



## Clinical trial results:

### A Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Tideglusib Versus Placebo for the Treatment of Children and Adolescents with Congenital Myotonic Dystrophy (REACH CDM)

#### Summary

EudraCT number	2016-004623-23
Trial protocol	GB
Global end of trial date	04 April 2023

#### Results information

Result version number	v1 (current)
This version publication date	25 April 2024
First version publication date	25 April 2024

#### Trial information

##### Trial identification

Sponsor protocol code	AMO-02-MD-2-003
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03692312
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	AMO Pharma Ltd
Sponsor organisation address	Braeburn, Grove Road, Godalming, United Kingdom, GU7 1RE
Public contact	General Enquiries, AMO Pharma Ltd, +44 07775915639, clinicaltrials@amo-pharma.com
Scientific contact	General Enquiries, AMO Pharma Ltd, +44 07775915639, 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	11 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 April 2023
Global end of trial reached?	Yes
Global end of trial date	04 April 2023
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy, from baseline to end of treatment, of weight adjusted 1000 mg tideglusib compared to placebo in children and adolescents with CDM1 as measured by the Clinician-Completed CDM1 Rating Scale (CDM1-RS).

Protection of trial subjects:

For each study subject, written informed consent was obtained from the subject's parent/LAR prior to any protocol-related activities and assent obtained from the subject according to the local institutional policies and guidelines. Caregiver informed consent was also obtained, if the caregiver was not the parent/LAR. As part of the informed consent procedure, the principal investigator or one of his/her associates explained orally and in writing the nature, duration, purpose of the study, and the action of the study drug in such a manner that the parent/LAR was aware of the potential risks, inconveniences, or adverse effects that may occur.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 March 2021
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 States: 34
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	New Zealand: 3
Worldwide total number of subjects	56
EEA total number of subjects	0

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)	33
Adolescents (12-17 years)	23
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:

A screening visit was conducted at least 1 week prior to the run-in visit. Eligible subjects were then entered into the placebo run -in period.

### Period 1

Period 1 title	Placebo run-in period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

### Arms

Arm title	Placebo
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Arm description:

2 week placebo run-in

Arm type	Placebo
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:

Matching placebo was administered once a day at approximately the same time each day. Food intake was to be prevented for at least 4 hours prior to, and at least 2 hours after taking the medication. Administration by gastrostomy tube was also permissible, provided the food restrictions, dose preparation, and administration instructions were followed.

Number of subjects in period 1	Placebo
Started	56
Completed	53
Not completed	3
Run-in failure	3

### Period 2

Period 2 title	Randomized treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

**Arms**

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Tideglusib
Arm description: -	
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:

Tideglusib dosing was weight-adjusted at 400 mg, 600 mg, or 1000 mg dose levels, with each subject randomized to tideglusib starting at a weight-adjusted 400 mg dose level for 2 weeks, then up titrating to a weight-adjusted 600 mg dose level for the next 2 weeks until they reached the final dose level of weight-adjusted 1000 mg tideglusib. Food intake was to be prevented for at least 4 hours prior to, and at least 2 hours after taking the medication. Administration by gastrostomy tube was also permissible, provided the food restrictions, dose preparation, and administration instructions were followed.

<b>Arm title</b>	Placebo
Arm description: -	
Arm type	Placebo
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:

Matching placebo was administered once a day at approximately the same time each day. Food intake was to be prevented for at least 4 hours prior to, and at least 2 hours after taking the medication. Administration by gastrostomy tube was also permissible, provided the food restrictions, dose preparation, and administration instructions were followed.

<b>Number of subjects in period 2</b>	Tideglusib	Placebo
Started	27	26
Completed	25	25
Not completed	2	1
Consent withdrawn by subject	1	1
Adverse event, non-fatal	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo run-in period
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Reporting group description: -

Reporting group values	Placebo run-in period	Total	
Number of subjects	56	56	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	33	33	
Adolescents (12-17 years)	23	23	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	20	20	
Male	36	36	

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: 2 week placebo run-in	
Reporting group title	Tideglusib
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

### Primary: Change from Baseline to End of Treatment in Clinician-completed Congenital Type I Myotonic Dystrophy Rating Scale (CDM1-RS)

End point title	Change from Baseline to End of Treatment in Clinician-completed Congenital Type I Myotonic Dystrophy Rating Scale (CDM1-RS)
End point description:	
End point type	Primary
End point timeframe: From Baseline to End of Treatment	

End point values	Tideglusib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: n/a				
least squares mean (standard error)	-1.65 (± 0.620)	-3.40 (± 0.618)		

### Statistical analyses

Statistical analysis title	Analysis of Change in CDM1-RS
Statistical analysis description: Analysis of Change from Baseline to End of Treatment in Clinician-Completed CDM1-RS Total Score (Tideglusib - Placebo) – Intent to treat analysis set	
Comparison groups	Tideglusib v Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0514
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.75

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	3.51
Variability estimate	Standard error of the mean
Dispersion value	0.875

### Post-hoc: Multi-domain responder index analysis (MDRI)

End point title	Multi-domain responder index analysis (MDRI)
End point description:	
End point type	Post-hoc
End point timeframe:	
From Baseline to End of Treatment	

End point values	Tideglusib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: Efficacy score				
arithmetic mean (standard error)	0.8 (± 0.31)	-0.1 (± 0.25)		

### Statistical analyses

<b>Statistical analysis title</b>	Treatment comparison of MDRI analysis
Comparison groups	Tideglusib v Placebo
Number of subjects included in analysis	48
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.0428
Method	t-test, 2-sided

### Post-hoc: Creatine Phosphokinase (CPK) - MMRM analysis

End point title	Creatine Phosphokinase (CPK) - MMRM analysis
End point description:	
End point type	Post-hoc
End point timeframe:	
From Baseline to End of Treatment	



End point values	Tideglusib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: Ratio				
least squares mean (standard error)	0.81 ( $\pm$ 0.070)	1.05 ( $\pm$ 0.091)		

## Statistical analyses

Statistical analysis title	Treatment comparison of CPK MMRM analysis
Comparison groups	Placebo v Tideglusib
Number of subjects included in analysis	48
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.0379
Method	Mixed models analysis

## Post-hoc: Responder analysis

End point title	Responder analysis
End point description:	
For each endpoint, response was defined as a 10% or greater improvement from baseline at Visit 11 (Week 20). For the 10 metre walk and creatine phosphokinase a reduction was considered an improvement, while for the other endpoints an increase was considered an improvement. Subjects without a baseline and a Visit 11 (Week 20) value were excluded from the analysis.	
End point type	Post-hoc
End point timeframe:	
From Baseline to End of Treatment	

End point values	Tideglusib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	26		
Units: Responders				
10 metre walk/run - preferred speed	9	6		
Hand grip strength - dominant hand	13	9		
Creatine phosphokinase	11	9		
Lip strength	8	7		
DXA Scan - Total lean muscle mass	2	1		
Peabody picture vocabulary test	7	1		
NIH Toolbox: DCCS - computed score	4	7		
NIH Toolbox: PSMT - computed score	7	5		

Vineland adaptive behaviour - daily living	8	6		
Vineland adaptive behaviour - communication	9	5		
Vineland adaptive behaviour - socialization	8	10		
DXA scan - bone mineral density - total Z-score	5	7		

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose until last subject visit.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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### Reporting groups

Reporting group title	Tideglusib
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Tideglusib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 28 (3.57%)	0 / 25 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Scoliosis surgery			
subjects affected / exposed	1 / 28 (3.57%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tideglusib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 28 (71.43%)	19 / 25 (76.00%)	
Vascular disorders			
Peripheral coldness			
subjects affected / exposed	1 / 28 (3.57%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Sinus operation			

subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 25 (0.00%) 0	
Wisdom teeth removal subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 25 (0.00%) 0	
General disorders and administration site conditions			
Vaccination site pain subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 3	1 / 25 (4.00%) 1	
Fatigue subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 2	0 / 25 (0.00%) 0	
Influenza like illness subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 25 (4.00%) 1	
Immune system disorders			
Hypersensitivity subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 25 (4.00%) 1	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 4	0 / 25 (0.00%) 0	
Rhinorrhoea subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3	1 / 25 (4.00%) 1	
Epistaxis subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 3	0 / 25 (0.00%) 0	
Hypoventilation subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 25 (0.00%) 0	
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 25 (0.00%) 0	
Nasal congestion			

subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 25 (8.00%) 2	
Dyspnoea subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 25 (4.00%) 1	
Psychiatric disorders Attention deficit hyperactivity disorder subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 25 (4.00%) 1	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 25 (0.00%) 0	
Haemoglobin decreased subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 25 (0.00%) 0	
Transaminases increased subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 25 (0.00%) 0	
Weight decreased subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 25 (8.00%) 2	
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	0 / 25 (0.00%) 0	
Skin abrasion subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	0 / 25 (0.00%) 0	
Road traffic accident subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 25 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3	0 / 25 (0.00%) 0	

Dyskinesia subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 25 (4.00%) 1	
Eye disorders Eye pruritus subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 25 (4.00%) 1	
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)  Oral pain subjects affected / exposed occurrences (all)  Abdominal pain upper subjects affected / exposed occurrences (all)  Anal incontinence subjects affected / exposed occurrences (all)  Faeces discoloured subjects affected / exposed occurrences (all)  Palatal disorder subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3  2 / 28 (7.14%) 5  1 / 28 (3.57%) 1  0 / 28 (0.00%) 0  0 / 28 (0.00%) 0  0 / 28 (0.00%) 0  0 / 28 (0.00%) 0	2 / 25 (8.00%) 2  5 / 25 (20.00%) 6  0 / 25 (0.00%) 0  2 / 25 (8.00%) 2  1 / 25 (4.00%) 1  1 / 25 (4.00%) 1  1 / 25 (4.00%) 1	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)  Skin discolouration subjects affected / exposed occurrences (all)  Perioral dermatitis	1 / 28 (3.57%) 1  1 / 28 (3.57%) 1	0 / 25 (0.00%) 0  0 / 25 (0.00%) 0	

subjects affected / exposed occurrences (all)  Rash macular subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0  0 / 28 (0.00%) 0	1 / 25 (4.00%) 1  1 / 25 (4.00%) 1	
Renal and urinary disorders Glycosuria subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 25 (0.00%) 0	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)  Arthralgia subjects affected / exposed occurrences (all)  Myalgia subjects affected / exposed occurrences (all)  Pain in extremity subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2  1 / 28 (3.57%) 1  1 / 28 (3.57%) 1  1 / 28 (3.57%) 1	1 / 25 (4.00%) 1  0 / 25 (0.00%) 0  0 / 25 (0.00%) 0  0 / 25 (0.00%) 0	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)  Upper respiratory tract infection subjects affected / exposed occurrences (all)  COVID-19 subjects affected / exposed occurrences (all)  Bronchitis subjects affected / exposed occurrences (all)  Influenza	3 / 28 (10.71%) 4  3 / 28 (10.71%) 4  2 / 28 (7.14%) 2  1 / 28 (3.57%) 2	3 / 25 (12.00%) 3  2 / 25 (8.00%) 2  1 / 25 (4.00%) 1  0 / 25 (0.00%) 0	

subjects affected / exposed	1 / 28 (3.57%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Otitis externa			
subjects affected / exposed	1 / 28 (3.57%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	1 / 28 (3.57%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	1 / 28 (3.57%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Coronavirus infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Ear infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	0 / 28 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 February 2022	<p>The purpose of this protocol amendment was to add clarification to exclusion criterion #10 to note that current evidence of second or third degree heart block, atrial flutter, atrial fibrillation or ventricular arrhythmias were exclusionary and also that a cardiac arrhythmia which requires medication for treatment was also exclusionary.</p> <p>Section 9.5 of the protocol, "Laboratory Alerts, Stopping Rules and Discontinuation Criteria" was updated for clarity, including clarification that appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia must occur simultaneously with the ALT or AST &gt; 3x ULN for the stopping criterion to apply. Further, clarification was added for the factors that should be considered to fully identify eosinophilia (i.e. both &gt;5% of white blood cells as well as an absolute eosinophil count above the normal reference range). Additionally, an additional home healthcare vendor was added.</p>
15 June 2022	<p>The purpose of this protocol amendment was to update the number of subjects to be randomized in this study as a result of the Blinded Sample Size Re-estimation Exercise (SSRE) to allow an increase in the total sample size from 56 up to 66 subjects. In addition, clarification was added to allow subjects to delay Visit 2 or Visit 3 if they were unable to attend due to COVID-19. Finally, the name of the Data Management and Statistical CRO was updated.</p>
02 February 2023	<p>The purpose of this protocol amendment was to add sample size calculations to support the close of enrollment into the study. Approximately 56 children were originally planned to be randomized into the study, assuming a dropout rate of 10- 13%. After a blinded SSRE, the protocol was amended to allow enrollment of between 56 and 66 children randomized into the study, if feasible. Due to feasibility considerations and taking into account the current low actual dropout rate, enrollment was closed after 53 subjects were randomized.</p>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported