3.3. Prior/Concomitant Medication Review

Site study staff will record all medications taken for ALS and all current medication within 1 month prior to screening visit in the CRF. Also, the following parameters will be recorded for all concomitant medications: drug name, route of administration, total daily dose, unit, frequency, start/stop dates, indication, and whether the medication was started after last dose of study medication. The concomitant medications will subsequently be coded using the World Health Organization Drug Dictionary (WHO-DD).

Subjects who are not currently taking riluzole will be started on riluzole 50 mg QD for the first 7 days and then 50 mg BID for the next 3 weeks prior to entry into the study.

8.8.3.4. Physical/Neurological Examination

The physical exams must be performed by the PI or qualified designee (physician, physician's assistant or nurse practitioner) listed on the Form FDA 1572. Clinically significant changes from the signing of the informed consent form (ICF) should be captured as AEs in the CRF.

A complete physical examination includes the following assessments: general appearance, head, eyes, ears/nose/throat, neck, lymph nodes, skin, lungs, heart, abdomen, and musculoskeletal. If the subject is discontinued for any reason, every attempt should be made to perform a final physical and neurological examination.

8.8.3.5. Vital Signs, Height, and Weight

Blood pressure (BP), heart rate (HR) measurements will be taken in a sitting position. Respiratory rate and temperature will also be measured and all measurements will be recorded in the CRF. Clinically significant changes, as defined by the PI, from the signing of the ICF should be captured as AEs in the CRF.

Weight will be measured in pounds. Height will be measured in inches at Visit 1 (screening) and this height is the canonical height for the duration of the clinical trial.

8.8.3.6. Electrocardiogram (12-Lead ECG)

All subjects will have standard resting 12-lead ECGs performed and interpreted. Subjects are to be supine for at least 5 minutes prior to ECG assessments. The time the ECG is performed will be recorded (using a 24-h clock).

The PI or a qualified designee listed on Form Food and Drug Administration (FDA) 1572 must review, initial, and date the report, which must be filed in the subject's study chart.

Clinically significant findings from the screening report must be captured in the medical history. Any clinically significant changes compared with screening must be captured as an AE in the CRF.

8.8.3.7. Manual Muscle Test

The manual muscle test (MMT) is a scored neurologic examination derived from the Medical Research Council scale. The scale is numerical, with scores between 0 and 5 per muscle, and is based on the examination of 42 muscles: neck flexors and extensors; shoulder abductors and external rotators; elbow flexors and extensors; wrist extensors and flexors; finger extensors and flexors, abductor pollicis brevis; first dorsal interosseus, abductor digiti minimi; index finger pinch, hip flexors, extensors, and abductors; knee extensors and flexors; ankle dorsiflexors; plantar flexors; and extensor hallucis longus. Each muscle is scored from 0 to 5, with 0 representing paralysis and 5 representing normal strength. If a muscle is rated between two scores, the lower score is entered into the CRF. The final MMT score is the mean of the scores of all 42 muscles.

8.8.3.8. Instrumented Hand Grip Measurement

Instrumented hand grip will be measured by Jamar Dynamometer. The best of two hand grips will be represented as Kg hand grip strength per hand and percent predicted. Results are represented in liters and percent predicted (Knudsen 1983).

8.8.3.9. Slow Vital Capacity

Slow vital capacity (SVC) is an index of respiratory function measured by a spirometry test to indicate potential respiratory compromise in ALS subjects. It measures the volume of air expired, non-forcefully, in one breath. The subject will be asked to inspire fully and then slowly expire all the air in their lungs.

8.8.3.10. Maximum Inspiratory Pressure / Negative Inspiratory Force

Maximum Inspiratory Pressure (MIP) / Negative Inspiratory Force (NIF) is a measure of diaphragm strength (Mendoza 2007, Roth 2010).

8.8.3.11. Forced Expiratory Volume in 1 Second measured by Slow Vital Capacity Protocol

Forced Expiratory Volume in 1 Second (FEV_1) will be measured by Slow Vital Capacity (SVC) protocol (Knudson et al 1983).

8.8.3.12. Maximal Voluntary Ventilation

Maximal Voluntary Ventilation (MVV) will be measured as the maximum amount of air that can be inhaled and exhaled within one minute. For the comfort of the patient this is done over a 15 second time period before being extrapolated to a value for one minute expressed as liters/minute (Berto et al 2007).

8.8.3.13. Non Invasive Ventilation Utilization

Non-invasive Ventilation Utilization will be measured by occurrence of prescription for NIV and time to occurrence of prescription for NIV (early ALS patients only).

8.8.3.14. Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRS-R)

The ALSFRS-R is a well-established and validated questionnaire to measure the progression of disability in patients with ALS. It is based on 12 items, each of which is rated on a 0 – 4 point scale. The rate of total functional disability thus ranges from 0 (maximum disability) to 48 (normal) points. The components of the scale group into four factors that encompass gross motor tasks, fine motor tasks, bulbar functions and respiratory function (Cedarbaum et al 1999).

8.8.3.15. Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-5)

The Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ) is a patient self-report questionnaire specifically designed to measure five areas of health: physical mobility, activities of daily living and independence, eating and drinking, communication and emotional functioning. The ALSAQ-5 is brief and easy to complete and has undergone rigorous testing for validity, reliability and sensitivity to change and has been shown to be a robust tool for assessing ALS (Jenkinson et al 2001).

8.8.3.16. Clinical Global Impression of Change

The Clinical Global Impression of Change (CGIC) scale is used to provide a global rating of illness severity, improvement, and response to treatment. It is a three-item observer rating scale and uses a seven-point rating scale. The scale is rated relative to the previous standard of care visit prior to randomization for entry. [-3 much much much worse, -2 much much worse, - 1 much worse, 0 no change, +1 much better, +2 much much better, +3 much, much, much better]. Rating will be provided by patient, caregiver or family member and physician on separate forms.

8.8.3.17. Adverse Event (AE) Monitoring

The PI or a qualified designee listed on Form FDA 1572 must assess the severity and relationship to study medication for all AEs (see Section 11.2).

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be recorded on the AE page(s) of the CRF.

The PI, sub-investigator (SI) and members of the clinical research team are responsible for identifying adverse events and reporting them to RN coordinator.

For all AEs, the Investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE (see Section 11.2) requiring immediate notification to the Sponsor or its designated representative.

For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE. The Investigator is required to assess causality and indicate that assessment on the CRF. For AEs with a causal relationship to the investigational product, follow-up by the Investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Sponsor concurs with that assessment.

Adverse events (serious and non-serious) including all Suspected Unexpected Serious Adverse Reactions (SUSARs) should be recorded on the CRF from the date of informed consent until the end of their participation in the study (i.e., the subject has discontinued or completed the follow-up visit).

8.8.3.18. Laboratory Evaluations

Laboratory evaluations will include the tests listed in Appendix 1. Samples will be sent to the local laboratory listed on Form FDA 1572.

Laboratory test results as they are reported will be tabulated per subject by date, time, test name, test result and reviewed by PI, SI, RN coordinator daily; if a clinically significant laboratory result is identified upon reporting, it will be reviewed with the PI or SI immediately.

9. STUDY DRUG MATERIALS AND MANAGEMENT

The investigational product is MN-166 30 or 60 mg.

9.1. Study Drug

Table 4: Study Drug Information

Investigational Drug:	MN-166
Formulation:	10 mg capsules or 10 mg placebo capsules
Frequency:	30 mg qd or 30 mg bid. Study drug dosing may be varied based on individual tolerability (e.g., 10 mg tid instead of 30 mg qd or 20 mg tid instead of 30 mg bid).
Storage Conditions:	Store at room temperature
Packaging Description:	Polyethylene bottles

9.2. Study Drug Packaging and Labeling

At a minimum the following information will be included on each bottle:

- Name of Sponsor
- Study number/Acronym/IND number
- Route of administration
- Quantity of dosage unit
- Directions for use
- Storage conditions
- Space for information to be completed by Investigator/designee:
    - Name and telephone number of Investigator
    - Dispensing date
    - Subject number
- Statement "Caution: New Drug – Limited by federal law to investigational use"
- Statement: "Keep out of reach of children"

9.3. Study Drug Storage

The study drug MN-166 should be stored at room temperature (preferably 18-23^{0}C, but 15-25^{0}C is acceptable).

9.4. Study Drug Administration

The study drug will be dispensed by appropriately qualified site study staff as indicated on the delegation of authority log. Subjects will self-administer the study drug orally at home following the directions given to them in the clinic. The subject will be instructed to return all unused study drug to the clinical trial site at each visit. The subject will be given a drug administration diary to complete and have available for telephone and clinic visits. Subject drug diary information will be transcribed into eCRF from the subject's diary at each monthly telephone or clinic visit. If the subject loses a diary he will be advised to keep drug administration data on a separate piece of paper until he had a replacement diary.

9.5. Study Drug Accountability

Investigational clinical supplies must be received by the PI or a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and/or designated assistants have access. Clinical supplies are to be dispensed only in accordance with the protocol.

The PI or designee is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the study. At the end of the study, all clinical supplies must be returned to the Sponsor, or designee, after confirmation with the CRA (Clinical Research Associate) or destroyed at the clinical site. Study drug will not be destroyed until written documentation is received from the study sponsor or designee. Proper documentation of the destruction of study drug must be provided by the site.

The following information is to be included in each subject's CRF: visit medication dispensed, dosing start/stop dates, dosage level, number of tablets dispensed and number of tablets returned.

10. ASSESSMENTS OF SAFETY AND CLINICAL ENDPOINT RESPONSIVENESS

10.1. Primary Endpoints

Safety will be assessed by the proportion of subjects with the following events:

- clinical and laboratory treatment emergent adverse events (TEAEs)
  - stratified by severity
  - stratified by persistence over time
  - stratified by relationship to study drug
- discontinuations due to TEAEs
- treatment emergent serious adverse events (TESAEs)

Safety (relationship and severity) and tolerability will further be assessed by statistical and clinical review of AEs, laboratory values, ECGs, physical examinations, vital signs and weight.

10.2. Secondary Endpoints

The secondary endpoints focused on clinical endpoint responsiveness are:

- Change from baseline in functional status (ALSFRS-R)
- Change from baseline in muscle strength as measured by a manual muscle test
- Change from baseline in instrumented hand grip strength
- Change from baseline in respiratory function as measured by Slow Vital Capacity (SVC)
- Change from baseline in respiratory function as measured by Maximum Inspiratory Pressure / Negative Inspiratory Force (MIP/NIF)
- Change from baseline in respiratory function as measured by Forced Expiration Volume in 1 second [FEV_1] under conditions of slow vital capacity.
- Change from baseline in respiratory function as measured by Maximum Voluntary Ventilation (MVV)
- Change from baseline in Amyotrophic Lateral Sclerosis Assessment Questionnaire-5 (ALSAQ-5)
- Change from anchored visit in Clinical Global Impression of Change (CGIC)

11. ADVERSE EVENTS

11.1. Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a study subject administered a medicinal (investigational) product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Adverse events may include the onset of a new illness and the exacerbation of pre-existing conditions.

Other untoward events occurring in the framework of a clinical study are also to be recorded as AEs (e.g., those occurring during treatment-free periods, including screening or post-treatment follow-up periods), in association with study-related procedures and assessments.

In this study, symptoms of progression/worsening of ALS, including 'normal' progression, will be recorded as adverse events. The following measures of disease progression will not be recorded as adverse events even if they worsen: vital capacity results, non-invasive ventilatory requirements, and ALSFRS-R, and ALSAQ-5. These measures will be recorded and analyzed separately.

11.2. Assessment of Adverse Events

The PI or an authorized physician will assess all AEs for severity, relationship with study medication, and whether it meets the criteria for classification as a SAE, requiring immediate notification to the Sponsor or designee (see Section 11.5). These assessments will be made in accordance with the standard ratings detailed in the following sections.

11.2.1. Severity Assessment

The severity of AEs will be determined as described in Table 4.

Table 5: Adverse Events Severity Definitions

Mild Grade 1	Ordinarily transient symptoms that do not influence performance of subject's daily activities. Treatment is not ordinarily indicated.
Moderate Grade 2	Marked symptoms sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Treatment may be necessary.
Severe Grade 3	Symptoms cause considerable discomfort. Substantial influence on subject's daily activities. May be unable to continue in the study and treatment may be necessary.

Life-threatening Grade 4	Extreme limitation in activity, significant assistance required; significant medical/therapy intervention required hospitalization probable.
Death Grade 5	Death.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted for that day. Any change in severity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended severity grade and the date (and time, if known) of the change.

11.2.2. Relationship to Study Drug

One of the following categories in Table 5 should be selected based on medical judgment, considering the definitions below and all contributing factors.

Table 6: Adverse Event Causality Definitions

Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which cannot be explained by concurrent disease or other medications or chemicals. The response to withdrawal of the treatment (dechallenge[a]) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge[b] procedure if necessary.
Probably related	A clinical event, including laboratory test abnormality, occurs within a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other medications or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
Possibly related	A clinical event, including laboratory test abnormality, occurs within a reasonable time sequence to administration of the treatment, but which could also be explained by concurrent disease or other medications or chemicals. Information on treatment withdrawal may be lacking or unclear.
Unlikely to be related	A clinical event, including laboratory test abnormality, occurs with a temporal relationship to treatment administration that makes a causal relationship improbable, and in which other medications, chemicals, or underlying disease provide plausible explanations.
Unrelated	A clinical event, including laboratory test abnormality, occurs with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors, or other medications or chemicals).

[a] Dechallenge is when a medication suspected of causing an AE is discontinued. If the symptoms of the AE disappear partially or completely, within a reasonable time from medication discontinuation, this is termed a positive dechallenge. If the symptoms continue despite withdrawal of the medication, this is termed a negative dechallenge. Note that there are exceptions when an AE does not disappear upon discontinuation of the medication, yet medication-relatedness clearly exists (e.g., as in bone marrow suppression, fixed medication eruptions, or tardive dyskinesia).

[b] Rechallenge is when a medication suspected of causing an AE in a specific subject in the past is readministered to that subject. If the AE recurs upon exposure, this is termed a positive rechallenge. If the AE does not recur, this is termed a negative rechallenge.

As this is a double-blind study, the causality assessment should be made under the assumption that the subject is receiving active study medication. If considering unblinding, this assessment should be made prior to unblinding to avoid bias.

11.3. Recording Adverse Events

Adverse events should be collected and recorded for each subject from the date the informed consent form (ICF) was signed until the end of their participation in the study, (ie, the subject has discontinued or completed the study) through the follow-up visit with the exception of those subjects who discontinue study medication during the study and are followed on a semi-annual basis. Subjects who discontinue study medication but continue follow-up within the study will not have AEs collected after study drug discontinuation. Only those AEs that occurred while on study drug that have not been resolved will be followed until resolution or stabilization.

Following the end of the subject's participation in the study, the PI or an authorized delegate should report SAEs "spontaneously" if considered at least possibly related to study medication.

Adverse events may be volunteered spontaneously by the study subject, or discovered by the study staff during physical examinations or by asking an open, non-leading question such as, "How have you been feeling since you were last asked?" All AEs and any required remedial action will be recorded in the subject's source documentation and transcribed onto the appropriate CRF page for the study period indicated. The nature of AE, date (and time, if known) of AE onset, date (and time, if known) of AE outcome to date, severity, and action taken of the AE will be documented together with the PIs or an authorized physician's assessment of the seriousness of the AE and causal relationship to study medication and/or study procedure (at the time of assessment).

All AEs should be recorded individually in the study subject's own words (verbatim) unless, in the opinion of the PI or an authorized physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual symptom. The AEs will subsequently be coded using the MedDRA.

11.4. Treatment and Follow-Up of AEs

Appropriate measures should be taken to treat AEs as necessary, and the response of the study subject should be monitored and recorded. Clinical, laboratory, and diagnostic

measures should be obtained as needed, and the results of which should be recorded in the subject's source documentation and transcribed onto the appropriate CRF page.

All SAEs will be followed until resolution, stabilization of the condition, the event is otherwise explained, or the subject is lost to follow-up.

11.5. Serious Adverse Events (SAEs)

An AE is considered serious if it meets one or more of the following criteria:

- Results in death
- Is life-threatening (i.e., a subject is at immediate risk of death at the time of the event, not an event where occurrence in a more severe form might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is another important medical event (see below).

Important medical events that do not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or in a physician's office, blood dyscrasias or seizures that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse. A distinction should be drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE, but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity, but would probably not be considered an SAE.

11.5.1. SAE Reporting Requirements

The PI or an authorized delegate is responsible for faxing the requested SAE information to the Sponsor or designee within 24 hours or as soon as possible after learning of the event. Following the end of the subject's participation in the study, the PI or an authorized delegate should report SAEs "spontaneously" if considered at least possibly related to study medication.

Notification should be made by fax or email a completed SAE Report Form to the Sponsor. Study sites in the US should fax or email a completed SAE Report Form to fax number 858-404-0048 or safetymonitors@medicinova.com**.** As a minimum requirement, the initial notification should provide the following information:

- Study number
- Subject number
- Gender
- Date of birth
- PI's name and full study site address
- Details of SAE
- Criterion/criteria for classification as "serious"
- Study medication name, or code if blinded, and treatment start date
- Date of SAE onset
- Causality assessment (if sufficient information is available to make this classification).

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (e.g., hospital reports, consultant reports, autopsy reports, etc.), with the study subject's personal identifiers removed. All relevant information obtained by the PI or an authorized delegate through review of these documents will be recorded on the AE eCRF page and/or a new SAE Report Form and faxed to the Sponsor or designee within 24 hours of receipt of the information. If a new SAE Report Form is faxed, the PI must sign and date the form. The Sponsor may also request additional information on the SAE, which the PI or an authorized delegate must fax to the Sponsor or designee within 24 hours of the request using a new SAE Report Form, bearing the PI's signature and date.

Any AE fulfilling the criteria for expedited reporting will be reported by the Sponsor to regulatory authorities and Investigators and IEC(s) in accordance with the Sponsor's standard operating procedures (SOPs) and local regulatory requirements.

The PI should report all Investigational New Drug Application safety alerts received from the Sponsor to the local IRB.

11.6. Guidance for Overdose

There is no clinical experience with MN-166 overdose in humans and there is no available specific antidote to the effects of MN-166. Standard symptomatic support measures should be used in the case of excessive pharmacological effects or overdose.

11.7. Reporting and Follow-up of Pregnancies

If any study subject or subject's partner becomes pregnant after receiving the first dose of study medication (MN-166 or placebo) and until the follow-up period specified in the protocol, the PI or an authorized delegate should submit a Pregnancy Report Form to the sponsor within 24 hours of the PI or an authorized delegate first becoming aware of the pregnancy. If a pregnancy is to be terminated, the anticipated date of termination should

also be provided in the "Additional Information/Comments" field of the Pregnancy Report Form. If a maternal SAE is reported for the study subject during the initial notification of pregnancy, a separate SAE Report Form should also be completed and submitted to the sponsor within 24 hours of the PI or an authorized delegate first becoming aware of the SAE.

Subjects who become pregnant while in the study should be followed for the duration of their pregnancy. If the pregnancy is discovered between regularly scheduled study visits, subjects should return for an unscheduled visit to return their study medication. A quantitative β-hCG should be obtained and subjects should be encouraged to return for follow-up visits. If follow-up visits are not possible, then the principal investigator should collect information about the pregnancy such as spontaneous or elective termination, details of birth, and presence or absence of birth defects, congenital abnormalities, or maternal and newborn complications.

The Sponsor will request that the PI follow the progress of the study subject's pregnancy with the doctor medically responsible for the pregnancy. A new Pregnancy Report Form should be submitted within 24 hours of the PI or an authorized delegate first becoming aware of any new information.

If additional information on the outcome of the pregnancy and/or the details of the birth/delivery is received "spontaneously" by the study site, the PI or authorized delegate should also submit a Pregnancy Report Form within 24 hours of becoming aware of the information. If the outcome of the pregnancy is reported as premature birth, or as elective termination due to a medical reason or as spontaneous or accidental miscarriage, the details of the outcome should be described in the "Additional Information/Comments" field of the Pregnancy Report Form. The pregnancy outcome will generally be reported as a follow-up report.

Complete an SAE Report Form if the delivery outcome meets the criteria for a SAE (e.g., congenital anomaly/birth defect, stillbirth, some other sickness, etc.). The SAE Report Form should be completed with the study subject's details (e.g., subject number, initials, date of birth, investigational product information, etc.) and the details of the fetal SAE and maternal complications should be described in the "Narrative" field of the SAE Report Form.

If a pregnancy is reported for the study subject's partner, the sponsor will provide instructions on how to collect pregnancy information in accordance with local requirements.

11.8. Preplanned Hospitalizations or Procedures

During the study, if a subject has a hospitalization or procedure (e.g., elective surgery) that was scheduled prior to the subject entering the study (i.e., before the subject signed the ICF) for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of an SAE. However, if the event/condition worsens during the study, it must be reported as an AE or SAE (if the event/condition results in a serious outcome such as prolongation of hospitalization.)

12. STATISTICAL CONSIDERATIONS

The Statistical Analysis Plan (SAP) will provide comprehensive details on the statistical methods planned for this study.

12.1. Data Analysis

12.1.1. Analysis Populations

Safety Analysis Set: The group of subjects who received at least one dose of study drug and had at least one post dose safety assessment.

Full Analysis Set (FAS): The group of randomized subjects who received at least 14 days of study drug and had at least one post-dose efficacy measurement.

12.1.2. Sample Size Justification

No prior data are available on which to base assumptions for sample size/power considerations. The results of this pilot study will be used to design future studies, and the sample size of 120 subjects is deemed to be appropriate for this purpose.

12.1.3. Safety Analysis

Safety analyses will be conducted on the Safety Analysis Set.

The incidence of treatment-emergent AEs (TEAEs, defined as AEs occurring from the time of first dose through 7 days after the last dose of study medication), SAEs and AEs leading to discontinuations will be summarized by treatment group. Incidence of TEAEs will also be summarized by severity (mild, moderate, or severe), as well as by relationship to treatment (not related, possibly related, or probably related) and by seriousness.

Changes from baseline in laboratory values will be summarized by treatment groups for continuous variables. Lab shift tables showing incidence of new or worsening clinically significant findings from baseline to the last visit will be displayed by treatment groups. Shift from baseline to the highest lab value, and from baseline to the lowest lab value will also be displayed.

Incidence of out-of-normal-range values and markedly abnormal change from baseline in laboratory safety test variables will be tabulated by treatment group.

Changes in vital signs from baseline to each visit will be summarized by treatment groups.

12.1.4. Clinical Endpoint Responsiveness Analysis

The clinical endpoints for early and advanced ALS subject will be analyzed separately. All clinical endpoints will be analyzed for responsiveness using analysis of covariance (ANCOVA) models with treatment group (three levels: placebo intent to treat, 60 mg/d

intent to treat and 30 mg/d down-titrated and unable to return to 60mg/d) as a factor and the baseline value of the corresponding endpoint as a covariate. The pairwise comparisons between 30 mg/d down titrated and placebo, 60mg/d completers and placebo, and between 60 mg/d intention to treat and placebo will be tested. All clinical endpoint analyses will be carried out using two-sided tests at the alpha=0.05 level of significance.

12.2. Direct Access to Source Data/Documents

By signing this protocol, the PI agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (GCP); and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The PI also agrees to allow monitoring, audits, and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The PI shall prepare and maintain complete and accurate study documentation in compliance with GCP standards and applicable federal, state, and local laws, rules, and regulations; and, for each subject participating in the study, provide all data, and upon completion or termination of the clinical study submit any other reports to the Sponsor, or its designee, as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor, or its designee, by the PI upon request and shall also be made available at the PI's site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The PI agrees to promptly take any reasonable steps that are requested by the Sponsor, or its designee, as a result of an audit to address deficiencies in the study documentation and worksheets/CRFs.

The PI will promptly inform the Sponsor or its designee of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The PI will immediately disclose in writing to the Sponsor or its designee if any person who is involved in conducting the study is debarred, or if any proceeding for debarment is pending or, to the best of the Investigator's knowledge, threatened.

12.3. Study Monitoring

Monitoring will include on-site monitoring to assure that the investigation is conducted according to protocol, to protect subject rights and safety, and to confirm data integrity and quality.

This study will be monitored through all phases of study conduct by the Sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with guidelines of GCP. On-site review of CRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject. Investigators will be required to store all source documents.

12.4. Audits and Inspections

The PI and appropriate personnel may be periodically requested to attend meetings organized by the Sponsor or its designee to assure acceptable protocol execution. The study may be subject to audit by the Sponsor/designee or by regulatory authorities. If such an audit occurs, the PI must agree to allow access to required subject records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring and auditing of all appropriate study documentation, as well as on-site review of the procedures employed in CRF generation, where clinically appropriate. The PI has to inform the Sponsor if he/she is approached for a regulatory audit.

12.5. Institutional Review Board (IRB)

Before initiation of the study, the PI must obtain approval of the research protocol, informed consent form (ICF), and any advertisement for subject recruitment from the IRB complying with the provisions specified in the Code of Federal Regulations (CFR) 21 Part 56 and applicable government regulations. A copy of written IRB approval of the protocol, ICF, and advertising (if applicable) must be provided to the Sponsor or their designee prior to initiation of the study.

12.6. Study Documentation

By signing a copy of Form FDA 1572, the Investigator acknowledges that he/she has received a copy of the investigational drug brochure on MN-166 and assures the Sponsor that he/she will comply with the protocol and the provisions stated in Form FDA 1572. No changes in this protocol can be made without the Sponsor's written approval.

The Investigator will supply the Sponsor with the following:

1. Original, signed Form FDA 1572;
2. Curricula vitae for all Investigators listed on Form FDA 1572;
3. Copy of the Investigator's medical licensure/medical registration number;
4. Signed protocol signature page;
5. Signed IB signature page;
6. Financial disclosure forms for all study staff listed on the FDA 1572.

13. QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the Sponsor and Clinical Study Site Principal Investigator agree to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures (SOPs) reviewed and approved by the sponsor to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

14. ETHICS

14.1. Ethics Review

Documented approval from the IRB will be obtained for all participating centers prior to clinical trial start, according to ICH (International Conference on Harmonisation) GCP, local laws, regulations and organization. When necessary, an extension, amendment or renewal of the CIRB approval must be obtained.

14.2. Ethical Conduct of the Study

The procedures set out in this clinical trial protocol pertaining to the conduct, evaluation, and documentation of this clinical trial, are designed to ensure that the Sponsor and Principal Investigator abide by Good Clinical Practice Guidelines (GCP in the appropriate current version). The clinical trial will also be carried out in accordance with applicable local law(s) and regulation(s). This may include an inspection by representatives from MediciNova Inc. and/or Regulatory Authority representatives at any time. The PI must agree to the inspection of clinical trial-related records by MediciNova, Inc. representatives, and must allow representatives direct access to source documents.

14.3. Written Informed Consent

An information and consent form will be provided to the subject. The process of obtaining informed consent must be in accordance with applicable regulatory requirements, and must adhere to GCP and ethical principles in the Declaration of Helsinki. Written informed consent must be obtained and documented before any clinical trial-specific procedure takes place. Participation in the clinical trial and date of informed consent given by the subject must be documented in the subject files.

14.4. Confidentiality

14.4.1. Confidentiality of Data

By signing this protocol, the Investigator affirms to the Sponsor that information furnished to the Investigator by the Sponsor will be maintained in confidence and such information will be divulged to the IRB or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

15. DATA HANDLING AND RECORDKEEPING

15.1. Review of Records

The results from Screening and data collected during the study will be recorded in the subject's CRF, which will be designed and provided by the sponsor or a designee. The Investigator will review all CRFs. The CRFs will be signed by the PI or a sub-Investigator who is listed on the Form FDA 1572 if the PI is unavailable. In order to maintain confidentiality, the subject will be identified only by his/her subject number and initials.

15.2. Retention of Records

The PI must arrange for retention of study records at the site for at least two years after the New Drug Application (NDA) is approved or Investigational New Drug (IND) is withdrawn, as required by the US Food and Drug Administration (FDA) regulations, or in accordance with local and/or national requirements, whichever is longer. The PI should take measures to prevent accidental or premature destruction of these documents. Documents cannot be destroyed without written Sponsor authorization. The Sponsor will inform the PI when the destruction of documents is permitted.

16. ADMINISTRATIVE AND REGULATORY DETAILS

16.1. Protocol Amendments and Study Termination

All revisions and/or amendments to this protocol must be approved in writing from the Sponsor and the IRB, except where necessary to eliminate an apparent immediate hazard to a study subject.

16.2. Discontinuation of the Study

The Sponsor reserves the right to discontinue the study at site(s) for safety or administrative reasons at any time. Should the study be terminated and/or the site closed for whatever reason, all documentation and study medication pertaining to the study must be returned to the Sponsor or its representative.

16.3. Compliance with Financial Disclosure Requirements

By signing this protocol, the PI agrees to provide to the Sponsor accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by the US FDA regulations (21 CFR Part 54). The PI further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by MediciNova, Inc. The Investigator will update this information if there are any relevant changes during the conduct of the study and for one year after completion of the study. This requirement also extends to sub-Investigators. The PI also consents to the transmission of this information to MediciNova, Inc. for these purposes.

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18. APPENDICES

Appendix 1: Laboratory Safety Tests for MN-166

Blood Chemistry Tests
aspartate aminotransferase (AST)
alanine aminotransferase (ALT)
albumin
alkaline phosphatase
bicarbonate
blood urea nitrogen
calcium
chloride
creatinine
gamma-glutamyl transferase
potassium
sodium
total bilirubin[a]
total protein
glucose
creatinine kinase
Endocrine Tests
serum beta-human chorionic gonadotropin (for females of childbearing potential)
urine beta-human chorionic gonadotropin
Hematology Tests
white blood cell count
white blood cell differential
eosinophilic leukocyte count
basophilic leukocyte count
neutrophil count
lymphocyte count
monocyte count
platelet count
hemoglobin
blood hematocrit
red blood cell count
red cell distribution width
red blood cell indices:
mean corpuscular volume
mean corpuscular hemoglobin concentration
mean corpuscular hemoglobin
Urinalysis Tests
color
appearance
total ketones
urobilinogen
bilirubin
red blood cells
leukocyte esterase
nitrite
pH

	protein
	specific gravity
	glucose
	microscopic evaluation[b]

[a] Bilirubin will be fractionated (direct serum bilirubin test/indirect serum bilirubin test) if elevated 2.0 times the upper limit of the normal range.

[b] Microscopic evaluation will be performed if dipstick analysis indicates the presence of any significant abnormality.

Appendix 2: ALS Functional Rating Scale-R

(Revised)	ALS	FUNCTIONAL	RATING	SCALE	2009
	4	3	2	1	0
Speech	☐ Normal	☐ Detectable speech disturbance	☐ Intelligible with repeating	☐ speech combined with non-verbal comm.	☐ loss of useful speech
Salivation	☐ Normal	☐ Slight but definite excess of saliva in mouth; may have nighttime drooling	☐ Moderately excessive saliva; may have minimal drooling	☐ Marked excess of saliva with some drooling	☐ Marked drooling
Swallowing	☐ Normal	☐ Early eating problems; occasional choking	☐ Dietary consistency changes	☐ Needs supplemental tube feedings	☐ NPO
Handwriting (dominant hand, no adaptive equip)	☐ Normal	☐ Slow or sloppy; all legible	☐ Not all words legible	☐ Able to grip pen; unable to write	☐ Unable to grip pen
Cutting food (without gastrostomy; ------ dominant hand, no adaptive equip)	☐ Normal	☐ Somewhat slow and clumsy; needs no help	☐ Can cut most foods; slow and clumsy; some help needed	☐ Foods cut by someone else; can still feed slowly	☐ Needs to be fed
(with gastrostomy) ---------	☐ Normal	☐ Clumsy; able to perform all manipulations	☐ Some help needed with closures and fasteners	☐ provides minimal assistance to caregiver	☐ Unable to perform any aspect of task
Dressing & Hygiene	☐ Normal	☐ Independent self care with effort or decreased efficiency	☐ Intermittent assistance or substitute methods	☐ Needs attendant for self care	☐ Total dependence
Turning in bed & Managing bedclothes (no adaptive equip)	☐ Normal	☐ Somewhat slow or clumps; needs no help	☐ Can turn alone or adjust sheets with great difficulty	☐ Can initiate; cannot turn or adjust sheets	☐ Helpless
Walking	☐ Normal	☐ Early ambulation difficulties	☐ Walks with assistance	☐ Non-ambulatory; functional movement only	☐ Unable to perform any aspect of talk
Climbing stairs	☐ Normal	☐ Slow	☐ Mild unsteadiness or fatigue	☐ Needs assistance	☐ Cannot do
Dyspnea	☐ None	☐ Occurs when walking	☐ Occurs with one or more: eating/bathing/dressing	☐ Occurs at rest: either sitting or lying	☐ Significantly difficult; considering mechanical support
Orthopnea	☐ None	☐ Some difficulty sleeping d/t SOB; does not routinely use > 2 pillows	☐ Needs extra pillows to sleep; (> 2)	☐ Can only sleep sitting up	☐ Unable to sleep
Respiratory Insufficiency	☐ None	☐ Intermittent use of BiPap	☐ Continuous use of BiPap at night	☐ Continuous use of BiPap day and night	☐ Continuous use of mechanical ventilation, intubation/trach
Totals	_____	_____	_____	_____	_____

Reviewed by:_____ Date:_____ Time:_____

Carolinas Medical Center
Department of Neurology
Carolinas Neurolmuscular/ALS Center
ALS FRS (revised)

Name:
DOB:
Medical Record #:

03/14/2011

Appendix 3: ALSAQ-5

Instructions to patient.

Please complete this questionnaire as soon as possible. If you have any difficulties filling in this questionnaire by yourself, please have someone help you. However, it is your responses that we are interested in.

The questionnaire consists of a number of statements about difficulties that you may have experienced during the last 2 weeks. There are no right or wrong answers: your first response is likely to be the most accurate for you. Please check the box that best describes your own experiences or feelings.

Please answer every question even though some may seem very similar to others, or may not seem relevant to you.

All the information you provide is confidential.

The following statements all refer to difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you cannot do the activity at all please check Always/cannot do at all.

How often during the last 2 weeks have the following been true?

Please check **one box** for each question.

Never Rarely Sometimes Often Always or cannot do at all

1. I have found it difficult to stand up.
2. I have had difficulty using my arms and hands.
3. I have had difficulty eating solid food.
4. I have felt that my speech has not been easy to understand.
5. I have felt hopeless about the future.

Appendix 4: Model Informed Consent Form

STATISTICAL ANALYSIS PLAN

A SINGLE-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED SIX-MONTH CLINICAL TRIAL FOLLOWED BY AN OPEN LABEL EXTENSION TO EVALUATE THE SAFETY, TOLERABILITY AND CLINICAL ENDPOINT RESPONSIVENESS OF IBUDILAST (MN-166) IN SUBJECTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Protocol No. MN-166-ALS-1201 (31 May 2016 (Amendment 4))

Sponsor: **MediciNova, Inc.**
4275 Executive Square, Suite 300
La Jolla, CA 92037

Prepared by: **MediciNova, Inc.**
4275 Executive Square, Suite 300
La Jolla, CA 92037

Contributor: **Charles S. Davis, Ph.D.**
CSD Biostatistics, Inc.
1005 W. Soft Wind Place
Oro Valley, AZ 85737

Version: **3**

Date: **01 MAY 2019**

CONFIDENTIALITY STATEMENT

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

6,7-DHD	6,7-dihydrodiol
AE	adverse event
ALS	amyotrophic lateral sclerosis
ALSFRS-R	amyotrophic lateral sclerosis functional rating scale-revised
ALSAQ-5	Amyotrophic Lateral Sclerosis Assessment Questionnaire-5
ALT/SGPT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST/SGOT	aspartate aminotransferase
b.i.d.	twice daily
BLQ	below limit of quantification
CGIC	clinical global impression scale
CI	confidence interval
CRF	case report form
CS	clinically significant
CSR	clinical study report
ECG	electrocardiogram
ET FAS	Early Termination Full Analysis Set
FEV_1	forced expiratory volume in one second
G	gram(s)
ISF	Investigator Site File
ISM	independent safety monitor
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
MIP	maximum inspiratory pressure
ms	millisecond(s)
MVV	maximal voluntary ventilation
NCS	not clinically significant
NIF	negative inspiratory force
NIV	non-invasive ventilator
OLE	open-label extension
PK	pharmacokinetic(s)
QTc	corrected QT interval
QTcB	QT interval corrected according to Bazett's method
QTcF	QT interval corrected according to Friderecia's method
RTF	rich text format
SAE	serious adverse event
SD	standard deviation
SE SOC	standard error system-organ-class
SVC	slow vital capacity
TEAE	treatment-emergent adverse event
TMF	trial master file
WHO	World Health Organization

DEFINITIONS

Adverse Event	An adverse event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product, regardless of causality assessment.
Full Analysis Set Population	Group of randomized subjects who received at least 14 days of study drug and had at least one post-dose efficacy measurement.
Safety Analysis Set Population	Group of subjects who received at least one dose of study drug and had at least one post-dose safety assessment.
Serious AE	An AE occurring at any dose that: results in death; is a life-threatening experience; requires inpatient hospitalization or prolongation of an existing hospitalization; results in a persistent or significant disability/incapacity; or is a congenital anomaly/birth defect in the offspring of a patient who received study drug.
Treatment-emergent AE	AEs occurring from the time of first dose through 7 days after the last dose
Treatment group "Placebo"	Subjects received placebo during the double-blind phase
Treatment group "MN-166"	Subjects received MN-166 during the double-blind phase
Treatment group Placbeo/MN-166	Subjects received placebo during double blind phase and received MN-166 druing open-label phase
Treatment group MN-166/MN-166	Subjects received MN-166 for both double-blind phase and open-label phase

1 INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of MediciNova, Inc. Protocol No. MN-166-ALS-1201 [**A SINGLE-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED SIX MONTH CLINICAL TRIAL FOLLOWED BY AN OPEN-LABEL EXTENSION TO EVALUATE THE SAFETY, TOLERABILITY AND CLINICAL ENDPOINT RESPONSIVENESS OF IBUDILAST (MN-166) IN SUBJECTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)**] (**NCT02714036**). The purpose of this plan is to provide specific guidelines from which the analysis will proceed. Any deviations from these guidelines will be documented in the clinical study report (CSR).

2 STUDY OBJECTIVES

The primary objective of this clinical study is to examine the safety and tolerability of MN-166 60 mg/d versus placebo when administred with riluzole in subjects with amyotrophic lateral sclerosis (ALS).

The secondary objective is to evaluate the clinical endpoint responsiveness of MN-166 60 mg/d versus placebo when administered with riluzole in subjects with ALS as measured by the following assessments:

- Functional activity as assessed by the Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRS-R) test battery.
- Respiratory function as measured by slow vital capacity (SVC), Maximum Inspiratory Pressure (MIP) also known as Negative Inspiratory Force (NIF), and Maximal Voluntary Ventilation (MVV).

3 STUDY DESIGN AND PLAN

This is a U.S.-based, single-center, randomized, double-blind, placebo-controlled, 6- month study. Each subject will receive MN-166 (ibudilast) or placebo administered orally (60 mg/d) as an adjunct to riluzole (50 mg bid) for ALS. Upon completion of the Double-blind Phase, subjects randomized to the placebo arm will continue for an additional 6 months and will receive open-label MN-166. The safety data will also be reviewed at Month 6 and if there are no safety or tolerability concerns in the MN-166 treated group, a decision will be made to extend participation to the MN-166 treated group into the Open-label Extension (OLE) Phase. Otherwise, only the placebo-treated patients will participate in the OLE Phase.

This study is designed to evaluate the safety, tolerability and clinical endpoint responsiveness of MN-166 (60 mg/d) when administered as an adjunct to riluzole (50 mg bid) in subjects with ALS. This study will consist of two treatment arms, MN-166 and matching placebo.

3.1 STUDY DESIGN

The study will consist of a Screening Phase (up to 3 months prior to baseline) followed by a double-blind Treatment Phase (6 months) and an Open-label Extension (OLE) Phase for the Placebo treatment arm (6 months). Safety, tolerability and clinical endpoint responsiveness will be monitored throughout the 6-month period with in-person visits at 3 and 6 months and monthly

phone calls at months 1, 2, 4, and 5. Plasma samples collected will be analyzed for MN-166. A follow-up visit will take place within 2 weeks after the last dose of study drug.

Patients will be randomized at enrollment to one of the following treatment groups in a 2:1 ratio.

	Double-Blind Phase	**Open-Label Extension Phase**	**ENTIRE STUDY**
Treatment (Treatment group)	MN-166 (MN-166)	MN-166 (MN-166/MN-166)	(MN-166/MN-166)
	Placebo (Placebo)	MN-166 (Placebo/MN-166)	(Placebo/MN-166)

3.2 RANDOMIZATION AND BLINDING

During the Double-blind Treatment Phase, subjects and all personnel involved with the conduct and interpretation of the study, including the investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by the third-party database vendor (ScienceTRAX) and accessible only to authorized persons (e.g., unblinded safety monitor) until the time of unblinding.

To ensure that treatment allocation remains concealed to both staff and participants, the following measures will be taken:

- Active drug and placebo will be identical in appearance
- Drug supplies to investigational pharmacy will be coded
- The randomization list will be held by ScienceTRAX to ensure that treatment allocation is concealed from the investigator's team and the participant, whilst providing provisions for emergency unblinding.

Details of the randomization process will be available in the Investigator Site File (ISF). Randomization roles in the trial outlining who has access to treatment allocation codes will be recorded in the trial master file (TMF).

The randomization system will be web-based and require a personal log-in and password. Only those individuals who are trained and are on the delegation-log can carry out this process.

Once a consented patient meets criteria for clinical trial entry and the subject has been randomly assigned, they will be given a card to indicate they are enrolled in the trial with the emergency contact numbers for medical advice. Patients will be instructed to show this card to any healthcare professional involved in their care who is not involved in the trial. Any trial participant who withdraws from the study will not be replaced.

Subjects will be informed of the treatment that they have received during the double-blind phase after the last subject has completed the open-label extension (OLE) or at the time defined by the principal investigator in consultation with MediciNova.

Randomization will occur in a 2:1 ratio (MN-166: placebo). To be eligible, subjects must have a diagnosis of sporadic or familial ALS with onset of ≤5 years ("early ALS") from first clinical weakness prior to screening or with onset of ≤10 years ("advanced ALS") from first clinical weakness prior to screening for ALS patients on non-invasive ventilator (NIV) support. All subjects must be on a stable dose of riluzole for at least 1 month prior to study drug treatment. All subjects will receive optimized standard of care in addition to MN-166 at an ALS Multidisciplinary Clinic affiliated with an academic medical center. A total of approximately 120 male and female subjects from 18 to 80 years old, inclusive, are planned to be enrolled.

Eligible subjects will be stratified by ALS stage (early, advanced). Approximately 60 subjects will be enrolled into the "early ALS" group with identifying subject numbers starting with the digits "00" and approximately 60 subjects will be enrolled into the "advanced ALS" group with identifying subject numbers starting with the digits "20". Within each stratum, subjects will be randomized in a 2:1 ratio to active drug and placebo (approximately 80 subjects in the MN-166 group; approximately 40 subjects in the placebo group). Upon completion of the Double-blind Phase, subjects randomized to the placebo arm will continue for an additional 6 months and will receive open-label MN-166.

3.3 SAFETY AND EFFICACY ANALYSIS PLAN

Periodic safety and efficacy evaluations will be performed by the unblinded Independent Safety Monitor (ISM) and independent unblinded biostatistician.

The safety and tolerability of MN-166 will be evaluated by an unblinded ISM during the interim safety monitoring assessment after approximately 20-30 subjects each for the early and advanced ALS groups have been followed for approximately 3 months. The safety data will also be reviewed at Month 6 and if there are no safety or tolerability concerns in the MN-166 treated group, a decision will be made to extend participation to the MN-166 treated group into the OLE Phase.

Two interim efficacy analyses will be performed by an independent biostatistician. The biostatistician will be unblinded to the treatment assignments. The first analysis will be performed after the 30th subject in the early ALS group completes 6 months of evaluation during the double-blind phase. The second analysis will be performed after the 30th subject in the advanced ALS group completes 6 months of evaluation during the double-blind phase period. This mid-study analysis will be summarized in a report. Any data collected after this cutoff, that is, from patients continuing to receive extended treatment, will be presented in a separate analysis. All data will be analyzed and summarized in a clinical study report when all patients have discontinued treatment and their data are collected.

4 DETERMINATION OF SAMPLE SIZE

The primary outcomes for the trial are safety and tolerability as measured by treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, ECG results, and discontinuations of study drug. No prior data are available on which to base assumptions for sample size/power considerations. The results of this pilot study will be used to design future

studies, and the sample size of approximately 120 subjects (n=60 early ALS; n=60 advanced ALS) is deemed to be appropriate for this purpose.

5 GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables and data listings. Unless otherwise noted, all statistical testing will be two-sided and will be performed at the 0.05 significance level. Tests will be declared statistically significant if the calculated p-value is <0.05. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. All summary tables will be presented by treatment group. Baseline summaries will also include a total summary column.

Individual subject data obtained from the case report forms (CRFs), clinical laboratory, spirometry testing, muscle and strength testing, ECG lab, pharmacokinetic (PK) data, and any derived data will be presented by subject in data listings.

The analyses described in this plan are considered *a priori*, in that they have been defined prior to database lock and prior to breaking the blind. Any analyses performed subsequent to breaking the blind will be considered post-hoc and exploratory. Post-hoc analyses will be labeled as such on the output and identified in the CSR.

All analyses and tabulations will be performed using SAS Enterprise Guide® Version 6.1 or higher on a PC platform. Tables and listings will be presented in RTF format. Upon completion, all SAS® programs will be validated by an independent programmer. In addition, all program output will undergo a senior level statistical review. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

6 ANALYSIS POPULATIONS

The Safety Analysis population will include all randomized subjects who received at least one dose of study drug and had at least one post dose safety assessment.

The Full Analysis Set (FAS) population will include all randomized subjects who received at least 14 days of study drug and had at least one post-dose efficacy measurement.

The exclusion of any subject from the FAS analysis population will be determined prior to database lock and unblinding.

7 STUDY POPULATION

7.1 SUBJECT DISPOSITION

Subject disposition information will be summarized for all subjects by treatment group. Summaries will include: the number of enrolled (randomized) subjects, the number of subjects in each analysis population, the number of subjects completing study visits at Months 1 to 6 during

the double-blind treatment, the number of subjects completing study visits at Months 7 to 12 during the open-label extension, the number completing the 2-week follow up after the end of treatment, and the primary reason for early termination.

7.2 PROTOCOL DEVIATIONS

Major protocol deviations that could potentially affect the safety or clinical endpoints of the study will be identified prior to database lock and unblinding of individual subject treatment information. Major protocol deviations may include:

- Randomized subjects who did not satisfy certain inclusion and exclusion criteria that would clearly impact efficacy interpretations;
- Subjects who received the wrong treatment or substantially incorrect dose;
- Subjects who received an excluded concomitant treatment that might markedly impact safety or efficacy (see Section 8.3 of the Protocol for Prohibited Medications).

Major protocol deviations will be summarized by deviation category and treatment group.

7.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic variables include: age, sex, ethnicity, and race. Other baseline characteristics include: medical history, weight, height, months since diagnosis. Demographic and baseline characteristics will be summarized for the Safety and Full Analysis Set (FAS) populations.

7.4 PRIOR AND CONCOMITANT MEDICATIONS

All medications will be recorded that were taken from 1 month prior to screening through study completion or early termination.

Concomitant medications will be summarized for each treatment.

8 SAFETY ANALYSES

All safety analyses will be based on the Safety population. All analyses will be stratified by early or advanced ALS. All summaries of safety variables will be given by treatment group for the double-blind phase, for the open-label extension phase and for the entire study (Double-Blind and Open Lable Phase).

8.1 EXTENT OF EXPOSURE

Study drug exposure will be summarized for each treatment using the average number of days on drug. The total subject number of discontinuations and the reasons for discontinuation will be summarized in the Subject Disposition table.

8.2 ADVERSE EVENTS

The incidence of treatment-emergent AEs (TEAEs, defined as AEs occurring from the time of first dose through 7 days after the last dose of MN-166), SAEs and AEs leading to discontinuations will be summarized by treatment group. Incidence of TEAEs will also be summarized by severity

(mild, moderate, or severe), as well as by relationship to treatment (not related, possibly related, or probably related) and by seriousness. If it cannot be determined whether the AE is treatment emergent due to a partial onset date then it will be counted as such.

Summaries that are displayed by system organ class (SOC) and preferred terms will be ordered by descending order of incidence of SOC and preferred term within each SOC.

Summaries of the following types will be presented:

- Subject incidence of TEAEs and total number of unique TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs by MedDRA SOC, preferred term, and highest severity. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported one or more events. AEs with missing severity will be considered severe for this summary.
- Subject incidence of TEAEs by MedDRA SOC, preferred term, and closest relationship to study drug (Related/Not Related). At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported one or more events. AEs with a missing relationship will be considered related for this summary.
- Subject incidence of serious TEAEs and total number of unique serious TEAEs by MedDRA SOC class and preferred term.
- Subject incidence of TEAEs leading to study discontinuation or death by MedDRA SOC and preferred term.

As this is a double-blind study, the causality assessment should be made under the assumption that the subject is receiving active study medication. If considering unblinding, this assessment should be made prior to unblinding to avoid bias.

8.3 CLINICAL LABORATORY EVALUATION

Changes from baseline in laboratory values will be summarized by treatment groups for continuous variables. Lab shift tables showing incidence of new or worsening clinically significant findings from baseline to the last visit will be displayed by treatment groups. Shift from baseline to the highest lab value, and from baseline to the lowest lab value will also be displayed. Incidence of out-of-normal-range values and markedly abnormal change from baseline in laboratory safety test variables will be tabulated by treatment group. Baseline is defined as the last non-missing value prior to the start of study drug administration.

8.4 VITAL SIGNS

Changes in vital signs from baseline to each visit will be summarized by treatment groups.

8.5 PHYSICAL EXAMINATION

Physical examination results will be included in data listings only.

8.6 ELECTROCARDIOGRAM

Investigator assessment (Normal, Abnormal NCS, Abnormal CS) of ECG results will be summarized using shift tables.

Descriptive statistics at baseline and at each post-baseline time point as well as changes from baseline will be summarized for each ECG parameter. In addition, a categorical summary of abnormal QTc values will be presented. At each time point, the number of subjects with QTcF and QTcB values of > 450 ms, > 480 ms, and > 500 ms will be presented. At each post-baseline time point, the number of subjects with change from baseline values in QTcF and QTcB of > 30 ms and > 60 ms will also be presented.

9 CLINICAL ENDPOINT RESPONSIVENESS VARIABLES

The Full Analysis Set (FAS) population will be used for all responsiveness analyses. All analyses will be stratified by early or advanced ALS.

9.1 RESPONSIVENESS VARIABLES

Secondary endpoints focused on clinical responsiveness at 6 months are as follows:

- Change from baseline in function status as measured by the ALSFRS-R
- Change from baseline in respiratory function as measured by Slow Vital Capacity (SVC)
- Change from baseline in respiratory function as measured by Maximum Inspiratory Pressure/Negative Inspiratory Force (MIP/NIF)
- Change from baseline in respiratory function as measured by Maximal Voluntary Ventilation [MVV]
- Change from baseline in Amyotrophic Lateral Sclerosis Assessment Questionnaire-5 (ALSAQ-5)
- Clinical Global Impression of Change
- Change from baseline in muscle strength as measured by manual muscle test
- Change from baseline in instrumented hand grip strength

Additional secondary endpoints are as follows:

- Latency to onset of ALS progression from baseline measured by ALSFRS-R
    - ALS progression is defined as the first decrease in the ALSFRS-R Total Score. Subjects without a decrease are censored on the last assessment date for ALSFRS-R.
- Latency to death (due to ALS) from date of randomization
    - Time to death will be calculated death date from randomization date. Subjects who did not die during the study are censored on last known living date.

Analyses based on unmonitored data are as follows:

- Latency to occurrence of prescription for NIV (early ALS patients only)
- Latency to onset of ALS milestone measured by ALS milestone (assessed by investigator)

9.2 BASELINE VALUES

The baseline value for each endpoint is defined as the last non-missing value prior to study drug initiation. For spirometry endpoints the baseline value will be the value collected during the screening period.

9.3 ADJUSTMENTS FOR COVARIATES

The primary analysis model comparing changes at 6 months in the secondary measures will include the baseline value as a covariate.

9.4 HANDLING OF DROPOUTS OR MISSING DATA

The secondary clinical responsiveness endpoints are assessed at the 3- and 6-month visits. The amount of missing data will be reported for each measure at both time points by treatment group. If a subject has a missing baseline value, the endpoint will be set to missing and will not be included in the analysis. Our primary responsiveness analysis focuses on subjects' 6-month data. For subjects missing 6-month data but with 3-month data, the missing value will be imputed using multiple imputation assuming the missing data are missing at random. The results of this imputation will be compared to an exploratory analysis using a linear mixed model on all post randomization data with contrasts for the between drug group comparison at 6 months. This method also assumes a missing at random missing data mechanism.

9.5 SAFETY MONITORING AND INTERIM EFFICACY ANALYSIS

9.5.1 SAFETY MONITORING

The safety and tolerability of MN-166 will be evaluated by an unblinded Independent Safety Monitor during interim safety monitoring assessments after approximately 20-30 subjects in each stratum (early ALS group and advanced ALS group) have been followed for approximately 3 months. The safety data will also be reviewed at Month 6 in each stratum and if there are no safety or tolerability concerns in the MN-166 treated group, a decision will be made to extend participation to the MN-166 treated group into the Open-label Extension (OLE) Phase. Otherwise, only the placebo-treated patients will participate in the OLE Phase.

Independent oversight of this study will be provided by an Independent Safety Monitor (ISM). The ISM will review safety data to assess risk in the context of possible benefit. Efficacy data will be made available to the ISM upon request. The ISM is empowered to recommend four courses of action with respect to continuing the study:

- The study should continue without modification;
- The study should continue but with modification to the protocol or with additional data presentation needs;

- The study should be temporarily suspended to further enrollment and treatment administration, pending further evaluation of data; or
- The study should be terminated because of safety concerns.
- The ISM is not empowered to recommend premature stopping of the study because of apparent extreme efficacy.

If the ISM determines that an unacceptably greater proportion of subjects is experiencing a safety problem and that there is no counterbalancing evidence of efficacy, the ISM may request a joint decision with MediciNova regarding stopping prematurely or recommending a change in the trial for safety reasons. The responsibility for the final decision regarding a ISM-recommended course of action will rest with MediciNova. Investigational sites will be advised in writing of the course of action recommended by the ISM after each of its review sessions. This information will be promptly forwarded to the Investigator at each study site.

9.5.2 INTERIM EFFICACY ANALYSIS

Two interim efficacy analyses will be performed by an indendent biostatistician who will be unblinded to the treatment. The first analysis will be performed after the 30th subject in the early ALS group completes 6 months of evaluation during the double-blind phase. The second analysis will be performed after the 30th subject in the advanced ALS group completes 6 months of evaluation during the double-blind phase period. This mid-study analysis will be summarized in a report. Any data collected after this cutoff, that is, from patients continuing to receive extended treatment, will be presented in a separate analysis.

The investigator, study staff, and sponsor will not be informed of the treatment assignments given to the subjects, i.e., they will not know the treatment received by individual subjects. Each analysis will focus on the clinical endpoint responsiveness for the early and advanced ALS patient groups separately. Clinical endpoint responsiveness assessments are as follows:

- Change from baseline in function status as measured by the ALSFRS-R
- Change from baseline in respiratory function as measured by Slow Vital Capacity (SVC)
- Change from baseline in respiratory function as measured by Maximum Inspiratory Pressure/Negative Inspiratory Force (MIP/NIF)
- Change from baseline in respiratory function as measured by Maximal Voluntary Ventilation [MVV]

9.6 EXAMINATION OF SUBGROUPS

Efficay analyses will be additionally carried out in the following subgroups:

- Patients with bulbar onset ALS
- Patients with limb onset ALS

9.7 MULTIPLE COMPARISON/MULTIPLICITY

No adjustments for multiplicity will be made in this study.

9.8 MULTICENTER STUDIES

This is a single-center study therefore no adjustments need to be made for multiple centers.

10 METHODS OF CLINICAL RESPONSIVENESS ANALYSIS

10.1 RESPONSIVENESS ANALYSES

The responsiveness comparison will explore the following hypotheses (ALSFRS-R used as an example):

H_0: The average change in the ALSFRS-R at 6 months is equal between the Placebo and MN-166 treatment groups;

H_1: The average change in the ALSFRS-R at 6 months is different between the Placebo and MN-166 treatment groups.

Treatment groups will be compared using an ANCOVA model that includes terms for treatment group, the randomization stratification factor, and baseline ALSFRS-R. Descriptive statistics will be presented as well as estimates of least-square (LS) means, LS mean difference, and p-value from the ANCOVA model. The same analysis approach will be used for all clinical responsiveness endpoints (muscle and respiratory measures) with the exception of the Clinical Global Impression of Change (CGIC) and the occurrence of prescription for NIV. The CGIC is an ordinal measure which will be categorized into "Better" versus "Worse/No Change" and compared between the two groups using the Mantel-Haenszel test stratified by the randomization stratification variable. The occurrence of prescription for NIV and the time to occurrence of prescription for NIV (for early ALS patients only) will be explored using Fisher's exact test and Kaplan-Meier curves with a log-rank test, respectively.

10.2 PHARMACOKINETIC ANALYSES

Specific details regarding the pharmacokinetic (PK) analysis of MN-166 and its metabolite, 6,7-dihydrodiol (DHD), will be documented elsewhere. As specific in the protocol, all plasma concentration-time data sets for MN-166 and 6,7-DHD will be evaluated by a non-compartmental model. Actual sampling time will be utilized for computation of PK parameters. All below limit of quantification (BLQ) values will be set to zero. Missing values will be treated as if they were never drawn. Summary statistics will be provided for all PK parameters. These include mean, median, standard deviation, percent, coefficient of variation, and maximum and minimum values.

11 CHANGES TO PROTOCOL-SPECIFIED ANALYSES

The following modifications have been made to the analyses described in the protocol:

- Added stratification by early and advanced ALS for all analyses
- Added missing data analysis plan

- Added steps to minimize unblinding due to adverse events
- Added analysis plan for CGIC
- Added analysis for latency to onset of ALS progression from baseline measured by ALSFRS-R
- Added latency to death (due to ALS) from date of randomization
- Added Analyses based on unmonitored data:
    - Latency to occurrence of prescription of NIV (early ALS patients only)
    - Latency to onset of ALS milestone measured by ALS milestone (assessed by investigator)

APPENDIX

APPENDIX A: LIST OF TABLES AND DATA LISTINGS

List of Tables: All Tables will be stratified by Early and Advanced ALS. Table numbers with an asterisk (*) will be provided as"Double-blind Phase", "Open-label Phase" and "Entire Study" separately.

Table Number	Table Description
1*	Subject Disposition (All Subjects)
2	Major Protocol Deviations (Safety Population)
3.1	Demographic and Baseline Characteristics (Safety Population)
3.2	Demographic and Baseline Characteristics (FAS Population)
4	Medical History (Safety Population)
5	Prior and Concomitant Medications (Safety Population)
6*	Study Drug Exposure (Safety Population)
7*	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
8*	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Severity (Safety Population)
9*	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug (Safety Population)
10	Treatment-Emergent Serious Adverse Events and Total Number of Unique Serious TEAEs by System Organ Class and Preferred Term (Safety Population)
11*	Treatment-Emergent Adverse Events Leading to Study Discontinuation or Death by System Organ Class and Preferred Term (Safety Population)
12*	Hematology (Safety Population)
13	Hematology – Shift from Baseline (Safety Population)
14*	Serum Chemistry (Safety Population)

Table Number	Table Description
1*	Subject Disposition (All Subjects)
2	Major Protocol Deviations (Safety Population)
3.1	Demographic and Baseline Characteristics (Safety Population)
15*	Serum Chemistry – Shift from Baseline (Safety Population)
16*	Vital Signs (Safety Population)
17*	Electrocardiogram – Investigator Assessment (Safety Population)
18*	Electrocardiogram (Safety Population)
19*	Electrocardiogram – Abnormal QTc Results (Safety Population)
20	ALSFRS-R – Change from Baseline (FAS Population)
21	Manual muscle test – Change from Baseline (FAS Population)
22	Instrumented hand grip – Change from Baseline (FAS Population)
23	Respiratory function as Measured by SVC, MIP/NIF, FEV1, and MVV – Change from Baseline (FAS Population)
24	ALSAQ-5 – Change from Baseline (FAS Population)
25	CGIC (FAS Population)
26	Latency to onset of ALS progression measured by ALSFRS-R (FAS Population)
27	Latency to onset of death due to ALS (FAS Population)

List of Data Listings

List of Listings: All Listings will be stratified by Early and Advanced ALS. Listings numbers with an asterisk (*) will be provided three times (double-blind phase, open label phase, entire study, and will be identified as ”Double-Blind Phase”,"Open-Label Phase” and “Entire Study," respectively).

Listing Number	Listing Description
1*	Subject Disposition
2	Major Protocol Deviations
3	Subject Eligibility
4	Demographics
5	Medical History
6	Serum Pregnancy Test (Female subjects)
7	Urine Pregnancy Test (Female subjects)
8	Prior and Concomitant Medications
9*	Study Drug Exposure
10	Slow vital capacity – Change from Baseline (FAS Population)
11	Maximum inspiratory pressure (MIP)/negative inspiratory force (NIF) – Change from Baseline (FAS Population)
12	Forced Expiratory Volume in One Second (FEV1) measured under SVC protocol (FAS Population)
13	Maximal voluntary ventilation (MVV) (FAS Population)
14	Muscle Strength (FAS population)
15	ALSFRS-R (FAS population)
16	ALSAQ-5 (FAS population)
17	CGIC (FAS polulation)
18	Plasma PK MN-166

Listing Number	Listing Description
19*	Adverse Events
20*	Serious Adverse Events
21*	Adverse Events Leading to Study Discontinuation or Death
22*	Hematology
23*	Serum Chemistry
24*	Urinalysis
25*	Vital Signs
26	Physical/Neurological Examination
27*	12-Lead Electrocardiogram