



## 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
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##### 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 <sup>[1]</sup>
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
<b>Arm title</b>	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
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Dosage and administration details:

Administration of placebo is as per active

<b>Arm title</b>	Cohort 2
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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.

<b>Number of subjects in period 1</b>	Cohort 1	Cohort 2
Started	8	8
Completed	8	8

## Baseline characteristics

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### Reporting groups

Reporting group title	Overall trial (overall period)
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Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	16	16	
Age categorical Units: Subjects			
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	11	11	
Gender categorical 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 <sup>[1]</sup>
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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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### Reporting groups

Reporting group title	Cohort 1 - 1000 mg
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Reporting group description: -

Reporting group title	Cohort 2 - 400 mg
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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			



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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 January 2017	<p>Protocol version 4.0 included the following changes:</p> <ul style="list-style-type: none"><li>- 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.</li><li>- 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.</li><li>- 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.</li><li>-Updated information on PK analysis methodology</li><li>-Inclusion of analysis to be performed once all subjects in cohort 1 had completed or discontinued from active treatment in the study</li><li>-Addition of exclusion criterion no. 29 where subjects were not allowed to enter the study if their BMI was less than 14.0 kg/m<sup>2</sup> or greater than 40.0 kg/m<sup>2</sup> to ensure that subjects were not over or under exposed to study drug respectively.</li><li>-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.</li><li>-Clarification of the description of the establishment of the DSMC</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported