CLINICAL STUDY PROTOCOL

A Multicenter, Randomized, Parallel Group, Double Blind, Multiple Dose, Placebo Controlled Study to Assess the Efficacy and Safety of MNK-1411 in Male Subjects 4 to 8 Years of Age With Duchenne Muscular Dystrophy

NCT03400852
Summary adjusted for disclosure

Protocol Number: MNK14112096

Date of Original Protocol: 22 August 2017

Date of Protocol Amendment 1: 16 November 2017

Date of Protocol Amendment 2: 22 August 2018

Date of Protocol Amendment 3: 23 May 2019

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PROTOCOL AMENDMENT 3

SUMMARY OF CHANGES

In order to accommodate subject needs, Protocol Amendment 3 was developed primarily to extend the Open Label Extension Period beyond Week 52 (to continue until the subject chooses to discontinue treatment, the investigator feels that treatment is no longer indicated, MNK-1411 is approved and marketed, or the sponsor ceases development of this compound for Duchenne Muscular Dystrophy [DMD]). Open label visits will continue every 12 weeks, with dispensing of study drug every 12 weeks. Along with this change, text has been added stating that if a subject requires a switch in dose during the Open Label Extension Period (eg, switch to low dose due to being unable to tolerate high dose, or switch to high dose based on increased weight [eg, as subject grows with age]), the investigator should consult with the medical monitor. Since subjects will be participating in the study longer, measurements of height have been added to all study visits.

Additional major protocol changes are summarized below and a more comprehensive Summary of Changes document, including minor protocol changes, is provided separately:

- To accommodate the needs of study sites in Israel, the combination of Sunday and Wednesday has been added as possible visit and/or dosage administration days.
- Text has been added specifying that subjects who have a hypersensitivity reaction to the study drug are not required to undergo the 2-week taper, or standard cosyntropin stimulation test (250 µg) at the follow-up visit.
- Varicella zoster testing has been added along with an inclusion criterion (Inclusion criterion 6) requiring subjects to test positive prior to study entry (since such infections may be serious in patients who are immunosuppressed).
- Pharmacokinetic analysis text has been corrected.
- Additional guidance regarding the administration of motor tests (10 Meter Walk/Run, Time to Climb 4 Standardized Stairs, Time to Stand from a Supine Position, North Starr Ambulatory Assessment [NSAA]) has been provided, along with modification of Exclusion criterion 7 to require that subjects be able to complete the 10 Meter Walk/Run test in 10 seconds or less at the Screening and Baseline Visits.

PROTOCOL AMENDMENT 2

SUMMARY OF CHANGES

Protocol Amendment 2 was developed to address the following considerations:

- In a randomized, double-blind, placebo controlled crossover study in patients ages 5 to 8 with Duchenne muscular dystrophy Beenakker et al, 2005 utilized a 2 month washout period between treatment periods with prednisone and placebo and this washout period appeared to be effective. Subsequently a Medical Advisory Board evaluated the current study design and based on their clinical experience recommended allowing the enrollment of subjects who have not received a therapeutic dose of corticosteroids within 2 months prior to the start of the study.
- Subjects with asthma are excluded from the study. Therefore, the concomitant use of inhaled corticosteroids (whose approved indication is for asthma) should not be permitted.

The following changes were made:

Section 12.2, Exclusion criterion 2 was revised to:

> 2. Subject has had previous systemic treatment with corticosteroids within 2 months prior to the Screening Visit. Exception: In subjects who were down-titrated to a physiological dose of corticosteroids (ie, 3 mg/m^2 of prednisone or deflazacort) a maximum of 1 month of no greater than a physiological dose followed by 1 month completely off corticosteroids prior to the Screening Visit will be acceptable for study entry. Transient previous use of corticosteroids will be evaluated on a case-by-case basis by the sponsor or designee. The use of topical or intra-articular corticosteroids is permitted during the study.

Section 13.1, the exception for inhaled corticosteroids was deleted.

PROTOCOL AMENDMENT 1

SUMMARY OF CHANGES

Protocol Amendment 1 was developed to address issues raised by the central institutional review board including adding a study drug taper followed by a cosyntropin stimulation test and clarifying parent and/or legal guardian consent.

Additional minor changes that do not impact study conduct or subject safety were also made.

The major protocol changes are summarized below:

- A mandatory study drug taper has been added. All subjects will complete a 2-week taper after their last full dose of study drug. In the first week of the taper, each subject will receive one-half of their original dose administered 2 times per week for 1 week, followed by one-half of their original dose administered 1 time per week for 1 week.
- All subjects will have a standard cosyntropin stimulation test (250 μg) at their Follow-up Visit.
- References to "legally authorized representative" have been removed from the protocol. Only a parent or legal guardian can give consent for subjects to participate.
- The listing of chemistry laboratory tests in Attachment 1, Section 32.1 has been clarified (creatine updated to creatine phosphokinase).

5. ABBREVIATIONS

Abbreviation	Term
2x/week	2 times per week
ACTH	Adrenocorticotropic hormone
AE	Adverse event
ANOVA	Analysis of variance
AUC	Area under the concentration time curve
CFR	Code of Federal Regulations
CL	Clearance
CL/F	Apparent clearance
C_{max}	Peak drug concentration
eCRF	Electronic case report form
DMD	Duchenne muscular dystrophy
ECG	Electrocardiogram
FDA	Food and Drug Administration
FVC	Forced vital capacity
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
HCV	Hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IGRA	Interferon gamma release assay
IM	Intramuscular, intramuscularly
IMP	Investigational medicinal product
IRB	Institutional Review Board
IXRS	Interactive Phone/Web Response System
MCR	Melanocortin receptor
mITT	Modified Intent-to-Treat
MM	Medical monitor
NSAA	North Star Ambulatory Assessment
PCR	Polymerase chain reaction
PD	Pharmacodynamics

Abbreviation	Term
PK	Pharmacokinetics
PODCI	Pediatric Outcomes Data Collection Instrument
SAE	Serious adverse event
SC	Subcutaneous, subcutaneously
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TFT	Timed function tests
US	United States
V	Volume of distribution
WT_{DMD}	Weight in kg of the DMD subject

6. SYNOPSIS

Study Title: A Multicenter, Randomized, Parallel Group, Double Blind, Multiple Dose, Placebo Controlled Study to Assess the Efficacy and Safety of MNK-1411 in Male Subjects 4 to 8 Years of Age With Duchenne Muscular Dystrophy	
Protocol Number: MNK14112096	Type: Phase 2
Condition/Disease:	Duchenne Muscular Dystrophy
Approximate Number of Subjects: 132	Approximate Duration of Subject Participation: 24 weeks for the Blinded Treatment Period, Open Label Extension Period until study termination.
Approximate Number of Study Centers: 50 globally	Approximate Duration of Study: The Blinded Treatment Period portion of the study is estimated to be 3 years.

Design:

This is a multicenter, double blind, placebo controlled, multiple dose study to examine the safety and efficacy of MNK-1411 in male subjects 4 to 8 years of age (inclusive) with Duchenne Muscular Dystrophy (DMD). Approximately 150 subjects will be screened in order to randomize 132 (44 per treatment group).

Following a screening period of up to 28 days, subjects will be randomized on a 2:2:1:1 basis to receive 24 weeks of treatment with 2 weight based doses of MNK-1411 or volume matched placebo administered 2x/week. Subjects will return to the clinic for visits at 4, 8, 12, 16, and 24 weeks after their first dose of study drug. Subjects who complete the 24-week Blinded Treatment Period will be eligible to enter an Open Label Extension Period where all subjects will receive treatment with MNK-1411. Participation in the Open Label Extension Period will continue until the subject chooses to discontinue treatment, the investigator feels that treatment is no longer indicated, MNK-1411 is approved and marketed, or the sponsor ceases development of this compound for DMD. All subjects will complete a 2-week drug taper after their last full dose of study drug and a follow-up visit 28 (± 7) days after their last full dose of study drug. The taper is not required for any subject who has a hypersensitivity reaction to the study drug.

Objectives:

Primary Objective

To determine the effect of MNK-1411 on motor function in subjects with DMD.

Secondary Objectives

To assess the effect of MNK-1411 on motor skills and strength.

To determine the safety and tolerability of MNK-1411 in subjects with DMD.

Exploratory Objectives

[redacted]

Entry Criteria:

Male subjects 4 to 8 years of age (inclusive) with a diagnosis of DMD confirmed by complete dystrophin deficiency, an identifiable mutation of the DMD gene, or complete dystrophin gene sequencing consistent with DMD, and a clinical profile consistent with DMD. Subjects should have serum potassium within the reference range at screening. Subjects taking approved treatments that target gene mutation (eg, eteplirsen or ataluren) may be enrolled in the study if they have been on a stable dose for 30 days prior to the first dose of study drug, and plan to remain on that dose throughout the study. Subjects will be excluded if they have symptomatic cardiomyopathy; have had any previous systemic treatment with corticosteroids within 2 months prior to the Screening Visit; or treatment with immunosuppressants or mineralocorticoids in the 3 months prior to the Screening Visit. Subjects must be able to complete the 10 Meter Walk/Run test in 10 seconds or less at the Screening and Baseline Visits.

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Concomitant Medications and Treatments: Subjects are not permitted to receive live or live-attenuated vaccines (with the exception of the varicella zoster vaccine, if needed per Inclusion criterion 6), systemic corticosteroids (eg, prednisone or deflazacort) for DMD, mineralocorticoids, or immunosuppressants during the study. All medications and nondrug therapies (eg, physical therapy, blood transfusions, oxygen supplementation, etc) taken from 30 days prior to the Screening Visit and throughout the study will be recorded.

Study Drug and Treatment Administration:

The following treatments will be administered during the 24 week Blinded Treatment Period:

- **Treatment A:** MNK-1411 0.5 mg (0.5 mL, for subjects weighing more than 20 kg) or 0.4 mg (0.4 mL, for subjects weighing less than or equal to 20 kg) administered SC 2 times per week (2x/week) (administered on either Sunday and Wednesday, Monday and Thursday, Tuesday and Friday, or Wednesday and Saturday).
- **Treatment B:** MNK-1411 0.25 mg (0.25 mL, for subjects weighing more than 20 kg) or 0.2 mg (0.2 mL, for subjects weighing less than or equal to 20 kg) administered SC 2x/week (administered on either Sunday and Wednesday, Monday and Thursday, Tuesday and Friday, or Wednesday and Saturday).
- **Treatment C:** Volume matched placebo (0.5 mL for subjects weighing more than 20 kg or 0.4 mL for subjects weighing less than or equal to 20 kg) administered SC 2x/week (administered on either Sunday and Wednesday, Monday and Thursday, Tuesday and Friday, or Wednesday and Saturday).
- **Treatment D:** Volume matched placebo (0.25 mL for subjects weighing more than 20 kg or 0.2 mL for subjects weighing less than or equal to 20 kg) administered SC 2x/week (administered on either Sunday and Wednesday, Monday and Thursday, Tuesday and Friday, or Wednesday and Saturday).

During the Open Label Extension Period, subjects will be treated with MNK-1411 at the dose administered during the Blinded Treatment Period. If a subject requires a switch in dose (eg, switch to low dose due to being unable to tolerate high dose, or switch to high dose based on increased weight [eg, as subject grows with age]), the investigator should consult with the medical monitor. No switches in dose are permitted during the Blinded Treatment Period.

All subjects will complete a 2-week taper after their last full dose of study drug. In the first week of the taper, each subject will receive one-half of their original dose administered 2x/week for 1 week, followed by one-half of their original dose administered 1 time per week for 1 week. The taper is not required for any subject who has a hypersensitivity reaction to the study drug.

Efficacy Evaluations:

The following efficacy assessments will be evaluated: 10 Meter Walk/Run, North Star Ambulatory Assessment (NSAA), Time to Climb 4 Standardized Stairs, Time to Stand from A Supine Position, quantitative muscle testing, pulmonary function tests, and biomarkers.

Pharmacokinetic and Pharmacodynamic Evaluations:

The pharmacokinetics (PK) of MNK-1411 in DMD patients will be characterized using population PK modeling with sparse PK sampling implemented in this study. The exposure response (selected efficacy and/or safety endpoints at Week 4) relationship will be explored.

Safety Evaluations:

The following safety assessments will be evaluated: adverse events, medical history, physical examinations, concurrent medical conditions, height, weight, clinical laboratory tests, vital signs, electrocardiograms, and antidrug antibodies.

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Quality of Life/ Health Outcome Evaluations:

The following quality of life /health outcome assessment will be evaluated: Pediatric Outcomes Data Collection Instrument (PODCI).

Statistical Methods:

Analysis Populations

The following analysis populations are defined for this study:

- The Modified Intent-to-Treat (mITT) Population will include all randomized subjects who receive 1 or more doses of study drug and who contribute any efficacy data to the study.
- The Safety Population will include all subjects who receive 1 or more doses of study drug.
- The PK Population will include all subjects who provide at least 1 quantifiable concentration of $ACTH_{1-24}$ following the administration of at least 1 complete dose of study drug, and without any major protocol deviations that compromise the PK samples.

Sample Size

A total of 132 subjects will be randomized in this study (44 per treatment group). The sample size was determined using the change from baseline in the 10 Meter Walk/Run time. With 37 subjects per treatment group expected to complete the Blinded Treatment Period, the trial will have an 80% power to detect a 1 second treatment difference comparing 2 groups at a significance level of 0.05. Taking into account a dropout rate of approximately 15%, the sample size for this study will be 44 subjects per treatment arm.

Efficacy Analysis

Unless otherwise specified, all statistical tests will be two-sided with a significance level of 0.05. Summary statistics will be provided for all study variables with descriptive statistics (number of observations, mean, SD, median, minimum, and maximum) for numerical (or continuous) variables, and frequency and percentages will be calculated for categorical variables. All data will be summarized by treatment groups as appropriate. The 2 placebo groups will be combined for all analyses. Data summary and analyses will be performed with SAS 9.4 or higher.

The primary efficacy endpoint is a change from baseline in 10 Meter Walk/Run time at Week 24. The primary statistical analysis method for the endpoint will be performed using an analysis of variance (ANOVA) model with treatment as a main factor and baseline value as a covariate.

The secondary efficacy endpoints will be analyzed using the same statistical method as that for the primary efficacy endpoint.

Additional exploratory analyses [redacted]

Pharmacokinetic Analysis

Population PK analysis for MNK-1411 will be conducted using nonlinear mixed effects modeling.

Safety Analysis

Treatment-emergent adverse events and serious adverse events will be summarized using the appropriate version of MedDRA by preferred term within system organ class. Other safety data will be listed and summarized descriptively or graphically, as appropriate.

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Quality of Life/Health Outcomes Analysis

The PODCI (sport and physical functioning domain and transfer/basic mobility domain) will be summarized at baseline and each study visit. Change from baseline to Weeks 4, 8, 12, 16, and 24 in PODCI domains also will be summarized. The change from baseline data will be analyzed using the same methods as those used for the primary efficacy endpoint.

Open Label Extension Analysis

In the Open Label Extension Period, efficacy data will be summarized at each visit. Safety data will also be summarized as appropriate.