Study Protocol	
Official Title:	A Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Tideglusib Versus Placebo for the Treatment of Children and Adolescents with Congenital Myotonic Dystrophy (REACH CDM)
NCT Number:	NCT03692312
Document Date:	02 February 2023

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

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Sponsor:

AMO Pharma Ltd.
Braeburn,
Grove Road,
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United Kingdom.

1. PROTOCOL SYNOPSIS

PROTOCOL TITLE	A Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Tideglusib versus Placebo for the Treatment of Children and Adolescents with Congenital Myotonic Dystrophy **(REACH CDM)**
PROTOCOL NO.	AMO-02-MD-2-003
COORDINATING INVESTIGATOR	[redacted]
SPONSOR	AMO Pharma Ltd.
INVESTIGATIONAL MEDICINAL PRODUCT	Tideglusib
PHASE OF DEVELOPMENT	2/3
INDICATION	Congenital Myotonic Dystrophy (Congenital DM1)
STUDY DESIGN	This is a randomized, double-blind study of weight adjusted 1000 mg tideglusib versus placebo across a [redacted] treatment period. The subjects are children between the ages of 6 to 16 years with Congenital Myotonic Dystrophy (Congenital DM1).

Approximately 56 children were planned to be randomized into the study, assuming a dropout rate of 10-13%. After a blinded sample size re-estimation (SSRE), the protocol was amended to allow enrollment of between 56 and 66 children randomized into the study, if feasible. [redacted]

The study will have 5 distinct phases:

- Screening [redacted] Subjects will be screened to ensure adherence to eligibility criteria.
- [redacted] run-in ([redacted]
- Double-blind dose [redacted]).

  Subjects randomized at [redacted] (Baseline) to the weight adjusted 1000 mg dose level will take tideglusib at a weight adjusted 400 mg dose level from weeks [redacted], then they will take tideglusib at a weight adjusted 600 mg dose level from weeks [redacted] and thereafter they will take tideglusib at a weight adjusted 1000 mg dose level from weeks [redacted]. Subjects randomized at [redacted] (Baseline) to placebo will remain on that treatment for weeks [redacted]
- Double-blind maintenance (Weeks [redacted]. Subjects will continue on the fixed dose of 1000 mg weight adjusted tideglusib or placebo, which they have been previously randomized to for [redacted]
- Follow-up Period (Weeks [redacted] for those subjects not participating in the extension study AMO-02-MD-2-004
  - Adverse events will be elicited at [redacted] and [redacted] ([redacted] post end of treatment visit via telephone by a member of the study team

- An in -clinic follow-up visit will occur 2 after end of treatment

Due to the global COVID-19 (Coronavirus Disease 2019) pandemic and the potential for resurgences of COVID-19, for the purposes of this protocol, 'in-clinic' visits, when pertaining to Visits Visi (Weeks , may be conducted via a combination of telehealth and home healthcare providers in the event COVID-19 related reasons, e.g. institutional restrictions, travel restrictions, quarantine or shielding, prevent subjects from being seen in-person at the investigator site. Home healthcare visits will not be conducted if the subject or a member of the family present in the home has, or is suspected to have, COVID-19.

Data Safety Monitoring Committee

An independent Data Safety Monitoring Committee (DSMC) consisting of clinical and other experts will be established by the Sponsor to review safety findings during the study and to help ensure the well-being of enrollees.

STUDY OBJECTIVES

Primary Objective:

- To evaluate the efficacy, from baseline to end of treatment, of weight adjusted 1000 mg tideglusib compared to placebo in children and adolescents with Congenital DM1 as measured by the Clinician-Completed Congenital DM1 Rating Scale (CDM1-RS)

Secondary Objectives:

- To evaluate the safety and tolerability of weight adjusted 1000 mg tideglusib compared to placebo in children and adolescents with Congenital DM1

- To evaluate the efficacy, from baseline to end of treatment, of weight adjusted 1000 mg tideglusib compared to placebo in children and adolescents with Congenital DM1 as measured by clinician-completed rating scales, caregiver-completed rating scales, functional assessments, and biomarker/physiological assessments
- To evaluate the blood pharmacokinetics of tideglusib and its main metabolite (NP04113) after repeat dosing in children and adolescents with Congenital DM1
- To evaluate the consistency of telehealth data and in-clinic data for the CDM1-RS and CGI rating scales

STUDY ENDPOINTS

Primary Efficacy Endpoint:

- Clinician-Completed Congenital DM1 Rating Scale (CDM1-RS)

Key Secondary Efficacy Endpoint:

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

Secondary Efficacy Endpoints:

- Top 3 Caregiver Concerns VAS score
- Caregiver Completed Congenital DM1 Rating Scale (CC-CDM1-RS)
- Clinical Global Impression - Severity Scale (CGI-S)
- Clinician-Completed Congenital DM1 Rating Scale (CDM1-RS) - Independent Central Rater Score
- Clinical Global Impression- Severity Scale (CGI-S) – Independent Central Rater Score

* Sometimes referred to as the CGI-C

- Clinical Global Impression- Improvement Scale (CGI-I) - Independent Central Rater Score
- 10-meter walk-run test (preferred speed and fastest speed)

Exploratory Endpoints:

- DXA Scan measurement of total body lean/muscle mass
- Measurement of lip strength (via lip force meter)
- Congenital and Childhood Myotonic Dystrophy Health Index (CC-MDHI) Parent Proxy Instrument
- Autism Behavior Inventory- Clinician (ABI-C)
- [redacted] and Adaptive Behavior Composite standard scores of the Vineland Adaptive Behavior Scale – [redacted]
- Quantitative myometric measure of hand grip strength
- NIH Toolbox Cognition Battery: Dimensional Change Card Sort Test
- NIH Toolbox Cognition Battery: Picture Sequence Memory Test
- Peabody Picture Vocabulary Test (PPVT)
- [redacted] levels
- [redacted] sample
- [redacted]
- Serial blood pharmacokinetics of tideglusib

Safety Endpoints:

- The incidence of Adverse events (AEs), including serious adverse events (SAEs), between Screening and end of treatment. The incidence will also be assessed during a [redacted] follow-up period after discontinuation of the study drug for those subjects not participating in the extension study AMO-02-MD-2-004.
- The incidence of abnormal findings in objective assessments (e.g. laboratory values, ECGs, vital signs and bone mineral density) between Screening and end of treatment. The incidence of abnormal findings in objective assessments will also be assessed during a [redacted] follow-up period after discontinuation of the study drug for those subjects not participating in the extension study AMO-02-MD-2-004.

SUBJECT POPULATION

Diagnosis and main criteria for inclusion:

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 children or adolescents with a diagnosis of Congenital DM1. For the purposes of this study, the following definitions apply.

   In addition to the genetic confirmation of DM1, one or more of the following clinically relevant (e.g. requiring medical intervention) signs or symptoms was evident within the first month after birth:

   - Hypotonia
   - Generalized weakness
   - Respiratory insufficiency
   - Feeding difficulties
   - Clubfoot or another musculoskeletal deformity

2. Diagnosis must be genetically confirmed
3. Subjects must be male or female children and adolescents aged ≥6 years and ≤16 years at Screening
4. Subjects must have a Clinical Global Impression – Severity (CGI-S) score of 4 or greater at Screening and start of Run-in [redacted]
5. Subjects must be ambulatory and able to complete the 10-meter walk-run test (orthotics/splints allowed, forearm crutches are not allowed)
6. Written, voluntary informed consent must be obtained before any study related procedures are conducted. Where a parent or LAR provides consent, there must also be assent from the subject (as required by local regulations)
7. Subject's caregiver must be willing and able to support participation for duration of study
8. Subject must be willing and able to comply with the required food intake restrictions as outlined per protocol

Exclusion Criteria:

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

1. Non-ambulatory (full time) wheel chair use
2. Body mass index (BMI) less than 13.5 kg/m² or greater than 40 kg/m²
3. Receiving other medications/therapies not stable (i.e. changed) within 4 weeks prior to Screening. For each enrollee, every effort should be made to maintain stable regimens (i.e. dose, as applicable, and frequency) of allowed concomitant medications (e.g. concomitant mexiletine or stimulants) and allowed non-medicine based therapies (e.g. occupational or physiotherapy) throughout the

course of the study, from the time of commencement of Screening until the last study assessment.

4. Use within 4 weeks prior to Baseline [redacted]) of strong CYP3A4 inhibitors. Examples include clarithromycin, telithromycin, ketoconazole, itraconazole, posaconazole, nefazodone, idinavir and ritonavir
5. Concurrent use of drugs metabolized by CYP3A4 with a narrow therapeutic window e.g. warfarin and digitoxin
6. Medical illness or other concern which would cause the investigator to conclude that the subject will not be able to perform the study procedures or assessments or would confound interpretation of data obtained during assessment
7. Current enrollment in a clinical trial of an investigational drug or enrollment in a clinical trial of an investigational drug in the last 6 months
8. Gastrointestinal disease which, in the opinion of the investigator, 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) neurological, cardiovascular, renal, hepatic, endocrine or respiratory disease that may impact the interpretability of the study results
10. Clinically significant heart disease (in the opinion of the investigator) or current evidence of second or third degree heart block, atrial flutter, atrial fibrillation, ventricular arrhythmias, or requires medication for treatment of a cardiac arrhythmia
11. Implantation of a cardiac pacemaker within the 12 months preceding Screening
12. Average QTcF value of >450 msec at Screening or at Run-In [redacted]** (may repeat to confirm)

13. Clinically significant abnormalities in safety laboratory tests, vital signs or ECG, as determined by the investigator at Screening or Run-In [redacted]**, as applicable (may repeat to confirm)
14. Females 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
15. Males, engaged in sexual relations with a female of child-bearing potential, not using an acceptable contraceptive*** method if not surgically sterile
16. Kidney disease requiring ongoing treatment
17. A history of chronic liver disease with current out of range values for ALT, clinically relevant hepatic steatosis or other clinical manifestations of liver disease
18. ALT value > 2X the upper limit of the normal reference range at [redacted] (may repeat to confirm)
19. 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). For subjects with a well known/well documented diagnosis of Gilbert's syndrome a total bilirubin value greater than 2 x the upper limit of the normal reference range at [redacted] (may repeat to confirm)
20. HbA1c values greater than 6% or 42.0 mmol/mol at Screening (may repeat to confirm)
21. TSH values outside of the normal reference range at [redacted] (may repeat to confirm)
22. Serum creatinine >1.7 mg/dL (>150 micromole/L) or creatinine clearance ≤ 60 mL/min (according to Cockcroft-Gault formula) at [redacted] (may repeat to confirm)
23. Clinical history of hepatitis or previous or current positive serological evidence for Hepatitis B or C
24. Serological evidence of Hepatitis A at [redacted] or in the [redacted] preceding [redacted]

25. A history of significant drug allergy (such as Steven-Johnson syndrome, anaphylaxis)
26. A history of alcohol or substance use disorders
27. Current malignancy or any history of malignancy except for surgically cured skin cancer or pilomatricoma (benign tumor of the hair follicle that is associated with Congenital DM1)
28. Severe arthritis or other medical condition (besides Congenital DM1) that would significantly impact ambulation or completion of myometric assessments
29. Hypersensitivity to tideglusib or any components of its formulation including allergy to strawberry
30. Unable to swallow liquids or may have trouble swallowing liquids (in the opinion of the investigator), unless medication to be administered via gastrostomy tube
31. 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.

**As the central ECG report for [redacted] will not be available prior to the subject commencing run-in, eligibility related to ECGs (exclusion criteria 12 and 13) will be based on the investigator's calculation of the mean QTcF value of all ECGs taken at [redacted] and their initial review of the ECG tracings at [redacted]. If there is a conflict between the investigator's initial assessment of the ECG and the central ECG report, whereby the subject would no longer be eligible for the study, the subject will be withdrawn from the study at or before [redacted], prior to randomization into the double-blind treatment period.

***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:

- Combined or progestogen-only hormonal contraception
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence, defined as true abstinence. True Abstinence: When this is in line with the preferred and usual lifestyle of the subjects [periodic abstinence (such as calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]
- Male or female condom with or without spermicide[1]
- Cap, diaphragm or sponge with spermicide[1]

[1]A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable birth control methods

TIDEGLUSIB FORMULATION/DOSE	Unit-dose packets of 'tideglusib [redacted] for oral suspension' and/or 'tideglusib [redacted] for oral suspension' will be constituted [redacted]. Dosing will be weight adjusted at tideglusib 400 mg, 600 mg or 1000 mg dose levels, [redacted]. For blinding purposes, each active dose has a corresponding matching placebo presentation i.e. 'placebo for tideglusib [redacted] for oral suspension' or 'placebo for tideglusib [redacted] for oral suspension' which will be dosed to those randomized to placebo and as required to blind at the 400 mg, 600 mg and 1000 mg dosing phases.

	Regardless of the dose a subject has been assigned to, study medication will always be [redacted] This can be a [redacted] packet combination, an [redacted] packet combination, or an [redacted] packet combination depending on which treatment group the subject has been assigned to and which dose they are taking, e.g. during [redacted]
ROUTE OF ADMINISTRATION	Oral
DURATION/FREQUENCY OF TREATMENT	Taken once daily at approximately [redacted], by oral route. [redacted]. Administration by gastrostomy tube is also permissible, provided the [redacted] are followed. Participation for individual subjects will consist of a [redacted] run-in phase. Subjects will be randomized to either weight adjusted 1000 mg tideglusib, or matched placebo, once daily for [redacted] weeks. Subjects randomized to weight adjusted 1000 mg tideglusib will receive the 400 mg weight adjusted dose level of tideglusib for [redacted] and then will advance to the 600 mg weight adjusted dose level for the next [redacted]. Thereafter, these subjects will take tideglusib at the weight adjusted 1000 mg dose level for the remaining [redacted]
EFFICACY ASSESSMENTS	The study will evaluate efficacy from four different perspectives (also referred to as efficacy domains): clinician-completed assessments, caregiver-completed assessments, functional assessments (i.e. assessments that require in-clinic performance by the enrollee), and biomarker/physiological assessments.

The efficacy domains will include the measures described below.

- Clinician-completed assessments:
  - Clinician-Completed Congenital DM1 Rating Scale (CDM1-RS)
  - Clinical Global Impressions (Severity and Improvement) scale
  - Clinician-Completed Congenital DM1 Rating Scale (CDM1-RS) Independent Central Rater Score
  - Clinical Global Impressions (Severity and Improvement) scale Independent Central Rater Score
  - Autism Behavior Scale- Clinician (ABI-C)
  - Vineland Adaptive Behavior Scale - [redacted]
- Caregiver-completed assessments:
  - Top 3 Caregiver Concerns VAS
  - Caregiver Completed Congenital DM1 Rating Scale (CC-CDM1-RS)
  - Congenital and Childhood Myotonic Dystrophy Health Index (CC-MDHI) Parent Proxy Instrument
- Functional assessments:
  - 10-meter walk-run test (preferred speed and fastest speed)
  - Quantitative myometric measure of hand grip strength
  - Measurement of lip strength via lip force meter
  - NIH Toolbox Cognition Battery: Dimensional Change Card Sort Test
  - NIH Toolbox Cognition Battery: Picture Sequence Memory Test
  - Peabody Picture Vocabulary Test (PPVT)

- Biomarker/physiological assessments:
  - Dual-energy X-ray absorptiometry (DXA) whole body scan of lean muscle mass
  - [redacted] levels and activity
  - [redacted] analysis
  - [redacted]

SAFETY ASSESSMENTS

This study will compare the incidence of adverse events (AE), including serious adverse events (SAE), between Screening and end of treatment with weight adjusted 1000 mg tideglusib versus placebo, for [redacted]. The incidence of abnormal findings in objective assessments (e.g. clinical laboratory values, urinalysis, physical examination findings, vital signs, weight, ECG and bone mineral density) during the course of the study will also be assessed. The incidence will also be assessed during a [redacted] follow-up period after discontinuation of the study drug for those subjects not participating in the extension study AMO-02-MD-2-004.

PHARMACOKINETIC ASSESSMENTS

Pharmacokinetic blood samples will be collected for measurement of tideglusib and its primary metabolite, NP04113. PK samples will be collected at Visits [redacted] and [redacted] (corresponding to Weeks [redacted] and [redacted]).

[redacted] samples will be collected at Week [redacted]). The time of administration of study medication will not be adjusted from the time the subject normally takes their dose of study medication. It will be noted in the CRF whether the subject dosed at home or in the clinic.

If the subject normally takes their dose of study medication where they would be in the clinic between [redacted] post dose, then ideally

the [redacted] PK sample should be taken between [redacted] post dose and the [redacted] PK sample should be taken between [redacted] post dose.

If the subject normally takes their dose of study medication [redacted] post dose, then the [redacted] PK samples can be taken at any time during the visit as long as there [redacted]

At Week [redacted] a total of [redacted] samples will be taken. All subjects, regardless of when they usually take their study medication, will take their study medication in clinic during this study visit. The [redacted] sample will be taken prior to the subject [redacted] study [redacted] in clinic, the [redacted] sample will be taken [redacted] and a [redacted] sample will be taken [redacted], a [redacted], and a [redacted] sample taken [redacted].

With the exception of Week [redacted] For Week [redacted] there should be [redacted] Week [redacted]).

Population pharmacokinetic modelling will be used to analyze the data. If PK parameters [redacted]

In order to determine whether there are associations between [redacted]

[redacted] These associations may be statistically tested using correlation coefficients and general linear models, if appropriate.

STATISTICAL ANALYSIS

Details of all planned analyses will be specified in a separate statistical analysis plan (SAP) which will be finalized 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.

Estimated Sample Size:

No clinical trial data are available on the CDM1-RS instrument. Twenty-five subjects per group will generate 70% power to detect the effect size of 0.6 at the 0.1 two-sided significance level. This sample size will also be sufficient to generate 80% power to detect the effect size of 0.82 at the 0.05 two-sided significance level. Accounting for a 10%-13% drop-out rate, approximately 28 subjects per group will be enrolled. A blinded sample size re-estimation (SSRE), based on the observed variance in the primary outcome measure, was performed once 33% of subjects had been enrolled and had completed [redacted]. The effect size assumptions were partially based on the Clinician VAS ([redacted] total score changes from baseline to end of study (6 points on drug vs. 1 point on placebo with the common standard deviation of 5.8). Based on these and other data, 29 and 22 subjects per group will be sufficient to generate 90% and 80% power at the 0.05 two-sided significance level. Based on these calculations, a suggested sample size of approximately 56 patients total was deemed to be

adequate to detect the treatment effect or at least a consistent trend.

Based on the blinded SSRE, the planned sample size is sufficient to detect the treatment difference between active and control arms based on the primary endpoint with at least 80% power at the 0.05 two sided significance level. However, the variability of the key secondary endpoint was slightly greater than that originally assumed. Respectively, it was recommended, if operationally feasible, to increase the total sample size to a maximum of 66 subjects.

Statistical Methods for Safety:

Analysis of safety will be performed based on the Safety Analysis Set (SAS). See section 11.2 for definition. All AEs will be coded using the MedDRA dictionary and will be summarized by treatment.

Other safety data, including laboratory, vital signs and ECG values including change from baseline will be summarized.

Statistical Methods for Efficacy:

Primary and key secondary analyses of efficacy will be based on the Intent to Treat (ITT) population. Other efficacy analyses will be performed based on the Full Analysis Set (FAS). See section 11.2 for definitions.

The primary efficacy endpoint will be calculated at each time point as a total score based on 11 domain ratings. Changes from Baseline [redacted] to post-treatment visits will be summarized by treatment group at each study visit. For the CGI-I the observed values will be summarized.

Change from baseline to end of treatment will be analysed using general linear model. Improvement during the [redacted] run-in period may be included as a covariate. The statistical significance of changes

from baseline over time may also be assessed using the linear mixed effects repeated measures model.

Due to COVID-19 related restrictions some of the data at certain visits may be collected using a telehealth approach while other data may be collected during in-clinic visits. To evaluate the consistency of telehealth data and in-clinic data for the CDM1-RS and CGI rating scales and to minimize the potential bias, Baseline ([redacted], Week [redacted] ([redacted]) and Week [redacted]) visits will be performed using both in-clinic and telehealth data collection approaches. Analysis to evaluate the consistency of these two methods of data collection will be performed.

According to the recommendations in the FDA Guidance "Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency", sensitivity analyses will be performed in addition to the primary analysis (FDA, 2020). The sensitivity analyses will include combined use of telehealth and in-clinic data; the impact of using telehealth data on outcomes will be evaluated.

The exploratory endpoint analysis will be outlined in the SAP. The details of the analysis methods will be determined after exploratory endpoint data review.

NUMBER OF STUDY CENTERS	Up to 14 sites in the US, UK, Canada, Australia, and New Zealand
ESTIMATED FIRST SUBJECT SCREENED	Q1 2021
ESTIMATED LAST SUBJECT LAST VISIT	Q4 2022

Table 1: Standard Schedule of Events

Visit[25]	Screening	Run-in	Baseline [h]	Interim [h]	Interim [h]	Interim [h,22]	Interim [h]	Interim [h, 22]	Interim [h]	Interim [i]	End of Treatment [i, 23]	AE Follow up [redacted] post EOT[24]	AE Follow up [redacted] post EOT[24]	[Follow-up][h ,24]
	[redacted]													
Week	[redacted]													
Informed Consent/Assent	[redacted]													
Eligibility Criteria														
Medical/Surgical History														
Caregiver DM1 Status														
Physical Examination														
Clinical Labs[2]														
Urinalysis[3]														
Pregnancy Test[4]														
Vital Sign Measures														
Height														
Weight														
12 Lead ECG[5]														
Grip Strength[6]														
Lip Strength[6]														
10-meter walk / run[7]														
DXA scan														
Autism Behavior Inventory- Clinician (ABI-C)														
Telehealth Test Session[8]														
CGI-S [9] In Clinic														
CGI-S Via Telehealth[10]														
CGI-I[9] In Clinic														

Visit[25]	Screening	Run-in	Baseline [h]	Interim [h]	Interim [h]	Interim [h,22]	Interim [h]	Interim [h, 22]	Interim [h]	Interim [i]	End of Treatment [i, 23]	AE Follow up		[Follow-up][h ,24]
												[redacted] post EOT[24]	[redacted] post EOT[24]	
Week	[redacted]													
CGI-I Via Telehealth[10]	[redacted]													
Vineland Adaptive Behavior Scale														
Clinician-Completed Congenital DM1 Rating Scale (CDM1-RS) In Clinic														
Clinician-Completed Congenital DM1 Rating Scale (CDM1-RS) via Telehealth[11]														
Independent Central Rating of the CGI-S[12]														
Independent Central Rating of the CGI-I[12]														
Independent Central Rating of the Clinician-Completed Congenital DM1 Rating Scale (CDM1-RS)[12]														
Caregiver Top 3 Concerns VAS														
CC-MDHI Parent Proxy Instrument														
Caregiver-Completed Congenital DM1 Rating Scale (CC-CDM1-RS)														

Visit[25]	Screening	Run-in	Baseline[h]	Interim[h]	Interim[h]	Interim[h,22]	Interim[h]	Interim[h, 22]	Interim[h]	Interim[i]	End of Treatment[i, 23]	AE Follow up		[Follow-up][h ,24]
												[redacted] post EOT[24]	[redacted] post EOT[24]	
Week	[redacted]											[redacted]	[redacted]	
NIH Dimensional Change Card Sort Test	[redacted]													
NIH Picture Sequence Memory Test														
Peabody Picture Vocabulary Test														
[redacted] **Sample[13]**														
Sample for PK analysis[14]														
[redacted]														
[redacted]														
Muscle RNA Sample (optional)[17]														
[redacted] **Sample[18]**														
Dosing and/or Dispensing[19] Randomization														
Subject Diary Issue/Review[20]														
Adverse Events[21]														
Concomitant Medication														

[redacted]

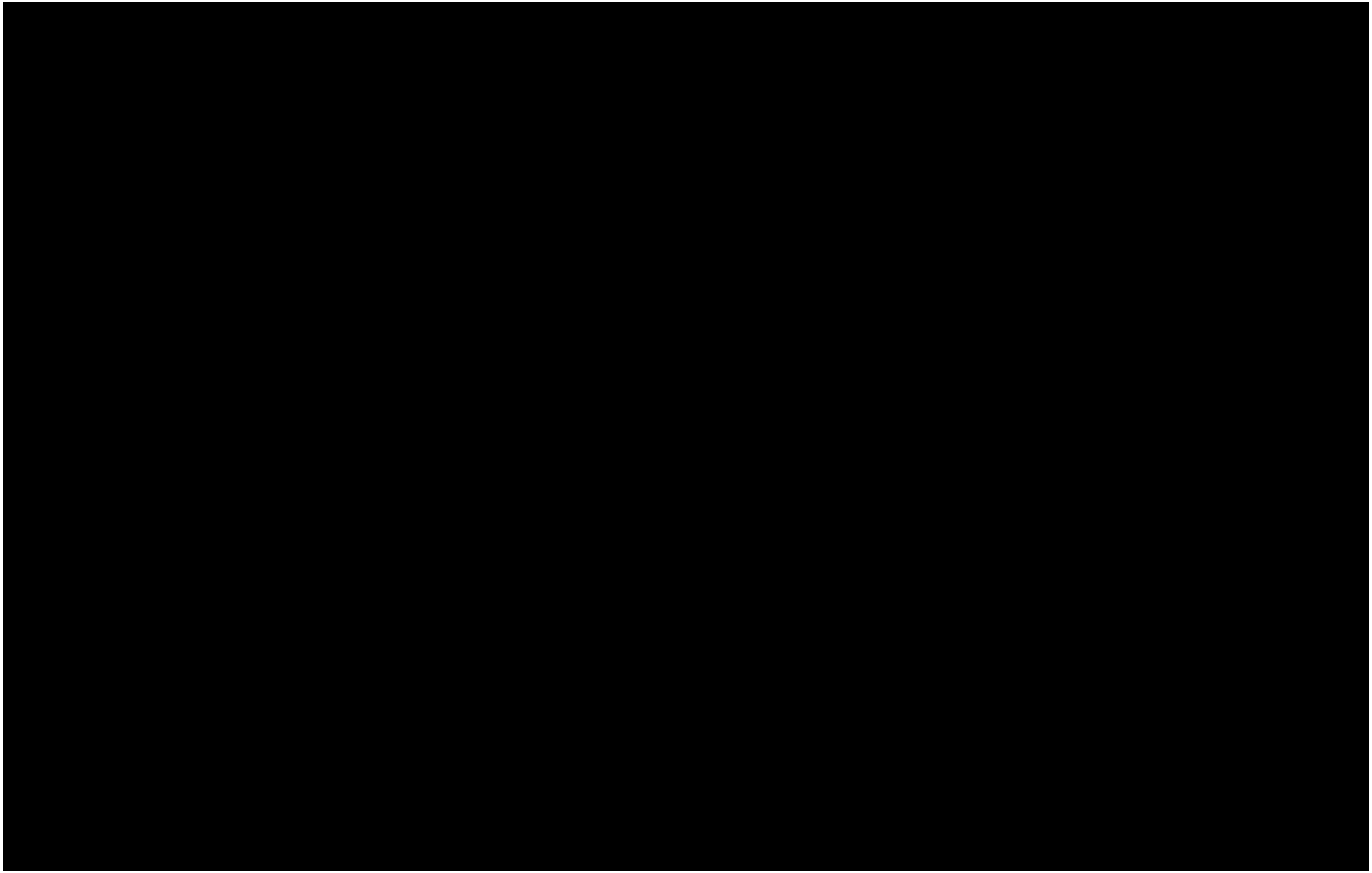

Table 2: Schedule of Events Where a Visit Needs To Be Conducted Via Telehealth and Home Healthcare Due to COVID-19[1]

Visit[15]	Screening[2]	Run-in[2]	Baseline [2 e]	Interim [e]	Interim [e]	Interim [e]	Interim [e]	Interim [e]	Interim [e]	Interim [f]	End of Treatment [f, 13]	AE Follow up		[Follow-up][e, 14]
												post EOT[14]	post EOT[14]	
Week														
Physical Exam[3]														
Clinical Labs[4, h]														
Urinalysis[5, h]														
Pregnancy Test[6, h]														
Vital Sign Measures [h]														
Height [h]														
Weight [h]														
6 Lead ECG[7, h]														
DXA scan[8]														
Autism Behavior Inventory- Clinician (ABI-C) [g]														
CGI-S[9, g]														
CGI-I[9, g]														
Independent Central Rating of CGI-S														
Independent Central Rating of CGI-I														
Vineland Adaptive Behavior Scale [g]														
Clinician-Completed Congenital DM1 Rating Scale (CDM1-RS) [g]														

Visit[15]	Screening[2]	Run-in[2]	Baseline 2 e	Interim e	Interim e	Interim e	Interim e	Interim e	Interim e	Interim f	End of Treatment [f, 13]	AE Follow up		[Follow-up][e, 14]
												post EOT[14]	post EOT[14]	
Week														
Independent Central Rating of the Clinician-Completed Congenital DM1 Rating Scale (CDM1-RS)														
Caregiver Top 3 Concerns VAS [i]														
CC-MDHI Parent Proxy Instrument [i]														
Caregiver-Completed Congenital DM1 Rating Scale (CC-CDM1-RS) [i]														
Dosing and/or Dispensing[10]														
Subject Diary Issue/Review[11, g]														
Adverse Events[12, g]														
Concomitant Medication[g]														

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3. LIST OF ABBREVIATIONS

ABI-C	Autism Behavior Inventory- Clinician
AD	Alzheimer's Disease
ADME	Absorption, Distribution, Metabolism and Excretion
ADR	Adverse Drug Reaction
AE	Adverse Event
ALCOAC	Attributable, Legible, Contemporaneous, Original, Accurate, Complete
ALT	Alanine amino transferase
ANCOVA	Analysis of Covariance
ASD	Autism Spectrum Disorder
AST	Aspartate amino transferase
AUC	Area Under the Curve
BMI	Body Mass Index
BP	Blood Pressure
BRIEF-2	Behavior Rating Inventory of Executive Function-Second Edition
CC-MDHI	Congenital and Childhood Myotonic Dystrophy Health Index
CC-CDM1-RS	Caregiver-Completed Congenital DM1 Rating Scale
CDM1-RS	Clinician-Completed Congenital DM1 Rating Scale
Congenital DM1	Congenital Myotonic Dystrophy
COVID-19	Coronavirus Disease 2019
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression- Improvement Scale
CGI-S	Clinical Global Impression- Severity 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 Organization
CSF	Cerebrospinal Fluid
CTG/CUG	Cytosine, Thymine/Uracil, Guanine nucleotides
CTIMP	Clinical Trial of an Investigational Medicinal Product
CYP	Cytochrome P450 enzymes
DCCS	Dimensional Change Card Sort Test
DM-1	Type 1 Myotonic Dystrophy
DM-2	Type 2 Myotonic Dystrophy
DNA	Deoxyribonucleic acid
DSMC	Data Safety Monitoring Committee
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DXA	Dual-energy X-ray absorptiometry
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End-of-Treatment

FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GLM	General Linear Model
GSK	Glycogen Synthase Kinase
HAV	Hepatitis A Virus
HCV	Hepatitis C Virus
IB	Investigator's Brochure
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IVR	Interactive Voice Recognition
LAR	Legally Authorized Representative
LFT	Liver Function Tests
MBNL1	Muscle Blind Like Splicing Regulator 1
MD	Multiple Dose
MRI	Magnetic Resonance Imaging
NCE	New Chemical Entity
NIH	National Institute of Health
PK	Pharmacokinetics
PKAS	Pharmacokinetics Analysis Set
PPS	Per-Protocol Set
PPVT	Peabody Picture Vocabulary Test
PSMT	Picture Sequence Memory Test
PSP	Progressive Supranuclear Palsy
PT	Prothombin Time
PV	Pharmacovigilance
QTcB	Corrected QT- Bazett's Formula
QTcF	Corrected QT- Fridericia's Formula
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SE	Standard Error

SERCA1	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	Half-life
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time to Maximum Concentration
TSH	Thyroid Stimulating Hormone
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VAS	Visual Analog Scale

4. INVESTIGATORS AND ADMINISTRATIVE STRUCTURE

Coordinating Investigator

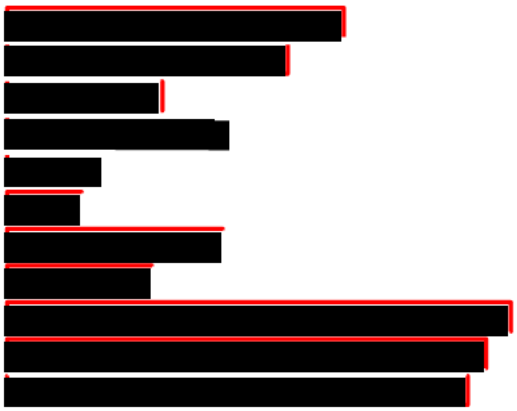
Medical Monitor

Contract Research Organization / Monitors

Data Management and Statistical CRO

Statistical Consultants

Pharmacovigilance



Central Laboratory

Central ECG Vendor

IWRS Vendor

Patient and Investigator Site Payments, Patient Travel Booking Service	[redacted]
Mobile Medical Services/Home Healthcare and Phlebotomy	[redacted]
	[redacted]

5. BACKGROUND INFORMATION

5.1 Myotonic dystrophy

Myotonic dystrophy is a monogenetic disorder caused by non-coding expansion repeats in the *DMPK* gene (myotonic dystrophy type 1 or adult onset DM1 or Steinert disease), which is located on chromosome 19, or the *CNBP* gene (myotonic dystrophy type 2 or DM2), which is located on chromosome 3. There are no symptomatic or disease-modifying treatments approved for the treatment of individuals with myotonic dystrophy.

DM1 may be present at birth (Congenital Myotonic Dystrophy), appear during childhood (Childhood Myotonic Dystrophy) or during adulthood (Classic Adult onset Myotonic Dystrophy and Late onset Myotonic Dystrophy).

Congenital Myotonic Dystrophy (Congenital DM1) 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 wheelchairs. Less than a quarter of Congenital DM1 patients were able to attend mainstream schooling due to intellectual disability, 15 percent were still fecally 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 noted learning disabilities in 95 and 89 percent of Congenital and Childhood DM1 patients, respectively. Ekström *et al.,* (2008) also reported that 68 percent and 50 percent, respectively, of individuals with Congenital and Childhood DM1 had an Autism Spectrum Disorder (ASD).

Current practice distinguishes between congenital, infantile, juvenile, adult, and late onset forms (Dogan *et al.,* 2016) of DM1. The condition is a multi-system disorder that affects muscle, brain, the heart, and liver amongst other organs. When DM1 has an onset in early adulthood, presentation is primarily characterized by a progressive distal weakness of the hands and arms, myotonia and excessive daytime sleepiness (Heatwole et al., 2012). Adult onset DM1 is associated with increased mortality, with mean survival age reported to be in the range of 55.4 years (Mathieu *et al.,* 1999) to 60 years (de Die-Smulders *et al.,* 1998).

Congenital DM1 is distinct from all other forms of DM1 in both time of onset, severity of disease, and genetic presentation.

- The expansion repeat size in individuals with Congenital DM1 is typically significantly larger than individuals with juvenile- or adult onset forms of DM1 (Ekström *et al.,* 2008).
- The congenital onset form of DM1 is by definition diagnosable at birth due to the presence of characteristic clinical signs that are not present in DM1 with onset at other ages (Genevieve *et al*., 2015).

- In particular, the CNS features of Congenital DM1 are much more severe than juvenile or adult onset forms. Almost all individuals with Congenital DM1 have intellectual disability, which is not the case with juvenile DM1 (Ekström *et al.,* 2008).
- Also, characteristic neuromuscular and skeletomuscular features, described below, are evident at birth in Congenital DM1.
- Congenital DM1 can be distinguished at the molecular and histological level. Congenital DM1 is associated with RNA splicing variants that are not present in the adult onset form (Thomas *et al.,* 2017). The presentation of muscle cell types in Congenital DM1 is different to that in juvenile and adult onset DM1 (Nakamori *et al.,* 2017).

Congenital DM1 may be a disorder in which muscle fibers fail to develop at the microscopic level, being therefore a developmental disorder. Adult onset DM1 can be considered a degenerative disorder of muscle, whose histopathological features may appear in adulthood in Congenital DM1. The genomic lesions in Congenital DM1 and Adult-onset DM1 may differ in respect somatic instability.

The hallmark clinical stigmata of neonates with Congenital DM1 include hypotonia, generalized weakness, respiratory insufficiency, feeding difficulties, and clubfoot or another musculoskeletal deformity. As infancy and young childhood progress, Congenital DM1 is associated with pronounced and unremitting oral facial weakness including diminished lip strength, respiratory difficulties, characteristic facies, often profound intellectual disability and behavioral disorders akin to ASD (Johnson *et al.,* 2016). These features are not central to Adult-onset DM1 which is associated with signs and symptoms that arise later in life, and in which fatigue, daytime sleepiness and milder cognitive deficits are associated with distal and proximal muscle weakness as well as myotonia.

As described previously, Congenital DM1 is associated with significant morbidity and mortality; life expectancy is significantly shortened with 25 percent of affected patients deceased by 18 months and less than 50 percent surviving to 30 years of age. Life-expectancy may be decreased in Adult-onset DM1 but to a lesser degree.

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. The IMP is ‘tideglusib for oral suspension’. It [redacted]

[redacted]

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

Signaling downstream of the insulin receptor is disrupted in DM1, given the significant splicing mis-regulation of the insulin receptor itself. Prior therapeutic trials (Heatwole, *et al.,* 2011) have focused on upregulating the insulin signal itself. The current approach targets the disrupted signaling downstream of the insulin receptor, at the GSK-3β site.

Jones *et al*., reported in 2012 that GSK-3β mediates muscle pathology in myotonic dystrophy based on increased GSK-3β activity in DM1 expressing cell lines, muscle biopsy samples from DM1 expressing transgenic mice and DM1 patient tissue samples. Tideglusib has also been shown to interact directly with an RNA construct containing the DMPK gene CUG repeat formed as a hairpin. Administration of tideglusib is also associated with fragmentation of the mutant *DMPK* gene RNA in Congenital DM1 patient tissue and reduction of *DMPK* gene RNA foci in muscle from the HSA^{LR} mouse (Wang et al 2019). Further, tideglusib reverses deficits in myodifferentiation of Congenital DM1 myoblasts *in vitro*. Tideglusib also significantly attenuates abnormalities in total levels and splice variants of key effectors such as BIN1 and SERCA1 in Congenital DM1 tissue *in vitro* and the HSA^{LR} transgenic mouse model of DM1 ([redacted].

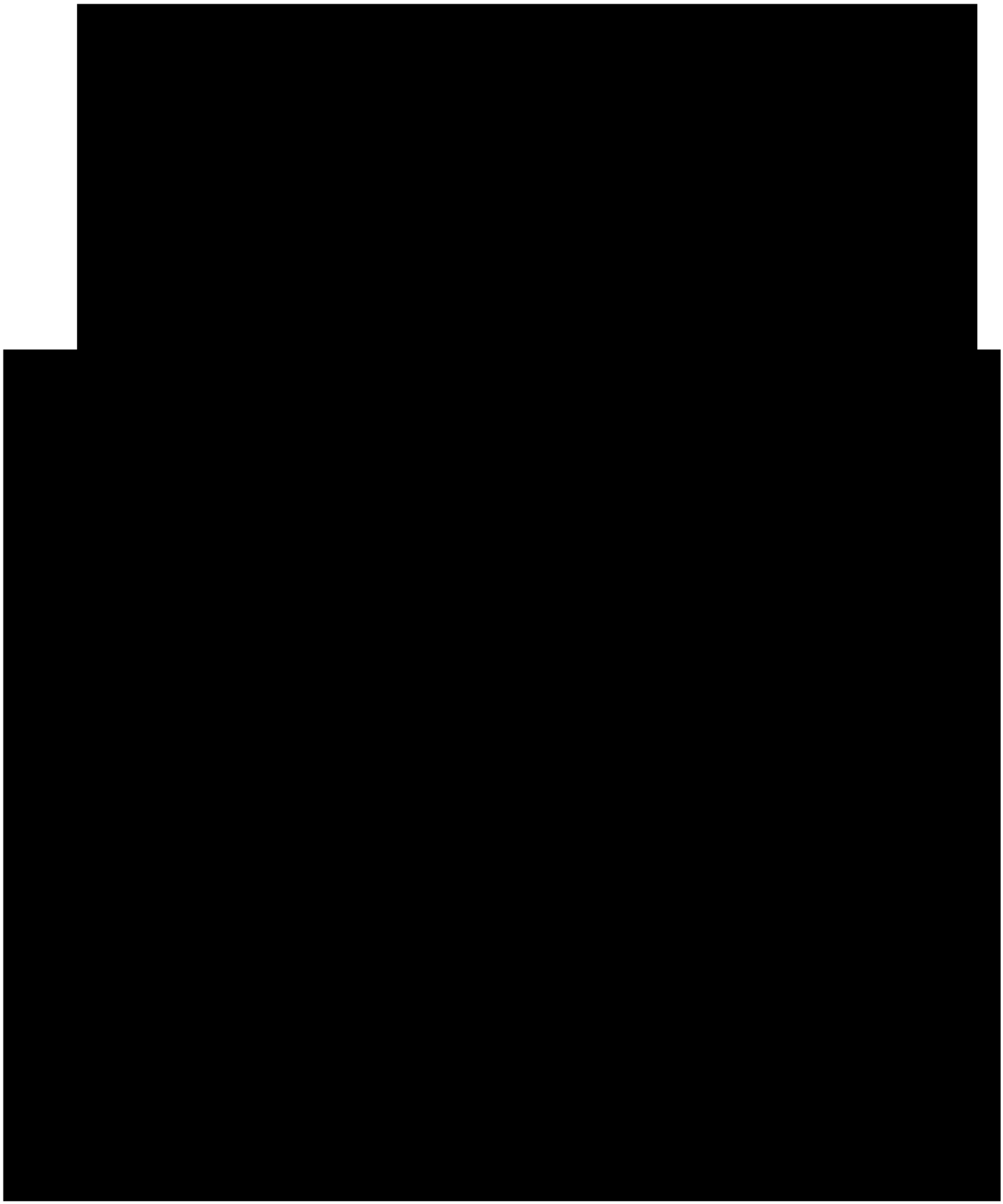
Refer to the current Investigator Brochure for additional information on tideglusib.

Given the above, the research intended by the Sponsor seeks to investigate the efficacy and safety of tideglusib in children and adolescents ages 6-16 years, affected by Congenital DM1.

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 is contained within the current version of the Investigator Brochure.



[redacted]

5.4 Clinical Experience

[redacted]

Table 3: [redacted]

Adverse Event	Active N=[redacted]	Placebo N=[redacted]
[redacted]		

[redacted]

Table 4: [redacted]

ADVERSE EVENT	[redacted]						[redacted]		TOTAL		[redacted]	
	[redacted]											
	n	%	n	%	N	%	n	%	N	%	n	%
[redacted]												

[redacted]

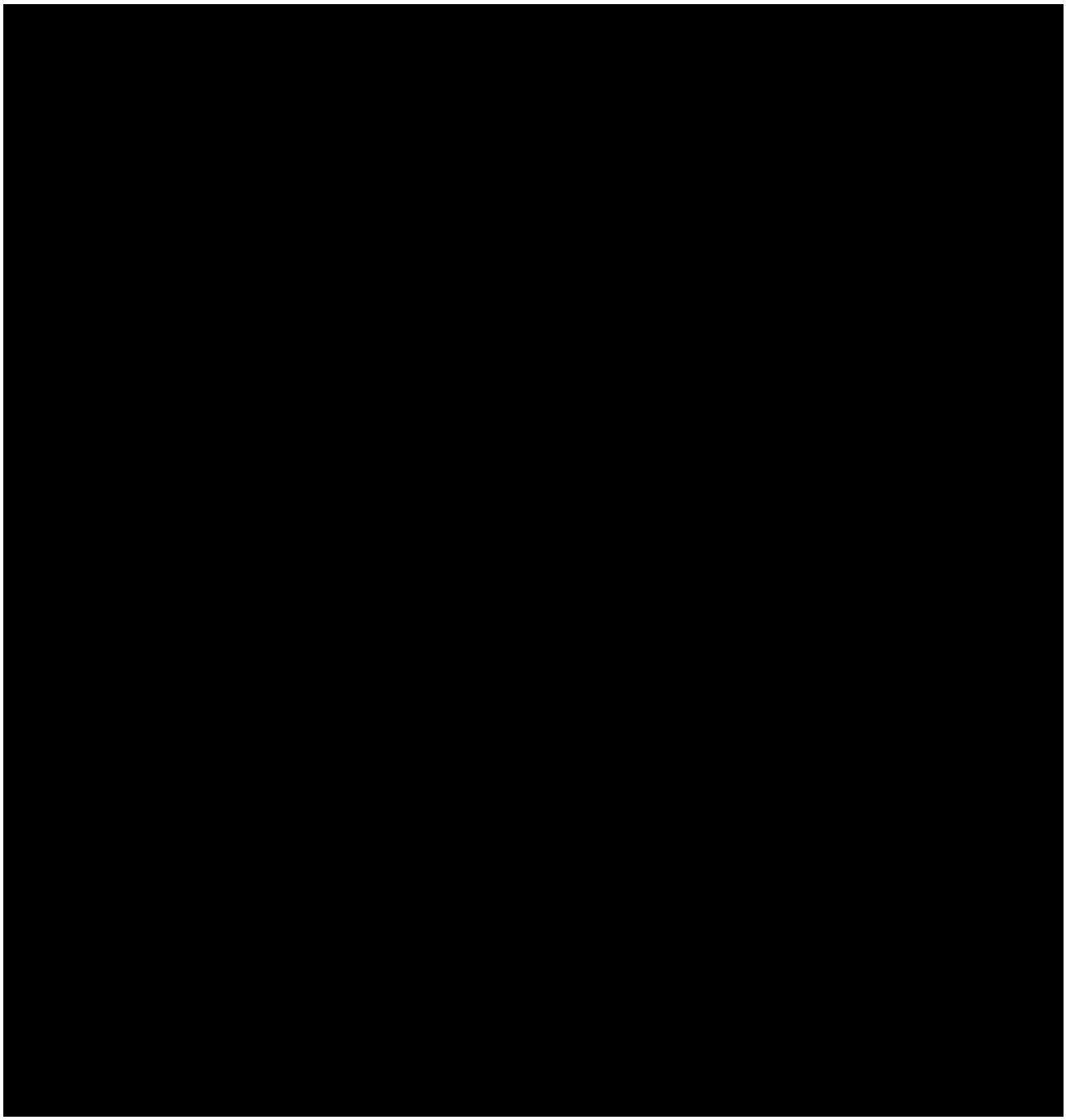


Table 5:

	n	%	n	%	n	%	n	%	n	%

Table 6: [redacted]

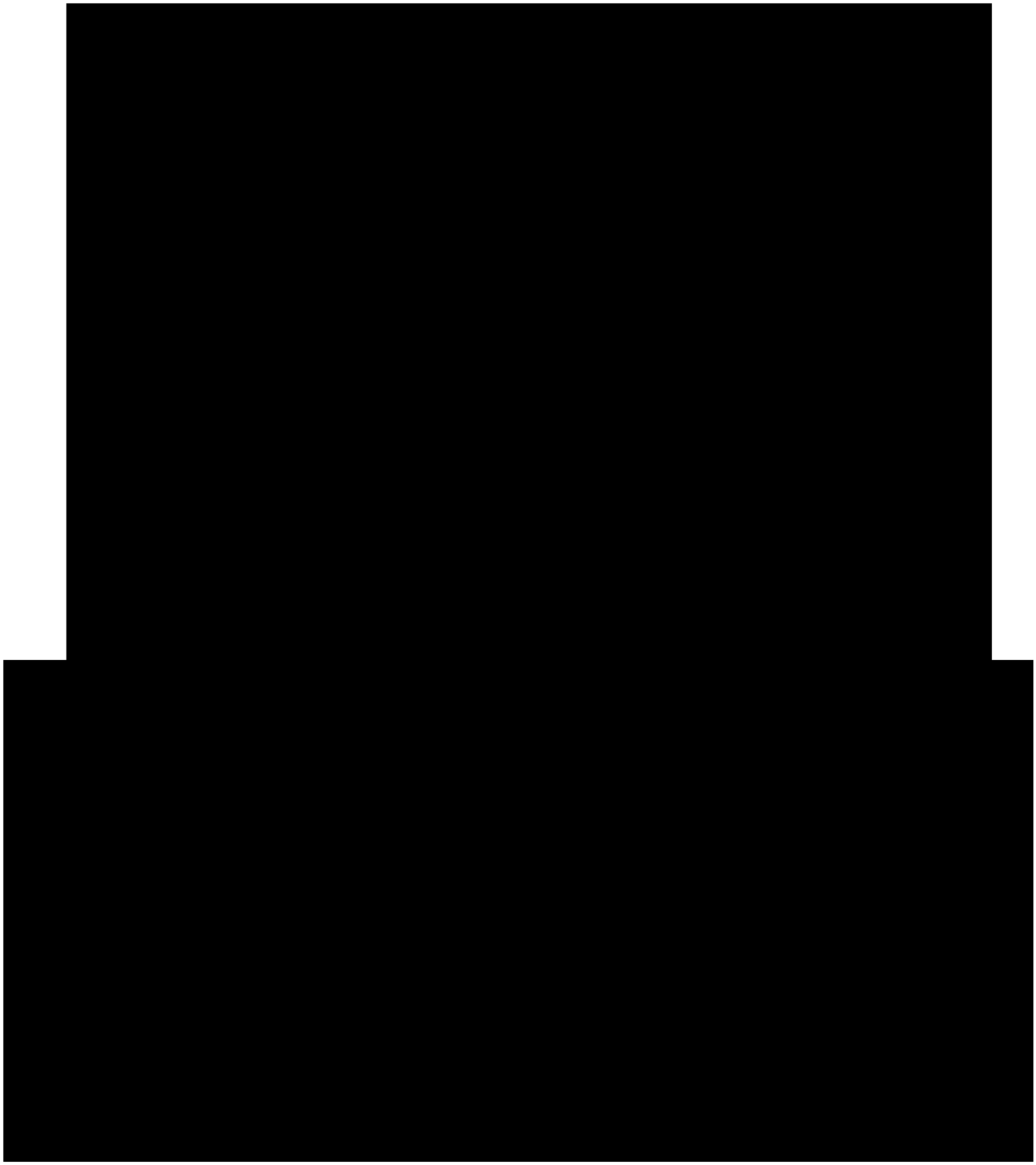
[redacted]	n	%	n	%	n	%
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7: [redacted]

[redacted]	n	%	N	%	n	%	n	%
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]



[redacted]

5.5 Rationale for this Study

There are currently no approved pharmacological treatments for individuals with DM1. Moreover, Congenital DM1 is a rare disease with a high mortality rate and as such has a significant unmet need for the development of pharmacological treatments. As described in Section 5.3, there is both pre-clinical and *in-vitro* clinical evidence to suggest that inhibition of GSK-3β could have the potential to reverse myotonia and improve muscle weakness in patients with Congenital DM1. Similarly, there is affirming preclinical evidence from neurodevelopmental models that suggest that tideglusib may have the potential to improve the associated neurocognitive and neuropsychiatric symptoms associated with DM1. This will be the first randomized, double-blind, placebo-controlled study of a GSK-3β inhibitor in children and adolescents with Congenital DM1. The following factors are taken into account:

Dose:

The dose of tideglusib that will be utilized in this study is within the dose range, and the weight-adjustment dosing strategy, that was implemented in the aforementioned Canadian TIDE study in children and adolescents with ASD. The doses for the TIDE study and for this study were selected based upon preclinical efficacy pharmacology studies as well as the safety data from prior clinical studies.

[redacted]

[redacted]

Clinical studies in adults have shown that chronic administration of an oral dose of 1000 mg tideglusib for six months or greater is generally safe and well tolerated.

In the recently completed AMO-02-MD-2-001 study, the study drug was well tolerated with all 16 subjects enrolled completing the study, and no early discontinuations or dose adjustments required. There were no SAEs or suspected unexpected serious adverse reactions (SUSARs) reported during the study and no serious AEs related to drug. There were no systematic irregularities in objective assessments (e.g. vital signs, ECGs, laboratory assessments). [redacted]

[redacted]

Pharmacokinetics:

[redacted]

[redacted]

Safety:

More than 496 adults and 65 children and adolescents have been administered tideglusib.

[redacted]

The safety and tolerability profile observed to date in both of these studies has been consistent with the information provided in the IB and no new safety or tolerability concerns have arisen in either of these two studies. Both studies were overseen by independent DSMC's.

[redacted]

[redacted]

Duration:

Based on data from a natural history study of this population and in consideration of the type of improvements anticipated to be measured, a duration of [redacted] weeks of treatment has been selected to investigate the effects of tideglusib on existing signs and symptoms. The effects of tideglusib and analogues on transgenic mouse models of myotonic dystrophy and on abnormal differentiation of Congenital DM1 muscle tissue *in vitro* revealed rapid onset following acute dosing. The time course over which tideglusib or any other pharmacological agent may demonstrate efficacy in ameliorating the symptoms of Congenital DM1 has not yet been established.

6. STUDY OBJECTIVES AND PURPOSE

6.1 Primary Objective

The primary objective of this study is to evaluate the efficacy, from baseline to end of treatment, of weight adjusted 1000 mg tideglusib compared to placebo in children and adolescents with Congenital DM1 as measured by the Clinician-Completed Congenital DM1 Rating Scale (CDM1-RS).

6.2 Secondary Objectives

Secondary Objectives of this study are:

- To evaluate the safety and tolerability of weight adjusted 1000 mg tideglusib compared to placebo in children and adolescents with Congenital DM1
- To evaluate the efficacy, from baseline to end of treatment, of weight adjusted 1000 mg tideglusib compared to placebo in children and adolescents with Congenital DM1 as measured by clinician-completed, caregiver-completed rating scales, functional assessments, and biomarker/physiological assessments
- To evaluate the blood pharmacokinetics of tideglusib and its main metabolite (NP04113) after repeat dosing in children and adolescents with Congenital DM1
- To evaluate the consistency of telehealth data and in-clinic data for the CDM1-RS and CGI rating scales

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Subject Numbers

Approximately 56 children were planned to be randomized into the study, assuming a dropout rate of 10-13%. After a blinded sample size re-estimation (SSRE), the protocol was amended to allow enrollment of between 56 and 66 children randomized into the study, if feasible. [redacted]

Randomization will occur in a 1:1 manner such that each treatment group will have approximately 28 subjects (assuming a 10-13% drop-out rate) contributing data to the primary efficacy analysis. Randomization will be stratified by age at the time of screening. [redacted]

Subjects that withdraw due to COVID-19 related reasons e.g. institutional restrictions, travel restrictions, subject in quarantine, or subject shielding, after receiving randomized

treatment may be replaced. Subjects that withdraw from the study after receiving randomized treatment for non-COVID-19 related reasons will not be replaced.

Subject eligibility will not be re-assessed after the [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 children or adolescents with a diagnosis of DM1. For the purposes of this study, the following definitions apply.

   In addition to the genetic confirmation of DM1, one or more of the following clinically relevant (e.g. requiring medical intervention) signs or symptoms was evident within the first month after birth:

   - Hypotonia
   - Generalized weakness
   - Respiratory insufficiency
   - Feeding difficulties
   - Clubfoot or another musculoskeletal deformity
2. Diagnosis must be genetically confirmed
3. Subjects must be male or female children and adolescents aged ≥6 years and ≤16 years at Screening
4. Subjects must have a Clinical Global Impression – Severity (CGI-S) score of 4 or greater at [redacted] and start of [redacted])
5. Subjects must be ambulatory and able to complete the 10-meter walk-run test (orthotics/splints allowed, forearm crutches are not allowed)
6. Written, voluntary informed consent must be obtained before any study related procedures are conducted. Where a parent or LAR provides consent, there must also be assent from the subject (as required by local regulations)
7. Subject's caregiver must be willing and able to support participation for duration of study
8. Subject must be willing and able to comply with the required food intake restrictions as outlined per protocol

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 use
2. Body mass index (BMI) less than 13.5 kg/m² or greater than 40 kg/m²
3. Receiving other medications/therapies not stable (i.e. changed) within 4 weeks prior to Screening. For each enrollee, every effort should be made to maintain stable regimens (i.e. dose, as applicable, and frequency) of allowed concomitant medications (e.g. concomitant mexiletine or stimulants) and allowed non-medicine based therapies (e.g. occupational or physiotherapy) throughout the course of the study, from the time of commencement of Screening until the last study assessment
4. Use within 4 weeks prior to Baseline ([redacted]) of strong CYP3A4 inhibitors. Examples include clarithromycin, telithromycin, ketoconazole, itraconazole, posaconazole, nefazodone, idinavir and ritonavir
5. Concurrent use of drugs metabolized by CYP3A4 with a narrow therapeutic window e.g. warfarin and digitoxin
6. Medical illness or other concern which would cause the investigator to conclude that the subject will not be able to perform the study procedures or assessments or would confound interpretation of data obtained during assessment
7. Current enrollment in a clinical trial of an investigational drug or enrollment in a clinical trial of an investigational drug in the last 6 months
8. Gastrointestinal disease which, in the opinion of the investigator, 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) neurological, cardiovascular, renal, hepatic, endocrine or respiratory disease that may impact the interpretability of the study results
10. Clinically significant heart disease (in the opinion of the investigator) or current evidence of second or third degree heart block, atrial flutter, atrial fibrillation, ventricular arrhythmias, or requires medication for treatment of a cardiac arrhythmia
11. Implantation of a cardiac pacemaker within the 12 months preceding Screening
12. Average QTcF value of >450 msec at [redacted] or at [redacted] ** (may repeat to confirm)
13. Clinically significant abnormalities in safety laboratory tests, vital signs or ECG, as determined by the investigator, at [redacted] or [redacted], ([redacted])**, as applicable (may repeat to confirm)

14. Females 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
15. Males, engaged in sexual relations with a female of child-bearing potential, not using an acceptable contraceptive*** method if not surgically sterile
16. Kidney disease requiring ongoing treatment
17. A history of chronic liver disease with current out of range values for ALT, clinically relevant hepatic steatosis or other clinical manifestations of liver disease
18. ALT value > 2X the upper limit of the normal reference range at [redacted] (may repeat to confirm)
19. 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). For subjects with a well known/well documented diagnosis of Gilbert's syndrome a total bilirubin value greater than 2 x the upper limit of the normal reference range at [redacted] (may repeat to confirm)
20. HbA1c values greater than 6% or 42.0 mmol/mol at [redacted] (may repeat to confirm)
21. TSH values outside of the normal reference range at [redacted] (may repeat to confirm)
22. Serum creatinine >1.7 mg/dL (>150 micromole/L or creatinine clearance ≤ 60 mL/min (according to Cockcroft-Gault formula) at [redacted] (may repeat to confirm)
23. Clinical history of hepatitis or previous or current positive serological evidence for Hepatitis B or C

24.24. Serological evidence of Hepatitis A at [redacted] or in the [redacted] preceding [redacted]

25. A history of significant drug allergy (such as Steven-Johnson syndrome, anaphylaxis)
26. A history of alcohol or substance use disorders
27. Current malignancy or any history of malignancy except for surgically cured skin cancer or pilomatricoma (benign tumor of the hair follicle that is associated with Congenital DM1)
28. Severe arthritis or other medical condition (besides Congenital DM1) that would significantly impact ambulation or completion of myometric assessments
29. Hypersensitivity to tideglusib or any components of its formulation including allergy to strawberry
30. Unable to swallow liquids or may have trouble swallowing liquids (in the opinion of the investigator), unless medication to be administered by gastrostomy tube
31. 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.

**As the central ECG report for [redacted] will not be available prior to the subject commencing run-in, eligibility related to ECGs (exclusion criteria 12 and 13) will be based on the investigator's calculation of the mean QTcF value of all ECGs taken at [redacted] and their initial review of the ECG tracings at [redacted] If there is a conflict between the investigator's initial assessment of the ECG and the central ECG report, whereby the subject would no longer be eligible for the study, the subject will be withdrawn from the study at or before [redacted], prior to randomization into the double-blind treatment period.

***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:

- Combined or progestogen-only hormonal contraception
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence, defined as true abstinence. True Abstinence: When this is in line with the preferred and usual lifestyle of the subjects [periodic abstinence (such as calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]
- Male or female condom with or without spermicide[1],
- Cap, diaphragm or sponge with spermicide[1],

  [1]A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable birth control methods

7.4 Withdrawal Criteria

A subject should be withdrawn from treatment if they meet the discontinuation criteria in section 9.5. 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 72 hours) 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 enrollment 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 or is consistently noncompliant with the pre- and post-dose food restrictions
- **Pregnancy:** The subject has either a positive urine or serum pregnancy test during the study.
- **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 Study Endpoints to be assessed:

Primary Efficacy Endpoint:

- Clinician-Completed Congenital DM1 Rating Scale (CDM1-RS)

Key Secondary Efficacy Endpoint:

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

* Sometimes referred to as the CGI-C

Secondary Efficacy Endpoints:

- Top 3 Caregiver Concerns VAS score
- Caregiver Completed Congenital DM1 Rating Scale (CC-CDM1-RS)
- Clinical Global Impression - Severity Scale (CGI-S)
- CDM1-RS Independent Central Rater Score
- CGI-I Independent Central Rater Score
- CGI-S Independent Central Rater Score
- 10 Meter Walk/Run (preferred speed and fastest speed)

Exploratory Endpoints:

- DXA Scan measurement of total body lean/muscle mass
- Measurement of lip strength (via lip force meter)
- Congenital and Childhood Myotonic Dystrophy Health Index (CC-MDHI) Parent Proxy Instrument
- Autism Behavior Inventory- Clinician (ABI-C)
- [redacted] and Adaptiv e Behavior Comp osite standard scores of the Vineland Adaptive Behavior Scale - [redacted]
- Quantitative myometric measure of hand grip strength
- NIH Toolbox Cognition Battery: Dimensional Change Card Sort Test
- NIH Toolbox Cognition Battery: Picture Sequence Memory Test
- Peabody Picture Vocabulary Test (PPVT)
- [redacted] levels
- [redacted] sample
- [redacted]
- Serial blood pharmacokinetics of tideglusib

Safety Endpoints:

- The incidence of Adverse events (AEs), including serious adverse events (SAEs), between Screening and end of treatment. The incidence will also be assessed during a [redacted] follow-up period after discontinuation of the study drug for those subjects not participating in the extension study AMO-02-MD-2-004.

- The incidence of abnormal findings in objective assessments (e.g. laboratory values, ECGs, vital signs and bone mineral density) between Screening and end of treatment. The incidence of abnormal findings in objective assessments will also be assessed during a [redacted] follow-up period after discontinuation of the study drug for those subjects not participating in the extension study AMO-02-MD-2-004.

8.2 Study Design

This is a randomized, double-blind, placebo controlled study of weight adjusted dose 1000 mg/day tideglusib versus placebo in the treatment of children 6-16 years of age with Congenital DM1 across a [redacted] treatment period.

Approximately 56 children will be randomized into the study. Randomization will occur in a 1:1 manner such that each treatment group will have approximately 28 children (assuming a 10-13% drop-out rate) contributing data to the primary efficacy analysis. The randomization will also be stratified by age group, [redacted].

The study will have 5 distinct phases (Figure 4, Study Design)

- Screening (Weeks [redacted]) Subjects will be screened to ensure adherence to eligibility criteria.
- [redacted] run-in (weeks [redacted]): Subjects and their caregiver will be dispensed [redacted] and 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 food intake and time of first meal after dosing. These will be reviewed by the investigator site at each visit.
- Double-blind dose [redacted] (weeks [redacted]): Subjects randomized to placebo remain on that treatment. Subjects randomized weight adjusted 1000 mg tideglusib will take tideglusib at a weight adjusted 400 mg dose level from week [redacted] then they will take tideglusib at a weight adjusted 600 mg dose level from weeks [redacted] and thereafter they will take tideglusib at the weight adjusted 1000 mg dose level from weeks [redacted]
- Double-blind maintenance (Weeks [redacted]): Subjects will continue on the fixed doses of weight adjusted 1000 mg tideglusib, or placebo, which they have been previously randomized to for [redacted] weeks. [redacted] and [redacted] may be completed at home using an AMO approved home healthcare vendor or as a standard clinic visit.
- Follow-up Period [redacted] after end of treatment (weeks [redacted]): for those subjects not participating in the extension study AMO-02-MD-2-004.

- Adverse Events will be elicited at [redacted]) and [redacted] ([redacted]) post end of treatment visit via telephone by a member of the study team
- An in-clinic follow-up visit will occur [redacted] weeks after end of treatment [redacted]

[redacted]

8.3 COVID-19 Impact to Study Design

Due to the global COVID-19 pandemic and the potential for resurgences of COVID-19, for the purposes of this protocol, 'in-clinic' visits, when pertaining to Visits [redacted] (Weeks [redacted]), may be conducted via a combination of telehealth and home healthcare providers if COVID-19 related reasons e.g. institutional restrictions, travel restrictions, quarantine or shielding prevent subjects from being seen in-person at the investigator site. Every effort will be made to resume the protocol-specific in-clinic visits for the affected subject, as soon as it is feasible and safe to do so. The type of device (e.g. tablet, mobile phone, computer) used by the clinician and subject/caregiver to conduct telehealth visits will be recorded, and should remain consistent throughout the study, if possible. Additionally, a test session prior to the first telehealth visit will be conducted to make sure that the technology works and the assessment can be easily collected.

Subjects who have completed Screening [redacted]) but are unable to attend Run-In [redacted] in-person due to COVID-19 related reasons will be allowed to either delay [redacted] (in the event that the rescheduled [redacted] can occur within [redacted] weeks of the originally planned date) or allowed the opportunity to rescreen for the study if study enrollment is still ongoing once they are able to attend the clinic again in person. Subjects who have attended the Run-In ([redacted]) and are unable to attend the Baseline [redacted] in-person due to COVID-19 related reasons will be allowed to delay [redacted] (and additional [redacted] IMP dispensed, if required) until they are able to return in-person for [redacted]

In the event a combined telehealth and home healthcare visit is required, or unscheduled visits as outlined in section 9.5, the following endpoints and procedures may be impacted, as follows:

- Clinician completed assessments (i.e. CDM1-RS, CGI-I, CGI-S, Vineland Adaptive Behavior Scale and ABI-C) will be completed via telehealth
- Caregiver-completed assessments (i.e. Top 3 Caregiver Concerns VAS, CC-MDHI and CC-CDM1-RS) will be completed remotely in the subject's home
- 10-meter walk-run test: will not be collected as it is unable to be completed safely in a subject's home
- Lip strength assessment will not be able to be completed as specialized physiotherapists are unavailable for home healthcare visits
- Grip strength assessment will not be able to be completed as specialized physiotherapists are unavailable for home healthcare visits
- NIH toolbox assessments (i.e. Dimensional Change Card Sort Test and Picture Sequence Memory Test) and the Peabody Picture Vocabulary Test (PPVT) will not be completed as telehealth administration is non-standard administration for these tests. Sensitivity analyses on the primary, key secondary and one secondary endpoint to support telehealth administration are intended to be performed, and therefore additional sensitivity analyses for these exploratory tests will not be performed.
- DXA scan: will need to be completed locally or may be unable to be completed
- [redacted]samples will be unable to be processed outside of a clinical laboratory, and therefore will not be collected
- Physical examinations will not be able to be completed outside of the clinic setting. If a subject is unable to complete Week[redacted] in-clinic, a physical exam will be completed locally.
- Vital signs, height and weight will be collected remotely in the subject's home using an AMO approved home healthcare vendor
- Safety laboratory and urinalysis samples will be collected remotely in the subject's home using an AMO approved home healthcare vendor
- Pregnancy testing will be completed via a serum sample collected by an AMO approved home healthcare vendor
- The standard 12-lead ECG will be replaced with a 6-lead ECG using equipment provided by the central ECG vendor and completed in the subject's home using an AMO approved home healthcare vendor

- PK samples will be unable to be processed outside of a clinical laboratory setting, and therefore will not be collected
- The diary review will need to be completed remotely by the study staff
- [redacted] will be unable to be processed outside of a clinical laboratory, and therefore will not be collected
- [redacted] will not be able to be collected or processed outside of the clinic setting
- Adverse event collection, concomitant medication review will be completed by telehealth or telephone
- IMP will need to be shipped from the investigator site to the subject's home and unused IMP returned via arranged shipment to the investigator site

Home healthcare visits will not be conducted if local restrictions prohibit it or if the subject or a member of the family present in the home has, or is suspected to have, COVID-19, and those assessments will not be completed. The details of telehealth and in-clinic data assessment are outlined in the SAP.

8.4 DSMC

An independent Data Safety Monitoring Committee (DSMC) consisting of clinical and other experts will be established by the Sponsor to review safety findings during the study and to help ensure subject 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, and considerations for any statistical items (e.g. data displays) that may be required for the data reviews.

The DSMC will meet 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 may suggest changes to the protocol. Based on the results of their data reviews, the DSMC will submit its recommendations in written form to the Sponsor who is responsible for responding to the recommendations of the DSMC and to take appropriate action.

9. STUDY MEDICATION AND ADMINISTRATION

9.1 Study Medication

Investigational Medicinal Product (IMP): Tideglusib for oral suspension

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

The IMP is a p[redacted]wder blend presented in individual[redacted] were developed for this study, namely 'tideglusib [redacted] or placebo for oral suspension' and 'tideglusib [redacted] or placebo for oral suspension' [redacted]. The IMP was developed to be dosed orally following [redacted] The formulation contains an [redacted]

A matching placebo powder blend formulation was developed according to protocol and study design. Placebo products are prepared for each strength. The products are filled dose-proportionally in identical unit-dose packets at the same total powder blend weight as the corresponding [redacted] active strength products. It is comprised of the same qualitative composition as the active product except that tideglusib [redacted]

The unit-dose packets (active and matching placebo) must be [redacted]

Tideglusib dosing will be weight-adjusted at 400 mg, 600 mg, or 1000 mg dose levels, with each subject randomized to tideglusib starting at a weight-adjusted 400 mg dose level for [redacted] weeks, then up [redacted] to a weight-adjusted 600 mg dose level for the next [redacted] weeks until they reach the final dose level of weight-adjusted 1000 mg tideglusib. Weight-adjusted dosing for 400 mg, 600 mg or 1000 mg dose levels of tideglusib result in target [redacted] respectively.

Subjects weighing [redacted] Run-in ([redacted]) will not need to make weight adjustments for their randomized dose of IMP and [redacted]

Subjects weighing [redacted] Run-in ([redacted] will need to make a weight adjustment to the dose of IMP they have been randomized to [redacted] The [redacted] APPENDIX G: [redacted]

[redacted]

There is an accompanying description of the dose preparation procedure that offers more specific details concerning the dosing methodology that will be utilized by caregivers.

The [redacted] will be provided to the subject and their caregiver at Run-in [redacted] and dosing is to commence the day following the completed visit i.e. if the run-in visit is completed over [redacted], then dosing will start the [redacted] t [redacted].

The double-blind IMP (active or placebo) will be provided to the subject and their caregiver at each clinic visit from Baseline [redacted] to end of treatment (EOT) ([redacted]. After completing each visit, [redacted], the medication dispensed should be used for the next scheduled dose after completing the full study visit. If a visit is split across 2 days, [redacted]

IMP (either active tideglusib or placebo) will be [redacted] At Visits [redacted] where the time between in-clinic visits may be [redacted] weeks, [redacted]

[redacted] wit [redacted] information using the [redacted]

[redacted]. The IMP (packets and cartons) label text will comply with all applicable regulatory requirements. For information on which cartons constitute which doses refer to **Table 8.**

The caregiver/ LAR will be given clear instructions that all unused packets 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/LAR must be informed to only use packets from the new cartons and return both sets of IMP at the next visit.

If Visits [redacted] Weeks [redacted]) are conducted via a combination of telehealth and home healthcare providers due to COVID-19 related reasons, shipment of the IMP from the investigator site directly to the subject's home will be arranged. Unused IMP may also be returned from the subject's home to the investigator site via arranged shipment.

Table 8: Dose Cartons

Dose	Cartons of Medication Dispensed per [redacted] timeframe
400 mg	[redacted]
600 mg	[redacted]
1000 mg	[redacted]
Placebo	[redacted]

9.2 Allocation to Treatment

Subject numbers are assigned to subjects as consent is obtained for them to participate in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to the IMP allocated to the subject. This will be allocated at Baseline, Week [redacted] once Run-In is completed.

The treatment the subject is randomized to is determined by a randomization scheme which will automatically be assigned by the IRT(Interactive Response Technology).

Randomization will occur in a 1:1 manner (e.g. 1000 mg weight adjusted tideglusib: placebo) such that each treatment group will have approximately 28 children contributing data to the primary efficacy analysis, stratified by age group, [redacted] years.

9.3 Study Treatment and Administration

IMP (tideglusib or placebo) will be administered [redacted], by oral route. [redacted]. Administration by gastrostomy tube is also permissible, provided [redacted], dose preparation, and administration instructions are followed. Method of administration will be recorded in the CRF. [redacted]

[redacted] this will be recorded in the source and the CRF.

To maintain study blind, all subjects will receive two packets of study medication at each dosing occasion. To initially prepare the IMP, [redacted] (see **Table 9:** [redacted]

[redacted] referenced in APPENDIX G: Weight-based Dosing Chart. For weight adjusted dosing, [redacted]

[redacted] should be discarded. [redacted]

[redacted].

The date and time of dosing 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).

Weight measurement at Run-In [redacted] will be used to determine the weight based dosing and will be kept throughout the study, even if the subject's weight changes.

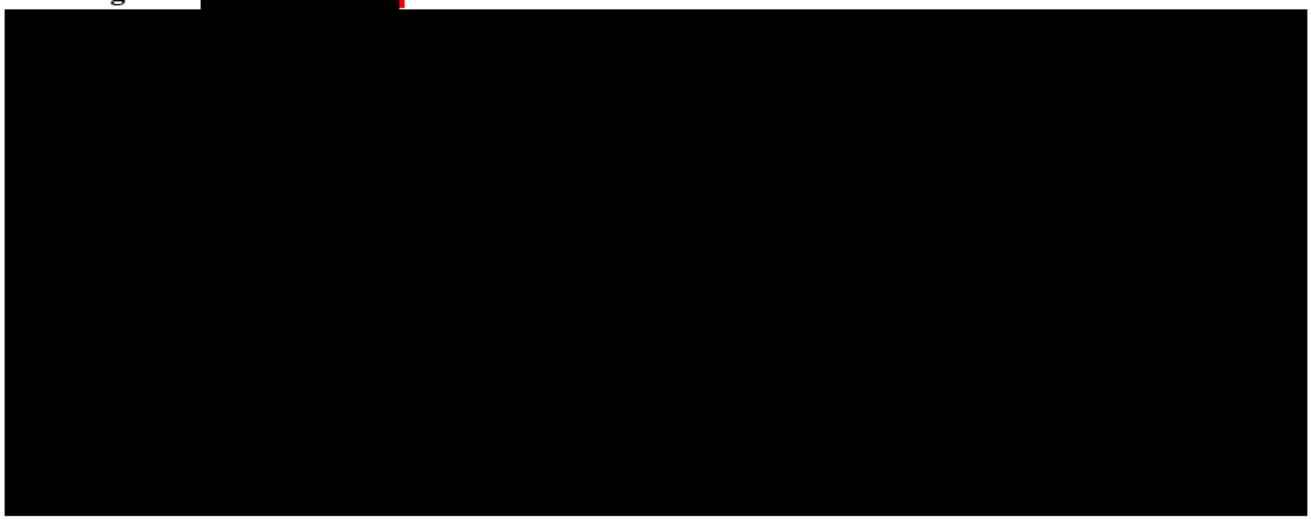
Table 9: [redacted]

Dose Level	400 mg Tideglusib [redacted]	600 mg Tideglusib [redacted]	1000 mg Tideglusib	Placebo
Packet Combination for Dose Administration	[redacted]	[redacted]	[redacted]	[redacted]

9.4 Duration of Subject Participation

The overall expected duration of subject participation is [redacted] weeks. Clinic visits will be completed per the schedule of events and visits can be completed across either one or two days as necessary. Participation for individual subjects will consist of up to 4 weeks of an initial Screening period followed by a [redacted] run-in treatment phase. After this, subjects will be randomized to either weight adjusted 1000 mg tideglusib, or matched placebo, once daily orally for [redacted] weeks. Subjects randomized to weight adjusted 1000 mg tideglusib will receive the 400 mg weight adjusted dose level of tideglusib for two weeks, and then will advance to the 600 mg weight adjusted dose level for the next two weeks. Thereafter, these subjects will take tideglusib at the weight adjusted 1000 mg dose level for [redacted] weeks (see **Figure 5**). All subjects will be followed up for [redacted] weeks after the end of treatment if they are not participating in the extension study AMO-02-MD-2-004.

Figure 5 [redacted]



9.5 Laboratory Alerts, Stopping Rules and Discontinuation Criteria

Laboratory Alerts:

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:

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 below are met.

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 ideally within 72 hours, and at that time, repeat laboratory work will be obtained [redacted], a physical examination will be conducted, and the protocol-defined study assessments for end-of-treatment will be completed. If possible, [redacted] PK sample will be obtained.

ii. Dose Adjustment

If a subject has either an [redacted]

As the study is double-blind, to maintain the blind, regardless of the dose of study medication the subject has been assigned to, all subjects will be given new medication as follows: [redacted]

[redacted] If a subject has [redacted]

Ideally, this procedure should not take more [redacted]

- If the [redacted]

The [redacted] will b assigned for statistical purposes (both for efficacy and safety analyses) to the [redacted] group where they have [redacted]

iii. Subject/Caregiver contacted by Investigator for further evaluation

If a subject has [redacted] (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. The investigator should at the minimum arrange for collection of clinical labs [redacted] ideally within [redacted] from the subject, and if these clinical labs are collected during an in-clinic visit should also conduct a brief physical examination, collect vital signs, collect [redacted] PK sample when possible, and check for any AEs or changes to concomitant medications. The investigator should also assess the need for continued follow-up before the next appointment, as appropriate.

If clinical laboratory tests are obtained with a home healthcare visit, a member of the study team should telephone the subject and/or caregiver to assess if there have been any AEs and collect any new or changed medications. This should be assessed again at the next in-clinic appointment to ensure accurate collection of information.

Management of Diarrhea

In case of [redacted]

9.6 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 packets 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.

At each in-clinic visit, the subject diary will be reviewed and compared to the accountability evidence to further ascertain compliance and ensure dose times are recorded for all dose administrations, including if dosing is done in-clinic.

Diary review may be completed remotely, if required due to a COVID-19 related reason. Unused packets of IMP will be returned to the investigator site at the next in-clinic visit, or if the situation requires, unused packets may be returned directly from the subject's home to the investigator site via arranged shipment.

At the end of the study, all unused IMP will be returned to the Sponsor's designee or destroyed by the site according to the Sponsor's instructions once it has been inventoried and the monitor has reviewed drug accountability records.

9.7 Treatment Blinding Code

An IRT will be employed in the study to manage the randomization of subjects, tracking and confirmation of shipments and returns, IMP supply management, inventory management and supply ordering, IMP expiration tracking, and emergency un-blinding of the IMP.

The IRT vendor will provide a user manual and training to each site with detailed instruction on the use of the IRT.

9.8 Unblinding the Treatment Assignment

The treatment assignment must not be broken during the study except in emergency situations where the identification of the subject treatment code is required for further treatment of the subject. The investigator should contact the medical monitor as soon as possible after the investigator has been unblinded if the medical monitor was not contacted prior to unblinding of treatment code.

In the event that the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code are recorded in the IRT and the source documents. Upon breaking the blind, the subject is withdrawn from the study, but should be followed up for safety purposes. Any code breaks that occur must be reported to the CRO and Sponsor.

Code break IRT access is held by the investigator and pharmacist/designated person at the site and by the medical monitor, or designee, for the study.

9.9 Permitted concomitant medication/ non- pharmacological therapies

All concomitant medications and non-pharmacological therapies (e.g. physiotherapy, occupational therapy, speech therapy, yoga) taken or implemented during the study will be recorded in the CRF with indication, dose information, frequency and dates of administration as applicable. The Investigator should inquire at each clinic visit whether there have been changes in any permitted concomitant medications or non-medical therapies or interventions, including those in the school setting (e.g. speech therapy).

With regard to any permitted medication (e.g. concomitant mexiletine or stimulants) or therapy (e.g. occupational or physiotherapy) that the subject was taking on entry to the study, every effort should be made to continue at the same dose (as applicable) and frequency throughout the study.

If the subject is taking [redacted].

9.10 Prohibited concomitant medications

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

Drugs metabolized 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 events where the subject is able to attend the investigator site in person.

Refer to **Table 2** for an adjusted schedule of events in the event that a subject is unable to attend the investigator site in person due to a COVID-19 related reason. If a subject is in quarantine due to COVID-19, home-health care visits/assessments will not be completed.

10.1 Efficacy Assessments

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

The study will evaluate efficacy from four different perspectives (also referred to as efficacy domains): clinician-completed assessments, caregiver-completed assessments, functional assessments (i.e. assessments that require in-clinic performance by the enrollee), and biomarker/physiological assessments. The efficacy domains will include the measures described below:

10.1.1 Clinician-Completed Assessments

10.1.1.1 Clinician-Completed Congenital DM1 Rating Scale (CDM1-RS)

The Clinician-completed Congenital DM1 Rating Scale is an 11-item rating scale completed by the clinician to score the symptom severity of the following domains that are clinically relevant in Congenital DM1:

- Limitations with mobility or walking
- Problems with hands or arms
- Signs of Fatigue
- Signs of Pain
- Gastrointestinal issues
- Communication difficulties
- Impaired sleep or daytime sleepiness
- Difficulty thinking
- Myotonia
- Breathing difficulties
- Choking or swallowing issues

This list of domains is informed by the Congenital and Childhood Myotonic Dystrophy Health Index (CC-MDHI) (Johnson *et al.,* 2016). The CC-MDHI is a rating scale developed from a Natural History Study of the symptoms and impact of Congenital DM1 (Johnson *et al.,* 2016). The CC-MDHI is a 168-item Likert scale that covers multiple aspects of the specific phenotype of Congenital DM1, intended for completion by the caregiver of the subject. The CDM1-RS is being developed in collaboration with the authors of the CC-MDHI. This new outcome measure utilizes domains informed by those reported for the CC-MDHI; the scale covers much of the breadth of the clinical phenotype of Congenital DM1.

The severity of the clinician's concern in each domain is scored by using a 5 point Likert Scale. Scores range from 0 = Not present to 4 = Very severe. The clinician is asked to rate the severity of each symptom, using a time frame of the past week including the day of the assessment for reference.

A standard interview and examination form will be provided to the sites to assist the rater making assessments and in eliciting commentary from the subject or their caregiver across each of the core domains of the affected individual's Congenital DM1, and also on associated symptoms. Every effort will be made to ensure that the same rater also observes the subject at each visit to the clinic or telehealth visit.

At Baseline ([redacted]), Week[redacted]) and Week [redacted]) the CDM1-RS will be rated twice for consistency evaluation purposes. One rating will be from an interview completed in-clinic and an another from an interview completed via telehealth within the [redacted] period before the in-clinic visit. Both the in-clinic and telehealth interviews will be video recorded.

In addition to the investigator ratings of the CDM1-RS, an independent central rater will also rate the CDM1-RS for both the in-clinic and telehealth interviews recorded at Baseline [redacted]), Week [redacted] and Week [redacted]

The CDM1-RS will be completed according to the schedule of events and will be assessed via telehealth instead of an in-clinic interview if required due to a COVID-19 related reason.

A copy is included in APPENDIX A: Clinician-Completed Congenital DM1 Rating Scale (CDM1-RS).

10.1.1.2 Clinical Global Impressions (Severity and Improvement)

The clinician administered Clinical Global Impression - Severity (CGI-S) and - Improvement (CGI-I) scale (Guy, 1976) will be performed in accordance with the schedule of events. 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 events.

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, sometimes referred to as the CGI-C, requires the clinician to rate how much the subject's illness has changed (improved, worsened or stayed the same) relative to a baseline state (Amer Psychiatric Pub Inc, 2000). A seven point Likert type scale is used with ratings of 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 subject's clinical presentation at Run-in [redacted]). For subsequent CGI-I ratings completed from [redacted] onwards, the assessment should be compared against the subject's clinical presentation at Baseline ([redacted].

In this study, score levels for the CGI-S and CGI-I are calibrated to standard scoring anchors which are specific to the Congenital DM1 phenotype. A standard interview and examination form will be provided to the sites as a guide to the rater in evaluating the subject and in eliciting commentary from the subject or their caregiver across each of the core domains of the affected individual's Congenital DM1 and also on associated symptoms. Every effort will be made to have the same rater also observe the subject at each visit to the clinic or telehealth visit.

At Baseline ([redacted]), Week [redacted]) and Week [redacted]) the CGI will be rated twice for consistency evaluation purposes. One rating will be from an interview completed in-clinic and another from an interview completed via telehealth within the [redacted] period before the in-clinic visit. Both the in-clinic and telehealth interviews will be video recorded.

In addition to the investigator ratings of the CGI-S and CGI-I scales, an independent central rater will also rate the CGI-S and CGI-I scales for both the in-clinic and telehealth interviews recorded at Baseline ([redacted]), Week [redacted]) and Week [redacted]). The CGI-I rating at Week [redacted] and Week [redacted]) should be rated against the independent central rater's assessment of the change in the subject's clinical presentation since Baseline [redacted].

The CGI-I and CGI-S will be completed according to the schedule events and will be assessed via telehealth instead of an in-clinic interview if required due to a COVID-19 related reason.

A copy of the CGI-S and CGI-I to be used in the study, along with instructions is included in APPENDIX B: Clinical Global Impressions (Severity and Improvement).

10.1.1.3 Autism Behavior Inventory - Clinician (ABI-C)

The Autism Behavior Inventory - Clinician (ABI-C) is a 14 item rating scale to assess the core features of ASD as well as common associated behaviors. Items are organized into the following areas: Social Communication, Restrictive Behaviors, Mood & Anxiety, Self-Regulation, and Challenging Behavior. Research studies to date demonstrate good test-retest reliability, as well as convergent and divergent validity with other commonly used ASD scales.

When completing the ABI-C, the clinician is asked to rate the overall severity/level of impairment of each item over the past week on a 7-point Likert type scale. In general, the ratings correspond to the following: 1. None, No symptoms present; 2. Minimal, Symptoms present; no effect on function or adaptation; 3. Mild, Rarely interferes with function or adaption; 4. Moderate, Occasionally interferes with function or adaptation; 5. Significant, Frequently interferes with function or adaptation; 6. Severe, Nearly always interferes with function or adaptation; or 7. Very Severe, Persistent interference with function or adaptation. The clinician will rate the subject based on both behavioral observation and clinician interview. The clinician interview to support the ABI-C ratings can be with the parent/caregiver, subject, or both.

The ABI-C will be administered according to the schedule events and will be assessed via telehealth if required due to a COVID-19 related reason.

A copy is included in APPENDIX C: Autism Behavior Inventory- Clinician (ABI-C).

10.1.1.4 Vineland Adaptive Behavior Scales- [redacted] – [redacted] (Vineland[redacted])

The Vineland Adaptive Behavior Scales – [redacted] (Vineland – [redacted] measures personal and social skills needed for everyday living. It provides a targeted assessment of adaptive behavior via a semi-structured parent or caregiver interview. [redacted] Test administration can be accomplished on a portable device such as an iPad or given via paper/pencil. The Vineland-[redacted] includes suggested interview questions as well as item-level probe questions. [redacted] The [redacted] version of the Vineland[redacted] can generally be completed within 20 minutes, ideally completed by a clinician with at least two years of experience working with individuals with ASD. The [redacted] version will be utilized in this study.

The Vineland[redacted] will be administered according to the schedule events and will be assessed via telehealth if required due to a COVID-19 related reason.

10.1.2 Caregiver-Completed Assessments

10.1.2.1 Congenital and Childhood Myotonic Dystrophy Health Index (CC-MDHI) Parent-Proxy Instrument

The Congenital and Childhood Myotonic Dystrophy Health Index (CC-MDHI) surveys the overall quality of life in relation to the subject's myotonic dystrophy symptoms. The CC-MDHI is a rating scale developed from a Natural History Study of the symptoms and impact of Congenital DM1 (Johnson *et al.,* 2016). The CC-MDHI Parent Proxy is a 19 question, 128-item Likert scale that covers multiple aspects of the specific phenotype of Congenital DM1, intended for completion by the caregiver of the subject. Each item offers 6 levels of severity ranging from "he/she doesn't experience this" to "it affects his/her life severely".

The CC-MDHI will be administered according the schedule events and will be completed remotely in the subject's home if required due to a COVID-19 related reason.

A copy of the CC-MDHI Parent Proxy can be found in APPENDIX D: Congenital and Childhood Myotonic Dystrophy Health Index (CC-MDHI) Parent Proxy Instrument.

10.1.2.2 Top 3 Caregiver Concerns Visual Analogue Scale (VAS)

The Top 3 concerns VAS allows 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.

Caregivers will be asked to rate three causes for concern by drawing a vertical mark on a 10 cm long VAS with anchors of "not at all severe" at the left end and "very severe" at the right end. Ideally, the caregiver should choose one item that relates to muscle function (such as problems with walking, drinking from a straw, or grip), one item that relates to cognitive abilities (such as problems with thinking, planning or concentration), and one item that relates to performing activities of daily living (for example, problems or difficulties brushing teeth, getting dressed or helping with household chores). 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 according to the schedule of events using the same scales and will be completed remotely in the subject's home if required due to a COVID-19 related reason.

A copy of the Top 3 concerns VAS is included in APPENDIX E: Caregiver Top 3 Concerns Visual Analog Scale (VAS).

10.1.2.3 Caregiver-Completed Congenital DM1 Rating Scale (CC- CDM1-RS)

This scale provides a caregiver assessment of the subject on symptoms that may occur in individuals with CDM1. There are a total of 11 symptoms that the caregiver is asked to rate:

- Limitations with mobility or walking
- Problems with hands or arms
- Signs of fatigue
- Signs of pain
- Gastrointestinal issues
- Communication difficulties
- Impaired sleep or daytime sleepiness
- Difficulty thinking
- Myotonia

- Breathing difficulties
- Choking or swallowing issues

These symptoms are rated on a score from 0 to 4 based on overall severity (e.g. severity of symptoms, frequency of symptoms, context in which it occurs and functional impact), where 0 = Symptom not present or is no longer present during the relevant time frame, and 4 = Very severe, symptom causes pronounced and consistent impairment and is highly disruptive with regard to daily life.

When rating each symptom, the caregiver will be asked to consider how the symptom influences how the subject feels and how it impacts his/her ability to perform everyday functions. Caregivers ratings should also incorporate important observations that they make of the subject, with regard to his/her symptoms. For example, caregivers should consider the subject's behaviors and verbalizations (what he/she says), as well as the symptoms that the caregiver can actually see. When making their ratings, the caregiver is asked to consider a time frame of the past week including the day of the assessment for reference.

The CC-CDM1-RS will be administered according to the schedule of events and will be completed remotely in the subject's home if required due to a COVID-19 related reason.

A copy of the CC-CDM1-RS is included in APPENDIX F: Caregiver Completed Congenital DM1 Rating Scale (CC-CDM1-RS).

10.1.2.4 Caregiver Myotonic Dystrophy Type 1 Status

Study staff will ask the caregiver for some optional basic information about themselves which will be recorded in the CRF. The information includes:

- Relationship of the caregiver to the subject (e.g. mother, father, sibling, other)
- If the caregiver has a diagnosis of DM1
- Which subtype of DM1 the caregiver has, if applicable

10.1.3 Functional Assessments

10.1.3.1 10-Meter walk-run test (preferred speed and fastest speed)

The 10-meter walk/run test is a performance measure used to assess walking speed in meters 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 events and will be performed at the subject's preferred walking speed and then at the fastest speed possible.

For each speed, the test should be repeated until 3 valid measures are obtained. No more than 6 trials per speed should be conducted, with 10-15 seconds of rest between trials to avoid fatigue. If needed, the rest period can be longer, until the subject has recovered.

The subject walks without assistance for 12 meters while the time taken to walk from meter 1 to meter 11 is recorded. The electronic timing system starts and stops when the subject crosses the 1 and 11-meter line, respectively. Assistive devices such as orthotics/splints are allowed, forearm crutches or walkers are not allowed. Use of assistive devices 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 valid assessments, this will also be recorded.

The 10-meter walk/run will not be collected remotely (i.e. if an in-clinic visit is not possible due to a COVID-19 related reason) as it is unable to be completed safely in a home environment.

10.1.3.2 Quantitative myometric measure of hand grip strength

Handgrip myometry is used as a measure of myotonia and muscle strength and has been validated as a reliable measure in patients with DM1 (Moxley *et al.,* 2007).

The force of concentration will be measured using the Jamar Handgrip Dynamometer and will be measured in kilograms (Kg).

Handgrip strength will be tested bilaterally, first on the right and then followed by the left hand. The subject will be asked to squeeze the Jamar Handgrip dynamometer for 3-5 seconds to allow for maximal muscle contraction, after which the subject will release their grip and relax their hand. This will be repeated until 3 valid measures are obtained. A maximal 6 trials per hand will be attempted, with a 5 to 10 second rest given between trials to avoid fatigue.

Handgrip strength will not be collected remotely (i.e. if an in-clinic visit is not possible due to a COVID-19 related reason) as specialized physiotherapists are unavailable for home healthcare visits.

10.1.3.3 Measurement of lip strength via lip force meter

Lip strength will be measured using a mouthguard adaptation for the digital force meter. Subject s will insert the mouthguard between their incisors and their lips and hold as force is applied for 10 seconds with increasing force until the mouthguard is dropped.

Measurements will be repeated until 3 valid times are obtained. No more than 6 trials will be conducted, with at least 10-15 seconds rest in between trials to avoid fatigue. If needed, the rest period can be longer.

Lip strength will not be collected remotely (i.e. if an in-clinic visit is not possible due to a COVID-19 related reason) as specialized physiotherapists are unavailable for home healthcare visits.

10.1.3.4 NIH Toolbox Cognition Battery: Dimensional Change Card Sort Test

The NIH Toolbox Cognition Battery: Dimensional Change Card Sort Test (DCCS) is a measure of cognitive flexibility and attention in individuals aged 3 years and older. Two target pictures are presented that vary along two dimensions (e.g., shape and color). Subjects are asked to match a series of bivalent test pictures (e.g., yellow balls and blue trucks) to the target pictures, first according to one dimension (e.g., color) and then, after a number of trials, according to the other dimension (e.g., shape). The relevant dimension for sorting is indicated by a cue word (e.g., “shape” or “color”) that appears on the screen for all subjects and that, for young children ages 3-11 years, is also spoken by a prerecorded audio file.

The NIH Toolbox Cognition Battery: Dimensional Change Card Sort Test is unable to be collected remotely as telehealth administration is non-standard administration and may alter the integrity of the data collected. Sensitivity analyses on the primary, key secondary and one secondary endpoint to support telehealth administration are intended to be performed, therefore additional sensitivity analyses for this exploratory test will not be performed.

10.1.3.5 NIH Toolbox Cognition Battery: Picture Sequence Memory Test

The NIH Toolbox Cognition Battery: Picture Sequence Memory Test (PSMT) is a measure developed for the assessment of episodic memory for ages 3-85 years. It involves recalling increasingly lengthy series of illustrated objects and activities that are presented in a particular order on the iPad screen, with corresponding audio-recorded phrases. The sequence of pictures appears one at a time in the center of the computer screen in a fixed order. As each picture appears, a recording briefly describes its content. This continues until all pictures in a sequence have been displayed and placed in their proper positions. Once all the pictures in the sequence are displayed, the pictures then are placed in a random spatial array at the center of the screen. The subjects are asked to recall the sequence of pictures demonstrated over two learning trials; sequence length varies from 6-18 pictures,

depending on age. Subjects are given credit for each adjacent pair of pictures they correctly place. The test takes approximately seven minutes to administer.

The NIH Toolbox Cognition Battery: Picture Sequence Memory Test is unable to be collected remotely as telehealth administration is non-standard administration and may alter the integrity of the data collected. Sensitivity analyses on the primary, key secondary and one secondary endpoint to support telehealth administration are intended to be performed, therefore additional sensitivity analyses for this exploratory test will not be performed.

10.1.3.6 Peabody Picture Vocabulary Test (PPVT)

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-color 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 PPVT will be performed according to the schedule of events.

The PPVT is unable to be collected remotely as telehealth administration is non-standard administration and telehealth administration is not included in the normative group. Sensitivity analyses on the primary, key secondary and one secondary endpoint to support telehealth administration are intended to be performed, therefore additional sensitivity analyses for this exploratory test will not be performed.

10.1.4 Biomarker/Physiological Assessments

10.1.4.1 Dual-energy X-ray absorptiometry (DXA) whole body scan of lean muscle mass

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

The primary assessment of interest in this study, from an efficacy perspective, is lean muscle mass. 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. Bone mineral

density (g/cm^2) will also be assessed as a safety parameter. The DXA scans will be administered in accordance with the schedule of events. DXA scans may be obtained locally rather than at the investigator site if required due to a COVID-19 related reason.

10.1.4.2 [redacted] levels and activity

A blood sample will be taken for the [redacted]

The levels of active [redacted]

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

[redacted] samples cannot be processed outside of a clinical laboratory. Therefore, these samples will not be collected if an in-clinic visit is not feasible due to a COVID-19 related reason.

10.2 Safety Assessments

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

10.2.1 Medical/Surgical and Medication history

The investigator must record all medically and clinically 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, hematological, neurological, psychiatric and any other diseases

- Any surgical procedures that have occurred during 1 year before the Screening Visit ([redacted]) and any history of having an implanted cardiac pacemaker
- History of use of mechanical ventilation, gastronomy tube or cough assist devices

10.2.2 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 occurring after the Screening Visit will 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.

Physical examinations will not be completed if an in-clinic visit is not feasible due to a COVID-19 related reason. If a subject is unable to attend Week [redacted] as an in-clinic visit, a physical examination will be obtained locally by a physician.

10.2.3 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.

Height will be collected remotely in the subject's home using an AMO approved home healthcare vendor, if required due to a COVID-19 related reason.

10.2.4 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 0.1 kg. Bulky items should be removed whenever possible to ensure the most accurate weight is recorded. All orthotics should be removed prior to weight measurement.

Weight will be collected remotely in the subject's home using an AMO approved home healthcare vendor, if required due to a COVID-19 related reason.

10.2.5 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?" AEs and SAEs will be collected from the time of informed consent.

At Week [redacted] or Week [redacted], a member of the study team should telephone the subject and/or caregiver to assess if there have been any AEs and collect any new or changed medications. This should be assessed again at the next in-clinic appointment to ensure accurate collection of information.

Adverse events will be elicited at [redacted] hours [redacted]) and [redacted] hours ([redacted]) post the end of treatment visit ([redacted] via telephone by a member of the study team.

Standard (i.e. non-leading) questions should be used but the clinician should bear in mind that the purpose of AE questioning is to elicit events specifically related to study drug dependency, abuse or withdrawal. However, all reported adverse events should be reported in the eCRF.

Adverse events will be collected by telehealth or telephone if required due to a COVID-19 related reason.

Refer to section 10.5 for additional details of AE collection and reporting.

10.2.6 Vital signs

Vital signs will include the following measures: 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.

Vital signs will be collected remotely in the subject's home using an AMO approved home healthcare vendor, if required due to a COVID-19 related reason.

10.2.7 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.

Safety laboratory and urinalysis samples will be collected remotely in the subject's home using an AMO approved home healthcare vendor for unscheduled visits as required or if required due to a COVID-19 related reason.

Biochemistry

A biochemistry sample will be collected as outlined in the schedule of events. Biochemistry blood samples can be drawn with the subject in either a fasting or non-fasting state. However, 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 the Screening [redacted] a virology panel (may be collected separately from the biochemistry sample in some regions) will 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 an additional blood sample may be collected from the subject.

[redacted]

At Screening [redacted] and EOT [redacted]), a [redacted] panel [redacted] should be obtained.

Additionally, at Screening [redacted] and EOT [redacted], [redacted] should also be obtained.

Hematology

A full blood count with differential should be collected as outlined in the schedule of events. This should include [redacted]

[redacted]

A [redacted] will be collected as outlined in the schedule of events. The actual [redacted] and the [redacted] will be reported from this sample.

Urinalysis

Urinalysis will be performed by dipstick and documented in source documents as outlined in the schedule of events. Abnormal results should be investigated further by sending to the study central 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. If a female subject of child bearing potential is seen at home for a visit, due to a COVID-19 related reason or an unscheduled visit requiring a pregnancy test, by a home health care professional, the central laboratory will perform a serum pregnancy test using the biochemistry sample.

10.2.8 ECG

All ECGs will be performed using equipment provided by the central ECG provider and all ECGs performed will be transmitted electronically to the central ECG provider for

interpretation. The investigator will perform the initial interpretation of the ECG immediately after collection to ensure the safety of each subject.

The central ECG provider will send a final report, including ECG source data within 72 hours. The study site will be required to print out at least 1 copy of the original tracing of the ECG. The original ECG(s), along with the final central ECG provider report, should be signed by the investigator, and maintained at the site with the subject's medical records. The investigator will be responsible for determining the clinical significance of each ECG (after review of both the ECG and the central ECG provider report).

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. For in clinic ECGs, a standard ECG recording device will be used with the standard paper rate of 25 mm/second and the standard scale setting of 10 mm/volt.

Triplicate ECGs will be obtained at the Screening Visit [redacted] to determine subject eligibility. The eligibility of a subject will be based on the ECG values from the central reader, the assessment of the ECG from the central reader (normal/abnormal) and the determination of clinical significance by the investigator, in consultation with the medical monitor if the ECG is determined to be abnormal per the central reader.

Triplicate ECGs will be obtained at two occasions during Run-In ([redacted]) (e.g. beginning and end of the visit), at least 2 hours apart. As the central ECG reports for [redacted] will not be available prior to the subject commencing run-in, eligibility related to these ECGs (exclusion criteria 12 and 13) will be based on the investigator's calculation of the mean QTcF value of all ECGs collected at [redacted] and their initial review of the ECG tracings at [redacted] If there is a conflict between the investigator's initial assessment of the ECG and the central ECG report, whereby the subject would no longer be eligible for the study, the subject will be withdrawn from the study at or before [redacted], prior to randomization into the double-blind treatment period.

Triplicate ECGs will also be obtained at two occasions during Baseline [redacted] (e.g. beginning and end of the visit), at least 2 hours apart.

For all other visits, where an ECG is requested according to the schedule of events, these will also be performed in triplicate (ideally separated by at least five minutes). For any abnormal, clinically significant ECGs a consultation with the medical monitor should occur. The investigator in conjunction with the medical monitor will evaluate the potential impact of an abnormal, clinically significant ECG on the continued participation of the subject.

For any visits completed in a subject's home due to a COVID-19 related reason, the standard 12-lead ECG will be replaced with a 6-lead ECG using equipment provided by the central ECG vendor and collected by an AMO approved home healthcare vendor.

At Week [redacted] where dosing occurs in-clinic for all subjects, triplicate ECGs will be collected pre dose and post dose at approximately 30-90 minutes after dosing. If this visit is completed in a subject's home due to a COVID-19 related reason, the standard 12-lead ECG will be replaced with a 6-lead ECG using equipment provided by the central ECG vendor and collected by an AMO approved home healthcare vendor. The ECGs will be collected pre dose and post dose at approximately 30-90 minutes after dosing.

All ECGs must be transmitted to the central ECG provider regardless of quality, result, or number of ECGs taken at a respective visit. No ECG should be deleted by study site personnel or AMO approved home healthcare vendor.

10.3 Pharmacokinetic Assessments

Pharmacokinetic samples will be collected for tideglus b and its primary metabolite, NP04113. PK samples will be collected at Visits [redacted] and [redacted] (corresponding to Weeks [redacted] and [redacted].

Two PK samples will be collected at Week [redacted] The time of administration of study medication will not be adjusted from the time the subject normally takes their dose of study medication. It will be noted in the CRF whether the subject dosed at home or in the clinic.

[redacted]

At Week [redacted] a total of [redacted] samples will be taken. All subjects, regardless of when they usually take their study medication, will take their study medication in clinic during this study visit. The [redacted]

With the exception of Week [redacted]), [redacted]

Actual PK blood sample collection date and time will be recorded. [redacted] at Week [redacted]) should also be recorded. At Week [redacted] PK sample should be recorded. In addition, at Week [redacted] should also be recorded. [redacted]

A single PK sample may also be collected at an unscheduled visit if in the opinion of the investigator this would provide useful information.

Population pharmacokinetic modelling will be used to analyze the data. If PK parameters cannot be estimated using the study data only, prior information on parameter distributions from a previously reported pharmacokinetic model of tideglusib will be used. 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 model-predicted PK parameters estimated for each subject. 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.

PK samples cannot be processed outside of a clinical laboratory setting. Therefore, these sample will not be collected if an in-clinic visit is not feasible due to a COVID-19 related reason.

10.4 Other Assessments

10.4.1 Diary

A diary will be provided to the subject/caregiver from Run-in ([redacted]) to Week [redacted] which should be completed every day. The diary should be reviewed at each subsequent visit 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 had [redacted]
- Time of [redacted] after dose
- Method of administration of study drug (oral or gastrostomy tube)

The diary review should be performed in addition to checking returned used and unused packets of IMP.

The diary will be reviewed remotely by study staff if required due to a COVID-19 related reason.

10.4.2 [redacted] Sample

For purposes of inclusion in the study, subjects need to have a confirmed genetic diagnosis of DM1. [redacted] defined as an inclusion or exclusion criterion, however where this information is available it will be recorded in the CRF. In addition, a [redacted] Run-in [redacted] from all subjects to [redacted] inherited for an individual subject. This will be related to baseline disease severity and potential treatment response.

Where possible and with [redacted], previously [redacted] samples collected for the purposes of [redacted] will be obtained for [redacted].

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

10.4.3 [redacted]

10.4.3.1 [redacted] Sample

A 5ml blood sample will be taken for [redacted]

[redacted] These samples will not be utilized for anything other than the tests described within this protocol.

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

[redacted] and [redacted] samples cannot be processed outside of a clinical laboratory, therefore will not be collected if an in-clinic visit is not feasible due to a COVID-19 related reason.

10.4.3.2 [redacted]

At Baseline ([redacted]) and end of treatment visits ([redacted] an optional [redacted] may be performed.

The [redacted]

If the subject has had a [redacted] Baseline [redacted] sample.

[redacted]

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

[redacted] samples cannot be collected or processed outside of the clinic setting therefore these samples will not be collected if an in-clinic visit is not feasible due to a COVID-19 related reason.

10.4.3.3 [redacted] Testing Sample

A blood sample will be taken for [redacted] testing at the timepoint described in the schedule of events. Testing [redacted] include both [redacted] testing as well as [redacted] testing. [redacted]

[redacted]

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

10.5 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.

10.5.1 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 unfavorable 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 an 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 hospitalization or prolongation of existing hospitalization (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 hospitalization, but may jeopardize 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.

Hospitalizations are defined as initial or prolonged admissions that include an overnight stay. Hospitalization or prolonged hospitalization 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 10.5.8. 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.

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 IMP).

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.

10.5.2 Severity Categorization

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

- **Mild (Grade 1)** Awareness of sign or symptom, but easily tolerated; no interference with activity
- **Moderate (Grade 2)** Sign or symptom causes discomfort, some interference with activity
- **Severe (Grade 3)** Sign or symptom of sufficient intensity to prevent activity
- **Potentially Life Threatening (Grade 4)** Requires emergent care or hospitalization

Examples of gradation for AEs can be found in the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (FDA, 2005).

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

10.5.3 Assessment of Causality

A study physician 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**

10.5.4 Outcome Categorization

All AEs should have an outcome recorded, which should be updated if it changes during the reporting and follow-up period (defined in section 10.5.9). 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 independent DSMC.

10.5.5 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) present before study entry should be recorded in the CRF. These symptoms should not be classed as AEs as long as changes are within the normal day to day fluctuation or expected progression of the disease; however, significant worsening of the symptoms, in the opinion of the investigator, should be recorded as an AE.

10.5.6 Clinical Laboratory Evaluations

Abnormal laboratory findings (e.g. [redacted]) 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 10.5.1.

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 ([redacted]) will be followed up until recovery or stabilization of the condition.

10.5.7 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.

10.5.8 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:	[redacted]
SAE Fax number:	[redacted]
	[redacted]
SAE Telephone contact:	[redacted]
	[redacted]

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 authorized 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 10.5.3 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 Week [redacted] follow-up visit ([redacted] will be followed until resolution or stabilization of subject condition, whichever occurs first. In such cases, follow-up SAE forms will be completed at the Week [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 independent 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 of the applicable Regulatory Authorities.

All investigators will receive a safety letter notifying them of relevant SUSAR reports. In accordance with 21 CFR 312.32 of the United States Code of Federal Regulations, the European Commission Directive 2001/20/EC, and C.05.014 of the Canadian Food and Drug Regulations, AMO Pharma Ltd or delegate will notify the relevant Institutional Review Board, Ethics Committees, and Research Ethics Board in concerned Regulatory Authorities 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.

10.5.9 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 is obtained) that do not result in the exclusion of the subject from participating in the study, should be recorded as Medical/Surgical History.

All SAE's and AEs occurring after informed consent 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

The details of all planned analyses will be specified in a separate statistical analysis plan (SAP) which will be finalized 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.

A blinded sample size re-estimation (SSRE), based on the observed variance in the primary outcome measure, will occur when approximately 33% of subjects are enrolled and have completed [redacted] The variability of key secondary and secondary endpoints may be assessed as well, if feasible. This SSRE was executed as planned.

Primary and key secondary analyses of efficacy will be based on the Intent To Treat (ITT) population and the summary of safety based upon the Safety Analysis Set (see definitions below in section 11.2). Other efficacy analyses will be based on the Full Analysis Set.

Statistical significance will be assessed at the 0.05 two-sided level, unless specified otherwise.

In general, statistical analyses will be performed using methods which account for known potential confounding data (e.g. sites/geographic locations, baseline characteristics, [redacted]

Changes in efficacy variables from Baseline [redacted] to post-treatment visits (or observed values for some variables such as CGI-I) will be summarized and compared between the weight adjusted tideglusib 1000 mg dose and placebo at each study visit. The primary comparison will be performed for changes from baseline to end of treatment. The model details and data displays will be described in the SAP.

Additionally, the changes from baseline over time will be compared using linear mixed effects repeated measures modelling.

For all analyses, the effects of the weight adjusted tideglusib 1000 mg dose versus placebo will be estimated at the end of treatment and presented along with associated 95% two-sided confidence intervals and p-values. The comparisons may also be performed at other

time points; however the p-values should be reviewed with caution due to potential multiplicity issue (high probability of chance-alone outcomes).

Subjects [redacted] and who discontinue the study will be classified as screening failures. Subjects [redacted] but who discontinue the study before taking a dose of tideglusib will be classified as run-in failures.

11.1 Estimated Sample Size

One of the study goals is to identify consistent efficacy trends in the primary and key secondary endpoints. Twenty-five subjects per group will generate 70% power to detect the effect size of 0.6 at the 0.1 two-sided significance level. This sample size will also be sufficient to generate 80% power to detect the effect size of 0.82 at the 0.05 two-sided significance level. Accounting for a 10%-13% drop-out rate, approximately 28 subjects per group were initially planned. No data are available on the CDM1-RS instrument. Based on the preliminary data observed in the AMO-02-MD-2-001 study, the assumed effect sizes look reasonable. The effect size assumptions are partially based on the Clinician VAS total score changes from baseline to end of study (6 points on drug vs. 1 point on placebo with the common standard deviation of 5.8). Based on these and other data, 29 and 22 subjects per group will be sufficient to generate 90% and 80% power at the 0.05 two-sided significance level. Based on these calculations, the suggested sample size of 56 patients total was considered adequate to detect the treatment effect or at least a consistent trend.

A blinded SSRE, based on the observed variance in the primary outcome measure, was performed during the conduct of the study. Based on the blinded SSRE, the planned sample size is sufficient to detect the treatment difference between active and control arms based on the primary endpoint with at least 80% power at the 0.05 two sided significance level. However, the variability of the key secondary endpoint was slightly greater than that originally assumed. Respectively, it was recommended, if operationally feasible, to increase the total sample size to a maximum of 66 subjects.

However, based on the blinded SSRE, the pooled standard deviation of change from baseline for the primary endpoint was 2.64. Assuming this standard deviation and as long as the difference in the primary endpoint mean change from baseline to EOT between drug and control is at least 2.2, the power to detect treatment differences will be 82% if n=25/group. [redacted]

The details of the SSRE and summary of scenarios and outcomes are outlined in the SAP.

11.2 Study Populations

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

The Intent to Treat Set (ITT) will include all randomized subjects. Subjects will be included in the analysis set according to their randomized treatment assignment regardless of actual treatment received. The ITT is the primary population for the analysis of efficacy data.

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

The Full Analysis Set (FAS) will include all randomised subjects in the SAF for whom any efficacy data were collected post randomisation. Subjects will be included in the analysis set according to the treatment they actually received.

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 prior to data lock and unblinding. Subjects excluded from the PPS will be determined prior to data unblinding. 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 PK samples that were taken were analyzable and for whom the corresponding dosing information prior to sample collection and sample collection information is available. Listings of study data will be based on all subjects who were randomised into the study.

11.3 Demographic and Baseline Characteristics

Summaries of demographic and baseline characteristics (including medical history, Congenital DM1 history, prior treatments) will be provided by treatment group 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 summarized by treatment using frequencies and percentages as appropriate.

Other safety data, including laboratory, vital signs and ECG values including change from baseline will be summarized. 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 two weeks of [redacted].

11.5 Statistical Methods for Efficacy

Primary analysis of efficacy will be based on the ITT population. Additional analysis will be performed based on FAS.

The primary efficacy endpoint (CDM1-RS) will be calculated at each time point as a total score based on 11 domain ratings. Changes in efficacy variables from the start of the [redacted] run-in [redacted] to Baseline [redacted] for each subject will be summarized and will be considered as indicative of the effect of two weeks of [redacted]. Changes from Baseline [redacted] to post-treatment visits will be summarized by treatment group (weight adjusted tideglusib 1000 mg versus Placebo) at each study visit. For the CGI-I the observed values will be summarized.

Change from baseline to end of treatment will be analysed using general linear model with terms for treatment group, baseline and treatment group by baseline interaction (observed values will be analysed for the CGI-I). [redacted].

The statistical significance of changes from baseline over time may also be assessed using the linear mixed effects repeated measures model with fixed effect terms for treatment group, follow-up visit and treatment group by follow-up visit interaction. Subject will be included as a random effect and baseline as a covariate. [redacted] If covariates/interactions in any model are not statistically significant at the 0.05/0.1 two-sided levels, respectively, they will be excluded from the model. The details will be specified in the SAP.

The key secondary efficacy endpoint for analysis is:

- CGI-I at the end of treatment

The secondary efficacy endpoints for analysis are:

- The change from baseline in the Top 3 Caregiver Concerns VAS total score to end of treatment
- The change from baseline in the CC-CDM1-RS total score to end of treatment

- The change from baseline in CGI-S to end of treatment
- The change from baseline in the CDM1-RS independent central rater total scoreto end of treatment
- The change from baseline in CGI-S independent central rater score to end of treatment
- CGI-I independent central rater score at the end of treatment
- The change from baseline in 10 Meter Walk/Run (preferred speed and fastest speed) to end of treatment

Due to COVID-19 related restrictions some of the data at certain visits may be collected using a telehealth approach while other data may be collected during in-clinic visits. To evaluate the consistency of telehealth data and in-clinic data for the CDM1-RS and CGI rating scales and to minimize the potential bias, Baseline [redacted]), Week [redacted]([redacted]) and Week [redacted] [redacted]) visits will be performed using both in-clinic and telehealth data collection approaches. The following analysis will be performed to evaluate the consistency of these two methods of data collection. The details of these and some other consistency analyses will be specified in the SAP.

- Telehealth data will be plotted against corresponding in-clinic data for visual evaluation; the changes from baseline to various time points based on the corresponding telehealth and in-clinic data will also be plotted.
- The various descriptive statistics for the difference between corresponding telehealth and in-clinic data will be evaluated; the changes from baseline for the corresponding telehealth and in-clinic data will be evaluated using various descriptive statistics and correlation analysis.

According to the recommendations in the FDA Guidance “Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency” the following sensitivity analyses will be performed in addition to the primary analysis performed (FDA, 2020).

- If the data is missing due to a subject’s inability to attend clinic due to COVID-19 related reasons, the corresponding telehealth data will be utilized, where applicable; the primary and key secondary analyses will then be performed.
- If the dataset includes both in-clinic and telehealth data, the analysis stratified by the data acquisition method will be performed. Alternatively, the indicator variable with the values corresponding to the data acquisition approaches may be utilized in the model to determine the significance of the data acquisition impact on outcomes.
- The missing data will be imputed using one of the imputation approaches described below and primary and key secondary analyses will be performed.

The details of the sensitivity analyses will be described in the SAP.

As a supporting analysis, should the primary endpoint be met, the primary, key secondary and secondary endpoints may be evaluated using the permutation test (Berry-Kravis *et al.*, 2020 (accepted); Glaze *et al*., 2017; Jessup *et al.*, 2011) based on the additional criteria for "success" specified in the SAP (for example, 3 secondary endpoints, including the key secondary, demonstrate numerical superiority of drug to placebo with the remaining secondary endpoints demonstrating non-inferiority of drug to placebo based on the pre-specified threshold). Full details of the resampling procedure will be included in the Statistical Analysis Plan.

The exploratory endpoint analysis will be outlined in the SAP. The details of the analysis methods will be determined after exploratory endpoint data review.

The following exploratory endpoints, the NIH toolbox assessments (i.e. Dimensional Change Card Sort Test and Picture Sequence Memory Test) and the Peabody Picture Vocabulary Test (PPVT) will not be completed by telehealth in the event that a subject cannot attend clinic due to a COVID-19 related reason, as telehealth administration is non-standard administration for these tests. As described above, sensitivity analyses will be performed on the primary, the key secondary and one secondary endpoint to support telehealth administration, but additional sensitivity analyses for these exploratory endpoints are not planned.

A subject-level (scorecard) analysis will be performed based on the composite of primary and secondary endpoints (details will be provided in the SAP).

11.6 Missing data

In the analysis of the primary, key secondary, and secondary endpoints, sensitivity analyses will be performed to examine the potential influence of missing data. Depending on the actual data patterns, various imputation methodologies may be employed. Multiple imputation methodology may be used with missing data imputed by randomized arm according to the within arm distribution of the observed, non-missing data. Alternatively, the mean value within treatment group at a given time point may be imputed. Full details of the approach to examine the influence of missing data will be included in the Statistical Analysis Plan. The missing data will not be imputed for mixed effects models. No imputations will be performed for per protocol analysis.

If in-clinic data are missing due to a subject's inability to attend clinic due to COVID-19 related reasons, the corresponding telehealth data can be utilized instead. If both in-clinic and telehealth data are missing, the imputations described above may be utilized.

11.7 Statistical Methods for Pharmacokinetics

Individual pharmacokinetic data will be tabulated and concentration vs. time curves presented by treatment dose. Derived parameters will be summarized 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 for those subjects not proceeding into the extension protocol AMO-02-MD-2-004, or the final study assessment for subjects who do proceed into the extension protocol.

13. ETHICS COMMITTEE REVIEW/INFORMED CONSENT

13.1 Independent Ethics Committee/Institutional Review Board and Relevant Authorities

The final study protocol, the parent/LAR information and consent form and the patient information and assent forms 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 parent/LAR prior to any protocol-related activities and assent obtained from the subject according to the local institutional policies and guidelines. As part of the informed consent procedure, the principal investigator or one of his/her 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 parent/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.

Local institutional policies and guidelines regarding assent should be followed.

14. STUDY AND DATA MANAGEMENT

14.1 Protocol Amendments

Once approved by the Regulatory Authority and Independent Review Board (IRB)/ Ethics Committee (EC)/Research Ethics Board (REB), 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 authorized by the Regulatory Authority and IRB/EC 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 “ALCOAC” principles:

- Attributable
- Legible
- Contemporaneous
- Original

- Accurate
- Complete

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 ALCOAC principles to apply.

14.5 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.

14.6 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 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.

14.7 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 25 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.

14.8 Communication and Publication of Results

This study will be registered in Clinicaltrials.gov and the EudraCT database. Study results will be submitted to EudraCT in accordance with timelines for pediatric studies according to The European Clinical Trials Directive 2001/20/EC.

In accordance with FDAAA 801 requirements this study will be registered and have results submitted to ClinicalTrials.gov according to the published guidelines.

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.

14.9 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.

Coordinating 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.

[redacted]	[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.

Name of Principal Investigator: Title: Date:	

17. APPENDICES

APPENDIX A: Clinician-Completed Congenital DM1 Rating Scale (CDM1-RS)

Date (dd/mmm/yyyy):	Site #:	Subject #:	Visit:

Clinician-Completed Congenital DM1 Rating Scale (CDM1-RS)

Please rate the subject on the following symptoms that may occur in individuals with congenital myotonic dystrophy Type 1 (CDM1). When rating each symptom, consider how the symptom influences how the subject feels and how it impacts the subject's ability to perform everyday functions. Your ratings should also incorporate important observations that you make during your clinical exam of the subject. The manual of procedures that accompanies this rating scale gives examples of observable aspects of each potential symptom that may be evident in the clinic. These examples include observable signs (e.g. findings on the physical exam), child behaviors and verbalizations (e.g. what the child tells the clinician during the clinic visit).

Ideally, you should complete the ratings after completing and/or reviewing all the relevant clinical information at the clinic visit. You can use the CGI/CDM1-RS Interview/Exam form as a guide to the clinical interview and to document information from the interview and relevant exam results. Ideally you should record as many relevant details (e.g. duration, frequency, context in which symptom occurs, adjustments needed, specific consequences) as possible about the rating scale item at baseline for more accurate assessment of changes across time.

Instructions to the rater:

The item should be scored as 0, 1, 2, 3, or 4 based on overall severity (e.g. severity of symptoms, frequency of symptoms, context in which it occurs and functional impact).

The possible 0 to 4 rating levels for each item are:

0 = **Symptom not present** or no longer present during the relevant time frame

1 = **Mild severity**, symptom is clearly present but not pronounced, interferes little with day-to-day functioning

2 = **Moderate severity**, symptom is readily evident, intrudes on daily life to a moderate extent

3 = **Severe**, symptom is serious, markedly evident, consistently intrudes on daily life, symptom has a distinct impact on daily life

4 = **Very severe**, symptom causes pronounced and consistent impairment and is highly disruptive with regard to daily life

When rating the item severity, please focus on the **past week, including today**.

Date (dd/mmm/yyyy):	Site #:	Subject #:	Visit:

1. Limitations with mobility or walking

Examples include not being able to run or walk fast, difficulties standing from the ground, using stairs, an inability to keep pace with others when playing, or difficulties with balance.

How severe is the symptom? Circle the number that indicates how bad you think the limitations with mobility or walking have been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

---

2. Problems with hands or arms

Examples include difficulties with opening jars or bottles, impaired fine motor skills (for example, when using a writing instrument), or difficulties with throwing or catching.

How severe is the symptom? Circle the number that indicates how bad you think problems with hands or arms have been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

---

3. Signs of fatigue

Examples include physical fatigue, poor endurance, decreased energy, or a need for prolonged recovery time after physical activity.

How severe is the symptom? Circle the number that indicates how bad you think fatigue has been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

Date (dd/mmm/yyyy):	Site #:	Subject #:	Visit:

4. Signs of pain

Examples include pain in the arms, legs, back, neck or shoulders.

How severe is the symptom? Circle the number that indicates how bad you think pain has been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

---

5. Gastrointestinal issues

Examples include abdominal pain, stool incontinence, diarrhea, bloating, severe constipation, secondary urinary incontinence due to chronic constipation, or dyspepsia.

How severe is the symptom? Circle the number that indicates how bad you think gastrointestinal issues have been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

---

6. Communication difficulties

Examples include slurred speech, difficulties with production of speech, or problems with expressive language.

How severe is the symptom? Circle the number that indicates how bad you think communication difficulties have been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

Date (dd/mmm/yyyy):	Site #:	Subject #:	Visit:

7. Impaired sleep or daytime sleepiness

Examples include problems with falling asleep and staying asleep at night, restless sleep, or problems with easily falling asleep during the day (excessive daytime sleepiness).

How severe is the symptom? Circle the number that indicates how bad you think impaired sleep or daytime sleepiness have been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

---

8. Difficulty thinking

Examples include an inability to focus, problems concentrating, troubles organizing activities or tasks, problems remembering, or learning difficulties in school that require special assistance.

How severe is the symptom? Circle the number that indicates how bad you think difficulty thinking has been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

---

9. Myotonia

Examples include myotonia in the hands, difficulties with releasing one's grip, muscle stiffness, or cramping.

How severe is the symptom? Circle the number that indicates how bad you think myotonia has been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

Date (dd/mmm/yyyy):	Site #:	Subject #:	Visit:

10. Breathing difficulties

Examples include breathlessness while walking, problems with breathing during the middle of the night, or problems with taking a deep breath.

How severe is the symptom? Circle the number that indicates how bad you think the breathing difficulties have been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

---

11. Choking or swallowing issues

Examples include not being able to eat easily, problems swallowing, or having actual choking episodes.

How severe is the symptom? Circle the number that indicates how bad you think the choking or swallowing issues have been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

Signature of clinician rater: _____

Date of Signature: _____

Caregiver informant: _____

APPENDIX B: 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:

Busner J, Targum SD, and Miller DS (2009), The Clinical Global Impressions scale: errors in understanding and use. Comprehensive Psychiatry 50:257-262

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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.

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.

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]

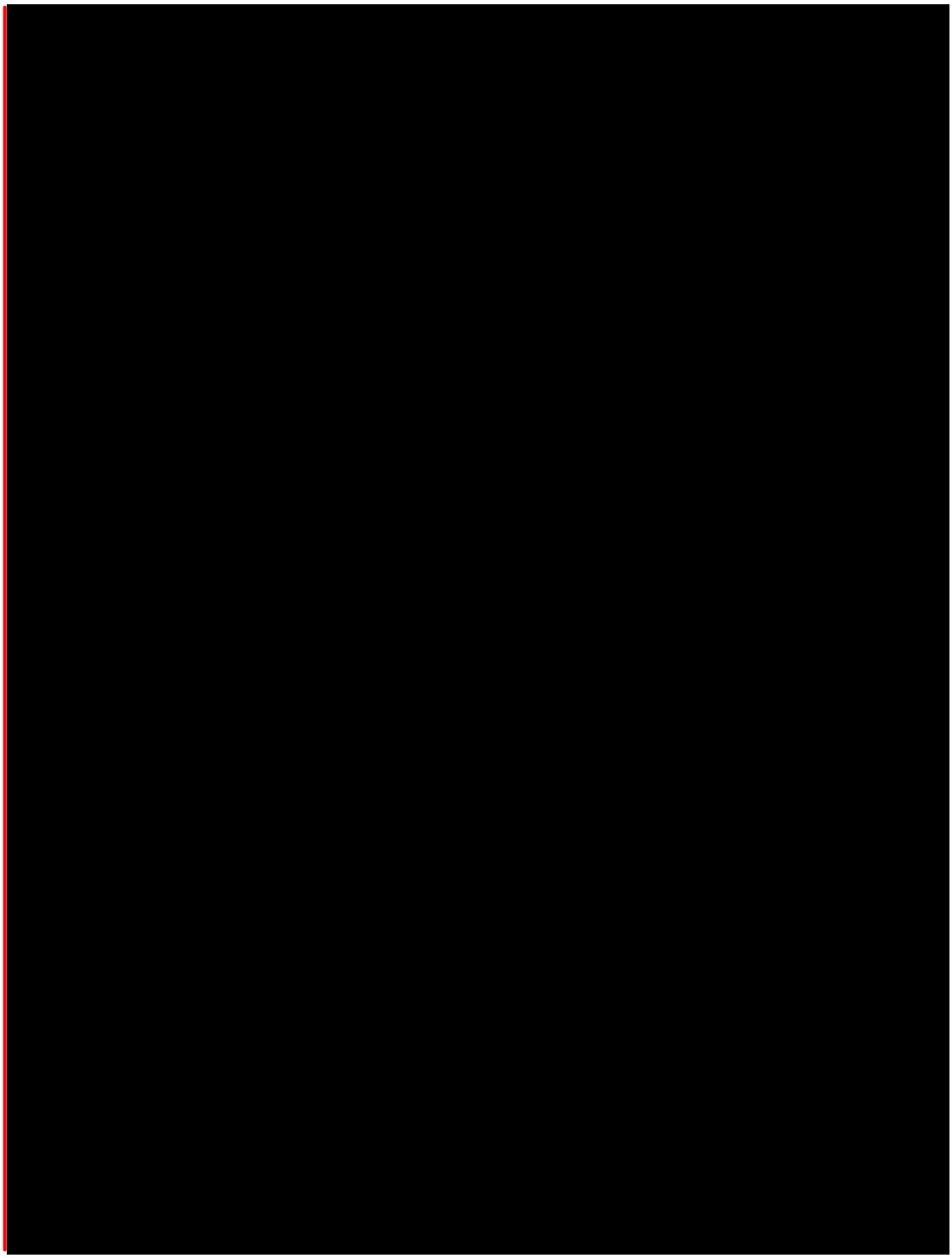
Score ____

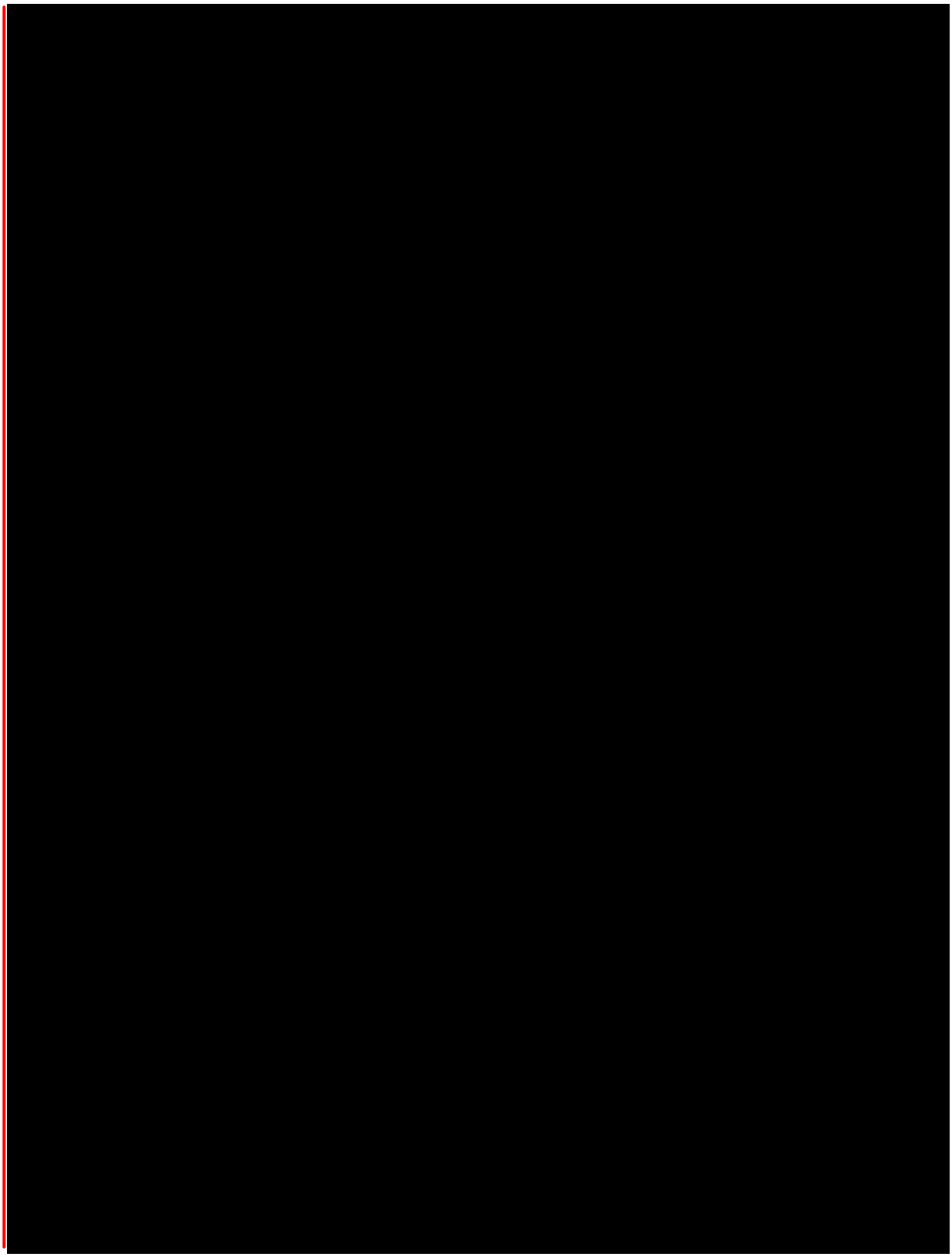
Evaluator name _____

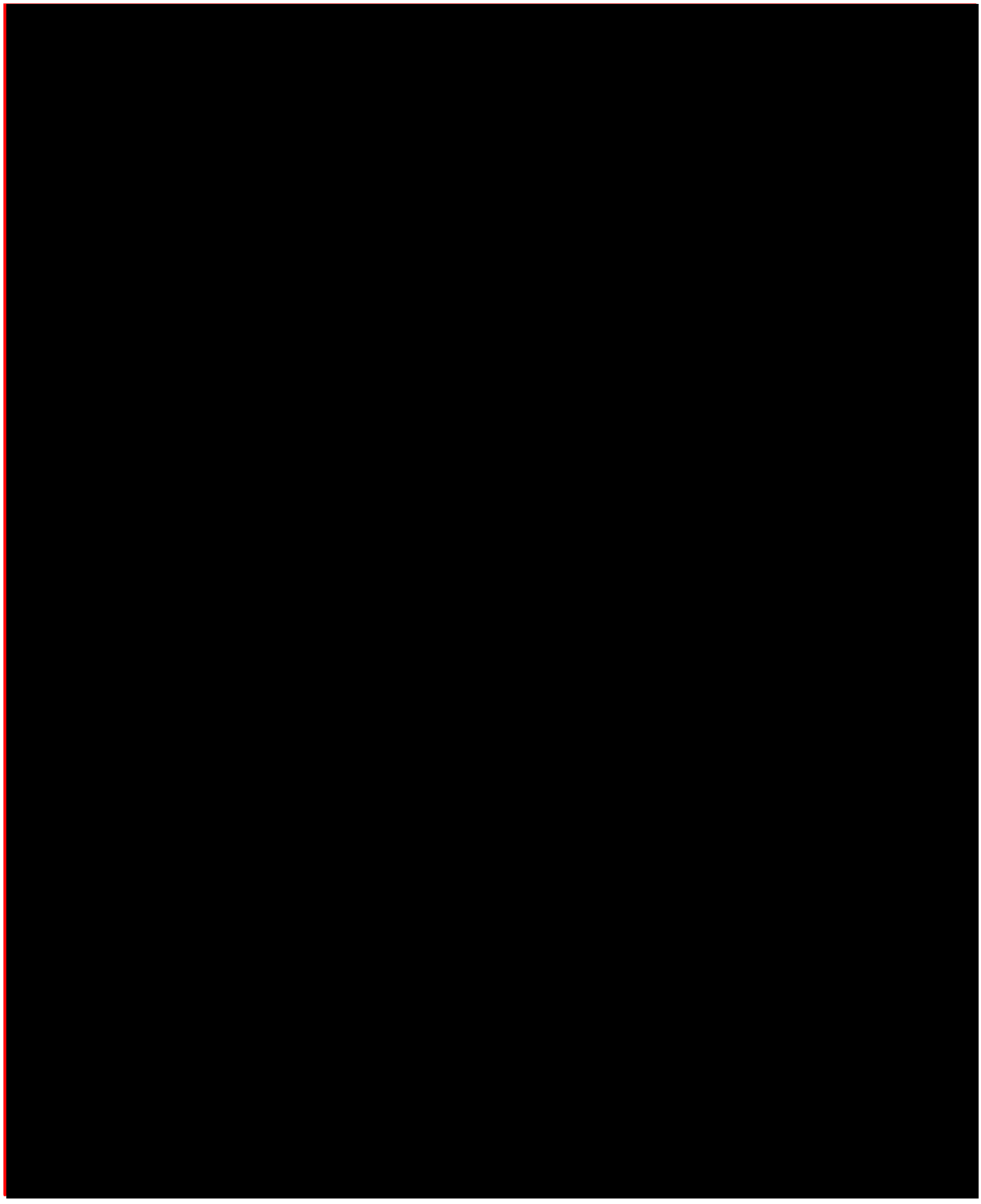
Evaluator signature _____

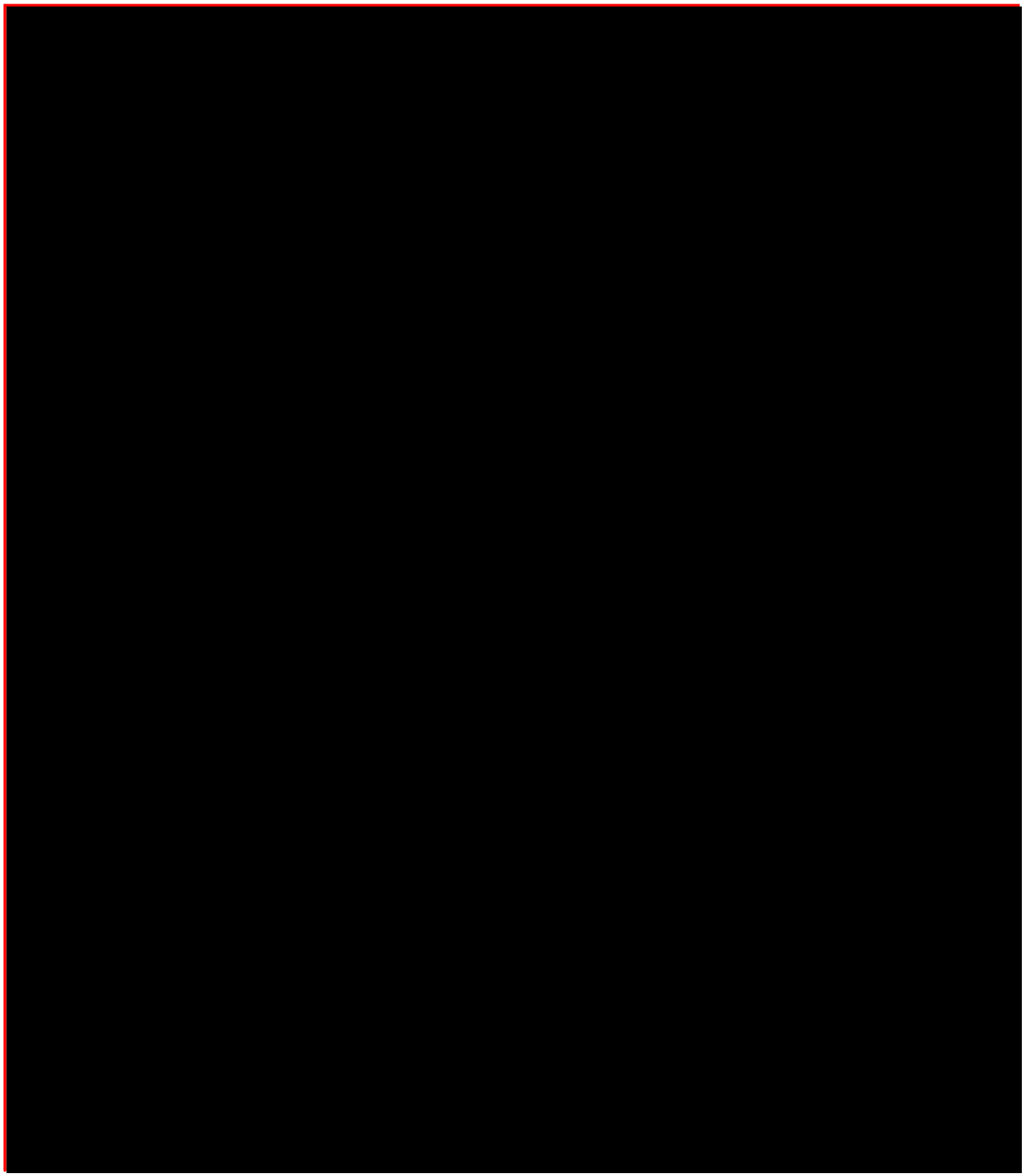
Date ____ ____ ____ (dd mmm yyyy)

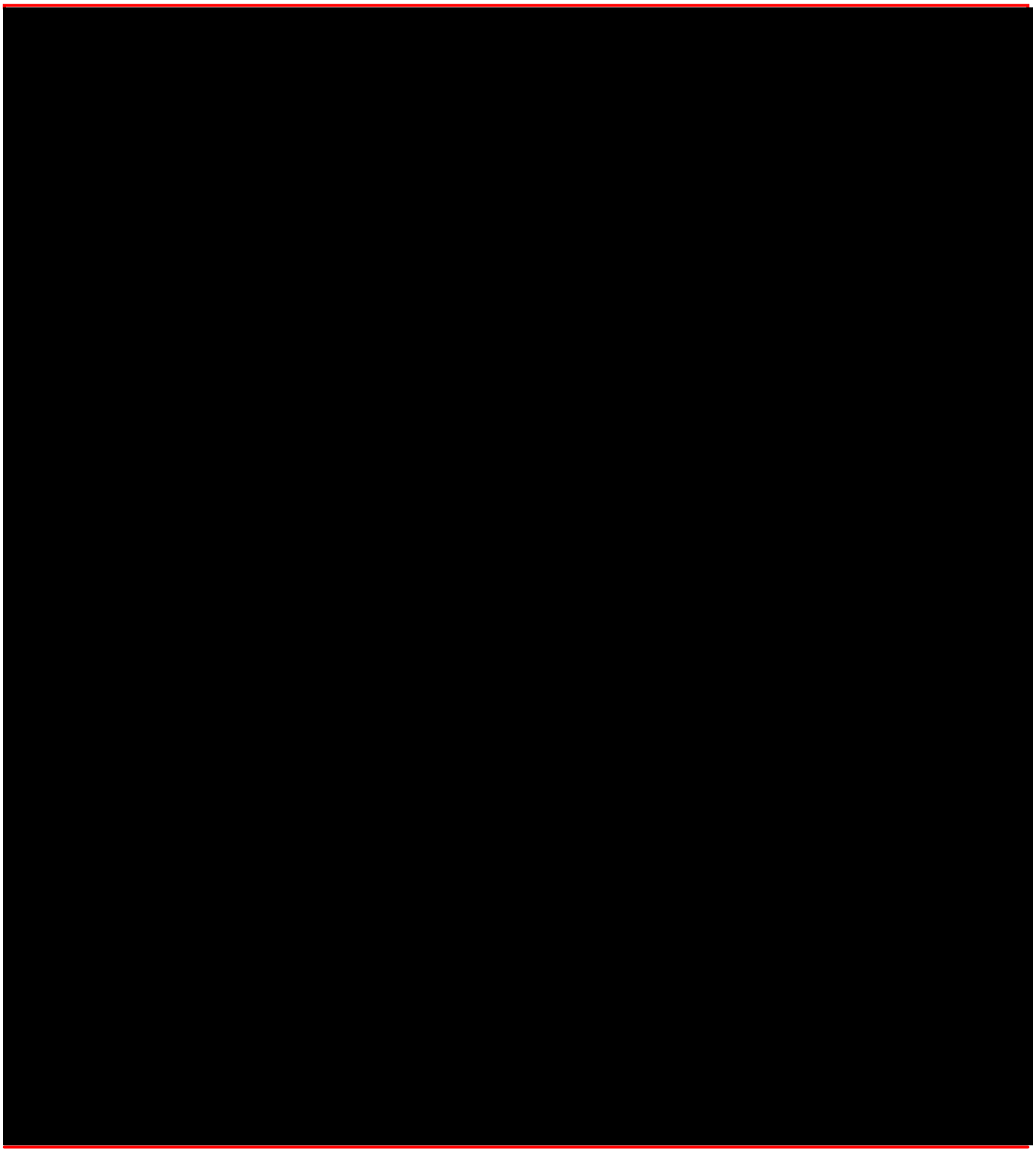
APPENDIX C: Autism Behavior Inventory- Clinician (ABI-C)

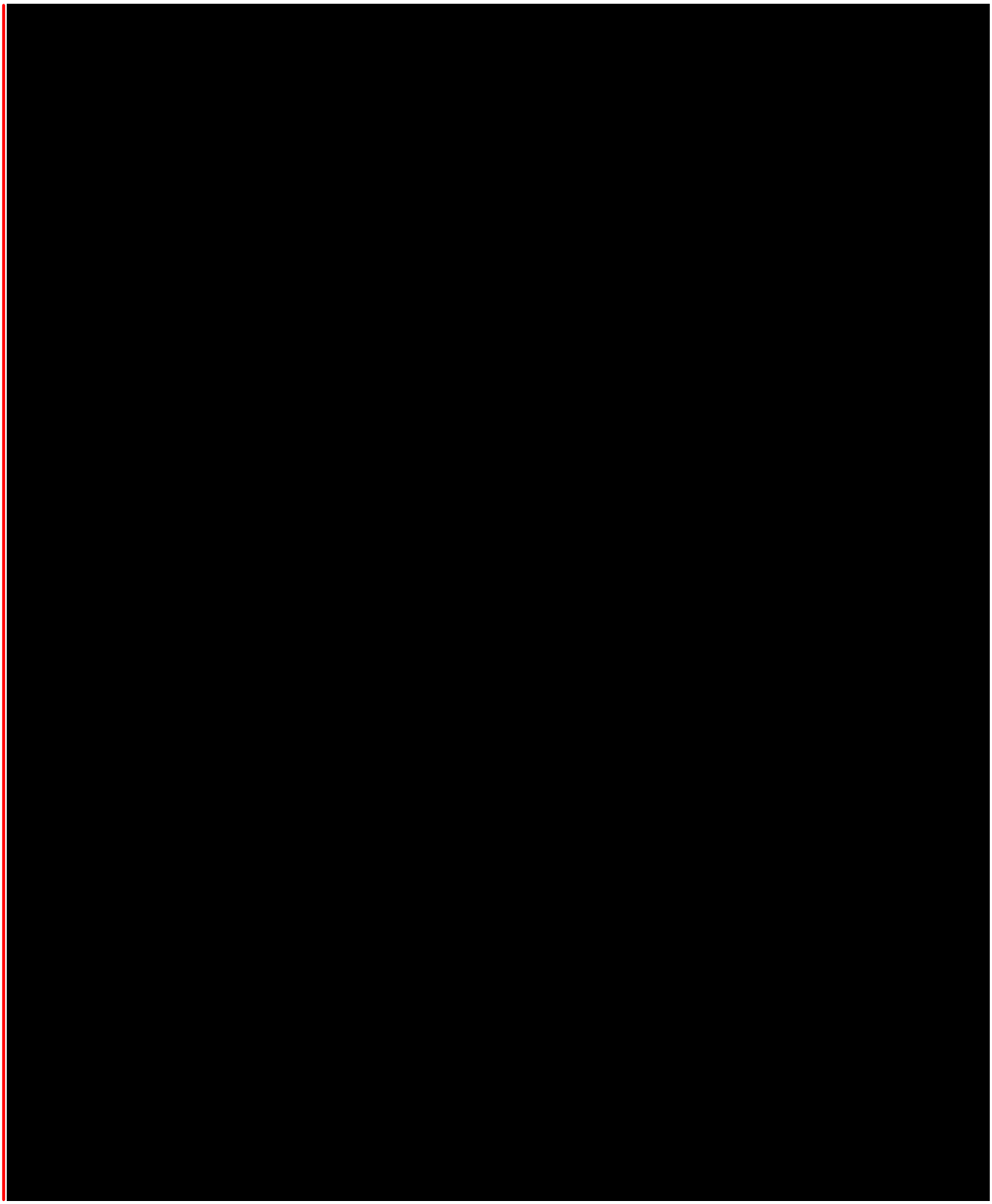


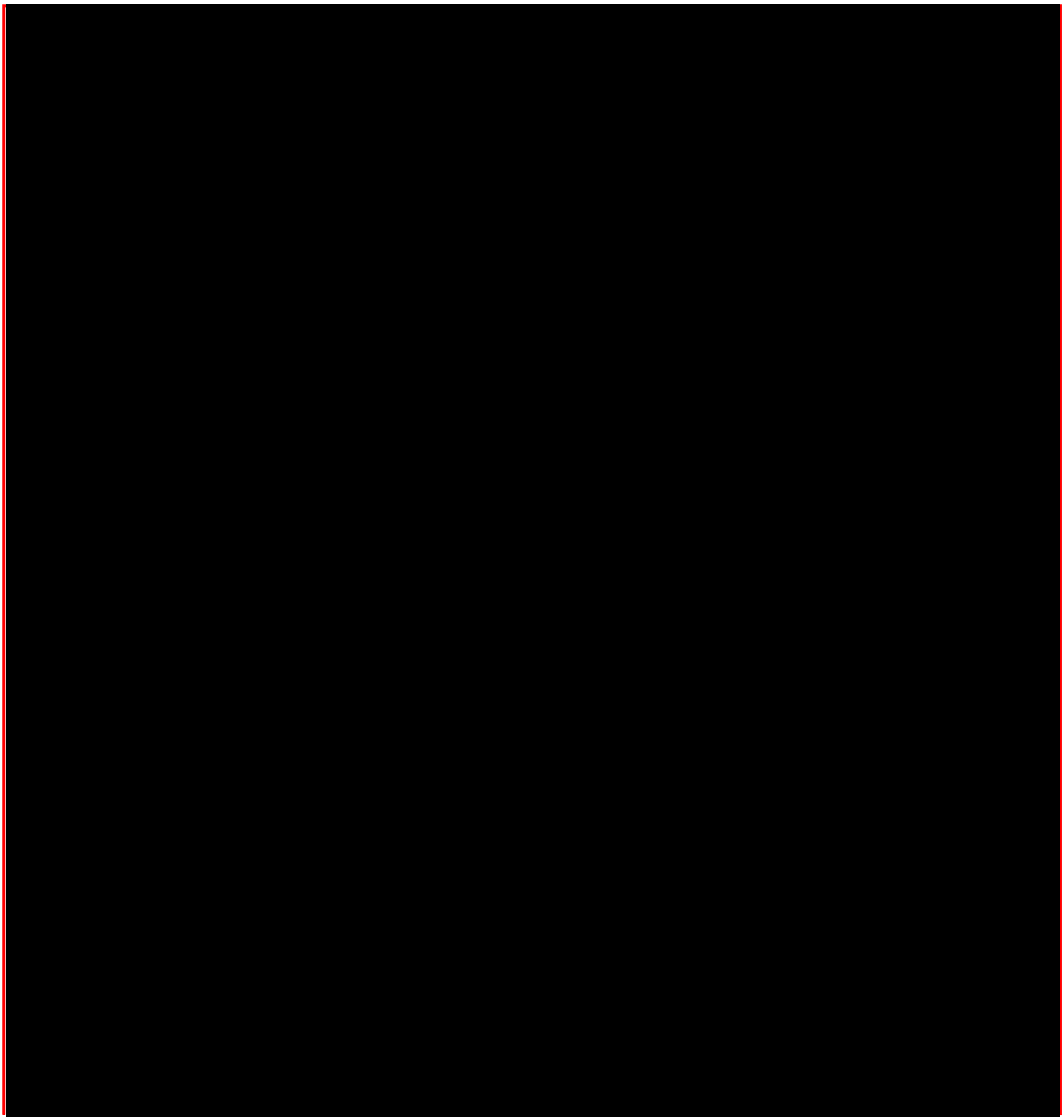




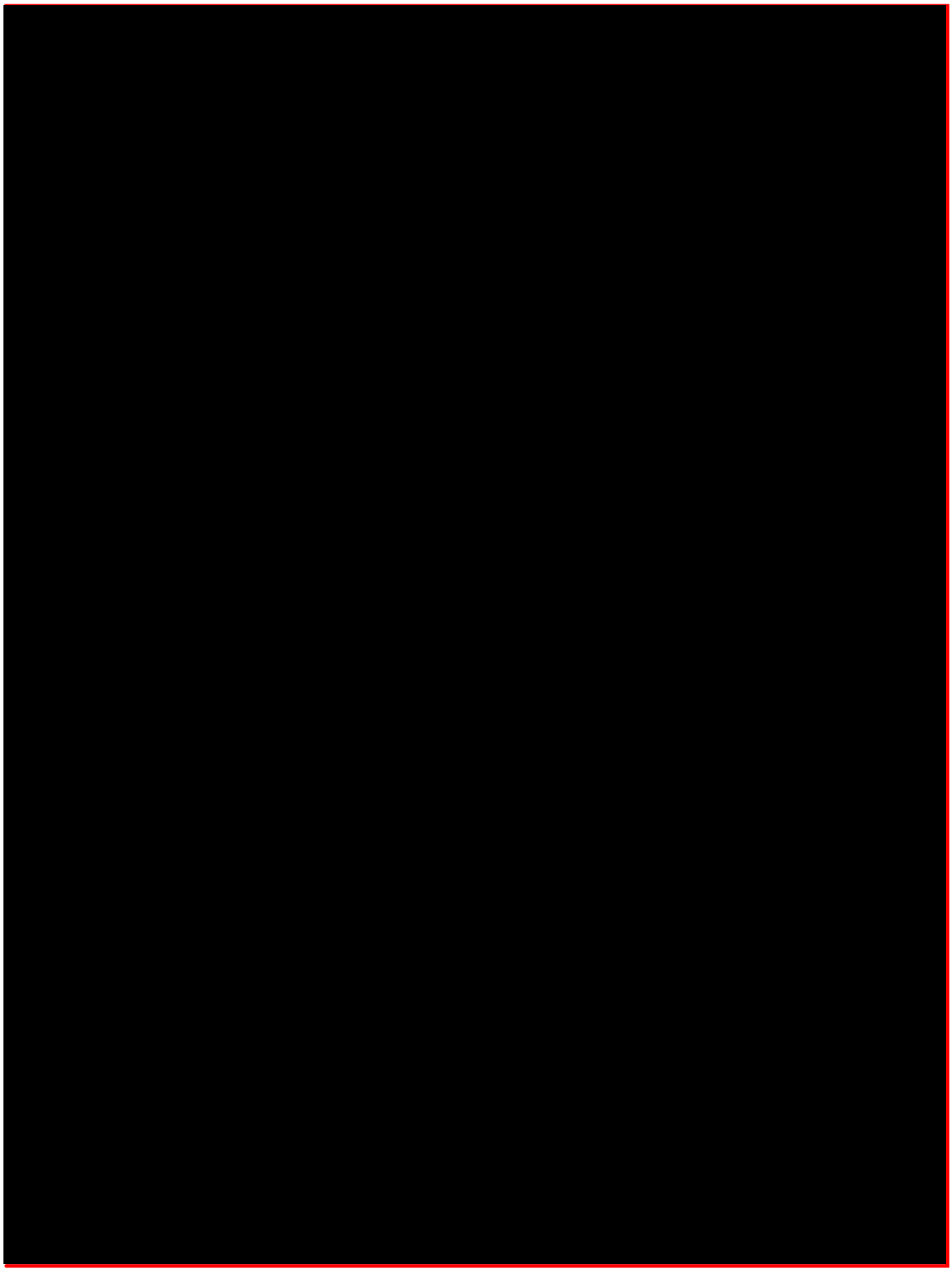


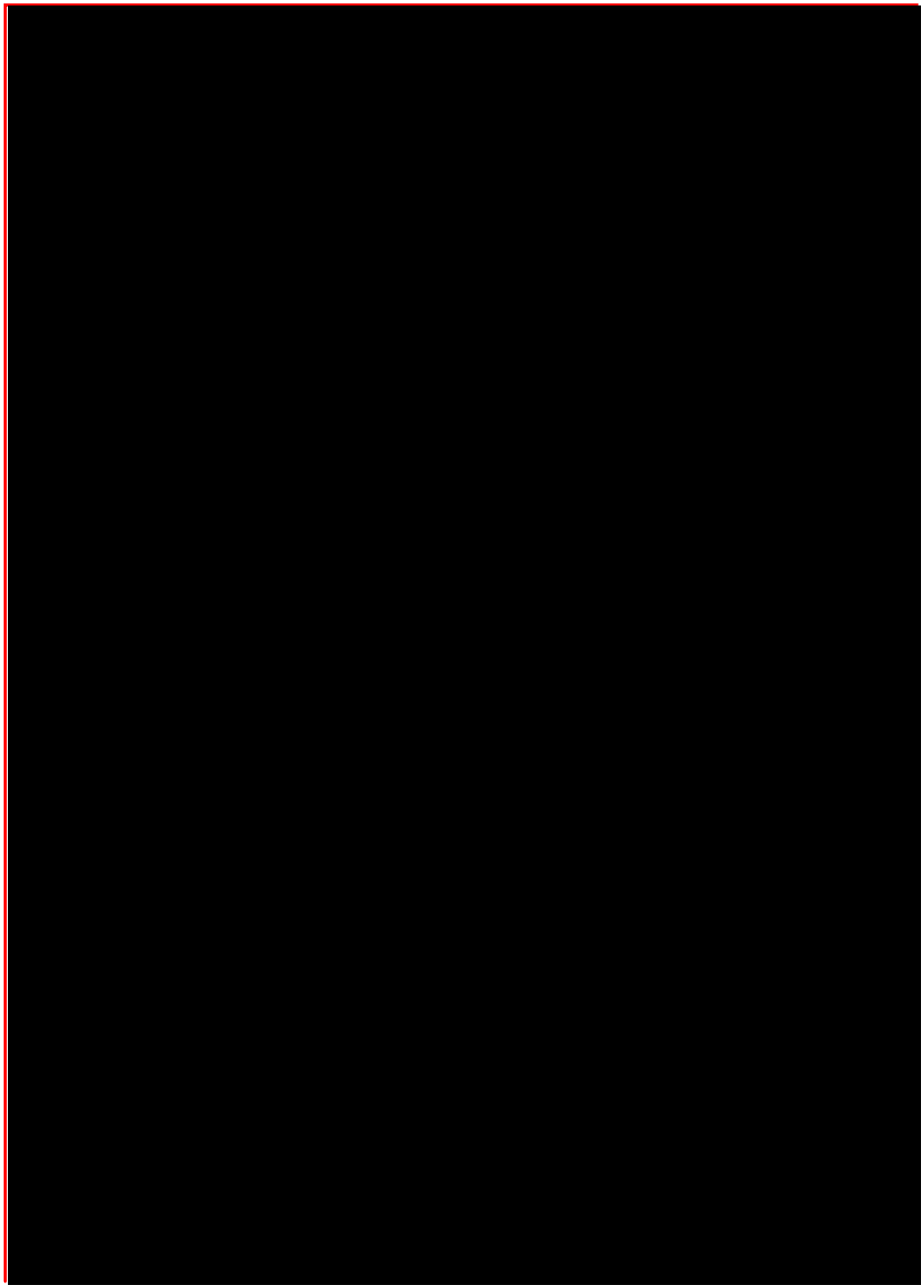


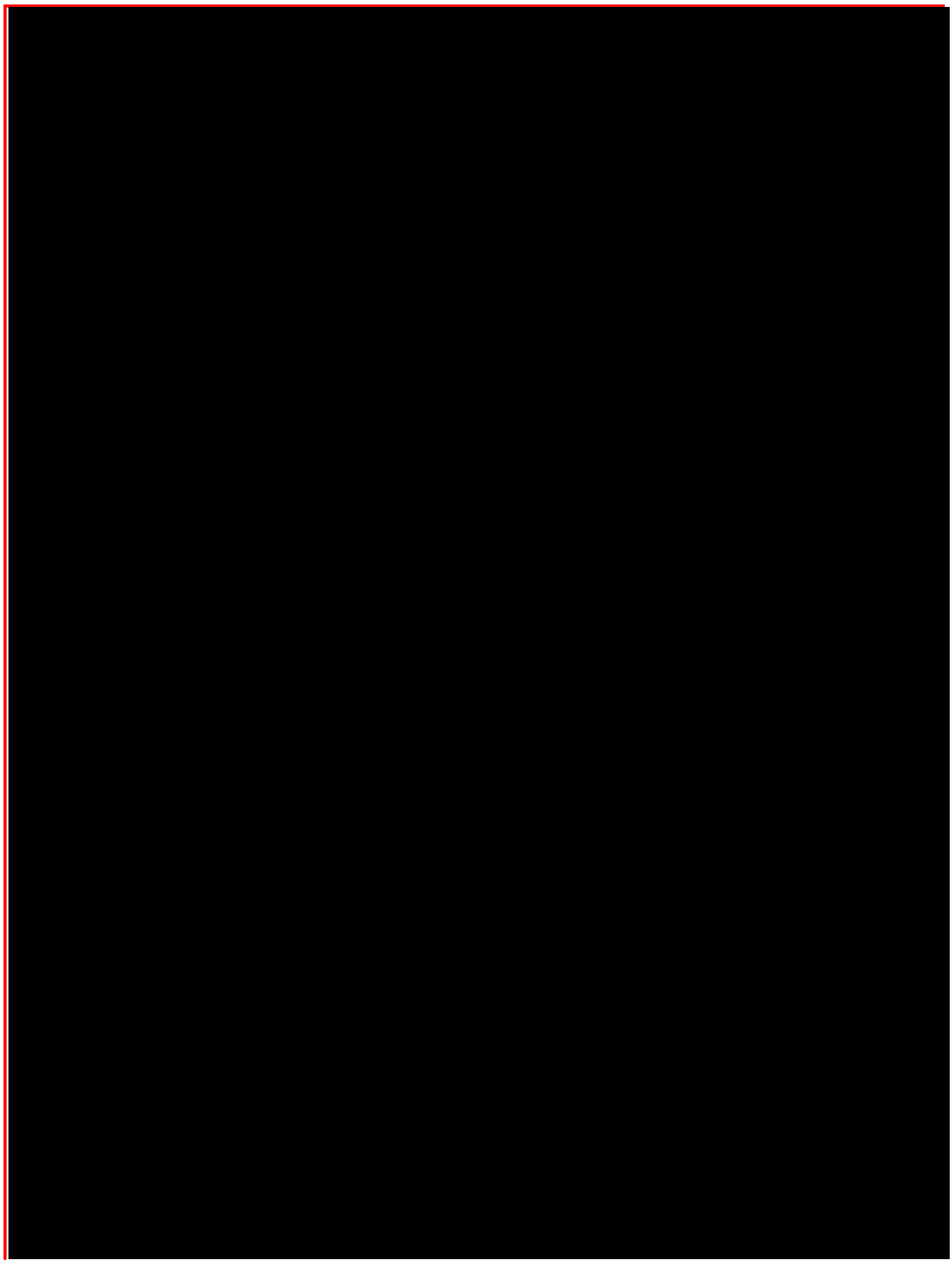


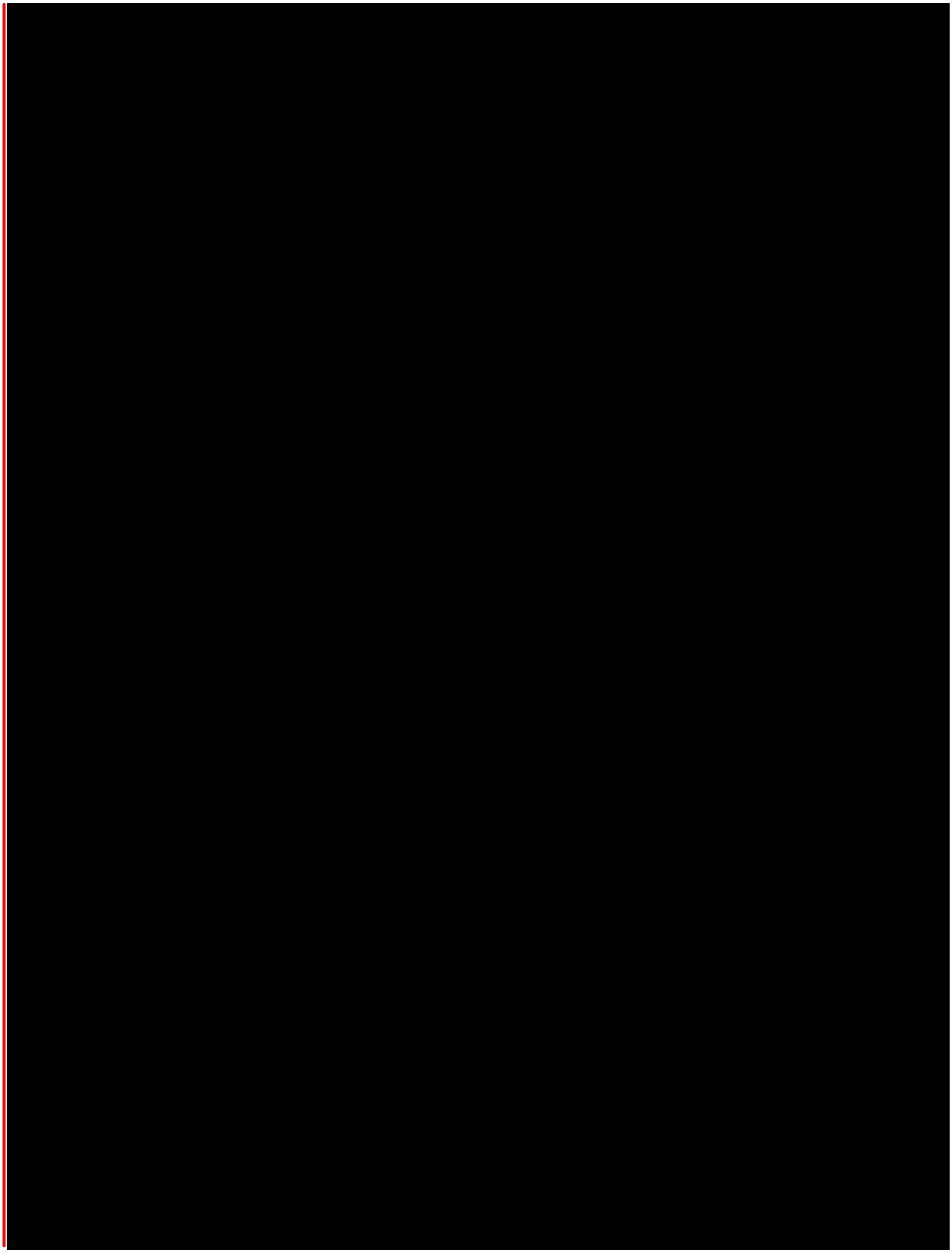


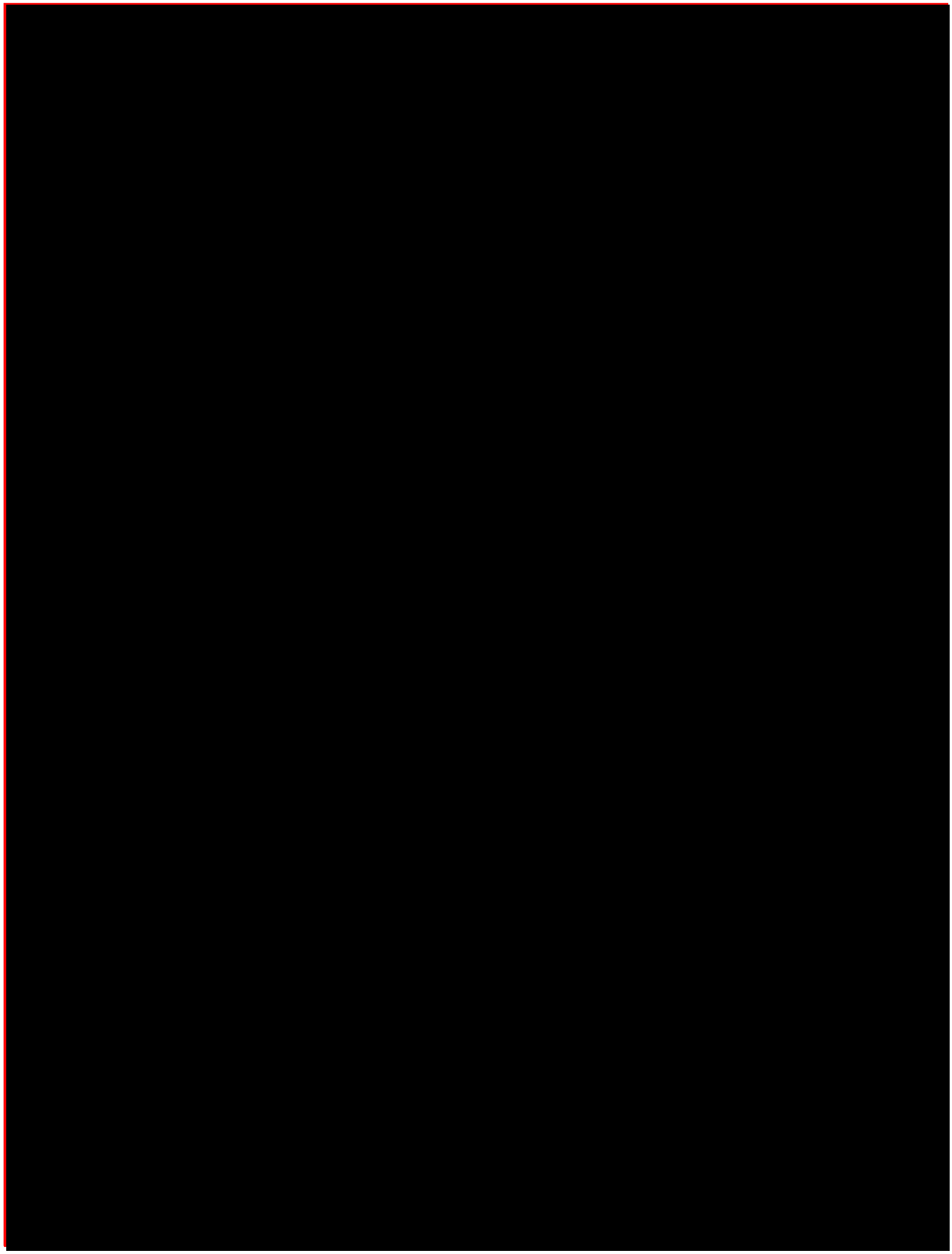
APPENDIX D: Congenital and Childhood Myotonic Dystrophy Health Index (CC-MDHI) Parent Proxy Instrument

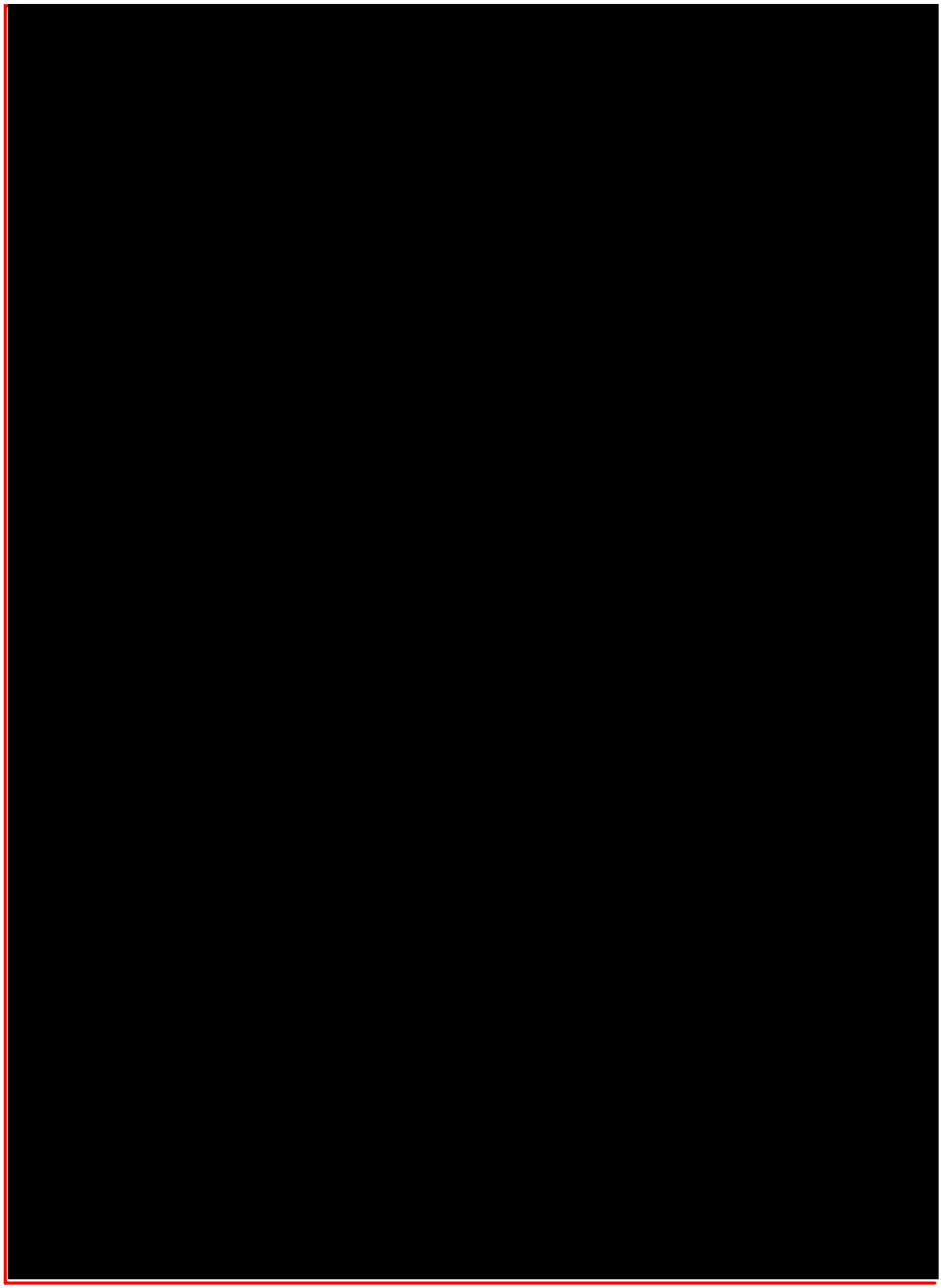












APPENDIX E: Caregiver Top 3 Concerns Visual Analog Scale (VAS)

Date (dd/mmm/yyyy):	Site #:	Subject #:	Subject Initials:	Visit:

Initials of Person Completing Form: _____ Relationship to Subject: _____

CAREGIVER TOP THREE CONCERNS-BASELINE

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. Ideally, you should choose one item that relates to muscle function (such as problems with walking, drinking from a straw, or grip), one item that relates to cognitive abilities (such as problems with thinking, planning or concentration), and one item that relates to performing activities of daily living (for example, problems or difficulties brushing teeth, getting dressed or helping with household chores).

Concern number 1:

The symptom causing concern is:

_____

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

Concern number 2:

The symptom causing concern is:

_____

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

Concern number 3:

The symptom causing concern is:

_____

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

Date (dd/mmm/yyyy):	Site #:	Subject #:	Subject Initials:	Visit:

Initials of Person Completing Form: _____ Relationship to Subject:_____

CAREGIVER TOP THREE CONCERNS-FOLLOW-UP

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 symptom causing concern was:

_____

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

Not at All Severe Very Severe

Concern number 2:

The symptom causing concern was:

_____

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

Not at All Severe Very Severe

Concern number 3:

The symptom causing concern was:

_____

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

Not at All Severe Very Severe

APPENDIX F: Caregiver Completed Congenital DM1 Rating Scale (CC-CDM1-RS)

Date (dd/mmm/yyyy):	Site #:	Subject #:	Visit:

Caregiver-Completed Congenital DM1 Rating Scale (CC-CDM1-RS)

Please rate the patient on the following symptoms that may occur in individuals with congenital myotonic dystrophy Type 1 (CDM1). When rating each symptom, consider how the symptom influences how this patient feels and how it impacts his/her ability to perform everyday functions. Your ratings should also incorporate important observations that you make of the patient, with regard to his/her symptoms. For example, you should consider the patient's behaviors and verbalizations (what he/she says), as well as the symptoms that you can actually see, when you are making your ratings.

Instructions to the rater:

The item should be scored as 0, 1, 2, 3, or 4 based on overall severity (e.g. severity of symptoms, frequency of symptoms, context in which it occurs and functional impact).

The possible 0 to 4 rating levels for each item are:

0 = **Symptom not present** or no longer present during the relevant time frame

1 = **Mild severity**, symptom is clearly present but not pronounced, interferes little with day-to-day functioning

2 = **Moderate severity**, symptom is readily evident, intrudes on daily life to a moderate extent

3 = **Severe**, symptom is serious, markedly evident, consistently intrudes on daily life, symptom has a distinct impact on daily life

4 = **Very severe**, symptom causes pronounced and consistent impairment and is highly disruptive with regard to daily life

When rating the severity of the item, please focus on the **past week, including today**.

Date (dd/mmm/yyyy):	Site #:	Subject #:	Visit:

1. Limitations with mobility or walking

Examples include not being able to run or walk fast, difficulties standing from the ground, using stairs, an inability to keep pace with others when playing, or difficulties with balance.

How severe is the symptom? Circle the number that indicates how bad you think the patient's limitations with mobility or walking have been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

---

2. Problems with hands or arms

Examples include difficulties with opening jars or bottles, impaired fine motor skills (for example, when using a writing instrument such as a pencil), or difficulties with throwing or catching.

How severe is the symptom? Circle the number that indicates how bad you think the patient's problems with hands or arms have been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

---

3. Signs of fatigue

Examples include physical fatigue, poor endurance, decreased energy, or a need for prolonged recovery time after physical activity.

How severe is the symptom? Circle the number that indicates how bad you think the patient's fatigue has been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

Date (dd/mmm/yyyy):	Site #:	Subject #:	Visit:

4. Signs of pain

Examples include pain in the arms, legs, back, neck or shoulders.

How severe is the symptom? Circle the number that indicates how bad you think the patient's pain has been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

---

5. Gastrointestinal issues

Examples include abdominal pain, stool incontinence, diarrhea, bloating, severe constipation, urinating in one's pants due to chronic constipation, or dyspepsia (also known as heartburn).

How severe is the symptom? Circle the number that indicates how bad you think the patient's gastrointestinal issues have been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

---

6. Communication difficulties

Examples include slurred speech, difficulties with production of speech, or problems with expressive language.

How severe is the symptom? Circle the number that indicates how bad you think the patient's communication difficulties have been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

Date (dd/mmm/yyyy):	Site #:	Subject #:	Visit:

7. Impaired sleep or daytime sleepiness

Examples include problems with falling asleep and staying asleep at night, restless sleep, or problems with easily falling asleep during the day (excessive daytime sleepiness).

How severe is the symptom? Circle the number that indicates how bad you think the patient's impaired sleep or daytime sleepiness have been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

8. Difficulty thinking

Examples include an inability to focus, problems concentrating, troubles organizing activities or tasks, problems remembering, or learning difficulties in school that require special assistance.

How severe is the symptom? Circle the number that indicates how bad you think the patient's difficulty thinking has been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

9. Myotonia

Examples include myotonia in the hands, difficulties with releasing one's grip, muscle stiffness, or cramping.

How severe is the symptom? Circle the number that indicates how bad you think the patient's myotonia has been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

Date (dd/mmm/yyyy):	Site #:	Subject #:	Visit:

10. Breathing difficulties

Examples include breathlessness while walking, problems with breathing during the middle of the night, or problems with taking a deep breath.

How severe is the symptom? Circle the number that indicates how bad you think the patient's breathing difficulties have been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

11. Choking or swallowing issues

Examples include not being able to eat easily, problems swallowing, or having actual choking episodes.

How severe is the symptom? Circle the number that indicates how bad you think the patient's choking or swallowing issues have been over the past week, including today.

0	1	2	3	4
Not present	Mild severity	Moderate severity	Severe	Very severe

Person completing the ratings (initials): _____

Date of rating: _____

Initials of clinical assessor reviewing the completion of ratings: _____

Date of review: _____

APPENDIX G: [redacted]