Study Protocol	
Official Title:	A Single-Blind, Phase 2 Study to Evaluate the Safety and Efficacy of Tideglusib 400mg or 1000mg for the Treatment of Adolescent and Adult Congenital and Juvenile-Onset Myotonic Dystrophy
NCT Number:	NCT02858908
Document Date:	09 January 2017

CLINICAL STUDY PROTOCOL

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

EudraCT No: 2016-000067-16
Protocol No.: AMO-02-MD-2-001
Version No: Version 4.0
Date of Protocol: 09 January 2017

Sponsor: AMO Pharma Ltd.
Throwsters,
The Street,
Wonersh,
Surrey,
GU5 0PF,
United Kingdom.

Confidentiality Statement:

This study will be conducted in compliance with Good Clinical Practice (GCP), the principles of the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements.

1. PROTOCOL SYNOPSIS

PROTOCOL TITLE	A Single-Blind, Phase 2 Study To Evaluate The Safety And Efficacy Of Tideglusib 400mg Or 1000mg For The Treatment Of Adolescent And Adult Congenital and Juvenile-Onset Myotonic Dystrophy
PROTOCOL NO.	AMO-02-MD-2-001
CHIEF INVESTIGATOR	[redacted]
SPONSOR	AMO Pharma Ltd.
INVESTIGATIONAL MEDICINAL PRODUCT	Tideglusib
PHASE OF DEVELOPMENT	II
INDICATION AND RATIONALE	Adolescent And Adult Congenital and Juvenile Myotonic Dystrophy
STUDY DESIGN	This is a single-blind, [redacted] week study in adolescent and adult subjects with congenital or juvenile-onset type 1 myotonic dystrophy (DM-1). Approximately 16 subjects are planned to be enrolled in total. The study will have 4 distinct phases: • Screening (weeks [redacted] Subjects will be screened to ensure adherence to eligibility criteria. • [redacted] run in (weeks [redacted]) • Single-blind treatment with tideglusib 1000mg (N = 8) (Cohort 1) or 400mg (N = 8) (Cohort 2) for 12 weeks (weeks 0 to 12)

- Follow-up visit [redacted] after end-of-treatment (EOT) (weeks [redacted])

Data Safety Monitoring Committee

A Data Safety Monitoring Committee (DSMC) consisting of clinical and other experts will be established by the sponsor to review interim safety findings during the study and to help oversee subject safety.

STUDY OBJECTIVES

Primary objective:

- 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.

Secondary objectives:

- To investigate the blood pharmacokinetics of tideglusib in adolescent and adult subjects with congenital or juvenile-onset myotonic dystrophy
- To investigate differences in outcomes reflective of efficacy, between baseline and end-of-treatment, with tideglusib in adolescent and adult subjects with congenital or juvenile-onset myotonic dystrophy.

STUDY ENDPOINTS

Primary endpoint:

- Incidence of adverse events (AE), including Serious adverse events (SAE). AEs will be evaluated between baseline and Follow-up Visit, while SAEs will be evaluated between screening and the last clinic visit or until resolution, whenever possible. The incidence of abnormal findings in objective assessments (e.g. laboratory values, ECGs, and vital signs) during the course of the study will also be assessed.

Secondary endpoints:

- Blood pharmacokinetics (PK) of tideglusib
- 10 metre walk/run test (self-selected and fastest velocity)
- Computerised handgrip myometer measure of grip strength and muscle relaxation time
- Respiratory Forced Vital Capacity (FVC)
- Dual-energy X-ray absorptiometry (DXA) whole body scan of lean muscle mass (g) legs, arms, and total
- Clinical Global Impressions– Severity and – Improvement (CGI-S and CGI-I)
- Actigraphy (measure daily averages of: number of bouts of activity, number of steps taken and energy expenditure)
- Nine Hole Peg Test (NHPT)
- Top 3 Concerns Visual Analogue Scale (VAS) (caregiver-completed and where possible, also subject-completed)
- OSU Autism Rating Scale (OARS)
- OSU Autism CGI
- Clinician-completed Domain Specific Causes for Concern VAS: Myotonic Dystrophy
- Peabody Picture Vocabulary Test (PPVT)
- [redacted] levels and activity

PLANNED SAMPLE SIZE AND STATISTICAL CONSIDERATIONS

16 Subjects are planned to be enrolled.

Adverse event and other safety data will be summarised as frequencies and percentages, and described in terms of severity and relationship to study treatment. Objective safety assessments, including laboratory and ECG values, will be summarised by treatment period (screening, run-in, [redacted] treatment) and treatment dose. Changes in safety parameters over time will be described, and shift tables at time points of interest will be generated as required.

Analyses of changes in efficacy variables from baseline will be performed where applicable using repeated measures

analysis of covariance (ANCOVA) models with study site (if more than one is used) and treatment dose as fixed effects, and baseline value as a covariate. Least square mean estimates will be produced by dose group and study visit and will be presented with 95% confidence intervals and two-sided p-values.

The safety and efficacy analyses will be specified in detail in the Statistical Analysis Plan (SAP).

SUBJECT POPULATION

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. Subjects under study must be adolescents or adults with a diagnosis of congenital or juvenile-onset type 1 myotonic dystrophy (DM-1). For the purposes of this study, the following definitions apply:

   Congenital: in addition to the genetic confirmation of DM-1, one or more of the following signs or symptoms was evident within the first week after birth:
   a) Hypotonia
   b) Generalized weakness
   c) Respiratory insufficiency
   d) Feeding difficulties
   e) Clubfoot or another musculoskeletal deformity

   Childhood/juvenile-onset: in addition to the genetic confirmation of DM-1, at least 2 signs or symptoms (not caused by another, unrelated condition) were evident prior to 12 years of age that can be clearly assigned to DM-1, for example:
   a) Muscle weakness
   b) Myotonia (delayed muscle relaxation)

c) Difficulty using hands, including fine motor problems
d) Excessive daytime sleepiness
e) Problems with upper or lower gastrointestinal functioning
f) Problems with concentration or focusing (including symptoms of attention-deficit/hyperactivity disorder)
g) Learning difficulties (including dyslexia)

2. Diagnosis must be genetically confirmed
3. Subjects must be male or female aged 12 years to 45 years (the first 3 subjects in Cohort 1 must be ≥18 years)
4. Subjects must have a Clinical Global Impression – Severity (CGI-S) score of 4 or greater at [redacted]
5. Subjects must be ambulatory and able to complete the 10 metre walk/run test (splints allowed)
6. Subject's legally authorised representative (LAR) must provide written informed consent and there must be written consent or assent (as age applicable and developmentally appropriate) by the subject before any study-related procedures are conducted
7. Subject's caregiver must be willing and able to support subject's participation for duration of study and if different from the LAR, must consent to this in writing

Exclusion Criteria:

1. Non-ambulatory (full time) wheel chair user
2. Receiving stimulant medication
3. Receiving other medications/therapies not stable (changed) within 4 weeks prior to Run-in [redacted]
4. Medical illness or other concern which would cause investigator to conclude subjects will not be able to perform the study procedures or

assessments or would confound interpretation of data obtained during assessment.

5. Current enrolment in a clinical trial of an investigational drug or enrolment in a clinical trial of an investigational drug in the last 6 months
6. Women of child bearing potential who are pregnant, lactating or not willing to use a protocol-defined acceptable contraception method if sexually active and not surgically sterile.
7. Men, if engaged in sexual relations with a female of child-bearing potential, not using an acceptable contraceptive method if not surgically sterile.
8. Gastrointestinal disease which may interfere with the absorption, distribution, metabolism or excretion of the study medication and impact the interpretability of the study results
9. Current clinically significant (as determined by the investigator) cardiovascular, renal, hepatic, endocrine or respiratory disease
10. Clinically significant heart disease (in the opinion of the investigator) or second or third degree heart block, atrial flutter, atrial fibrillation, ventricular arrhythmias, or is receiving medication for treatment of a cardiac arrhythmia
11. Average QTcF value of >450msec at [redacted]
12. Kidney disease requiring ongoing treatment
13. A history of chronic liver disease with current out of range values for ALT, clinically relevant hepatic steatosis or other clinical manifestations of ongoing liver disease
14. Current ALT value > 2X the upper limit of the normal reference range at [redacted] (may repeat to confirm)
15. Current total bilirubin value greater than the upper limit of the normal reference range at [redacted] (unless due to Gilbert's syndrome) (may repeat to confirm)
16. HbA1c values greater than 6% or 42.0mmol/mol at [redacted] (may repeat to confirm)

17. TSH values outside of the normal reference range [redacted] (may repeat to confirm)
18. Serum creatinine >150 µmol/L and creatinine clearance ≤ 60 mL/m (according to Cockcroft-Gault formula) [redacted] (may repeat to confirm)
19. Clinical history of hepatitis, previous or current positive serological evidence for hepatitis B or C
20. Serological evidence of Hepatitis A at [redacted] in the [redacted] preceding [redacted]
21. A history of significant drug allergy (such as Steven-Johnson syndrome, anaphylaxis)
22. A history of alcohol or substance use disorders
23. Current malignancy or any history of malignancy except for surgically-cured skin cancer or pilomatricoma (benign tumour of the hair follicle that is associated with DM-1).
24. Severe arthritis or other medical condition (besides DM-1) that would significantly impact ambulation
25. Use within 4 weeks prior to [redacted] of strong CYP3A4 inhibitors e.g. clarithyromycin, telithromycin, ketoconazole, itarconazole, posaconazole, nefazadone, indinavir, ritonavir
26. Concurrent use of drugs metabolised by CYP3A4 with a narrow therapeutic window e.g. warfarin and digitoxin
27. Judged clinically to be at risk of suicide (suicidal ideation, severe depression, or other factors) over the last three months, as assessed by the Investigator.
28. Hypersensitivity to tideglusib or any components of its formulation including allergy to strawberry
29. BMI of less than 14.0 kg/m^2 or greater than 40.0 kg/m^2 at [redacted]

TIDEGLUSIB	Unidose sachets of [redacted] and [redacted] dry powder to be [redacted]
FORMULATION/DOSE	

ROUTE OF ADMINISTRATION	Oral suspension.
DURATION/FREQUENCY OF TREATMENT	Once Daily, [redacted].
	A [redacted] treatment phase, followed by 12 weeks of 1000mg tideglusib in Cohort 1 and 400mg tideglusib in Cohort 2.
SAFETY ASSESSMENTS	The incidence of adverse events (AE), including Serious adverse events (SAE), between Screening (for SAEs) or Baseline (for AEs) and end-of-treatment with tideglusib 400mg or 1000mg for 12 weeks. Clinical laboratory values, urinalysis, physical exam findings, vital signs, weight and ECG will be assessed at Screening, during treatment and at follow-up visit.
EFFICACY ASSESSMENTS	The study will evaluate the main domains of the phenotype of congenital and juvenile-onset myotonic dystrophy type 1. These domains relate to muscle symptoms, CNS symptoms, disorder specific rating scales and biological markers pertinent to the molecular pathology of the disorder. The domains will be assessed using the measures described below. • Assessments of muscle functioning and muscle mass: o 10 metre/walk run test (self-selected and fastest velocity) o Computerised handgrip myometer measure of grip strength and muscle relaxation time o Respiratory Forced Vital Capacity (FVC) o Actigraphy (measure daily averages of: number of bouts of activity, number of steps taken and energy expenditure) o Nine hole peg test (NHPT) o Dual-energy X-ray absorptiometry (DXA) whole body scan of lean muscle mass

- Clinician and caregiver rating scales of syndrome-specific symptoms:
  - Clinician-completed Domain Specific Causes for Concern VAS: Myotonic Dystrophy
  - Clinical Global Impression Scales (Severity and Improvement)
  - Top 3 Concerns VAS (caregiver and where possible, subject; related to the subject's myotonic dystrophy)
- Assessments of cognitive functioning and associated neurodevelopmental symptoms:
  - Peabody Picture Vocabulary Test (PPVT)
  - OSU Autism Rating Scale (OARS)
  - OSU Autism CGI
- [redacted]
  - [redacted] levels and activity

PHARMACOKINETIC ASSESMENTS	Pharmacokinetic samples will be collected for tideglusib and metabolite NP04113. Pharmacokinetic samples will be collected at two clinic visits (Week [redacted] and Week [redacted] on each occasion two Pharmacokinetic samples will be taken separated by at least two hours, with the initial sample taken prior to the subject ingesting his/her daily dose of the study medication. Population pharmacokinetic methods of analysis will be used to analyze the data. If the data does not support a model on its own, the data may be combined with a previously developed model in order to strengthen the predictions. In order to determine whether there are associations between pharmacokinetic parameters and efficacy measures, change from baseline in efficacy measures over the course of the study will be correlated with Pharmacokinetic parameters estimated for each dose, if appropriate. These associations may be statistically tested using correlation coefficients and general linear models, if appropriate.

STATISTICAL METHODS	The present study is an initial Phase IIa study in a condition in which there are no published data that inform formal power analyses. Accordingly, no power analysis is reported here. Cohort 1 subject data will be analysed and evaluated once all subjects have completed their planned [redacted] treatment period (or discontinued prior to [redacted]).
NUMBER OF STUDY CENTRES	1-2 sites in the United Kingdom
ESTIMATED FIRST SUBJECT SCREENED	June 2016
ESTIMATED LAST SUBJECT LAST VISIT	June 2017

Table 1: Schedule of Events

Visit	Screening	Run-in	Baseline	Interim	Interim	Interim	Interim	Interim	EOT	Follow Up
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Informed Consent/Assent	[redacted]									
Eligibility Criteria										
Medical/Surgical History										
Physical Examination										
Clinical Labs[2]										
Urinalysis[3]										
Pregnancy Test[4]										
Vital Sign Measures										
Weight										
Height										
12 Lead ECG[5]										
Grip strength[6]										
10 metre walk/run[7]										
Pulmonary Function Test (FVC)										
Actigraphy[8]										
Nine Hole Peg Test										
Dual-energy X-ray Absorptiometry (DXA) Scan										
CGI-S[9]										
CGI-I[9]										
Clinician Completed Domain Specific Causes for Concern VAS: Myotonic Dystrophy										
Top 3 Concerns										
OSU CGI-S[9]										
OSU CGI-I[9]										
OSU Autism Rating Scale										
Peabody Picture Vocabulary Test										
PK samples[10]										
[redacted]										

[redacted] sample[12]	[redacted]
[redacted] sample[13]	
Dosing and/or dispensing	
Subject Diary Dispense/Review[14]	
Adverse Events[15]	
Concomitant Medication	

[redacted]

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3. LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse event
AKT	Protein kinase B
ALT	Alanine amino transferase
ANCOVA	Analysis of Covariance
ASD	Autism Spectrum Disorder
AST	Aspartate amino transferase
AUC	Area Under Curve
CGI	Clinical Global Impression
CGI-S	Clinical Global Impression - Severity scale
CGI-I	Clinical Global Impression - Improvement scale
C_{min}	Minimum Serum/Plasma Concentration
C_{max}	Maximum Serum/Plasma Concentration
CNS	Central Nervous System
CPK	Creatinine Phosphokinase
CRF	Case Report Form
CRO	Contract Research Organisation
CSF	Cerebro-spinal Fluid
C_{ss}	Steady State Concentration
CTG/CUG	Cytosine, Thymine/Uracil, Guanine nucleotides
CTIMP	Clinical Trial of an Investigational Medicinal Product
CYP	Cytochrome P450 Enzymes
DXA	Dual-energy X-ray absorptiometry
DM-1	Type 1 Myotonic Dystrophy
DM-2	Type 2 Myotonic Dystrophy
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
EOT	End-of-Treatment
FAS	Full Analysis Set
FVC	Forced Vital Capacity
FEV	Forced Expiratory Volume
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GSK3β	Glycogen Synthase Kinase 3 *beta*
HAV	Hepatitis A Virus
HCV	Hepatitis C Virus

ICH	International Council on Harmonisation
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
LAR	Legally Authorised Representative
LFT	Liver Function Tests
LDH	Lactate dehydrogenase
MREC	Multi-centre Research Ethics Committee
NCE	New Chemical Entity
NHPT	Nine Hole Peg Test
OARS	OSU Autism Rating Scale
OSU	Ohio State University
PK	Pharmacokinetics
PKAS	Pharmacokinetics Analysis Set
PPS	Per-Protocol Set
PPVT	Peabody Picture Vocabulary Test
PSP	Progressive Supranuclear Palsy
PV	Pharmacovigilance
PT	Prothrombin Time
QTcF	Corrected QT – Fridericia's Formula
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{½}$	Half-life
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time to Maximum Concentration
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale

4. INVESTIGATORS AND ADMINISTRATIVE STRUCTURE

List of Investigators and Affiliations [redacted]

Medical Monitor (Sponsor) [redacted]

Contract Research Organisation / Monitors [redacted]

Statistical Consultants [redacted]

	[redacted]
Pharmacovigilance	
Central Laboratory	

5. BACKGROUND INFORMATION

5.1 Myotonic dystrophy

GSK-3 is a serine/threonine protein kinase that recently emerged as a key target in drug discovery. GSK-3 has two isoforms - GSK3α and GSK3β. GSK3β is implicated in neurodevelopmental disorders. GSK3β is highly expressed in brain (Woodgett, 1990) and is important in central nervous system (CNS) ontology (Beurel *et al*., 2012) and is a key signalling element in activity dependent synaptic plasticity (Rui *et al*., 2013).

Myotonic dystrophy is a monogenetic disorder caused by expansion repeats in the DMPK gene (myotonic dystrophy type 1 or DM-1 or Steinert disease), which is located on chromosome 19, or the ZNF9 gene (myotonic dystrophy type 2 or DM-2), which is located on chromosome 3. DM-1 most commonly has an onset in early adulthood, where presentation is primarily characterised by a progressive muscle weakness that starts in the distal musculature (lower leg, hands, neck and face). Adult onset DM-1 is also associated with increased risk of cataracts, cardiac conduction block, excessive sleepiness, attentional problems and premature baldness and infertility in males.

DM-1 may also be present at birth (congenital myotonic dystrophy) or during childhood (juvenile myotonic dystrophy). Congenital myotonic dystrophy is a life threatening disorder, with a mortality rate of 25 percent by age 1.5 years and 50 percent by age 30 years (Reardon *et al*., 1993). This study reported that 50 percent of subjects were unable to walk unaided with 4 percent of subjects requiring wheel chairs. Less than a quarter of congenital myotonic dystrophy patients were able to attend mainstream schooling due to intellectual disability, 15 percent were still faecally incontinent at 5 years of age and in patients who lived to 20 years of age, 79 percent were unemployed. Complementary data were reported by Ekström *et al*., (2009), who reported learning disability in 95 and 89 percent of congenital and juvenile myotonic dystrophy patients, respectively. Ekström *et al*., (2008) also reported that 68 percent and 50 percent, respectively, of individuals with congenital and juvenile DM-1 had an autism spectrum disorder.

Whilst clinical practice commonly refers to “congenital onset” and “classical adult onset” forms of DM-1 myotonic dystrophy, these categorisations do not readily separate as biologically distinct medical entities. Rather, there is a continuum with a greater number of expansion repeats in the DMPK gene being associated with earlier onset and more severe symptoms (Turner and Hilton-Jones, 2012). However, there is large phenotypic variation and a number of known genetic modifiers within this general picture. For example, Ekström *et al*., (2009) define severe congenital DM-1, mild congenital DM-1 and childhood onset DM-1 on the basis of phenotype and age of diagnosis. These groups have substantially overlapping expansion repeat numbers (median and range 1600 (730 - 2400), 1000 (130 - 2100) and 930 (260 - 1300) for severe congenital, mild congenital and childhood groups respectively). Furthermore, congenital and childhood onset DM-1 defined as having an age of onset between one and ten years of age share many features (Ho *et al.,* 2015). Therefore, it is not apparent

that other than age of diagnosis there are clear distinctions between congenital onset and childhood onset DM-1. Conversely, the course and progression of congenital and childhood onset in later life parallels that of classical adult onset DM-1, albeit with emerging signs and symptoms superimposed on a different baseline. Accordingly, it is not readily apparent that the different ages of onset of DM-1 represent categorical differences, rather than a broad age and severity continuum of a condition in which there is substantial phenotypic variability, influenced in part by genetic mosaicism. As discussed above congenital and juvenile onset DM-1 is a life threatening disorder on which less than half of subjects survive to adulthood, and surviving subjects reaching adulthood will develop signs and symptoms of the classical adult onset form, which may in turn be life limiting. Within this broad analysis, Reardon et al., (1993) show that after the post-natal period, the increased probability of mortality in congenital DM-1 increases only relatively slowly until patients reach 40 years and above.

Given the above, the research intended by the Sponsor seeks to investigate the potential therapeutic utility of tideglusib in all age ranges of subjects affected by congenital, juvenile and classical adult onset DM-1. The present protocol is a safety study also assessing signals of efficacy in adolescents and adults with DM-1 documented to have a congenital or juvenile onset. Subject to the data obtained, future study will investigate the effects of this agent in children with congenital and juvenile onset DM-1. We have elected to define adolescence and adulthood as meaning 12 to 45 years (post puberty). The justification of safety and tolerability in this age range is discussed in section 5.5.

5.2 Tideglusib

Tideglusib (4-benzyl-2-naphtalen-1-yl-1,2,4-thiadiazolidine-3,5-dione) is a new chemical entity (NCE) from the thiadiazolidindiones chemical family. It is an irreversible inhibitor of Glycogen synthase kinase 3 beta (GSK-3 β).

Tideglusib is a brain penetrant and can be orally administered. It is formulated as a powder for oral suspension filled into unit dose sachets. [redacted] The [redacted] obtained is orally administered to patients/subjects.

One of the potential indications of this product is for the treatment of patients with some neurodegenerative disorders, such as Alzheimer's disease (AD). However, additional indications where GSK-3 is implicated, such as autistic spectrum disorder (ASD), Progressive Supranuclear Palsy (PSP) and DM-1 may also be a target for tideglusib. Tideglusib has been subject to clinical investigation in AD and PSP.

Jones *et al.* reported in 2012 that GSK3β mediates muscle pathology in myotonic dystrophy based on increased GSK3Kβ activity in DM-1 expressing cell lines, muscle biopsy samples from DM-1 expressing transgenic mice and DM-1 patient tissue samples. Further, tideglusib and related

compounds reverse the phenotype of transgenic mouse models of [redacted] and myotonic dystrophy.

Refer to the current Investigator Brochure for additional information on tideglusib.

5.3 Pre-clinical Research

A comprehensive ICH-compliant pre-clinical program has been conducted with tideglusib. Summary information is described in this section with additional information on the non-clinical studies conducted to date contained within the current version of the Investigator Brochure.

[redacted]

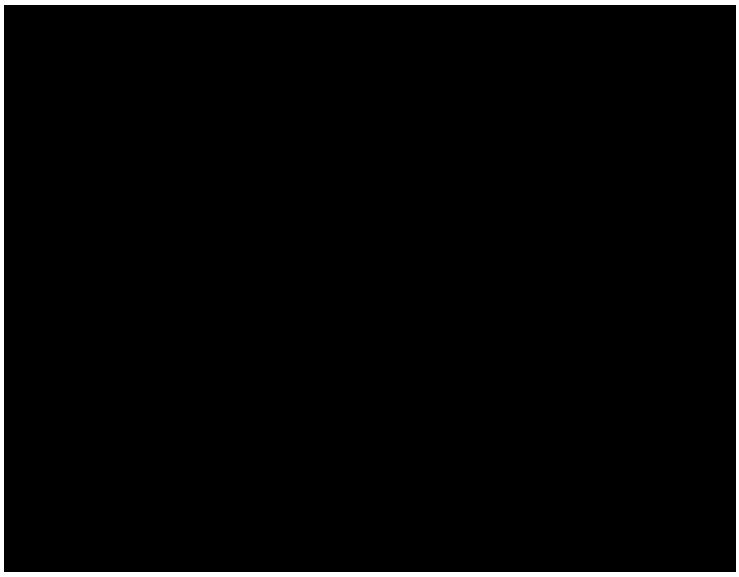


Figure 1:

[redacted]

[redacted]

5.4 [redacted]

[redacted]

[redacted]

[redacted]

More detailed summaries of the clinical trials can be found in the Investigator Brochure.

Safety Summary

Phase I studies

[redacted]

[redacted]

[redacted]

[redacted]

Adverse Event	Active	Placebo
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Patient studies

[redacted]

[redacted]

Table 3: [redacted]

ADVERSE EVENT			9				=10		TOTAL			
	n	%	n	%	n	%	n	%	n	%	n	%

[redacted]

In conclusion, tideglusib has been administered to 499 human subjects and has generally been well tolerated. With respect to the population intended to be investigated in the present protocol, there are no clear safety signals that could be considered specifically relevant.

Table 4:

	n	%	n	%	n	%	n	%	n	%

Table 5:

	n	%	n	%	n	%

Table 6:

	n	%	n	%	n	%	n	%

[redacted]

Efficacy Summary

[redacted]

[redacted]

5.5 Rationale for this Study

As described in Section 5.3, there is pre-clinical and in-vitro clinical evidence to suggest that inhibition of GSK3β could have the potential to reverse myotonia and improve muscle weakness in patients with myotonic dystrophy. This will be the first study of a GSK3β inhibitor in myotonic dystrophy patients and will investigate the safety and signals of efficacy of oral administration of tideglusib as an oral dose of either 1000mg or 400mg for twelve weeks in male and female adolescents and adults with congenital and juvenile Type 1 myotonic dystrophy (DM-1). The following factors are taken into account:

Dose: The doses of tideglusib that will be explored in this study are derived from extrapolation from doses administered orally to adult human subjects and shown to be generally safe and well tolerated during placebo controlled administration for up to [redacted] months. These same doses have been shown to produce effects consistent with on target effects in human subjects in relevant organs, such as the

[redacted] These doses are also estimated to produce plasma levels of tideglusib that are in the range shown to be safe according to toxicology studies with the oral formulation of tideglusib intended to be used here. The safety and toxicology data gathered with the proposed oral formulation to be used is extensive, covering mice, rat, mini-pigs and primates, for oral treatment periods of up to [redacted] months. The dose formulation is a dry powder for suspension with flavouring that is suitable for use in subjects that have potentially have swallowing difficulties as a consequence of DM-1 and may therefore not be able to manage solid dose forms.

Pharmacokinetics: [redacted] In these studies the [redacted]

Safety: Tideglusib has been administered to 499 human subjects and has generally been well tolerated. With respect to the population intended to be investigated in the present protocol, there are no clear safety signals that could be considered specifically relevant. A [redacted]

Duration: The duration of treatment (twelve weeks) is appropriate in light of the rapidity of onset of tideglusib and analogues in CNS and muscle tissue in relevant transgenic models of DM-1 and [redacted] (Jones *et al*., 2012; Franklin *et al*., 2013). This duration is also less than that used in previous clinical studies in which the doses proposed in the present protocol were generally safe and well tolerated during double blind, placebo controlled administration for periods of either [redacted] or [redacted] months. This period is longer than the period of assessment used in previous studies to show benefit of intervention in the DM-1 myotonic dystrophy population (Logigian *et al*., 2010).

6. STUDY OBJECTIVES AND PURPOSE

6.1 Primary objectives

The primary objective of this study is 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.

6.2 Secondary objectives

Secondary objectives of this study are:

To investigate the blood pharmacokinetics of tideglusib in adolescent and adult subjects with congenital or juvenile-onset myotonic dystrophy

To investigate differences in outcomes reflective of efficacy, between baseline and end-of-treatment, with tideglusib in adolescent and adult subjects with congenital or juvenile-onset myotonic dystrophy.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Subject numbers

A total of 16 subjects are planned to be enrolled in the study to receive active IMP. Subjects that withdraw during the [redacted] run-in phase, will be replaced. Subjects that withdraw from the study after receiving active IMP, will not be replaced.

Subject eligibility will not be re-assessed [redacted] run-in period; the run-in period is for the purposes of analysis.

7.2 Inclusion criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Subjects under study must be adolescents or adults with a diagnosis of congenital or juvenile-onset type 1 myotonic dystrophy (DM-1). For the purposes of this study, the following definitions apply:

   Congenital: in addition to the genetic confirmation of DM-1, one or more of the following signs or symptoms was evident within the first week after birth:

   a) Hypotonia
   b) Generalized weakness
   c) Respiratory insufficiency
   d) Feeding difficulties
   e) Clubfoot or another musculoskeletal deformity

   Childhood/juvenile-onset: in addition to the genetic confirmation of DM-1, at least 2 signs or symptoms (not caused by another, unrelated condition) were evident prior to 12 years of age that can be clearly assigned to DM-1, for example:

   a) Muscle weakness
   b) Myotonia (delayed muscle relaxation)
   c) Difficulty using hands, including fine motor problems
   d) Excessive daytime sleepiness
   e) Problems with upper or lower gastrointestinal functioning
   f) Problems with concentration or focusing (including symptoms of attention-deficit/hyperactivity disorder)
   g) Learning difficulties (including dyslexia)
2. Diagnosis must be genetically confirmed
3. Subjects must be male or female aged 12 years to 45 years (the first 3 subjects in Cohort 1 must be ≥18 years)

4. Subjects must have a Clinical Global Impression – Severity (CGI-S) score of 4 or greater at [redacted]
5. Subjects must be ambulatory and able to complete the 10 metre walk/run test (splints allowed)
6. Subject's legally authorised representative (LAR) must provide written informed consent and there must be written consent or assent (as age applicable and developmentally appropriate) by the subject before any study-related procedures are conducted
7. Subject's caregiver must be willing and able to support subject's participation for duration of study and if different from the LAR, must consent to this in writing

7.3 Exclusion criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Non-ambulatory (full time) wheel chair user
2. Receiving stimulant medication
3. Receiving other medications/therapies not stable (changed) within 4 weeks prior to Run-in ([redacted])
4. Medical illness or other concern which would cause investigator to conclude subjects will not be able to perform the study procedures or assessments or would confound interpretation of data obtained during assessment
5. Current enrolment in a clinical trial of an investigational drug or enrolment in a clinical trial of an investigational drug in the last 6 months
6. Women of child bearing potential who are pregnant, lactating or not willing to use a protocol-defined acceptable* contraception method if sexually active and not surgically sterile
7. Men, if engaged in sexual relations with a female of child-bearing potential, not using an acceptable* contraceptive method if not surgically sterile
8. Gastrointestinal disease which may interfere with the absorption, distribution, metabolism or excretion of the study medication and impact the interpretability of the study results
9. Current clinically significant (as determined by the investigator) cardiovascular, renal, hepatic, endocrine or respiratory disease
10. Clinically significant heart disease (in the opinion of the investigator) or second or third degree heart block, atrial flutter, atrial fibrillation, ventricular arrhythmias, or is receiving medication for treatment of a cardiac arrhythmia
11. Average QTcF value of >450msec at [redacted]
12. Kidney disease requiring ongoing treatment
13. A history of chronic liver disease with current out of range value for ALT, clinically relevant hepatic steatosis or other clinical manifestations of ongoing liver disease
14. Current ALT value > 2X the upper limit of the normal reference range at [redacted] ([redacted]) (may repeat to confirm)

15. Current total bilirubin value greater than the upper limit of the normal reference range at [redacted] (unless due to Gilbert's syndrome) (may repeat to confirm)
16. HbA1c values greater than 6% or 42.0mmol/mol at [redacted] (may repeat to confirm)
17. TSH values outside of the normal reference range at [redacted] (may repeat to confirm)
18. Serum creatinine >150 µmol/L and creatinine clearance ≤ 60 mL/m (according to Cockcroft-Gault formula) at [redacted] (may repeat to confirm)
19. Clinical history of hepatitis, previous or current positive serological evidence for hepatitis B or C
20. Serological evidence of Hepatitis A at [redacted] or in the [redacted] preceding [redacted]
21. A history of significant drug allergy (such as Steven-Johnson syndrome, anaphylaxis)
22. A history of alcohol or substance use disorders
23. Current malignancy or any history of malignancy except for surgically-cured skin cancer or pilomatricoma (benign tumour of the hair follicle that is associated with DM-1).
24. Severe arthritis or other medical condition (besides DM-1) that would significantly impact ambulation
25. Use within 4 weeks prior to [redacted] of strong CYP3A4 inhibitors e.g. clarithyromycin, telithromycin, ketoconazole, itarconazole, posaconazole, nefazadone, indinavir, ritonavir
26. Concurrent use of drugs metabolised by CYP3A4 with a narrow therapeutic window e.g. warfarin and digitoxin
27. Judged clinically to be at risk of suicide (suicidal ideation, severe depression, or other factors) over the last three months, as assessed by the Investigator.
28. Hypersensitivity to tideglusib or any components of its formulation including allergy to strawberry
29. BMI of less than 14.0 kg/m^2 or greater than 40.0 kg/m^2 at [redacted]

* Acceptable contraception is considered to be using one of the following birth control methods and should be in place for the duration of the study and for 30 or 90 days after last dose of IMP, respectively for female and male subjects:

- Surgical sterilisation of either the female subject in study (e.g., bilateral tubal ligation) or of her male partner (vasectomy with documented azoospermia) if he is the sole partner of that subject
- Established hormonal contraception (implantable, patch, oral or intramuscular [IM]) administered for at least one month prior to study medication administration
- An intrauterine device (IUD) or intrauterine system (IUS) with failure rate of less than 1% per year inserted by qualified physician at least one month prior to study medication administration

7.4 Withdrawal criteria

A subject should be withdrawn from treatment if they meet the discontinuation criteria in section 9.6. If a subject is discontinued at any time after Run-in [redacted], the investigator will make every effort to see the subject and complete the EOT visit as soon as possible (ideally within [redacted]) after being discontinued from IMP treatment and then attend the follow-up visit, [redacted] after final dose.

Subjects may withdraw from the study at any time without stating a reason and without prejudice to further treatment. The Investigator may withdraw a subject from the study and discontinue study treatment and assessments at any time.

Early discontinuation of any subject who has given informed consent to participate will be recorded including the reason for discontinuation. The primary reason for a subject withdrawing prematurely will be selected from the following standard categories of early discontinuations:

- **Failed to meet enrolment criteria.**
- **Adverse Event**: Clinical events occurred or laboratory results are reported that in the medical judgment of the investigator are grounds for discontinuation in the best interests of the subject.
- **Withdrawal of Consent**: The subject desired to withdraw from further participation in the study. The subject is not obliged to provide any reason for withdrawal of consent, but where a reason is given this will be recorded on the CRF.
- **Protocol Violation**: The subject failed to adhere to the protocol requirements, at the investigator's discretion e.g. the subject requires initiating a medication from the prohibited medications list (section 9.10).
- **Lost to Follow-Up**: The subject stopped coming for visits and study personnel were unable to contact the subject or caregiver. Every effort should be made to re-contact the subject prior to declaring a subject as lost to follow-up, which must be at least 3 documented attempts. The 3rd must be in writing and confirmed to have been received (e.g. registered post).
- **Other:** The subject was terminated for a reason other than those listed above, such as theft or loss of study drugs or termination of study by Sponsor.

8. STUDY DESIGN

8.1 Primary endpoints

Incidence of adverse events (AE), including Serious adverse events (SAE). AEs will be evaluated between baseline and Follow-up Visit, while SAEs will be evaluated between screening and the last clinic visit or until resolution, whenever possible.

The incidence of abnormal findings in objective assessments (e.g. laboratory values, ECGs, and vital signs) during the course of the study will also be assessed.

8.2 Secondary endpoints

Secondary endpoints will include the following:

- Blood pharmacokinetics (PK) of tideglusib
- 10 metre walk/run test (self-selected and fastest velocity)
- Computerised handgrip myometer measure of grip strength and muscle relaxation time
- Respiratory Forced vital capacity (FVC)
- Clinical Global Impressions– Severity and –Improvement (CGI-S and CGI-I)
- Actigraphy (measure daily averages of: number of bouts of activity, number of steps taken and energy expenditure)
- Nine Hole Peg Test (NHPT)
- Dual-energy X-ray absorptiometry (DXA) whole body scan of lean muscle mass (g) legs, arms, and total
- Top 3 Concerns VAS (caregiver-completed and where possible, subject-completed also)
- OSU Autism Rating Scale (OARS)
- OSU Autism CGI
- Clinician-completed Domain Specific Cause for Concern VAS: Myotonic Dystrophy
- Peabody Picture Vocabulary Test
- [redacted] levels and activity

8.3 Study design

This is a single-blind, [redacted] week study in adolescent and adult subjects with congenital or juvenile onset type 1 myotonic dystrophy (DM-1).

Approximately 16 subjects in total are planned to be enrolled and receive active IMP.

Participation for individual subjects will consist of an initial Screening of up to [redacted] weeks (minimum of [redacted] week) followed by a [redacted] treatment phase. After this, subjects in Cohort 1 will be treated [redacted] once daily orally for 12 weeks and Cohort 2 will be treated [redacted] once daily orally for 12 weeks.

Once [redacted] out of the [redacted] subjects from Cohort 1, who have received active treatment with 1000mg of tideglusib, have completed or discontinued from the study ([redacted]), the DSMC will meet to review the available data and a recommendation will be made to the Sponsor whether Cohort 2 should be initiated. [redacted]. No screening will take place for Cohort 2 until after the recommendation has been made from the DSMC, to the Sponsor, on if Cohort 2 should be initiated.

The study will have 4 distinct phases:

- Screening (weeks [redacted])

  Informed consent and assent (as applicable – see section 13.3) must be performed before any protocol procedures are carried out. Subjects will be screened to ensure adherence to eligibility criteria. This must be performed at least 1 week prior to Run-in ([redacted]). Laboratory tests may be repeated once during the screening window if laboratory exclusion criteria are met.

- [redacted] run in (weeks [redacted])

  Subjects and their caregiver will be dispensed [redacted] provided with instructions on when and how to administer the medication. Subject diaries will be dispensed to record the date and time of dose, any issue with taking the dose, information on the subject's [redacted] status, time of first meal after dosing and the type of food eaten. These will be reviewed by the investigator site at each visit.

- Single-blind treatment with tideglusib 1000mg (N = 8) (Cohort 1) or 400mg (N = 8) (Cohort 2) for 12 weeks (weeks 0 to 12)

In cohort 1, the first 3 subjects will be dosed sequentially. The safety Week [redacted] ([redacted]) laboratory data of the previous subject will be reviewed by the investigator and the medical monitor before the next subject will be dosed. The first 3 subjects will all be ≥18 years old.

After the review of laboratory results obtained at Week [redacted] for the third subject, the remaining subjects in Cohort 1 can be dosed, including subjects of ≥12 to ≤17 years.

Subjects will attend clinic for visits every [redacted] weeks where diaries will be collected and accountability checked before dispensing additional IMP. Safety, efficacy and pharmacokinetic assessments will be performed according to the schedule of assessments.

Cohort 2 can begin after data collected in Cohort 1 ([redacted]) has been reviewed by the DSMC. Cohort 2 subjects will be treated as above with 400mg dose, however there will be no initial restriction on enrolment.

- Follow-up visit [redacted] after end-of-treatment (weeks [redacted])

The follow-up visit will take place in clinic, approximately [redacted] after the EOT visit. Safety and efficacy assessments will be performed in line with the schedule of assessments.

[redacted]

Data Safety Monitoring Committee (DSMC)

A Data Safety Monitoring Committee (DSMC) consisting of clinical and other experts independent of the Sponsor and free from any conflict of interest will be established by the sponsor to review interim safety findings during the study and to safeguard patient's interest and safety. The DSMC will form a Charter prior to their first data review; that Charter will include a description of the Committee, the Members and their responsibilities, timing of the reviews, process for communicating with the Sponsor, and considerations for any statistical items (eg, data displays) that may be required for the data reviews.

The initial DSMC review will take place after the 3rd subject has completed Week [redacted] to review all available safety and tolerability data available up to that point. Then the DSMC will meet at least quarterly to review safety and tolerability data for the total study population. The DSMC review will be unblinded. The DSMC will make a recommendation to either proceed with the protocol with no modification or to suggest changes to the protocol e.g. replacement of subjects if appropriate. Based on the results of their data reviews, the DSMC will submit its recommendations in written form to the sponsor who is charged with responding to the recommendations of the DSMC and to take appropriate action.

The DSMC will have an additional meeting to review data from Cohort 1 prior to any screening of subjects for Cohort 2. This additional meeting will be triggered once [redacted], but will include all Cohort 1 data available.

9. STUDY MEDICATION AND ADMISTRATION

9.1 Study medication

Investigational Medicinal Product: Tideglusib

Chemical Name: 4-benzyl-2-naphthalen-1-yl-1,2,4-thiadiazolidine-3,5-dione

The Investigational Medicinal Product is a powder for oral suspension designated as formulation F06-037F. This powder is filled into sachets containing one dose of powder of either [redacted] or [redacted] The content of the sachets must be [redacted]

A similar formulation to F06-037F has been developed to be used as placebo according to protocol and study design. The placebo drug product (coded F07-101) is supplied in the same type of units containing sachets of the same strength as the active product. It is a powder for oral suspension in [redacted]

The single dose sachets should be stored in refrigerated conditions [redacted]) prior to reconstitution. Shelf life periods may be extended if justified by stability results and use-by-dates will be modified on the packaging. Sponsor approval must be sought prior to re-labelling.

The single-blind IMP will be provided to the subject and their caregiver at each visit [redacted]

IMP (either active tideglusib or matched placebo) will be packaged in cartons of 18 sachets. With 18 sachets per carton, there is sufficient medication to cover a [redacted] An additional 2 sachets of medication are also included in the carton in the event that during the process of opening the sachets, medication is inadvertently lost. In this event, the subject/caregiver will be instructed not to use the sachet from which drug has been lost, but to open a new replacement sachet from the same carton so that the full dose can be given.

Each sachet and carton will be externally labelled with a medication ID number, expiry date and clinical trial information. The IMP (sachets and cartons) will be labelled according to Annex 13, Volume 4 of EUDRALEX and will be in accordance with all other applicable regulatory requirements.

9.1.1 Subjects in Cohort 1 will receive the following cartons of medication:

Run-in Phase (dispensed at [redacted]):

1 x carton containing 18 sachets [redacted]

1 x carton containing 18 sachets [redacted]

Active Phase (dispensed at [redacted]):

1 x carton containing 18 sachets [redacted]

1 x carton containing 18 sachets [redacted]

Subjects/caregivers will be instructed to take 1 sachet from each carton to achieve the subject's assigned dose of 1000mg. [redacted]

9.1.2 Subjects in Cohort 2 will receive the following cartons of medication:

Run-in Phase (dispensed at [redacted])

1 x carton containing 18 sachets [redacted]

Active Phase (dispensed at [redacted])

1 x carton containing 18 sachets [redacted]

The caregiver will be given clear instructions that all unused and used sachets should be returned at each visit and they will be provided with new medication at the subsequent visit. If IMP is not returned at a visit, the caregiver must be informed to only use sachets from the new carton(s) and return both sets of IMP at the next visit.

9.2 Selection of doses in the study

Cohort 1 (n=8) will be administered 1000mg tideglusib once daily, with an initial sentinel group of 3 subjects being dosed individually with safety laboratory data being reviewed after [redacted] of active treatment [redacted] before the next subject is dosed. Once the 3rd subject has had their safety laboratory data reviewed after [redacted] of active treatment [redacted] by the investigator in consultation with the medical monitor, if acceptable, then the remaining subjects in the cohort can be enrolled.

Following DSMC review of Cohort 1 data, Cohort 2 will be administered 400mg once daily. In both cohorts, a [redacted] week run-in [redacted]

The doses of 1000mg and 400mg of tideglusib are derived from extrapolation from doses administered orally to adult human subjects and shown to be generally safe and well tolerated during placebo controlled administration for up to twelve months. These same doses have been shown to produce effects consistent with on target effects in human subjects in relevant organs, such as the [redacted] These

doses are also estimated to produce plasma levels of tideglusib that are in the range shown to be safe according to toxicology studies with the oral formulation of tideglusib intended to be used here. The safety and toxicology data gathered with the proposed oral formulation to be used is extensive, covering mice, rat, mini-pigs and primates, for oral treatment periods of up to [redacted] months. The dose formulation is a dry powder for suspension with flavouring that is suitable for use in subjects that potentially have swallowing difficulties as a consequence of DM-1 and may therefore not be able to manage solid dose forms.

As described above, the first cohort of subjects in this study will be dosed with 1000mg of tideglusib given orally once daily. This dose has previously been shown to be generally safe and well tolerated over periods of administration longer than presently proposed. As additional safeguards, sentinel dosing of the first 3 subjects in Cohort 1 has been included in the study design with these first 3 subjects needing to be ≥18 years old and a DSMC will be in place.

[redacted]

9.3 Allocation to Treatment

This study is single-blind, where the Sponsor/delegate and the Investigator site will know what treatment the subjects is receiving at each point during the study, but the subject and caregiver will be blinded to know if they are receiving active or placebo. Subjects will be allocated into Cohort 1 (1000mg) or 2 (400mg) in sequence.

9.4 Study Treatment and Administration

IMP and placebo will be administered orally once daily by dispersing one or two sachets (depending on dose) in [redacted].

The IMP must be administered in an [redacted]; [redacted]

The whole content of the sachet(s) should be a[redacted].

The date and time should be recorded in the subject diary along with confirmation that the dose was administered without issue or a description of any issues (e.g. incomplete dose).

9.5 Duration of Subject Participation

The overall expected duration of subject participation is [redacted] weeks. Subjects undergo up to [redacted] week screening period, followed by a[redacted]. Subjects will then receive [redacted] treatment for up to 12 weeks. There will be a follow-up visit at week [redacted] (approximately [redacted] after the last dose).

9.6 Discontinuation criteria

Stopping Rules for Individual Subjects

If a subject meets one or more of the following criteria, they should be immediately discontinued from the study

- [redacted]

The subject will be instructed to return to the clinic for a follow-up assessment within [redacted], and at that time, repeat blood work will be obtained (e.g. [redacted], a physical examination will be conducted, and the protocol-defined study assessments for end-of-treatment will be completed.

Laboratory Alerts for Stopping Rules

The laboratory will inform immediately (within 24 hours after obtaining the result) the investigator or designee and medical monitor if the following laboratory values are observed for a subject:

- [redacted]

[redacted]

Depending on the laboratory value(s) for the subject, there are 3 possible actions; the subject will be withdrawn from the study, the dose of their study medication will be reduced or the subject/caregiver will be contacted by the investigator for further evaluation:

i. Withdraw from Study

The subject/caregiver should be contacted to discontinue their study medication immediately and to be withdrawn from the study, if any of the stopping rules for individual subjects described above are met.

ii. Dose Adjustment (Only applicable for subjects on 1000mg Tideglusib)

[redacted] conduct a brief physical examination, collect vital signs and check for any AEs or changes to concomitant medication. As the study is single-blind to the subject/caregiver on whether they are receiving placebo or active medication rather than dose strength, the subject/caregiver will be instructed to bring both cartons of dispensed medication with them to the unscheduled visit. The carton containing the [redacted] sachets will be collected from the subject/caregiver and they will be instructed to re-start taking the [redacted] sachets. There will be no adjustment of clinic visits from the originally scheduled appointment.

- This procedure should not take more than 5 days from the time that the investigator is informed of the increased laboratory value, to the time the subject stops medication and starts taking the lower dose of medication
- [redacted] (see withdraw from study above)

[redacted] to the treatment group where they have been most of the time during the study.

iii. Subject/Caregiver contacted by Investigator for further evaluation

[redacted] If yes, the subject should be immediately discontinued from the study (see withdraw from study above). If no, the subject/caregiver should be instructed to call the investigator immediately if they experience any of these symptoms before the next scheduled clinic visit. In addition, the subject should attend clinic within 5 days to allow for collection of clinical labs ([redacted]), conduct of a brief physical examination, collection of vital signs and check for any AEs or changes to concomitant medication.

[redacted]

9.7 Treatment Accountability and Compliance Checks

In accordance with regulatory requirements, the Investigator or designated site staff must document the amount of IMP dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to the Sponsor (or representative) when applicable. Product accountability records must be maintained throughout the course of the study.

Every effort should be made to collect cartons and unused sachets of IMP from the subjects at each visit to allow for accountability and for compliance to be checked. It is essential that subjects and caregivers are given information not to use medication from the previous visit if they do not return all medication. This is to maintain the single-blind and therefore should have equal importance at each visit.

At each visit, the subject diary will be reviewed and compared to the accountability evidence to further ascertain compliance and ensure dose times are recorded for PK sample visits (Week [redacted] and Week [redacted]

[redacted] of IMP from 1000mg to 400mg, the number of sachets for both [redacted] or placebo and [redacted] or placebo should be counted and documented in medical notes before returning the [redacted] sachets to the subject and caregiver.

9.8 Treatment Blinding Code

The study is single-blind, with the subject/caregiver/LAR being blind to whether the subject is receiving placebo or active medication. Therefore a blinding code will not be required.

9.9 Permitted concomitant medications/non-pharmacological therapies

All concomitant medications and non-pharmacological therapies (e.g. physiotherapy, yoga) taken or implemented during the study will be recorded in the CRF with indication, dose information, frequency and dates of administration as applicable.

Any permitted medication or therapy that the subject was taking on entry to the study should be continued at the same dose (as applicable) and frequency throughout the study.

If the subject is taking [redacted].

9.10 Prohibited concomitant medication

Strong CYP3A4 inhibitors e.g. clarithyromycin, telithromycin, ketoconazole, itarconazole, posaconazole, nefazadone, indinavir, ritonavir are not permitted during this study.

Stimulant medication is not permitted during the study.

Drugs metabolised by CYP3A4 with a narrow therapeutic window e.g. warfarin and digitoxin, are not permitted during the study.

Treatment with any other IMP is not permitted during this study or within 6 months prior to screening.

10. STUDY SCHEDULE

Refer to Table 1 for a schedule of assessments for each timepoint.

10.1 Safety assessments

All assessments will be performed by the investigator or appropriately delegated and trained personnel.

10.1.1 Medical/Surgical and Medication History

The investigator must record all medically and clinical relevant information regardless of the time since the date of diagnosis

History should include (but is not limited to):

- All current and past medications taken during 1 year before the Screening Visit [redacted]
- All current and past non-pharmacologic therapies taken 3 months before the Screening Visit [redacted]
- History of respiratory, cardiovascular, renal, gastro-intestinal, hepatic, endocrine, haematological, neurological, psychiatric and any other diseases

10.1.2 Physical Examination

A full physical examination will be conducted. This will be completed by a delegated physician.

A full physical examination is composed of a review of the following body systems:

- General appearance
- Skin
- Head, eyes, ears, nose and throat
- Respiratory
- Cardiovascular
- Abdomen (including liver and kidneys)
- Musculoskeletal
- Neurological

Any abnormalities that are identified at the Screening Visit [redacted] will be documented in the subject's source and on the medical/surgical history CRF page. Any changes (including new and worsening findings) between the Screening Visit [redacted] and Run-in Visit [redacted] will be recorded either on the

medical/surgical history CRF page if a non-serious medical occurrence, or as a baseline sign or symptom if a non-serious sign or symptom. Any changes between the Run-in Visit [redacted] and end of study should be captured as AEs on the AE CRF page, as determined by the Investigator.

If an improvement/resolution of a physical examination finding documented in the subject's medical history occurs during the study, it should be recorded in the source document. If there is resolution of a physical examination finding previously noted as an AE, then the event resolution and stop date should be recorded on the AE CRF page.

10.1.3 Height

A calibrated stadiometer should be used to measure height. Height should be measured in centimetres without shoes with the subject standing on a flat surface and with their chin parallel to the floor. The body should be straight but not rigid. The subject's height should be recorded to the nearest 0.5cm.

10.1.4 Weight

The same calibrated scale should be used for all weight measurements for a subject. Weight should be measured in kilograms without shoes and recorded to the nearest 0.1kg. Bulky items should be removed whenever possible to ensure the most accurate weight is recorded.

10.1.5 Adverse Event Collection

Subjects will be questioned in a non-leading way to determine if AEs have occurred since the last visit e.g. have you had any health problems since your last visit?" SAEs will be collected from the time of informed consent. Non-serious AEs will be collected from the time of single-blind dosing. Any non-serious medical occurrences occurring between Screening [redacted] and Run in [redacted] will be recorded as Medical/Surgical History. Any non-serious signs and symptoms occurring between Screening [redacted] and Run in [redacted]) will be recorded and classified as baseline signs and symptoms. Refer to section 10.4 for additional details of AE collection and reporting.

10.1.6 Vital Signs

Vital signs will include the following measures: oral temperature, pulse, systolic and diastolic blood pressure and respiratory rate. Blood pressure and pulse will be determined after the subject has been in the sitting position for 5 minutes.

Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study). A BP cuff appropriate for the subject's arm length and girth should be used for all BP measurements. The cuff should be approximately two-thirds the length/width of the subject's arm (from elbow to shoulder). The cuff should be calibrated and ideally the same cuff should be used on a subject throughout the study. All BP measurements should be performed by the same study site personnel (if possible) throughout the study.

Any vital signs which in the opinion of the investigator are deemed to be clinically significant are to be recorded as an AE. Any clinically significant abnormalities at the follow-up visit should be followed up and repeated until they have returned to baseline or are, in the opinion of the investigator, no longer clinically significant.

10.1.7 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the study laboratory's normal procedures. Reference ranges will be supplied by the study laboratory and will be used to assess the laboratory data for clinical significance and out of range changes.

Biochemistry

A biochemistry sample will be collected at every visit. Biochemistry blood samples can be drawn with the subject in either a fasting or non-fasting state (this state should be kept consistent for blood sampling throughout the study). If a sample needs to be repeated, the subsequent sample should be drawn from the subject in the same fasting/non-fasting state.

The biochemistry analysis will include [redacted]

At screening [redacted] biochemistry sample will also be analysed to determine if there is serological evidence of Hepatitis A at [redacted] or in the past [redacted] or an active Hepatitis B or C infection (Anti-HAV IgM, anti-HBc IgM, Hep B surface antigen, HCV). If an initial positive result is obtained indicating an active Hepatitis C infection, the result will need to be confirmed and a further 4mL blood sample will be collected from the subject.

Additionally, at screening [redacted], run-in [redacted], baseline [redacted] Week [redacted] and EOT, it should also be requested to get a [redacted] analysed.

Haematology

A full blood count with differential should be collected at each visit. This should include [redacted] Additionally, at screening [redacted] baseline [redacted], Week [redacted] and EOT, [redacted] should also be analysed.

[redacted]

[redacted]

Urinalysis

Urinalysis will be performed by dipstick and documented in source documents. Abnormal results should be investigated further by sending to the study laboratory.

Pregnancy Test

Serum pregnancy test for female subjects of child bearing potential at screening will be performed. At subsequent visits, a urine pregnancy test is sufficient if acceptable and preferable according to local practice.

10.1.8 ECG

The HR, PR interval, QRS interval, and QT interval will be measured and QTcB and QTcF will be calculated for all ECGs.

Subjects will be assessed in a quiet state (after 5 minutes of rest) in the supine position. A standard ECG recording device will be used with the standard paper rate of 25 mm/second and the standard scale setting of 10mm/volt.

Three ECGs will be obtained at the Screening Visit [redacted] to determine subject eligibility. For all other visits, where ECG is requested according to schedule of assessment, these will also be performed in triplicate (ideally separated by at least five minutes) with the average values calculated and documented prior to recording in the eCRF.

10.2 Efficacy assessments

All assessments will be performed by the investigator or appropriately delegated and trained personnel.

The study will evaluate the main domains of the phenotype of congenital and juvenile-onset DM-1. These domains relate to muscle symptoms, CNS symptoms, disorder specific rating scales and biological markers pertinent to the molecular pathology of the disorder. Each domain will be assessed using the measures described below.

Assessment of Muscle Functioning

10.2.1 10 metre walk/run test

The 10 metre walk/run test is a performance measure used to assess walking speed in metres per second over a short distance. It can be used as an assessment of functional mobility. The test will be conducted according to the schedule of assessments (Table 1) and will be performed at the subject's preferred walking speed and then at the fastest speed possible. For each speed, 3 assessments will be completed with a rest period until the subject has recovered.

The subject walks without assistance for 12 metres while the time taken to walk from metre 1 to meter 11 is recorded. The timing starts and stops when the toes of the leading foot cross the 1 and 11 metre marks respectively. If assistive devices are needed, these can be used but must be documented and kept consistent for that subject throughout the study.

For the fastest speed possible, the assessor will document whether the subject was able to run, walk fast or walk for each assessment. Whether the subject is running is defined as both feet being off the floor at the same time. If the subject is not able/willing to perform the fastest speed possible for all 3 assessments, this will also be recorded.

Appendix A provides further information on the test including verbal instructions to give to the subject.

10.2.2 Computerised handgrip myometer measure of grip strength and relaxation time

Handgrip myometry is used as a measure of myotonia and muscle strength and has been validated as a reliable measure in patients with myotonic dystrophy type 1 (Moxley *et al.,* 2007).

The force of concentration exerted on the handle of a handgrip dynamometer is measured in addition to the time of contraction and relaxation. A computer stores the force curves for analysis to calculate the force of contraction/grip strength (Kg) and the time taken for the hand to relax from 90% contracted to 5% contracted (seconds).

Each assessment session consists of two trials per hand, each with three squeezes (maximum voluntary isometric contraction) on the handgrip dynamometer. Sessions are performed in accordance with the schedule of assessments. Both hands will be assessed.

The tester will allow an adequate amount of time after the first squeeze for the force curve to return to and remain at the level at the beginning of the trial (approx. 20 seconds) prior to proceeding with the remaining two grip contractions within the trial. The subsequent two squeezes will be approximately 3 seconds of contraction followed by 10 seconds of relaxation. After the first trial (3 squeezes), the subject will rest that hand for approximately one minute. While one hand is recovering, the other hand can be tested.

10.2.3 Respiratory - FVC

Forced Vital Capacity (FVC) is a measure of lung function which is obtained via spirometry. FVC is the total amount of air exhaled during a Forced Expiratory Volume (FEV) test using a spirometer. Measurements will be taken according to the schedule of assessments.

The subject should be sitting in a chair for the test. The evaluator will either explain or demonstrate the procedure to the subject and explain that they will be performing the test at least 3 times. The specific wording of instructions is detailed in Appendix B.

The test should be repeated at least 3 times, making sure that the subject has recovered between attempts. If at each attempt there is an improvement in the results, further tests can be conducted until the subject has achieved his/her best result.

10.2.4 Actigraphy

Actigraphy is a non-invasive method of monitoring physical activity via an actigraph device. The Actigraph device will be worn on the waist during waking hours, according to the device's instruction manual.

In this study, actigraphic assessments will occur on a regular basis throughout the study as detailed in the schedule of assessments. Each assessment will consist of approximately 7 full days of activity information from subjects, and this information will be used to calculate the average number of steps per day, bouts of activity and total energy expenditure.

10.2.5 Nine Hole Peg Test (NHPT)

The NHPT is a measure of fine manual dexterity.

The NHPT is composed of a square board with 9 pegs. At one end of the board are holes for the pegs to fit into, and at the other end a shallow round dish to store the pegs. The NHPT is administered by asking the subject to take the pegs from a container, one by one, and placing them into the holes on the board as quickly as possible. Subjects must then remove the pegs from the board, one by one, and replace them back in the container.

Subjects are scored on the time taken to complete the activity in seconds. Timing begins when the subject touches the first peg and finishes when the last peg hits the container.

Both the dominant and non-dominant arm should be tested; the dominant hand should be tested first. One practice trial should be completed with each hand prior to performing the actual test, which will include 1 attempt with each hand. The evaluator should demonstrate the test to the subject prior to the practice test and should be sitting next to the subject.

The NHPT will be administered in accordance with the schedule of assessments. Detailed instructions on the NHPT are contained in Appendix C.

10.2.6 Dual-energy X-ray absorptiometry (DXA) scan

DXA (previously DEXA) utilises two low energy X-ray beams, with different energy levels, which are aimed at the subject's bones. The DXA scan is more typically used to measure bone mineral density, however it can also be used to measure total body composition, lean muscle mass and fat content. The amount of radiation used in a DXA scan is very low.

Subjects will have their lean muscle mass determined by a whole body DXA scan and the following parameters recorded in grams; arms, legs and total. The DXA scans will be administered in accordance with the schedule of assessments.

Clinician and caregiver rating scales of syndrome-specific symptoms

10.2.7 Clinical Global Impressions Severity and Improvement

The clinician administered Clinical Global Impressions of Severity (CGI-S) and Improvement (CGI-I) scale (Guy, 1976) will be performed in accordance with schedule of assessment (Table 1). The CGI rating scale permits a global evaluation of the subject's improvement over time and will be administered as detailed in the schedule of assessments.

The CGI-S is a 7-point Likert type scale that requires the clinician to rate the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis. Considering total clinical experience, a subject is assessed on severity of illness at the time of rating 1, normal, not at all ill; 2, borderline ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.

The CGI-I requires the clinician to rate how much the subject's illness has improved or worsened relative to a baseline state. A seven point Likert type scale is used from 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse.

The CGI-I at Baseline [redacted] should be rated against the CGI-S at Run-in [redacted] For subsequent CGI-I ratings completed from Week [redacted] onwards, the assessment should be compared against the CGI-S, done at Baseline [redacted]

In this study, a standard set of probes/prompts will be provided to the sites to assist the evaluator in eliciting commentary from the subject or their caregiver across each of the core domains and also on associated symptoms. Every effort will be made so that the same evaluator will also observe the subject at each visit to the clinic.

As part of the physician evaluation of the subject for the CGI-S and CGI-I ratings, if additional information is volunteered by the subject and/or caregiver which the physician feels supports the ratings, but is not captured elsewhere in the CRF, this information will be recorded in the source and captured within a comments field within the eCRF.

A copy of the CGI-S and CGI-I to be used in the study, along with instructions is included in Appendix D.

10.2.8 Top 3 Concerns VAS

The Top 3 concerns VAS allows subjects and caregivers to identify their main three causes of concern, related to the subject's myotonic dystrophy, rather than these being pre-specified within a scale and then rating how these concerns have changed at specific time-points during the study.

Subjects, where possible, and caregivers will be asked to rate three causes for concern by drawing a vertical mark on a 10cm long visual analogue scale with anchors of "not at all severe" at the left end and "very severe" at the right end. The 3 concerns related to the subject's myotonic dystrophy will be chosen and rated at baseline. These 3 signs and symptoms will be rated again at Week [redacted] and EOT using the same scales.

A copy of the Top 3 concerns VAS is included in Appendix E.

10.2.9 Clinician completed Domain Specific Causes for Concern VAS: Myotonic Dystrophy

The Clinician-completed Domain Specific Concerns is a Visual Analogue Scale (VAS) completed by the clinician that scores the severity of concerns in the following domains that are clinically relevant in myotonic dystrophy:

- Limitations with mobility or walking
- Problems with hands or arms
- Inability to do activities
- Fatigue
- Pain
- Gastrointestinal issues
- Problems with vision
- Communication difficulties
- Impaired sleep or daytime sleepiness
- Emotional issues
- Difficulty thinking
- Decreased satisfaction in social situations
- Decreased performance in social situations
- Myotonia
- Breathing difficulties
- Choking or swallowing issues
- Hearing difficulties

This list of domains is derived from the 17 subscales of the Myotonic Dystrophy Health Index (MDHI) (Heatwole *et al*., 2014). The severity of the clinician's concern in each domain is scored by using a 10-cm visual analogue scale (VAS), with anchors of "not at all severe" at the left end and "very severe" at the right end. The clinician is asked to make a vertical line indicating his/her level of concern in each domain, using a time frame of the past week for reference. A score for each domain is determined by measuring the number of centimetres on the 10-cm VAS line from the anchor point on the left side of the line. A total VAS score for each subject is calculated as the sum of the scores for the 17 domains and is reported as both an absolute number and a percentage of the total possible line length (e.g. 170 cm).

The Clinician-completed Domain Specific Causes for Concern-VAS: Myotonic Dystrophy will be administered according the schedule of assessments.

A copy of the Clinician Domain Specific Causes for Concern VAS: Myotonic Dystrophy is included in Appendix F.

Assessments of cognitive functioning and associated neurodevelopmental symptoms

10.2.10 The OSU Autism Rating Scale—DSM-IV (OARS-4)

The OARS-4 contains the autism signs and symptoms in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM—IV). These should be rated with the degree of impairment the subject experiences for the given symptom. The symptoms should be elicited in a semi-structured interview with the subject's primary caregiver. While scoring, the assessor should try to take both frequency/duration and degree of impairment into account as well as how much the item interferes with relationships, learning, and/or activities of daily living. Thus, rituals or preoccupations that severely interfere with most attempts to transition or that are present most of the time should be scored 2 or 3. Conversely, a ritual or preoccupation that is very mild, occupies little time, and interferes only mildly with daily events may be scored as 1.

The OARS-4 provides two summary scores (a) A weighted score based on severity of autism or autism spectrum symptoms derived from the clinical interview and (b) A symptom count, based on the same clinical interview

The OARS-4 should be completed according to the schedule of assessments, a copy of the scale is included in Appendix G.

10.2.11 OSU Autism CGI scale

The OSU Autism CGI scale contains separate subscales for symptom severity and for global improvement. These are rated in a similar way to the NIMH CGI Severity scale (see Clinical Global Impressions Severity and Improvement section in 10.2.6), but it is focused on autism spectrum symptoms. Symptoms frequently associated with autism spectrum—such as compulsions, hyperactivity, and self-injury should also be considered.

The CGI-I at Baseline ([redacted]) should be rated against the CGI-S at Run-in ([redacted]). The subsequent CGI-I ratings should be compared against the second CGI-S, done at Baseline ([redacted]).

The OSU Autism CGI scale provides 2 summary score (a) A global severity scale for autism, which takes autism spectrum and related symptoms (e.g., compulsions, problems transitioning, SIB) into account; and (b) A global improvement scale for autism.

The OSU Autism CGI scale (CGI-S and CGI-I) should be completed according to the schedule of assessments, a copy of the scale is included in Appendix G.

10.2.12 Peabody Picture Vocabulary Test

The PPVT–4 scale is a norm-referenced instrument for measuring the receptive (hearing) vocabulary of children and adults. It contains training items and 228 test items, each consisting of four full-colour pictures as response options on a page. For each item, the examiner says a word, and the examinee responds by selecting the picture that best illustrates that word's meaning.

Each administration of the test produces a raw score as well as a standard score, derived from the number of responses attempted and the number of correct responses. The percent of correct responses is also reported.

The test will be performed at Run-in [redacted] Baseline [redacted] and End-of-Treatment [redacted] to compare scores prior and after single-blind placebo and single-blind tideglusib respectively.

10.2.13 [redacted]

- [redacted]
  A 4ml blood sample will be taken for [redacted]

  [redacted]

Details on collection, handling, storage, processing and shipment of the [redacted] sample will be provided in a separate laboratory manual.

10.2.14 Pharmacokinetics

[redacted] PK samples will be collected for tideglusib and the major metabolite NP04113 at both [redacted]

Individual concentration data will be determined and T_{max}, $T_{½}$, $AUC_{(0\text{-}12hr)}$, C_{max}, C_{min} and C_{ss} will be calculated. Population pharmacokinetic methods of analysis will be used to analyze the data. If the data does not support a model on its own, the data may be combined with a previously developed model in order to strengthen the predictions.

In order to determine whether there are associations between pharmacokinetic parameters and efficacy measures, change from baseline in efficacy measures over the course of the study may be correlated with PK parameters estimated for each dose. These associations may be statistically tested using correlation coefficients and general linear models, if appropriate.

Instructions for the collection, handling, storage, processing and shipment of the pharmacokinetic samples will be provided in a separate laboratory manual.

10.3 Other Assessments

10.3.1 Diary

A diary will be provided to the subject/caregiver at each visit from Run-in [redacted] to Week [redacted] which should be completed every day. The diary should be returned at each subsequent visit and the diary should be reviewed by a delegated member of the study team.

The diary should be completed in full so that the following can be ascertained:

- Time and date of each dose
- If there was any issue with taking the dose
- Whether the subject [redacted]
- Time of [redacted]
- Type of food [redacted]

If any information is missing, this should be discussed with the caregiver so that missing information can be completed from the caregiver's recollection. It must be documented in the medical notes which information has been completed retrospectively.

The diary review should be performed in parallel with checking returned used and unused sachets of IMP.

10.3.2 [redacted]

For purposes of inclusion in the study, subjects need to have a confirmed genetic diagnosis of myotonic dystrophy type 1 [redacted]

Where possible and with additional consent, [redacted]

Instructions for the collection, handling, storage, processing and shipment of the [redacted] will be provided in a separate laboratory manual.

10.3.3 [redacted]

A 5ml blood sample will be taken for [redacted] analysis at the timepoints described in the schedule of assessments.

Instructions for the collection, handling, storage, processing and shipment [redacted] will be provided in a separate laboratory manual.

10.4 Adverse events

Adverse events may be volunteered spontaneously by the subject, or discovered as a result of general, non-leading questioning. All adverse events should be recorded in the CRF and source document.

10.4.1 Definitions

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Abnormal laboratory findings should be reviewed by a delegated physician to determine whether they are clinically significant. Clinically significant abnormal laboratories should be reported as an AE. Where possible and underlying diagnosis should be reported as the AE.

Adverse Drug Reaction (ADR)

All events considered to be untoward and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Serious Adverse Event (SAE)

An adverse event that at any dose:

- Results in death
- Is life-threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation (see explanation below)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is considered to be an important medical event

Based upon medical and scientific judgment, important medical events that may not be immediately life-threatening, or result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above may be considered a serious adverse event.

Hospitalisations are defined as initial or prolonged admissions that include an overnight stay. Hospitalisation or prolonged hospitalisation for technical, practical or social reasons, in the absence of an adverse event is not an SAE.

Pregnancy

Pregnancy itself is not considered an AE. However, any pregnancy complication, spontaneous or elective abortion (for medical reasons), still birth, neonatal death, or congenital anomaly will be recorded in both the clinical and safety database.

If the investigator becomes aware of a pregnancy in a female subject, or in a female partner of a male subject in this study, every effort will be made to follow the pregnancy until termination or delivery.

In the event of pregnancy (either in a female subject or a female partner of a male subject in the study), it will be reported on a pregnancy form, and reported as per the information in section 10.4.8. This report will be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities. The outcome will be documented in the CRF if feasible. In the case of a female subject, the subject must be withdrawn from the study.

Due to the disease under study and the potential intellectual disability of the study subjects, along with the age of some of the potential study subjects, information on how and to whom, a positive pregnancy result will be communicated will be addressed in the study information sheet.

Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with applicable product information (e.g., Investigators Brochure for an unapproved Investigational Medicinal Product).

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious AE that is suspected to be related to the administered medicinal product and the nature or severity of which is not consistent with applicable product information.

Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events.

10.4.2 Severity Categorisation

The severity (intensity) of each AE will be classified as:

- **Mild** Awareness of sign or symptom, but easily tolerated

- **Moderate** Sign or symptom causes discomfort, but does not interfere with normal activities
- **Severe** Sign or symptom of sufficient intensity to interfere with normal activities

A change in severity should be captured as a new AE.

10.4.3 Assessment of Causality

A delegate physician/investigator must assess the relationship to the IMP for each AE. The likely relationship of each AE to the IMP will be assessed according to the definitions below:

- Unrelated
- Related

10.4.4 Outcome Categorisation

All AEs should have an outcome recorded, which should be updated if it changes during the reporting and follow-up period (defined in section 10.4.9). The possible outcomes should be:

- Fatal
- Recovered/Resolved
- Recovering/Resolving
- Recovered/Resolved with sequalae
- Not recovered/not resolved

For fatal outcomes, every effort should be made to ensure source documentation (e.g. autopsy report, death certificate) to confirm the cause of death will be available to be reviewed by the DSMC.

10.4.5 Symptoms of Disease Under Study

Symptoms of the disease under study (e.g. problems with ambulation, fine motor difficulties, fatigue, speech difficulties, and gastrointestinal issues) should not be classed as AEs as long as they are within the normal day to day fluctuation or expected progression of the disease; however, significant worsening of the symptoms should be recorded as an AE.

10.4.6 Clinical Laboratory Evaluations

Abnormal laboratory findings (e.g. haematology, liver function, biochemistry, urinalysis) or other abnormal assessments (e.g. ECGs, vital signs) that are judged by the Investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 10.4.1

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study and significantly worsen following the start of the study will be reported as AEs or SAEs.

The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

Subjects with any TEAE laboratory abnormality (especially LFT abnormalities) will be followed up until recovery or stabilisation of the condition.

10.4.7 Abuse, Misuse, Overdose or Medication Error

Subjects should not exceed the maximum daily doses or take any two doses within an 8 hour interval. There is no specific antidote to tideglusib. In the event of an overdose, appropriate supportive measures should be employed as clinically indicated and the Medical Monitor must be informed immediately. The investigator should determine appropriate supportive assessments which may include a thorough assessment for potential hepatotoxicity, including assessment of serum chemistries, with particular attention to ALT and bilirubin levels, after the cessation of drug. Repeat examinations should be conducted as clinically indicated.

10.4.8 Serious Adverse Event Reporting

Once an Investigator or delegate becomes aware that an SAE or pregnancy has occurred in a study subject, she/ he will report the information to the Sponsor's appointed agent within 24 hours of awareness by completing the SAE or Pregnancy form and e-mailing (or faxing if e-mail is not possible) this and any available supporting documentation to the details below:

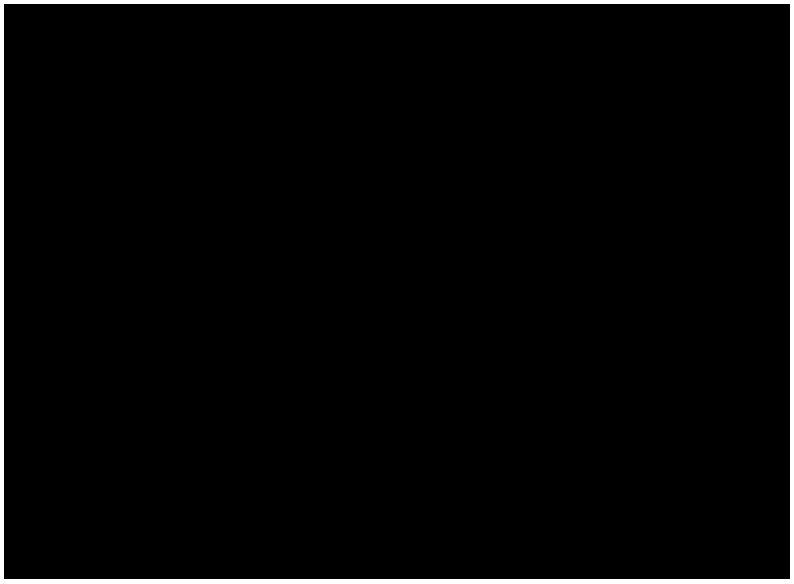
Pharmacovigilance (PV) Provider	[redacted]

SAE email contact:

SAE Fax number:

SAE Telephone contact:

Medical monitor contact:



The SAE/Pregnancy form will always be completed as thoroughly as possible with all available details of the event, and signed by the Investigator (or authorised designee). If the Investigator does not have all information regarding an SAE or Pregnancy, he/she will not wait to receive additional information before notifying the PV Provider / Medical Monitor of the event and completing the form. The form will be updated when additional information is received.

The Investigator will always provide an assessment of causality at the time of the initial report as described in Section 10.4.3 of this protocol.

The PV provider will contact the Investigator should it be necessary to clarify any of the event information. The Investigator should provide follow-up information for the event to the PV provider as soon as it becomes available.

Any event that in the opinion of the Principal Investigator may be of immediate or potential concern for the subject's health or well-being will be reported to the Medical Monitor with parallel notification to the PV Provider.

SAEs that are ongoing at the [redacted] follow-up visit [redacted] will be followed until resolution or stabilisation of subject condition, whichever occurs first. In such cases, follow-up SAE forms will be completed at the [redacted] follow-up visit [redacted] and on resolution or stabilisation, whichever occurs first.

SAEs occurring to a subject after the subject has completed the clinical trial and for which a reasonable possibility of a causal relationship is assessed by the investigator, should be reported by the investigator to the sponsor if the investigator becomes aware of them regardless of the time that has elapsed (post-trial events).

All SAE and AE data will be reviewed by the DSMC at scheduled meetings.

AMO Pharma Ltd is required to expedite to worldwide regulatory authorities, reports of Serious Adverse Events, Serious Adverse Drug reactions or Suspected Unexpected Serious Adverse Reactions (SUSARs) in line with the relevant legislation, including the European Commission Clinical Studies Directive (2001/20/EC).

All investigators will receive a safety letter notifying them of relevant SUSAR reports. In accordance with the European Commission Directive 2001/20/EC, AMO Pharma Ltd or delegate will notify the relevant Ethics Committees in concerned Member States of applicable SUSARs as individual notifications or through a periodic line listing.

AMO Pharma Ltd or delegate will submit to the regulatory authorities all safety updates and periodic reports, as required by applicable regulatory requirements.

10.4.9 Time Period, Frequency, and Method of Detecting AEs and SAEs

Any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e., before on-study informed consent obtained) that do not result in the exclusion of the subject from participating in the study, should be recorded as Medical/Surgical History. In addition, any non-serious medical occurrence which is reported after informed consent is obtained, but prior to the subject receiving single-blinded study medication, should be documented as Medical/Surgical History. Medical occurrences that meet the definition for an SAE should be recorded and reported as an SAE.

Any non-serious signs and symptoms present at the time before the first dose of single-blinded study medication is administered should be documented as baseline signs and symptoms. If a baseline sign or symptom worsens following dosing, then this should be recorded as an AE or SAE.

All AEs occurring after administration of the dose of single-blinded study medication and on or before the final visit must be reported. All AEs must be recorded irrespective of whether they are considered drug related.

At each visit/assessment in the period defined above, AEs will be evaluated by the Investigator and recorded.

Any AEs already documented at a previous assessment and designated as ongoing, should be reviewed at subsequent visits. If these have resolved, this should be documented.

11. STATISTICAL CONSIDERATIONS

Details of all planned analyses will be specified in a separate statistical analysis plan (SAP) which will be finalised prior to hard-lock of the study database. The SAP will contain details of all the analyses including specifications for all tables, listings and figures. All statistical programming will be performed using SAS software. An analysis and evaluation of study data will be performed once all subjects in Cohort 1 have either completed or discontinued from active treatment. The analysis and evaluation will be performed on a subset of the study data as described in the SAP.

The study data will be reported using summary tables, figures and data listings. Continuous variables will be summarised using mean, standard deviation (SD), coefficient of variation (CV%, as appropriate), median, minimum, maximum and, as appropriate, geometric mean. Categorical variables will be summarised by presenting the number (frequency) and percentage in each category. Separate summaries will be provided for subjects in each dose group, as well as overall.

Statistical analyses will be performed using methods and modelling techniques which are appropriate for the types variables (continuous, categorical, ordinal, binary, censored etc.) being analysed and which account for the data structure (e.g. study visits and assessments, methods for handling missing data) and known potential confounding data (e.g. baseline characteristics, treatment dose). Estimates will be presented with appropriate two-sided 95% confidence intervals. The results of statistical tests will be presented with two-sided p-values.

Subjects who [redacted] will be classified as screening failures. Subjects who [redacted] will be classified as run-in failures.

11.1 Estimated Sample Size

Sufficient subjects will be entered into the study to ensure at least 16 are dosed with tideglusib. Enrolment will occur at one, or maybe two, study sites. Eight subjects will be dosed in each of the two dose groups.

No formal sample size calculation was performed.

11.2 Study Populations

Assignment of subjects to analysis populations will be agreed prior to database lock.

The Safety Set (SAF) will include all subjects who took at least one dose of tideglusib. The SAF will be used for all summaries of safety data.

The Full Analysis Set (FAS) will include all subjects in the SAF for whom any efficacy data were collected after first dose of tideglusib. The FAS is the primary population for analyses of efficacy data.

The Per Protocol Set (PPS) will include all subjects in the FAS who did not have any major protocol violations. Definitions of major and minor protocol violations will be included in the SAP. If no subjects are excluded from the PPS, the PPS will not be required. The PPS will be used for secondary analyses of efficacy data.

The Pharmacokinetic Analysis Set (PKAS) will consist of all subjects for whom Pharmacokinetic samples were taken for the derivation of Pharmacokinetic parameters and for whom the corresponding time since last dose prior to sampling is available.

Listings of study data will be based on all subjects who were enrolled in the study.

11.3 Demographics and Baseline Characteristics

Summaries of demographic and baseline characteristics (including medical history, DM-1 history, prior treatments) will be provided by treatment dose and overall for the SAF.

11.4 Statistical Methods for Safety

All safety summaries and analyses will be performed using the SAF.

All AEs will be coded using the MedDRA dictionary and will be summarised by treatment using frequencies and percentages as appropriate.

Other safety data, including laboratory, vital signs and ECG values including change from baseline will be summarised. Changes in safety parameters from baseline [redacted] over time will be described by treatment dose, and shift tables at time points of interest will be generated. Changes from the start of the [redacted] run-in period [redacted] to baseline [redacted] will also be produced as indicative of the effect of [redacted] of [redacted] treatment.

11.5 Statistical Methods for Efficacy

Analyses of efficacy will be based primarily on the FAS.

Changes in efficacy variables from the start of the [redacted] run-in [redacted] to baseline [redacted] for each subject will be summarised and will be considered as indicative of the effect of [redacted] of [redacted] treatment. Changes from baseline [redacted] to post-treatment visits will be summarised by treatment dose at each study visit.

Analyses of changes from baseline will be performed where applicable using repeated measures analysis of covariance (ANCOVA) models with study site (if more than one is used) and treatment dose as fixed effects, and baseline value as a covariate. Least square mean estimates will be produced by dose group by study visit and will be presented with 95% confidence intervals and two-sided p-values.

11.6 Statistical Methods for Pharmacokinetics

Individual concentration data will be tabulated and concentration vs. time curves presented by treatment dose if warranted. Derived parameters will be summarised by dose group. Detailed information will be outlined in the pharmacokinetic analysis plan.

12. END OF THE STUDY

The end of the study is defined as the last subject's last study assessment, which for this protocol is the final follow-up visit conducted [redacted] post-treatment.

13. ETHICS COMMITTEE REVIEW/INFORMED CONSENT

13.1 Independent Ethics Committee (IEC) and Relevant Authorities

The final study protocol, the patient assent and consent forms and the caregiver/guardian information and consent form will be approved by an appropriately constituted independent ethics committee (IEC). Approval will be received in writing before initiation of the study.

Clinical Study Authorisation will be obtained prior to initiation of the study from the relevant Regulatory Authority.

13.2 Ethical Conduct of the Study

The study will be performed in accordance with the local regulations, the principals of Good Clinical Practice (GCP) as described by the International Council on Harmonisation (ICH), and the ethical principles that have their origins in the Declaration of Helsinki.

13.3 Informed Consent and/or Assent

For each study subject, written informed consent will be obtained from the subject's legally authorised representative (LAR) prior to any protocol-related activities. Where the subject lacks the mental capacity to give informed consent, the LAR will be acting as the subject's consultee. The consultee must be informed that, when being asked to act as a consultee for a person who lacks mental capacity, they are being asked to consider what they believe the potential subject would have decided themselves, had they the mental capacity to give informed consent. The personal consultee must themselves have capacity and be prepared to be consulted by the researcher about the possible involvement of the subject who lacks capacity.

As part of this procedure, the principal investigator or one of his associates will explain orally and in writing the nature, duration, purpose of the study, and the action of the study drug in such a manner that the LAR is aware of the potential risks, inconveniences, or adverse effects that may occur. They will be informed that the subject's medical records may be reviewed by appropriately qualified monitors of the Sponsor or Sponsor Representative, and by auditors or regulatory authorities to ensure the accuracy of the details recorded as part of the study. They will be informed that they or the subject may withdraw from the study at any time without prejudice to further treatment. They will receive all information that is required by local regulations and ICH guidelines.

The subject will provide assent or informed consent depending on the subject's age and on the investigator's assessment of what is developmentally appropriate. This must be documented prior to any protocol-related activities being conducted.

For subjects under 16 years old, a children's assent form and information sheet should be used in conjunction with parent/guardian Informed Consent Form.

For adults (16 years or older), the investigator or delegated sub-investigator must assess the subject's capacity to consent. Then, the appropriate Participant Information Sheet and Informed Consent Form or Assent Form should be used.

The assessment of capability to consent should be done following guidelines in the Clinical Trials Regulation for CTIMPs. Consent from the LAR remains valid but the participant should be informed and his/her wishes respected for inclusion and withdrawal to this study.

If the person providing day to day care for the subject and, will be fulfilling the role of caregiver in this study, is not the appropriate person to give consent on behalf of the subject or act as their consultee, consent will also be obtained from the caregiver for their own participation in the study. In this case, the LAR will consent for the patient to take part in the study while the caregiver will consent to their own involvement.

14. STUDY AND DATA MANAGEMENT

14.1 Protocol Amendments

Once approved by the Regulatory Authority and Ethics Committee, the protocol cannot be amended without approval by AMO Pharma Ltd. Unless a substantial amendment needs to be implemented urgently in the interests of safety, substantial amendments to the protocol must be authorised by the Regulatory Authority and Ethics Committee prior to implementation.

14.2 Monitoring

The investigator and institution will permit study-related monitoring, providing direct access to source data/documents.

14.3 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the investigator and institution will permit study-related audits, IRB/IEC review, and regulatory inspections, providing direct access to source data/documents.

14.4 Data Recording

14.4.1 Data to be Considered as Source Data

Source data is defined as the first place that data is documented. Source data must meet the following "ALCOA" principles:

- Attributable
- Legible
- Contemporaneous
- Original
- Accurate

For this study, source data can include, but is not limited to, medical records, study specific source sheets (as applicable), laboratory reports, laboratory sample collection forms, ECG traces, clinician correspondence, subject, caregiver and clinician completed tests, scales and questionnaires. Source data can be recorded electronically or on paper. Electronic records must be in a validated system that allows ALCOA principles to apply.

14.4.2 CRF

An electronic Case Report Form (eCRF) will be used to capture subject data. Access to enter data in the eCRF will be limited to delegated and trained investigator site staff only.

Data in the eCRF will be verified by monitors according to a risk-appropriate monitoring strategy.

14.5 Confidentiality

The Investigator must assure that the subject's anonymity will be maintained. On all study documentation, with the exception of the consent form and subject ID logs, subjects will only be identified by their unique identification code and initials and will not be referred to by name.

The sponsor may transfer some data collected during the study to a different company or regulatory authority within/outside Europe for the purpose of processing, review, analysis or storage. Whenever the subject's personal data is transferred, it will be kept confidential and secure, and will be used only for the purpose for which it was collected.

14.6 Retention of Study Data

Following closure of the study, the Investigator must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/ regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The Investigator must assure that all reproductions are legible and are a true and accurate copy of the originals, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the Investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

AMO Pharma Ltd. will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or AMO Pharma Ltd. or delegated CRO's SOPs; otherwise, the retention period will default to 15 years.

The Investigator must notify AMO Pharma Ltd. of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the Investigator leaves the site. The Investigator may not dispose of any records without prior approval from AMO Pharma Ltd.

14.7 Communication and Publication of Results

This study will be registered in the EudraCT database. A clinical study report will be submitted to EudraCT in accordance with timelines for paediatric studies according to The European Clinical Trials Directive 2001/20/EC.

The investigator has the right to publish study results from his/her specific site. However, any publication that includes AMO Pharma confidential information cannot be submitted for publication without AMO Pharma's prior written approval.

Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

14.8 Indemnification

In the event of study-related damage or injuries, the public liability insurance of the Sponsor provides compensation for claims that arise in accordance with the regulatory requirements of the countries involved, except for claims that arise from wilful misconduct or gross negligence. A copy of the insurance certificates will be held in the Trial Master File and in the Investigator Site File.

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16. SIGNATURES AND AGREEMENT WITH THE PROTOCOL

Sponsor Approval

I have reviewed and approved the protocol and confirm that the protocol follows GCP.

Signature: [redacted] Date: 10th Jan 2017

Sponsor CEO

Signature: [redacted] Date: 10-JANUARY-2017

Clinical Project Lead

Signature: Date:

[redacted]

Sponsor Medical Expert

Signature: [redacted] Date: 10 Jan 2017

Study Statistician

16. SIGNATURES AND AGREEMENT WITH THE PROTOCOL

Sponsor Approval

I have reviewed and approved the protocol and confirm that the protocol follows GCP.

Signature: [redacted] Date: 10th Jan 2017

Sponsor CEO

Signature: [redacted] Date: 10-January-2017

Clinical Project Lead

Signature: [redacted] Date: 10 January 2017

Sponsor Medical Expert

Signature: [redacted] Date:

Study Statistician

Chief Investigator Approval

I agree to conduct the study according to the terms and conditions of this protocol, current Good Clinical Practice and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

Signature: [redacted] Date: 09/01/2017

[redacted]

Principal Investigator Approval

I agree to conduct the study according to the terms and conditions of this protocol, current Good Clinical Practice and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

Signature: _____ Date:

_____

Name of Principal Investigator:

_____

Title

17. APPENDICES

Appendix A: 10 Metre Walk Test Instructions

Appendix B: Pulmonary Function Test Instructions

Appendix C: Nine Hole Peg Test

Appendix D: Clinical Global Impressions Severity and Improvement

Appendix E: Subject and Caregiver Top 3 Concerns

Appendix F: Clinician-completed Domain Specific Causes for Concern: Myotonic Dystrophy (VAS)

Appendix G: OSU Autism Rating Scale—DSM-IV (OARS-4) and OSU Autism CGI

17.1 Appendix A: 10 Metre Walk Test Instructions

Timed 10-Meter Walk/Run Test (adapted from Standard Procedure from OMMYD-3/IDMC-10 - June 8th, Paris, France)

Description

This test measures the short duration walking speed.

Equipment

- Stopwatch
- Walkway with at least 12 meters of walking course

Draw lines on the wall with tape at 0, 1, 11 and 12 meters.

Instructions

Patient preparation:

- Patient should wear comfortable clothing, appropriate shoes for walking and any orthosis if patient wears it daily;
- Patients should use their usual walking aids during the test (cane, walker, etc.) and it should be recorded.

Administration:

- Give the participant the following instructions: "You are going to walk a distance of about 12 meters at your normal comfortable speed. We will repeat the distance 3 times. Do you have any questions?"
- Position the participant at the 0m-line. Before the first trial, tell to the participant: "You are going to walk at a comfortable speed until I say stop (do not refer to the tape on the wall). Continue walking until I say "STOP" and start when I say "Ready, GO"."
- When the participant is ready, say "Ready, GO".
- Start the stopwatch when the toes of the leading foot crosses the 1-meter mark and stop the stopwatch when the toes of the leading foot crosses the 11-meter mark. Have the participant continue walking until he or she reaches the chair after the 12-m line.
- To ensure accuracy of the recorded time, the evaluator must follow the participant by standing behind him/her all the time to avoid influencing the walking speed.
- Record the time (in seconds to the hundredths) to walk the 10-m distance.
- The participant can rest until recovered. The participant can rest on a chair if needed. Repeat the same procedure as described above at a comfortable speed 2 more times (total of 3 trials).

- Repeat for 3 other trials but this time at the maximum speed the participant can manage. Instruct the participant that he/she must walk or run as fast as possible for the same distance as above.
- Document whether the participant walks, walks fast or runs (both feet off the ground).

17.2 Appendix B: Pulmonary Function Test Instructions

Pulmonary Function test (FVC - SITTING)

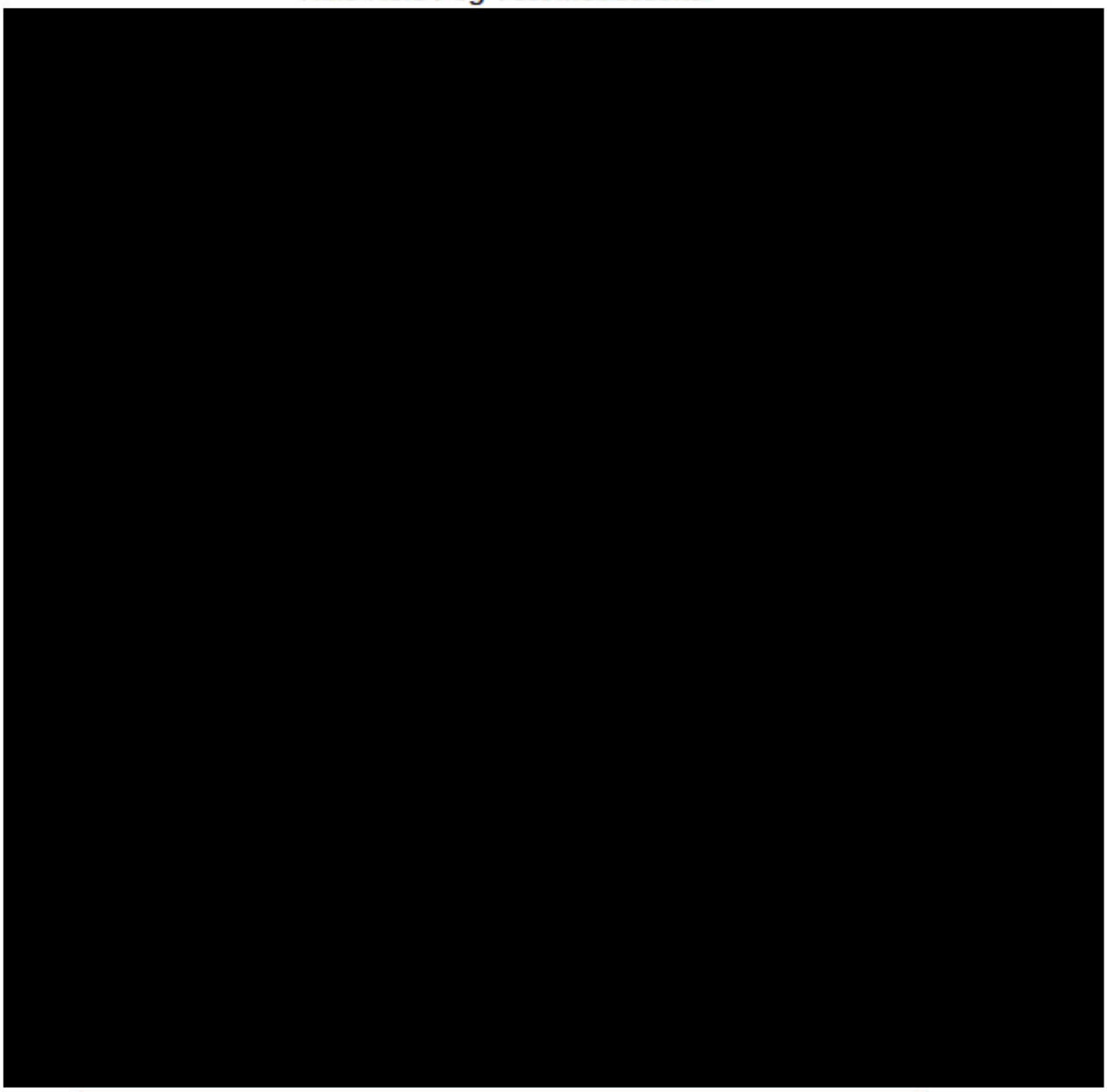
Forced Vital Capacity (FVC) will be performed in the sitting position.

The patient should be sitting comfortably in a chair. The evaluator explains /demonstrates the procedure to the subject and explains that they will be performing the test at least 3 times. The specific wording of instructions should be followed closely.

- Ask the patient to *'take as big a breath in as possible and then blow out through the mouth as hard and as long as you can'*. The evaluator should verbally encourage the subject to keep going for as long as possible. ATS criteria state a 6 second plateau is required.
- The test should be repeated three times making sure that the patient has recovered between attempts. If at each attempt there is an improvement in the results further tests can be conducted until the subject has achieved his best result.
- The subject can place the mouthpiece in his own mouth unless he is unable to reach his mouth with his hands or flexes his head and shoulders to reach the tube. In this case the evaluator should place the tube into the subject's mouth.
- The tube can be placed in the mouth either before the beginning of inspiration (closed circuit technique) or at the end of inspiration just prior to expiration (open circuit technique) whichever the subject finds most comfortable.
- Whichever technique is used the same method should be used at each evaluation and documented on the worksheets.
- A nose clip should be applied just prior to expiration. If a tight seal cannot be made around the tube then a mask may be used.
- The subject should not be allowed to flex forward during expiration.
- Calibrate the spirometry system on the day of testing

17.3 Appendix C: Nine Hole Peg Test

Nine Hole Peg Test Instructions



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17.4 Appendix D: Clinical Global Impressions Severity and Improvement

CGI-S and CGI-I

The Clinical Global Impression – Severity of Illness (CGI-S) and Clinical Global Impression – Improvement of Illness (CGI-I) are brief, easy to administer, clinician-rated measures (Guy, 1976). The CGI-S asks the clinician to rate the patient's current severity of illness based on the clinician's total clinical experience with the relevant population. The CGI-S is rated on a 7-point scale, with a range of responses from 1 (normal, not at all ill) through 7 (amongst the most extremely ill patients). The CGI-I asks the clinician to rate the patients' total improvement since baseline, whether or not the improvement is judged to be due entirely to the experimental treatment. The CGI-I is rated on a 7-point scale, with a range of responses from 1 (very much improved) to 7 (very much worse). For both the CGI-S and the CGI-I, the clinician is allowed to use all available information at the time of the rating.

The CGI-I has emerged as a convention for bifurcating clinical trial subjects into "responders" and "non-responders". In this application, the CGI-I can be a useful tool for gaining a general overview of the therapeutic potential of an experimental treatment. One of the relative detriments of both the CGI-S and –I is the lack of the measures' assessment of specific sign or symptoms associated with the disorder under study (Busner et al., 2009). An approach that has been developed to enhance the precision and clinical meaningfulness of CGI ratings is to utilize anchor points that are specific to the signs and symptoms of the disorder under study.

References:

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Clinical Global Impression – Severity of Illness Scale (CGI-S):

"Considering your total clinical experience with myotonic dystrophy patients, how severely ill is this patient at this time?"

1- *Normal, not at all ill*: The patient is indistinguishable from other individuals that do not have myotonic dystrophy (DM). The patient has no overt DM symptoms and no persistent dysfunction in the wake of having been diagnosed with DM.
2- *Borderline ill*: The patient has very occasional DM symptoms that seem modestly excessive in intensity, frequency or duration compared to individuals that have not been diagnosed with DM. These symptoms have only a transient impact on functioning, with no need for any special intervention.
3- *Mildly ill*: The patient has occasional DM symptoms that seem modestly excessive in intensity or duration, or the patient experiences very occasional DM symptoms that are modestly excessive both in intensity and duration as compared to individuals without a DM diagnosis. These symptoms have a limited impact on the patient's functioning, generally only in one setting, and require that others make some adjustments or accommodations in interacting with this patient.
4- *Moderately ill*: This DM patient is clearly distinguishable from other individuals because of his/her DM symptoms and the impairment that they cause. The patient's DM symptoms are clearly excessive in frequency, intensity or duration compared to others that have not received a DM diagnosis, and have limited impact on the patient's functioning in multiple settings or moderate impact in one setting. Caregivers, family members, teachers and co-workers make adjustments when interacting with this patient to avoid exacerbation of his/her symptoms and to deal with them when they occur.
5- *Markedly ill*: This patient's DM symptoms occur frequently and are noticeable in intensity or duration to even casual observers or occur infrequently but are quite intense or long-lasting. There is moderate impact on the patient's functioning in multiple settings or extreme impact in one setting. Caregivers, family members, teachers and co-workers utilize interventions that are necessary in order to deal with this patient's symptoms. Special accommodations related specifically to the patient's DM symptoms are likely necessary at home, at school or in the workplace.
6- *Severely ill*: The patient's DM symptoms occur very frequently and are noticeable in intensity or duration to even casual observers or occur infrequently but are severely intense or extremely long-lasting. Often there is marked impairment of normal day–to–day capabilities or skills necessary to function at school or in the workplace. Multiple interventions are required to address the patient's DM symptoms to minimize consequences.
7- *Among the most extremely ill patients*: The patient's DM symptoms occur the majority of the time and are very disruptive to functioning in multiple areas. There are very few times, if any, of normal functioning. There are often serious concerns about the patient's ability to provide adequate care for him/herself as a consequence of the DM symptoms. The patient requires almost constant monitoring by caregivers or others.

Study AMO-02-MD-2-001	Site no. ⌊__⌋ Subject no. ⌊__⌋	AMO PHARMA

Clinical Global Impression - Severity of Illness Scale (CGI-S)

Date of assessment ⌊__dd__ __mmm__ __yyyy__⌋

Considering your total clinical experience with myotonic dystrophy patients, how severely ill is this patient at this time?

1- Normal, not at all ill
2- Borderline ill
3- Mildly ill
4- Moderately ill
5- Markedly ill
6- Severely ill
7- Among the most extremely ill patients

Score ⌊__⌋

Evaluator name _____

Evaluator signature _____

Date ⌊__dd__ __mmm__ __yyyy__⌋

CGI—Improvement – A User's Guide

1. *Very Much Improved* designates marked improvement, across settings and/or across multiple problem areas. Although a CGI-I of 1 does not strictly require that the patient qualify for a CGI-S rating better than baseline, usually the CGI-S does also improve. Such improvement must be very substantial and is usually accompanied by considerable patient and/or caregiver enthusiasm. Such patients are usually noticeably improved in the clinic as well.

2. *Much Improved* may denote moderate improvement in a single symptom area, especially if seen across settings. Likewise, moderate improvements in several areas, even if confined to one setting, may warrant a rating of "Much improved." Durability of the change should be taken into account. For example, a change reported for the last few hours probably would not warrant such a rating. On the other hand, a change that was clearly in evidence for the last several days or longer probably would warrant a rating of 2. It is not necessary that the patient qualify for a CGI-S rating better than baseline to receive a CGI—I rating of 2, but often (not always) the CGI-S also improves.

3. *Minimal Improvement* indicates modest improvements, especially if confined to one setting. Trivial changes or changes that are possibly present or require guesswork usually would be scored as 4 (the level below this one).

4. *No Change* indicates, by definition, the absence of change in behavior or clinical presentation from baseline to subsequent assessments. Chance fluctuations and equivocal improvements or declines should be included here.

5. *Minimally Worse* indicates some worsening in symptoms that are mild to moderate or may be confined to one setting.

6. *Much Worse* designates moderate to moderately serve worsening. This may include moderate levels of worsening in a single symptom area when observed across settings. Moderately severe changes that are confined to one setting may warrant a rating of "Much Worse."

7. *Very Much Worse* designates significant worsening, across settings and/or across multiple symptoms.

N.B. The CGI-I is a rating of *change*; normalization is not necessary for a rating of 1, although if the clinical presentation is unequivocally improved and is evident across settings, it suggests an Improvement score of 1. A CGI-I of 2 is appropriate for definite, unequivocal improvement of a magnitude that makes the clinician confident that the treatment is helping. An improvement score of 3 (or 5) is appropriate if variations in ratings and other criteria appear to represent more than random chance or rating error, but are not definite and unequivocal. A score of 4 is appropriate for slight variation in either direction of a magnitude that is likely due to chance, natural history, external events, or rating error.

Study AMO-02-MD-2-001	Site no. ___ Subject no. ___	AMO PHARMA

Clinical Global Impression - Global Improvement Scale (CGI-I)

Date of assessment ___ (dd mmm yyyy)

Compared to the baseline assessment* in this study, if you consider the signs and symptoms associated with this patient's myotonic dystrophy, how much has he/she changed? Rate his/her total improvement whether or not, in your judgement, it is due entirely to the study drug.

1- Very much improved
2- Much improved
3- Minimally improved
4- No change
5- Minimally worse
6- Much Worse
7- Very much worse

[redacted]

Score ___

Evaluator name _____

Evaluator signature _____

Date ___ (dd mmm yyyy)

17.5 Appendix E: Subject and Caregiver Top 3 Concerns

Study AMO-02-MD-2-001	Site no. ⌊___⌋ Subject no. ⌊___⌋	AMO PHARMA

Caregiver Top Three Concerns Baseline

Date of assessment ⌊dd⌋⌊mmm⌋⌊yyyy⌋

Please rate the three causes for concern associated with your relative and their myotonic dystrophy that you would most like to see change during treatment. You can select any sign or symptom.

Your Concerns

Concern number 1

The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been in the past week, including today.

Completely Absent — Very Severe

Concern number 2

The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been in the past week, including today.

Completely Absent — Very Severe

Concern number 3

The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been in the past week, including today.

Completely Absent — Very Severe

Study AMO-02-MD-2-001	Site no. ⌊___⌋ Subject no. ⌊___⌋	AMO PHARMA

Subject Top Three Concerns Baseline

Date of assessment ⌊dd⌋⌊mmm⌋⌊yyyy⌋

Please rate the three causes for concern associated with your myotonic dystrophy that you would most like to see change during treatment. You can select any sign or symptom.

Your Concerns

Concern number 1

The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been in the past week, including today.

Completely Absent — Very Severe

Concern number 2

The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been in the past week, including today.

Completely Absent — Very Severe

Concern number 3

The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been in the past week, including today.

Completely Absent — Very Severe

Study AMO-02-MD-2-001	Site no. ⌊___⌋ Subject no. ⌊___⌋	AMO PHARMA

Caregiver Top Three Concerns Follow-Up

Date of assessment ⌊__dd__⌋⌊__mmm__⌋⌊__yyyy__⌋

At baseline, you rated the three causes for concern, related to your relative and their myotonic dystrophy that you most liked to see change during treatment. You selected the following signs or symptoms.

Your Concerns

Concern number 1
The sign or symptom causing concern was:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Completely Absent ——— Very Severe

Concern number 2
The sign or symptom causing concern was:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Completely Absent ——— Very Severe

Concern number 3
The sign or symptom causing concern was:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Completely Absent ——— Very Severe

Study AMO-02-MD-2-001	Site no. ⌊___⌋ Subject no. ⌊___⌋	AMO PHARMA

Subject Top Three Concerns Follow-Up

Date of assessment ⌊__dd__⌋⌊__mmm__⌋⌊__yyyy__⌋

At baseline, you rated the three causes for concern, related to your myotonic dystrophy that you most liked to see change during treatment. You selected the following signs or symptoms.

Your Concerns

Concern number 1
The sign or symptom causing concern was:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Completely Absent — Very Severe

Concern number 2
The sign or symptom causing concern was:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Completely Absent — Very Severe

Concern number 3
The sign or symptom causing concern was:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Completely Absent — Very Severe

17.6 Appendix F: Clinician-completed Domain Specific Causes for Concern: Myotonic Dystrophy (VAS)

Study AMO-02-MD-2-001	Site no. ⌊ ⌋ Subject no. ⌊ ⌋	AMO PHARMA

Clinician Domain-Specific Causes for Concern: Myotonic Dystrophy - Page 1 of 5

Date of assessment ⌊ ⌋ dd mmm yyyy

Please rate the causes for concern you would most like to see change during treatment in the categories below. Your choice should be associated with the subject's myotonic dystrophy. You can select any sign or symptom fitting the category. You should choose one specific concern for each category. If there is no concern in any symptom area, write "None" and mark at the end "Not at all severe". When rating the severity of the item, please focus on the past week.

1. Limitations with mobility or walking
Examples might include ankle turning, not being able to walk to the front door fast enough when there is a caller, needing help to move around the home. You can choose a different example.
The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Not at All Severe ——— Very Severe

2. Problems with hands or arms
Examples might include not being able to do up buttons, or type at a computer keyboard. You can choose a different example.
The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Not at All Severe ——— Very Severe

3. Inability to do activities
Examples might include not being able to visit family, do cleaning in the home, take a bath or shower. You can choose a different example.
The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Not at All Severe ——— Very Severe

Study AMO-02-MD-2-001	Site no. ⌊__⌋ Subject no. ⌊__⌋	AMO PHARMA

Clinician Domain-Specific Causes for Concern: Myotonic Dystrophy - Page 2 of 5

Please rate the causes for concern associated with the subject's myotonic dystrophy that you would most like to see change during treatment in the categories below. You can select any sign or symptom fitting the category.

4. Fatigue
Examples include lacking the energy to perform work activities, or finding walking too exhausting.
You can choose a different example.
The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Not at All Severe — Very Severe

5. Pain
Examples include pain in the hands or feet. You can choose a different example.
The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Not at All Severe — Very Severe

6. Gastrointestinal issues
Examples include fecal incontinence or dyspepsia. You can choose a different example.
The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Not at All Severe — Very Severe

7. Problems with vision
Examples include blurred vision, ptosis, or ocular myotonia. You can choose a different example.
The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Not at All Severe — Very Severe

Study AMO-02-MD-2-001	Site no. ⌊ ⌋ Subject no. ⌊ ⌋	AMO PHARMA

Clinician Domain-Specific Causes for Concern: Myotonic Dystrophy - Page 3 of 5

Please rate the causes for concern associated with the subject's myotonic dystrophy that you would most like to see change during treatment in the categories below. You can select any sign or symptom fitting the category.

8. Communication difficulties
An example would be difficulties with production of speech. You can choose a different example.
The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Not at All Severe — Very Severe

9. Impaired sleep or daytime sleepiness
Examples include insomnia, or falling asleep after lunch. You can choose a different example.
The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Not at All Severe — Very Severe

10. Emotional issues
Examples include feeling depressed or anxious. You can choose a different example.
The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Not at All Severe — Very Severe

11. Difficulty thinking
Examples include difficulties in concentrating for long enough to complete tasks, or remembering important information. You can choose a different example.
The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Not at All Severe — Very Severe

Study AMO-02-MD-2-001	Site no. ⌊⌋⌋⌋ Subject no. ⌊⌋⌋⌋	AMO PHARMA

Clinician Domain-Specific Causes for Concern: Myotonic Dystrophy - Page 4 of 5

Please rate the causes for concern associated with the subject's myotonic dystrophy that you would most like to see change during treatment in the categories below. You can select any sign or symptom fitting the category.

12. Decreased satisfaction in social situations
Examples include not enjoying the attention of others, or not being able to participate in social activities.
You can choose a different example.
The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Not at All Severe — Very Severe

13. Decreased performance in social situations
Examples include feeling self-conscious of speaking in public, or not being able to follow group dialogues.
You can choose a different example.
The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Not at All Severe — Very Severe

14. Myotonia
Examples include myotonia in the hands or ocular myotonia. You can choose a different example.
The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Not at All Severe — Very Severe

15. Breathing difficulties
Examples breathlessness whilst walking, or sleep apnea. You can choose a different example.
The sign or symptom causing concern is:

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Not at All Severe — Very Severe

Study AMO-02-MD-2-001	Site no. ⌊ ⌋ Subject no. ⌊ ⌋	AMO PHARMA

Clinician Domain-Specific Causes for Concern: Myotonic Dystrophy - Page 5 of 5

Please rate the causes for concern associated with the subject's myotonic dystrophy that you would most like to see change during treatment in the categories below. You can select any sign or symptom fitting the category.

16. Choking or swallowing issues

An example would be not being able to eat easily. You can choose a different example.
The sign or symptom causing concern is:

_____

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Not at All Severe ——————————— Very Severe

17. Hearing difficulties

Examples include hearing loss or inability to follow conversations in a group situation. You can choose a different example.
The sign or symptom causing concern is:

_____

How severe is the sign or symptom? Place a vertical mark on the line below to indicate how bad you think the sign or symptom has been over the past week, including today.

Not at All Severe ——————————— Very Severe

Evaluator name _____

Evaluator signature _____

Date ⌊dd⌋ ⌊mmm⌋ ⌊yyyy⌋

17.7 Appendix G: OSU Autism Rating Scale—DSM-IV (OARS-4)

OSU Autism Rating Scale—DSM-IV (OARS-4)

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[redacted]

References**:**

The OSU Research Unit on Pediatric Psychopharmacology (2005, November): OSU Autism Rating Scale—DSM-IV (OARS-4). Columbus, OH: Author.