

**Clinical trial results:****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****Summary**

| | |
|--------------------------|------------------|
| EudraCT number | 2017-004139-35 |
| Trial protocol | ES BG IT |
| Global end of trial date | 25 February 2020 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 18 February 2021 |
| First version publication date | 06 September 2020 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Correction of typing error: For non-serious adverse events, 5% reporting threshold is corrected to 3% reporting threshold |

Trial information**Trial identification**

| | |
|-----------------------|-------------|
| Sponsor protocol code | MNK14112096 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03400852 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Mallinckrodt ARD LLC |
| Sponsor organisation address | 1425 U.S. Route 206, Bedminster, NJ, United States, 07921 |
| Public contact | Medical Information Call Center, Mallinckrodt ARD LLC, 1 1 800-844-2830 Ext 5, clinicaltrials@mnk.com |
| Scientific contact | Medical Information Call Center, Mallinckrodt ARD LLC, 1 1 800-844-2830 Ext 5, clinicaltrials@mnk.com |

Notes:

Paediatric regulatory details

| | |
|--|-----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 02 May 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 February 2020 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to determine the effect of MNK-1411 on motor function in subjects with Duchenne Muscular Dystrophy (DMD). Information has been collected only from caretakers who are fluent in English, using the Pediatric Outcomes Data Collection Instrument (PODCI). The PODCI is a validated 86-question instrument completed by the parent or legal guardian of children 2 to 10 years of age to assess a variety of health outcome measures (Uzark et al, 2012). This study will only collect information for the PODCI domains of sports and physical functioning and transfer/basic mobility.

Protection of trial subjects:

The study was conducted in full compliance with applicable international, national and local regulatory requirements; US Food and Drug Administration (FDA) regulations including 21 CFR 314.106 and 312.120, (where applicable); and ICH guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 27 July 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | Bulgaria: 2 |
| Country: Number of subjects enrolled | Israel: 1 |
| Country: Number of subjects enrolled | Italy: 2 |
| Country: Number of subjects enrolled | United States: 10 |
| Country: Number of subjects enrolled | Mexico: 18 |
| Country: Number of subjects enrolled | Serbia: 2 |
| Country: Number of subjects enrolled | Turkey: 3 |
| Worldwide total number of subjects | 44 |
| EEA total number of subjects | 10 |

Notes:

| Subjects enrolled per age group | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 44 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After screening, 44 patients were randomized into blinded treatment groups at 16 sites in 8 countries.

Period 1

| | |
|------------------------------|------------------------------|
| Period 1 title | Blinded Treatment Period |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer |

Blinding implementation details:

Patients were randomized 2:1 to receive MNK-1411:placebo at the dose appropriate for their weight

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes |
| Arm title | MNK-1411 |

Arm description:

All patients who received any dose of MNK-1411 in Period 1

| | |
|--|----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Cosyntropin acetate |
| Investigational medicinal product code | MNK-1411 |
| Other name | Tetracosactide Hexaacetate |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

MNK-1411 suspension for subcutaneous injection

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

All patients who received placebo in Period 1

| | |
|--|--------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | Matching placebo |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Matching placebo suspension for subcutaneous administration

| Number of subjects in period 1 | MNK-1411 | Placebo |
|--------------------------------|----------|---------|
| Started | 29 | 15 |
| Completed | 20 | 9 |
| Not completed | 9 | 6 |
| Physician decision | - | 1 |
| Adverse event, non-fatal | 1 | 1 |
| Study terminated by sponsor | 8 | 4 |

Period 2

| | |
|------------------------------|-------------------|
| Period 2 title | Open Label Period |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

All patients entering open label period received MNK-1411

Arms

| | |
|-----------|----------|
| Arm title | MNK-1411 |
|-----------|----------|

Arm description:

All patients who entered the open label extension period receive MNK-1411

| | |
|--|----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Cosyntropin acetate |
| Investigational medicinal product code | MNK-1411 |
| Other name | Tetracosactide Hexaacetate |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

MNK-1411 1 mg/ml [milligram(s)/milliliter] suspension for subcutaneous injection

| Number of subjects in period 2 ^[1] | MNK-1411 |
|---|----------|
| Started | 24 |
| Completed | 2 |
| Not completed | 22 |
| Physician decision | 1 |
| Study terminated by sponsor | 21 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Patients who chose to discontinue double-blind period prior to Week 24, entered OLE

period. Patients who did not enter OLE Period were followed-up to Week 28.

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | MNK-1411 |
|-----------------------|----------|

Reporting group description:

All patients who received any dose of MNK-1411 in Period 1

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

All patients who received placebo in Period 1

| Reporting group values | MNK-1411 | Placebo | Total |
|---|----------|---------|-------|
| Number of subjects | 29 | 15 | 44 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 29 | 15 | 44 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 5.7 | 6.3 | |
| standard deviation | ± 1.49 | ± 1.18 | - |
| Gender categorical Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 29 | 15 | 44 |

End points

End points reporting groups

| | |
|---|----------|
| Reporting group title | MNK-1411 |
| Reporting group description: All patients who received any dose of MNK-1411 in Period 1 | |
| Reporting group title | Placebo |
| Reporting group description: All patients who received placebo in Period 1 | |
| Reporting group title | MNK-1411 |
| Reporting group description: All patients who entered the open label extension period receive MNK-1411 | |

Primary: Time to Complete 10 Meter Walk/Run

| | |
|--|---|
| End point title | Time to Complete 10 Meter Walk/Run ^[1] |
| End point description: 10 Meter Walk/Run is a motor function test to measure the functional capability in patients with DMD. | |
| End point type | Primary |
| End point timeframe: Baseline, Week 24 | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analyses were performed to arrive at these descriptive statistics | |

| End point values | MNK-1411 | Placebo | | |
|-------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 15 | | |
| Units: Seconds | | | | |
| median (full range (min-max)) | | | | |
| at Baseline | 5.9 (4.7 to 22.3) | 7.8 (3.9 to 13.0) | | |
| at Week 24 (n=16,9) | 5.4 (4.1 to 8.9) | 8.7 (3.3 to 18.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: North Star Ambulatory Assessment (NSAA) Score

| | |
|---|---|
| End point title | North Star Ambulatory Assessment (NSAA) Score |
| End point description: The NSAA is comprised of 17 items, each of which is graded using the standard scorecard. Each assessment is rated as 0 - unable to achieve independently, 1 - modified method but achieves goal independent of physical assistance from another, or 2 - normal with no obvious modification of activity. The subscale scores are summed for a total score ranging from 0 to 34. The higher the total score, the better the outcome. | |

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 24 | |

| End point values | MNK-1411 | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 15 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| at Baseline | 17.9 (± 6.80) | 17.1 (± 6.40) | | |
| at Week 24 (n=17,9) | 20.5 (± 7.94) | 16.6 (± 8.82) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Climb 4 Standardized Stairs

| | |
|--|-------------------------------------|
| End point title | Time to Climb 4 Standardized Stairs |
| End point description: | |
| Time to climb 4 standardized stairs is a motor performance test. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 24 | |

| End point values | MNK-1411 | Placebo | | |
|--------------------------------------|------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 15 | | |
| Units: Seconds | | | | |
| arithmetic mean (standard deviation) | | | | |
| at Baseline | 8.528 (± 8.8832) | 8.467 (± 4.3353) | | |
| at Week 24 (n=15,9) | 4.711 (± 2.4547) | 15.087 (± 13.8414) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Stand from a Supine Position

| | |
|-----------------|--------------------------------------|
| End point title | Time to Stand from a Supine Position |
|-----------------|--------------------------------------|

End point description:

Time to stand from a supine position is a motor function test to measure the functional capability in subjects with DMD.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 24

| End point values | MNK-1411 | Placebo | | |
|--------------------------------------|------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 13 | | |
| Units: Seconds | | | | |
| arithmetic mean (standard deviation) | | | | |
| at Baseline | 11.141 (\pm 9.0756) | 15.031 (\pm 12.4518) | | |
| at Week 24 (n=16,9) | 7.645 (\pm 4.9939) | 24.889 (\pm 26.4763) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Quantitative Muscle Testing Scores at Baseline

| | |
|-----------------|--|
| End point title | Quantitative Muscle Testing Scores at Baseline |
|-----------------|--|

End point description:

Quantitative muscle testing measured strength-knee flexion and extension measured in Newtons, using a dynamometer.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

at Baseline

| End point values | MNK-1411 | Placebo | | |
|--------------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 15 | | |
| Units: Newton | | | | |
| arithmetic mean (standard deviation) | | | | |
| Knee flexion | 26.610 (\pm 14.1697) | 29.870 (\pm 14.1697) | | |
| Knee extension | 28.987 (\pm 16.2362) | 26.643 (\pm 15.2748) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Quantitative Muscle Testing Scores at Week 24

| | |
|--|---|
| End point title | Quantitative Muscle Testing Scores at Week 24 |
| End point description: Quantitative muscle testing measured strength-knee flexion and extension measured in Newtons, using a dynamometer. | |
| End point type | Secondary |
| End point timeframe: Week 24 | |

| End point values | MNK-1411 | Placebo | | |
|--------------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 9 | | |
| Units: Newtons | | | | |
| arithmetic mean (standard deviation) | | | | |
| Knee flexion | 33.636 (\pm 15.7832) | 25.267 (\pm 13.3471) | | |
| Knee extension | 26.610 (\pm 14.1697) | 29.870 (\pm 15.1330) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Adverse Events in the Blinded Treatment Period

| | |
|--|---|
| End point title | Summary of Adverse Events in the Blinded Treatment Period |
| End point description: Clinically significant changes in vital signs, height, weight, immunogenicity and laboratory assessments were reported as adverse events (AEs) | |
| End point type | Secondary |
| End point timeframe: within 28 weeks | |

| End point values | MNK-1411 | Placebo | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 15 | | |
| Units: Patients | | | | |
| Number of patients exposed | 29 | 15 | | |
| Number affected by serious adverse events | 0 | 1 | | |
| Total number affected by non-serious AEs | 22 | 15 | | |
| Total number of deaths (all causes) | 0 | 0 | | |

| | | | | |
|-----------------------------|---|---|--|--|
| Number of deaths due to AEs | 0 | 0 | | |
|-----------------------------|---|---|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of AEs in the Open Label Extension Period

| | |
|-----------------|---|
| End point title | Summary of AEs in the Open Label Extension Period |
|-----------------|---|

End point description:

Clinically significant changes in vital signs, height, weight, immunogenicity and laboratory assessments were reported as AEs

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

within 28 weeks

| | | | | |
|--|-----------------|--|--|--|
| End point values | MNK-1411 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 | | | |
| Units: Patients | | | | |
| Number of patients exposed | 24 | | | |
| Number affected by SAEs | 2 | | | |
| Total number affected by non-serious AEs | 11 | | | |
| Total number of deaths (all causes) | 0 | | | |
| Number of deaths due to AEs | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

within 28 weeks

Adverse event reporting additional description:

Clinically significant changes in vital signs, height, weight, immunogenicity and laboratory assessment were reported as AEs

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------------------|
| Reporting group title | MNK-1411 (Blinded Treatment Period) |
|-----------------------|-------------------------------------|

Reporting group description:

All patients who received MNK-1411 during the blinded treatment period

| | |
|-----------------------|------------------------------------|
| Reporting group title | Placebo (Blinded Treatment Period) |
|-----------------------|------------------------------------|

Reporting group description:

Patients who received placebo during the blinded treatment period

| | |
|-----------------------|---------------------------------|
| Reporting group title | MNK-1411 (Open Label Extension) |
|-----------------------|---------------------------------|

Reporting group description:

Patients who received MNK-1411 during the open label extension period

| Serious adverse events | MNK-1411 (Blinded Treatment Period) | Placebo (Blinded Treatment Period) | MNK-1411 (Open Label Extension) |
|---|-------------------------------------|------------------------------------|---------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 15 (6.67%) | 2 / 24 (8.33%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle disorder | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 15 (6.67%) | 0 / 24 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 15 (0.00%) | 1 / 24 (4.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Urinary tract infection | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 15 (0.00%) | 1 / 24 (4.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events | MNK-1411 (Blinded Treatment Period) | Placebo (Blinded Treatment Period) | MNK-1411 (Open Label Extension) |
|---|-------------------------------------|------------------------------------|---------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 22 / 29 (75.86%) | 15 / 15 (100.00%) | 11 / 24 (45.83%) |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 1 | 0 | 2 |
| General disorders and administration site conditions | | | |
| Face oedema | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 15 (13.33%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injection site bruising | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 15 (6.67%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Injection site erythema | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 1 / 15 (6.67%) | 1 / 24 (4.17%) |
| occurrences (all) | 4 | 1 | 1 |
| Injection site haematoma | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injection site haemorrhage | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 15 (6.67%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|--|----------------------|----------------------|---------------------|
| Injection site induration subjects affected / exposed occurrences (all) | 4 / 29 (13.79%) 4 | 1 / 15 (6.67%) 1 | 2 / 24 (8.33%) 2 |
| Injection site irritation subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 24 (0.00%) 0 |
| Injection site mass subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 3 / 15 (20.00%) 3 | 1 / 24 (4.17%) 1 |
| Injection site pain subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 1 / 15 (6.67%) 1 | 0 / 24 (0.00%) 0 |
| Injection site swelling subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 15 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 2 / 15 (13.33%) 2 | 1 / 24 (4.17%) 1 |
| Swelling face subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 15 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Immune system disorders Allergy to arthropod bite subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 15 (6.67%) 2 | 1 / 24 (4.17%) 2 |
| Respiratory, thoracic and mediastinal disorders Bronchial hyperreactivity subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 24 (0.00%) 0 |
| Cough subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 3 | 2 / 15 (13.33%) 2 | 0 / 24 (0.00%) 0 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 15 (6.67%) 1 | 0 / 24 (0.00%) 0 |
| Asthma | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 15 (0.00%) 0 | 1 / 24 (4.17%) 1 |
| Psychiatric disorders | | | |
| Affect lability | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 15 (6.67%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Mood swings | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Separation anxiety disorder | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 15 (6.67%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 1 | 1 |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 7 / 29 (24.14%) | 0 / 15 (0.00%) | 3 / 24 (12.50%) |
| occurrences (all) | 9 | 0 | 3 |
| Nerve stimulation test abnormal | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 15 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 15 (6.67%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 15 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 0 | 1 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 15 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 0 | 2 |
| Nervous system disorders | | | |
| Headache | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 0 / 15 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Motor dysfunction subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 15 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Psychomotor hyperactivity subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 15 (0.00%) 0 | 1 / 24 (4.17%) 1 |
| Blood and lymphatic system disorders Leukocytosis subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 15 (0.00%) 0 | 1 / 24 (4.17%) 1 |
| Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 15 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Abdominal pain subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 0 / 15 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Aphthous ulcer subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 15 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 2 | 0 / 15 (0.00%) 0 | 1 / 24 (4.17%) 1 |
| Food poisoning subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 1 / 15 (6.67%) 1 | 0 / 24 (0.00%) 0 |
| Irritable bowel syndrome subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 15 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 15 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Acne | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hirsutism | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypertrichosis | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Seborrhoeic dermatitis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Swelling face | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lipohypertrophy | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 15 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 0 | 1 |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Glycosuria | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 15 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 0 | 3 |
| Endocrine disorders | | | |
| Cushing's syndrome | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cushingoid | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-----------------------------|----------------|-----------------|----------------|
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 15 (6.67%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 15 (6.67%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 15 (6.67%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 3 / 15 (20.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 4 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 15 (6.67%) | 1 / 24 (4.17%) |
| occurrences (all) | 2 | 1 | 1 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Enterobiasis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 15 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 0 | 1 |
| Otitis media acute | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 15 (6.67%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 15 (13.33%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pharyngotonsillitis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 3 / 29 (10.34%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Scarlet fever | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 15 (6.67%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tonsillitis bacterial | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tooth abscess | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 15 (13.33%) | 1 / 24 (4.17%) |
| occurrences (all) | 1 | 2 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 15 (6.67%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Viral pharyngitis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 15 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 0 | 1 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 15 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 0 | 1 |
| Upper respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 15 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyperphagia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Increased appetite | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 15 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 15 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 0 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 16 November 2017 | <p>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.</p> <p>Additional minor changes that do not impact study conduct or subject safety were also made.</p> |
| 22 August 2018 | <p>Protocol Amendment 2 was developed to address the following considerations:</p> <ul style="list-style-type: none">- 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. |
| 23 May 2019 | <p>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:</p> <ul style="list-style-type: none">-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 on the administration of motor tests 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. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|--|--------------|
| 25 February 2020 | The trial was permanently discontinued because of slow enrollment. | - |

Notes:

Limitations and caveats

None reported