# Clinical trial results:
# A Single-Blind, Phase 2 Study To Evaluate The Safety And Efficacy Of Tideglusib 400 mg Or 1000 mg For The Treatment Of Adolescent And Adult Congenital And Juvenile-Onset Myotonic Dystrophy

## Summary

| | |
|---|---|
| EudraCT number | 2016-000067-16 |
| Trial protocol | GB |
| Global end of trial date | 04 January 2018 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 19 July 2018 |
| First version publication date | 19 July 2018 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | AMO-02-MD-2-001 |

### Additional study identifiers

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

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | AMO Pharma Ltd |
| Sponsor organisation address | Throwsters, The Street, Wonersh, Surrey, United Kingdom, GU5 0PF |
| Public contact | General enquiries, AMO Pharma Ltd, +44 01483 898 448, clinicaltrials@amo-pharma.com |
| Scientific contact | General enquiries, AMO Pharma Ltd, +44 01483 898 448, clinicaltrials@amo-pharma.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? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 01 February 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 04 January 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 January 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To investigate the safety and tolerability between baseline and end-of-treatment of tideglusib in adolescent and adult subjects with congenital or juvenile-onset myotonic dystrophy

Protection of trial subjects:

The study was conducted in accordance with ICH principles of Good Clinical Practice (GCP), as required by European Directive 2001/20/EC and 2005/28/EC and local rules relevant to the use of new therapeutic agents within the United Kingdom, and adherence to the general principles that have their origins in the Declaration of Helsinki.
Consideration was made of the fact that this study required recruitment of patients from 12 years of age who had been diagnosed with Type 1 Myotonic Dystrophy (DM-1). DM-1 patients have varying phenotypes but congenital and juvenile-onset DM-1 patients often suffer from intellectual disability. To address this, the primary Informed Consent was to be given by the subject's parent/caregiver/spouse/Legally Authorised Representative (LAR). The subject was to provide assent or informed consent depending on their age and on the investigator’s assessment of the subject’s developmental level. This was documented prior to any protocol-related activities being conducted.

| | |
|---|---|
| Background therapy: - | |
| Evidence for comparator: - | |
| Actual start date of recruitment | 20 July 2016 |
| 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 | United Kingdom: 16 |
| Worldwide total number of subjects | 16 |
| EEA total number of subjects | 16 |

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) | 0 |
| Adolescents (12-17 years) | 5 |
| Adults (18-64 years) | 11 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Subjects were to be male or female aged 12 to 45 years with a diagnosis of genetically confirmed congenital or juvenile-onset type 1 myotonic dystrophy. Subjects were to have a Clinical Global Impression- Severity (CGI-S) score of 4 or greater at Screening and Run-in (V2) and were to be ambulatory and able to complete the 10-metre walk/run test.

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 16 |
| Number of subjects completed | 16 |

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Single blind[1] |
| Roles blinded | Subject, Carer |

Blinding implementation details:

The study was single blinded, where the Sponsor/delegate and the Investigator site knew what treatment the subjects were receiving at each point during the study, but the subject and parent/caregiver/spouse/LAR were blinded as to whether the subject was receiving active or placebo. It is noted that all subjects and parents/caregivers/spouses/LARs were informed that the study subjects would receive the study drug at some time during the study.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Cohort 1 |

Arm description:

Subjects were given a placebo run in (weeks -2 to 0) followed by tideglusib 1000 mg for 12 weeks (weeks 0 to 12)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Tideglusib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

IMP was administered orally once daily by dispersing two packets in water. The product was to be consumed immediately after constitution. The product could be administered via a percutaneous endoscopic gastrostomy (PEG) if applicable. The IMP was to be administered in an overnight fasted state; food intake was to be prevented for at least 1 hour after taking the medication. The whole content of the packets was added to 100 mL of tap water in a glass and mixed with a spoon until dispersed. After drinking this constituted dispersion, another 50 mL of tap water was added to the glass and stirred with a spoon to disperse any remnants of the powder in the glass before drinking.

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for oral suspension |

| | |
|---|---|
| Routes of administration | Oral use |

Dosage and administration details:

Administration of placebo is as per active

| **Arm title** | Cohort 2 |
|---|---|

Arm description:

Subjects were given a placebo run in (weeks -2 to 0) followed by tideglusib 400 mg for 12 weeks (weeks 0 to 12)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Tideglusib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

IMP was administered orally once daily by dispersing one packet in water. The product was to be consumed immediately after constitution. The product could be administered via a percutaneous endoscopic gastrostomy (PEG) if applicable. The IMP was to be administered in an overnight fasted state; food intake was to be prevented for at least 1 hour after taking the medication. The whole content of the packet was added to 100 mL of tap water in a glass and mixed with a spoon until dispersed. After drinking this constituted dispersion, another 50 mL of tap water was added to the glass and stirred with a spoon to disperse any remnants of the powder in the glass before drinking.

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Administration of placebo is as per active

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Due to the patient population, both the patient and carer were blinded to ensure results remained objective.

| **Number of subjects in period 1** | Cohort 1 | Cohort 2 |
|---|---|---|
| Started | 8 | 8 |
| Completed | 8 | 8 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Overall trial (overall period) |

Reporting group description: -

| Reporting group values | Overall trial (overall period) | Total | |
|---|---|---|---|
| Number of subjects | 16 | 16 | |
| Age categorical<br>Units: Subjects | | | |
| Adolescents (12-17 years) | 5 | 5 | |
| Adults (18-64 years) | 11 | 11 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 6 | 6 | |
| Male | 10 | 10 | |

## End points

### End points reporting groups

| Reporting group title | Cohort 1 |
|---|---|

Reporting group description:

Subjects were given a placebo run in (weeks -2 to 0) followed by tideglusib 1000 mg for 12 weeks (weeks 0 to 12)

| Reporting group title | Cohort 2 |
|---|---|

Reporting group description:

Subjects were given a placebo run in (weeks -2 to 0) followed by tideglusib 400 mg for 12 weeks (weeks 0 to 12)

### Primary: Safety

| End point title | Safety[1] |
|---|---|

End point description:

| End point type | Primary |
|---|---|

End point timeframe:

From start of active treatment to end of study

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: An overall summary of TEAEs was produced, however no formal statistical analysis was required per protocol.

| End point values | Cohort 1 | Cohort 2 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 8 | | |
| Units: Subjects | | | | |
| Total no. of TEAEs | 8 | 6 | | |
| Total no. of serious TEAEs | 0 | 0 | | |
| Total no. TEAEs leading to discontinuation of IMP | 0 | 0 | | |
| Total no. TEAEs leading to withdrawal | 0 | 0 | | |
| Total no. TEAEs leading to death | 0 | 0 | | |
| Severity: Mild | 3 | 1 | | |
| Severity: Moderate | 5 | 4 | | |
| Severity: Severe | 0 | 1 | | |
| Unrelated to active treatment | 6 | 6 | | |
| Related to active treatment | 2 | 0 | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| From start of active treatment to end of study | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.1 |

| Reporting groups | |
|---|---|
| Reporting group title | Cohort 1 - 1000 mg |
| Reporting group description: - | |
| Reporting group title | Cohort 2 - 400 mg |
| Reporting group description: - | |

| Serious adverse events | Cohort 1 - 1000 mg | Cohort 2 - 400 mg | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Cohort 1 - 1000 mg | Cohort 2 - 400 mg | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 8 (100.00%) | 6 / 8 (75.00%) | |
| Injury, poisoning and procedural complications | | | |
| Back injury | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fall | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Laceration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Limb injury | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 2 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nervous system cyst | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 8 (25.00%) | |
| occurrences (all) | 1 | 2 | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 8 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Post-tussive vomiting | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 8 (12.50%) | |
| occurrences (all) | 1 | 1 | |

| | | | |
|---|---|---|---|
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Erythema | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash papular | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Axillary mass | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 3 / 8 (37.50%) | |
| occurrences (all) | 2 | 4 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 8 (12.50%) | |
| occurrences (all) | 1 | 1 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|---|---|---|---|
| Metabolism and nutrition disorders<br>Vitamin D deficiency<br>subjects affected / exposed<br>occurrences (all) | 1 / 8 (12.50%)<br>1 | 0 / 8 (0.00%)<br>0 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 09 January 2017 | Protocol version 4.0 included the following changes:<br>- Change to exclusion criterion no. 16 relating to HbA1c to re-define the exclusion levels using absolute values to avoid ambiguity and to remove the need for further HbA1c value to be normal at run-in as each HbA1c test is applicable to a 2-3 month period. The value taken at screening was sufficient to determine eligibility. HbA1c was no longer collected at run-in.<br>- Clarification that a "prothrombin time test" would be completed as part of the clinical lab tests collected in the event of elevated liver function values occurring as detailed in the Discontinuation Criteria. Prothrombin time tests had been stated as being completed at every visit in the schedule of assessments but not consistently throughout the protocol.<br>- Correction of blood volume required for the GSK3B biomarker analysis. It was not possible to source a 3mL sodium citrate tube to collect this sample, therefore a 4 mL sodium citrate tube, requiring a 4mL blood sample was provided in all relevant kits.<br>-Updated information on PK analysis methodology<br>-Inclusion of analysis to be performed once all subjects in cohort 1 had completed or discontinued from active treatment in the study<br>-Addition of exclusion criterion no. 29 where subjects were not allowed to enter the study if their BMI was less than 14.0 kg/m2 or greater than 40.0 kg/m2 to ensure that subjects were not over or under exposed to study drug respectively.<br>-Inclusion of a text field in the CRF to record pertinent information that was reported by the subject and/or caregiver and not captured elsewhere in the CRF, that supported the CGI-S and CGI-I rating.<br>-Clarification of the description of the establishment of the DSMC |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported