STATISTICAL ANALYSIS PLAN

Protocol Title	A Randomized, Double-Blind, Placebo-Controlled, Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single and Multiple-Doses of AOC 1001 Administered Intravenously to Adult Myotonic Dystrophy Type 1 (DM1) Subjects (MARINA™)
Protocol Number	AOC 1001-CS1
Investigational Product	AOC 1001
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Version History

This Statistical Analysis Plan (SAP) for study AOC 1001-CS1 is based on the protocol V5.0 dated 21 October 2022.

SAP Version History Summary

SAP Version	Version Date	Change	Rationale
1	16SEP2022	Not Applicable	Original version
2	24MAR2023	See Summary of Changes	

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LIST OF ABBREVIATIONS

Abbreviation	Definition
10MWRT	10-Meter walk/run test
9HPT	9-Hole peg test
%	Percent
ADA	Anti-drug antibodies
AE	Adverse event
Ae	Amount excreted in urine
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
AOC	Antibody oligonucleotide conjugate
AST	aspartate Aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
AV01mAb	humanized IgG1 antibody
CGIC	Clinical global impression of change
CGIS	Clinical global impression of severity
CI	Confidence interval
CK	Creatine kinase
CL	Clearance
cm	Centimeter
C_{max}	Maximum plasma concentration
C-SSRS	Columbia-suicide severity rating scale
CSR	Clinical study report
CTG	Trinucleotide composed of cytosine, thymine, and guanine nucleotides in sequence
DM1	Myotonic Dystrophy Type 1
DM1-Activ	DM1 activity and participation scale
DM1-NSM	DM1 neuromuscular severity measure
DM1-NSM-PGIC	DM1 neuromuscular severity measure patient global impression of change
DM1-NSM-PGIS	DM1 neuromuscular severity measure patient global impression of severity
DMPK	DM1 protein kinase
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOPT	End of post treatment
EOT	End of Treatment
EQ VAS	EQ visual analogue scale
Fe	Percent of administered dose excreted unchanged in urine
FDSS	Fatigue and daytime sleep scale
FIVC after Ex	Forced inspiratory vital capacity after expiration

Abbreviation	Definition
FVC	Forced Vital Capacity
g/dL	grams per deciliter
GGT	Gamma glutamyl transferase
GLDH	Glutamate dehydrogenase
Hb	Hemoglobin
HbA1C	Hemoglobin A1c
HR	Heart Rate
IA	Interim Analysis
INR	International normalized ratio
IRR	Infusion related reaction
IRT	Interactive response technology
kg	Kilogram
L	Liter
LLN	Lower limit of normal
LLOQ	lower limit of quantification
Ln	Natural logarithm
m^2	Square meter
m/s	Meters per second
MAD	Multiple ascending dose
MBNL	Muscle blind-like protein
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDHI	Myotonic Dystrophy Health Index
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Maximal expiratory pressure
mg/kg	Milligram per kilogram
MIP	Maximal inspiratory pressure
MIRS	Muscular impairment rating scale
mL	Milliliter
MM	sponsor medical monitor
mm	Millimeter
MMT	Manual muscle test
MRC	Medical research council
mRNA	Messenger ribonucleic acid
ms	Millisecond
PD	Pharmacodynamic
PI	principal investigator
PK	Pharmacokinetic
PSI	Percent Spliced-in

Abbreviation	Definition
QMT	Quantitative myometry testing
QRS	Combination of the Q wave, R wave and S wave
QT	Interval between Q and T waves
QTc	Corrected interval between Q and T waves
QTcB	QT interval with Bazett's correction
QTcF	QT interval with Fridericia's correction
RA	Accumulation index based on appropriate PK parameter
RBC	Red blood cell
RDW	Red cell distribution width
Rel Day	Relative study day
retic	reticulocyte
RR	time elapsed between two successive R-waves
RSS	Raw Sum Score
SAP	Statistical analysis plan
SD	Standard deviation
SE	standard error
SI	International System of Units
SiRNA	Small interfering ribonucleic acid
SOA	Schedule of Assessments
SOC	System organ class
SRC	Safety review committee
TEAE	Treatment-emergent adverse event
TIBC	Total iron binding capacity
t_{max}	Time to maximum peak observed concentration
TSAT	Transferrin saturation
TUG	Timed up and go
TVA	total infusion volume administered
TVP	total infusion volume prepared
U/L	units per liter
ULN	Upper limit of normal
ULOQ	upper limit of quantification
vHOT	Myotonia video recording
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) provides details of the statistical analyses that have been outlined within the protocol for AOC 1001-CS1 Version 5.0 dated 21 October 2022. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to evaluate the safety and tolerability of single and multiple ascending doses (MAD) of AOC 1001 in DM1 subjects.

2.2. Secondary Objectives

The secondary objectives are the following:

- To evaluate the pharmacokinetic (PK) profile of single dose and multiple doses of AOC 1001 in DM1 subjects
- To evaluate the pharmacodynamic (PD) profile of single dose and multiple doses of AOC 1001 in muscle biopsies in DM1 subjects
- To evaluate the efficacy of multiple doses of AOC 1001 in DM1 subjects as measured by spliceopathy

2.3. Exploratory Objectives

The exploratory objectives are the following:

- To evaluate the exploratory efficacy of multiple doses of AOC 1001 in DM1 subjects on measures of mobility, muscle strength, muscle function, and patient-reported outcomes
- To evaluate immunogenicity and metabolite PK of AOC 1001

2.4. Additional Safety Objectives

An additional safety objective is to further characterize the safety and tolerability profile of AOC 1001.

3. STUDY DESIGN

3.1. General Study Design

This study is designed to evaluate the safety, tolerability, PK, PD, and clinical activity of AOC 1001 in a randomized, placebo-controlled, double-blind manner and will be conducted in two parts in subjects with adult onset DM1. Part A is designed to test the safety and tolerability of a single dose, while Part B will test single and multiple ascending doses in a nested manner. These cohorts will be initiated in a staggered fashion based on safety data review of preceding cohort(s). Part A will enroll approximately 8 adult DM1 subjects, whereas Part B is a nested single and multiple ascending dose (MAD) design enrolling up to 44 adult DM1 subjects.

Part A – The length of participation in Part A is approximately 7.5 months that includes an up to 6-week screening period, a one-day dosing period, a 6-month post-treatment period. Muscle needle biopsies will occur at Baseline, Day 43, and Day 92 to characterize the PK and PD profile of AOC 1001.

Part B – The length of participation in Part B is approximately 7.5 months, which includes an up to 6-week screening period, a 3-month treatment period, and a 3-month post-treatment period. Part B is designed to have both single-dose and multiple-dose treatment periods in a nested design. Subjects will receive a single dose of study drug (AOC 1001 or placebo) on Day 1 followed by safety assessments through Day 29, which will comprise the single dose treatment period. Given an acceptable safety profile, as determined by the principal investigator (PI) and the sponsor medical monitor (MM) (or designee), subjects will enter the multiple-dose treatment period and receive 2 additional doses on Days 43 and 92. After the third dose, subjects will enter a 3-month post-treatment period. Muscle needle biopsies will occur at Baseline, Day 92, and Day 183 to characterize the PK and PD profile of AOC 1001.

The AOC 1001 doses planned are as follows:

Table 1: Cohort Dose Levels

Cohort	siRNA Component Level*	Total AOC 1001 Weight*
A1	1 mg/kg	11.94 mg/kg
B1	2 mg/kg	23.88 mg/kg
B2	4 mg/kg	47.76 mg/kg
B3	8 mg/kg	95.52 mg/kg

*Per dose for Part B cohorts

3.2. Study Population

The study will include adult subjects with DM1 aged 18 to 65 years (inclusive) with a genetic diagnosis of DM1 with *DMPK* CTG repeat length ≥ 100. A full list of eligibility criteria is presented in protocol AOC 1001-CS1 version 5.0, Section 5.1.

3.3. Blinding and Randomization Methods

Eligible subjects will be randomly assigned on Day -1 or Day 1 to AOC 1001 or placebo via Interactive Response Technology (IRT). Subjects within each dose cohort will be randomized in a 3:1 AOC 1001:placebo allocation. A sentinel group of 2 subjects (1:1 active: placebo) will be utilized in each cohort.

Investigators and site personnel will remain blinded to each subject's assigned study intervention (AOC 1001 vs placebo) throughout the course of the study. The site pharmacy and a few sponsor representatives will be unblinded to study drug treatment. The study drug will be administered under the supervision of the blinded investigator. To maintain this blind, an otherwise uninvolved pharmacist will be responsible for the reconstitution and dispensation of study drug and will endeavor to ensure that site personnel and subjects remain blinded to the treatment.

3.4. Sample Size Determination

The sample size was selected based on practical considerations and is consistent with this type of early phase study. The cohort size is chosen considering the detectable event rate and the safety management rule (Buöen 2003). This sample size is deemed to be able to provide sufficient evidence of safety and tolerability of AOC 1001 in DM1 patient subjects while limiting unnecessary subject exposure. The sample size for this study was not based on statistical power considerations.

The study will enroll approximately 44 adult DM1 subjects – 8 in one single dose cohort (Part A) (6 active and 2 placebo) and at least 12 subjects in the 3 planned nested single and MAD cohorts (Part B). The maximum enrollment for the trial, including replacements, will be limited to 52 subjects.

3.5. Interim Analysis

No formal interim analyses (IA) are planned within this study. Preliminary assessments on outcomes such as safety, tolerability, key biomarkers may be performed. Details for the preliminary analysis will be specified in a separate specification document.

A Safety Review Committee (SRC) will perform ongoing blinded reviews of safety and tolerability data collected in all study parts (Parts A and B) with the primary purpose of protecting the safety of subjects. The SRC will be responsible for recommending decisions to dose escalate from Part A to Part B and from cohort B1 to cohort B2 based on safety and tolerability data of preceding cohorts. After the Independent Data Monitoring Committee (IDMC) (see Section 4.2.2) has been put in place, the SRC safety oversight responsibilities will be transferred to the IDMC. The details regarding meeting frequency, data to be reviewed, the data review process, and information dissemination to clinical sites, are included in a separate SRC Charter.

An IDMC will be responsible for recommending the decision to dose escalate from cohort B2 to B3 (upon protocol implementation of protocol version 5.0). The IDMC will also conduct regular meetings to review the safety and tolerability. The details regarding membership, responsibilities, meeting frequency, data to be reviewed, and process for communication with the Sponsor are included in the IDMC charter.

4. STUDY ENDPOINTS AND COVARIATES

4.1. Primary Endpoint

The primary endpoint is the frequency of treatment emergent adverse events (TEAEs).

4.2. Secondary Endpoints

The secondary endpoints are the following:

- AOC 1001 levels in plasma, urine, and muscle tissue
- Estimation of PK parameters, including Cmax, tmax, t1/2, AUC, and fraction excreted in urine
- Change and percentage change from baseline in DMPK mRNA levels
- Change from baseline in spliceopathy

4.3. Exploratory Endpoints

The exploratory endpoints are change from baseline of the following measurements:

- Myotonia
- Ankle dorsiflexion strength by Quantitative Myometry Test (QMT)
- Multiple Muscle Strength by QMT
- Grip Strength
- Pinch Strength
- 10-Meter Walk/Run Test (10MWRT)
- Timed Up and Go (TUG)
- Timed 4 Stair Climb
- Timed 4 Stair Descend
- Pulmonary Function Parameters by Spirometry
- Multiple Muscle Strength by Manual Muscle Test (MMT)
- 9-Hole Peg Test (9HPT)
- Percentage of subjects needing to start myotonia medications after dosing

- Muscular Impairment Rating Scale (MIRS)
- DM1-Neuromuscular Severity Measure (DM1-NSM)
- Myotonic Dystrophy Health Index (MDHI)
- DM1-Activity and Participation Scale for Clinical Use (DM1-Activ)
- DM1-NSM Patient Global Impression of Severity (DM1-NSM-PGIS)
- DM1-NSM Patient Global Impression of Change (DM1-NSM-PGIC)
- Fatigue and Daytime Sleepiness Scale
- Clinician Global Impression of Severity (CGIS)
- Clinician Global Impression of Change (CGIC)
- EuroQol 5 Dimension 5 Level Quality of Life Scale (EQ-5D-5L)

4.4. Exploratory Pharmacokinetic Endpoints

The exploratory PK endpoints are the following:

- Measurement of ADA
- Measurement of potential metabolites

4.5. Additional Safety Endpoints

Additional safety endpoints are the following:

- Laboratory parameters
- Vital signs
- Infusion related reactions (IRR)
- Electrocardiographic (ECG) measures
- Echocardiographic measures
- Columbia-Suicide Severity Rating Scale (C-SSRS)

4.6. Subgroups

Analyses within subgroups may be performed. Subgroups may be defined by normative data or response status for select measures. Subgroup analysis by baseline disease severity or baseline characteristics may be explored as permitted by the sample size.

5. DEFINITIONS AND DERIVED VARIABLES

5.1. Baseline and Change from Baseline

Baseline is defined as the last non-missing value prior to first dose of study drug, unless otherwise stated in the table below. For subjects randomized but not treated, baseline is defined as the last non-missing value prior to randomization.

Table 2: Other Baseline Definitions

Parameter(s)	Baseline Definition
Liver function tests: plasma ALT, AST, ALP, total bilirubin, direct bilirubin, indirect bilirubin, total protein, albumin, GGT, GLDH, CK, myoglobin, creatinine, eGFR, urine protein/creatinine ratio	Average of 2 most recent values prior to the first dose administered
Iron homeostasis: ferritin, transferrin, transferrin saturation, TIBC, Hb, MCV, RBC, MCHC, MCH, RDW, retic %, retic absolute, iron	Average of all pre-dose values
C-SSRS	Result from C-SSRS Baseline Form
ECG	Average of all pre-dose values on study day 1
DM1-NSM	Average of pre-dose assessments performed within 28 days of first dose date
Remote Hand Grip Strength	Best (maximum) result from the three trials from the last assessment prior to first dose
Pinch Strength	Best (maximum) result from the three trials from the last assessment prior to first dose
9HPT – Average	Average of the two trials from the last assessment prior to first dose
9HPT – Fastest	Fastest (minimum) time of the two trials from the last assessment prior to first dose
vHOT	Average of the two trials from the last assessment prior to first dose
10MWRT – First	From the last assessment prior to first dose, if there is more than one result documented, use the result from the first test, else use the sole documented result
10MWRT – Average	Average result across test(s) from the last assessment prior to first dose

Change from baseline will be calculated as $y_i - y_0$, where y_i denotes the post-baseline value assessed at time *i* and y_0 is the baseline value. Percent change from baseline will be calculated as:

$$Percent\ change\ from\ baseline = 100 \times \left(\frac{y_i - y_0}{y_0}\right)$$

5.2. Study Day

Study day 1 is defined as the date of first dose of study drug. For assessment occurring on or after study day 1, study day is calculated for a subject as:

Assessment date – first dose date + 1.

For assessments occurring prior to study day 1, study day is calculated for a subject as:

Assessment date – first dose date.

5.3. Duration of Exposure and Follow-up

Duration of study drug exposure in days will be calculated as:

Date of last dose – date of first dose + 91.

Duration of on-study follow-up in days will be calculated as:

End of study date – date of first dose + 1.

5.4. Study Drug Administration

The formula for total dose volume of study drug to be infused calculated by IRT, information on the total infusion volume prepared (study drug + saline) and additional information on study drug preparation can be found in the Pharmacy Manual. The total dose volume of study drug to be infused, total infusion volume prepared (TVP; mL) and total infusion volume administered (TVA; mL) at each study visit are captured in the eCRF. Total dose volume (mL) is calculated in IRT based on the following equation:

$$Dose\ Level\left(\frac{mg}{kg}\right) \times 11.94 \times Subject\ Weight(kg) \times \frac{8mL}{175mg}.$$

Derivations planned for study drug administration are detailed in Table 3.

Note: Dose level (mg/kg) in the equation above and table below is in terms of the siRNA component weight of AOC 1001 and siRNA weight is used to designate drug dose in the protocol. As AOC 1001 is composed of an antibody linked to an siRNA, the total weight of AOC 1001 can be calculated by multiplying the siRNA weight by the appropriate factor.

Table 3: AOC 1001 Administration

Parameter (unit)	Detail
siRNA component of AOC 1001 administered per kg body weight (mg/kg)	• $\left(Dose\ level\left(\frac{mg}{kg}\right)\right) \times \left(\frac{TVA(mL)}{TVP(mL)}\right)$ if AOC 1001 • 0 if Placebo
siRNA component of AOC 1001 administered per person (mg)	wt (kg) × (siRNA component of AOC 1001 administered (mg/kg))
Total weight of AOC 1001 administered per body weight (mg/kg)	11.94 × (siRNA component of AOC 1001 administered (mg/kg))
Total weight of AOC 1001 administered per person (mg)	11.94 × (siRNA component of AOC 1001 administered (mg))
Percentage of study drug administered (%)	$100 \times \left(\frac{TVA(mL)}{TVP(mL)}\right)$

5.5. DM1 History

The following derivations will be made for DM1 history parameters:

- Duration (years) since DM1 symptom onset: (Date of informed consent – date of symptom onset + 1)/365.25.
- Duration (years) since DM1 diagnosis: (Date of informed consent – date of DM1 diagnosis + 1)/365.25.
- Age (years) at symptom onset: age at screening – years since DM1 symptom onset.
- Age (years) at DM1 diagnosis: age at screening – years since DM1 diagnosis.

5.6. Prior, Baseline and Concomitant Medication

Prior, baseline and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug Global B3-March 1, 2021 or later).

- Prior medications are defined as medications with a stop date prior to the first dose of study drug.
- Baseline medications are defined as medications with a start date prior to the first dose of study drug and are ongoing at the time of first dose.

- Concomitant medications are defined as medications that started after the first dose. Medications that start on the first dose date without information to discern whether the medication stated before first dose will be classified as being a concomitant medication.

5.7. Efficacy Assessments – Measures of Function and Strength

5.7.1. Muscular Impairment Rating Scale (MIRS)

The Muscular Impairment Rating Scale (MIRS) is an ordinal five-point rating scale, established in accordance with clinically recognized distal to proximal progression of the muscular involvement in DM1. It is based on manual muscle testing of 11 muscle groups. The scores and responses are: 1 = 'Grade 1 - No muscular impairment', 2 = 'Grade 2 - Minimal signs', 3 = 'Grade 3 - Distal weakness', 4 = 'Grade 4 - Mild to moderate proximal weakness' and 5 = 'Grade 5 - Severe proximal weakness'.

5.7.2. Quantitative Myometry Testing (QMT)

At screening, the dominant side of the body will be chosen for QMT testing and will be the side tested throughout the trial. Muscle groups that will be tested are: elbow flexion, ankle dorsiflexion, elbow extension, knee flexion, knee extension and hand grip. A minimum of two trials will be performed for each muscle group; additional trials (maximum of 5) may be performed at the evaluator's discretion. The maximum force (kilogram; kg) from the valid trials will be recorded in the eCRF.
Missing assessments for individual muscle groups will imputed to 0 kg if the reason for missing is due to weakness.

For each muscle group the percent of predicted normal will be calculated. Percent of predicted normal will be calculated as:

$$\text{Percent of Predicted Normal} = 100 \times \frac{\textit{measured strength (kg)}}{\textit{predicted strength (kg)}}.$$

Equations for percent of predicted normal are in Table 4.

Table 4: Equations for QMT % of Predicted Normal

Muscle Group	Gender	Regression Equation
Right elbow flexion	Male	MS*9.8*100/(EXP(5.0254-(0.00335*age)+(0.00430*height)))
	Female	MS*9.8*100/(EXP(3.1534-(0.00335*age)+(0.01298*height)))
Left elbow flexion	Male	MS*9.8*100/(EXP(4.1605-(0.00266*age)+(0.00863*height)))
	Female	MS*9.8*100/(EXP(2.8467-(0.00266*age)+(0.01442*height)))
Right elbow extension	Male	MS*9.8*100/(EXP(4.0617-(0.00232*age)+(0.00737*height)))
	Female	MS*9.8*100/(EXP(3.5597-(0.00232*age)+(0.00737*height)))
Left elbow extension	Male	MS*9.8*100/(EXP(3.7628-(0.00151*age)+(0.00864*height)))
	Female	MS*9.8*100/(EXP(3.2676-(0.00151*age)+(0.00864*height)))
Right hand grip	Male	MS*100/(-9.7022 - (0.1732 * age) + (0.3696 * height))
	Female	MS*100/(-24.8027-(0.1732 * age)+(0.3696 * height))
Left hand grip	Male	MS*100/(-26.9062 - (0.1329 * age) + (0.4374 * height))
	Female	MS*100/(-39.5766 - (0.1329 * age) + (0.4374 * height))
Right ankle dorsiflexion	Male	MS*9.8*100/(EXP(4.9847-(0.00277*age)+(0.00435*height)))
	Female	MS*9.8*100/(EXP(4.6962-(0.00277*age)+(0.00435*height)))
Left ankle dorsiflexion	Male	MS*9.8*100/(EXP(4.6332-(0.00241*age)+(0.00607*height)))
	Female	MS*9.8*100/(EXP(4.3991-(0.00241*age)+(0.00607*height)))
Right knee flexion	Male	MS*9.8*100/(EXP(4.9481-(0.00641*age)+(0.00524*height)))
	Female	MS*9.8*100/(EXP(2.0670-(0.00641*age)+(0.02020*height)))
Left knee flexion	Male	MS*9.8*100/(EXP(4.9876-(0.00591*age)+(0.00499*height)))
	Female	MS*9.8*100/(EXP(2.1190-(0.00591*age)+(0.01994*height)))
Right knee extension	Male	MS*9.8*100/(EXP(6.4124-(0.00701*age)+(0.00104*height)))
	Female	MS*9.8*100/(EXP(3.4479-(0.00701*age)+(0.01557*height)))
Left knee extension	Male	MS*9.8*100/(EXP(5.1832-(0.00837*age)+(0.00789*height)))
	Female	MS*9.8*100/(EXP(4.7644-(0.00837*age)+(0.00789*height)))

Age measured in years at baseline; height measured in cm; MS = muscle strength measure in kg

Three composite QMT scores to be assessed are:

- Total composite QMT score, calculated as the mean percent of predicted normal across the six muscle groups tested
- Upper extremity muscle group composite QMT score, calculated as the mean percent of predicted normal for elbow flexion, elbow extension and hand grip strength
- Lower extremity muscle group composite QMT score, calculated as the mean percent of predicted normal for ankle dorsiflexion, knee flexion and knee extension.

A composite score will not be computed if any of its components are missing.

5.7.3. Manual Muscle Testing (MMT)

Thirteen muscle groups/motions on both sides of the body, neck flexion and neck extension will be test throughout the study. Each muscle group will be scored using a modified Medical Research Council (MRC) scale, in accordance with a protocol that standardizes the subject's

position, direction of movement, and joint angle of resistance, as well as the examiner's stabilization and hand placement. Muscle groups/motions tested are neck extensors and flexors; shoulder abductors; elbow flexors and extensors; wrist flexors and extensors; thumb flexors; hip flexors, extensors, and abductors; knee flexors and extensors, ankle dorsiflexors and ankle plantar flexors. Possible MRC grades and numeric values for summarization are listed in Table 5.

Table 5: **MRC Grades for MMT**

Converted Numeric Value	Grade	Criteria
5	5	Normal strength
4.67	5-	Uncertain muscle weakness
4.33	4+	Ability to move through full range of motion and hold against strong pressure
4	4	Ability to move through full range of motion and hold against moderate pressure
3.67	4-	Ability to move through full range of motion and hold against slight pressure: or breaks abruptly against minimal pressure
3	3	Ability to move through full range of motion and hold against gravity
2.67	3-	Ability to move through partial range of motion against gravity
2	2	Ability to move through any range of motion only with gravity eliminated
1	1	A flicker of movement is seen or felt in the muscle
0	0	No contraction palpable

Four composite MMT scores to be assessed are:

- Total MMT composite score, defined as the mean MMT score across all 28 muscle groups tested
- Total muscle MMT composite score, defined as the mean MMT score across all muscle groups tested excluding thumb flexors (average across 26 muscles groups)
- Upper extremity MMT composite score, defined as the mean MMT score across all 10 upper extremity muscles only (shoulder abductors; elbow flexors and extensors; wrist flexors and extensors)
- Lower extremity MMT composite score, defined as the mean MMT score across all 14 lower extremity muscles only (hip flexors, extensors, and abductors; knee flexors and extensors, ankle dorsiflexors; plantar flexors).

A composite score will not be computed if any of its components are missing.

5.7.4. Pinch Strength by Dynamometer

The dominant hand will be chosen for pinch strength testing and will be the hand tested throughout the trial. Key (lateral) pinch will be measured in kg using a standalone pinch dynamometer. Three successive trials will be recorded. The best (maximum) pinch strength from the three trials will be used for summarization.

5.7.5. Remote Hand Grip Strength

The remote hand grip strength assessment will be performed using the dominant hand and will be the hand tested throughout the trial. Hand grip strength will be measured in kg using a grip dynamometer. Subjects are to perform three trials and record the score in a diary. The best (maximum) score from the three trials will be used for summarization. Percent of predicted normal based on the best score will also be summarized (Table 4).

5.7.6. 10-Meter Walk/Run Test (10MWRT)

From a standing start, the subject will be asked to go 10 meters as quickly as possible, whether walking or running. 10MWRT was modified during the study. Initially, one 10MWRT was performed per planned visit; subsequently two 10MWRT tests are performed for every visit where 10MWRT is required. The time in seconds to complete the test will be recorded. Orthotics and ankle braces are allowed. Walk/run status will be recorded. 10MWRT time and velocity will be separately summarized using the first and average trial result.

For the analysis of first trial result, if there is more than one result documented, the result from the first valid test will be used, else the sole documented result will be used. 10MWRT velocity (m/s) is calculated as 10/time(sec). Velocity for tests that were not completed will be imputed to 0.

5.7.7. Timed up-and-go (TUG)

Subjects will be asked to rise from a chair, walk 3 meters, turn around, and return to the chair and sit. The time in seconds to complete the timed up-and-go (TUG) task will be recorded. TUG will be performed twice, once at a comfortable pace and once at a maximum pace. Results will be presented separately for the comfortable pace and for the maximum pace. Assistive devices, orthoses, and ankle braces are allowed.

5.7.8. Timed 4-Stair Climb and Timed 4-Stair Descend

Subjects will be asked to climb up and down (timed as separate tests) 4 stairs as quickly as possible. The time it takes to complete the task, use of railings, and manner of ascent and descent (i.e., step-to or step-over-step pattern) will be recorded. The time in seconds and velocity (steps/sec) to complete the ascent and descent will be summarized separately. Orthotics and ankle braces are allowed. Velocity (steps/sec) is calculated is 4/time (sec). Velocity for tests that were not completed will be imputed to 0.

5.7.9. 9-Hole Peg Test (9HPT)

The 9HPT is a quantitative measure of distal upper extremity function. Subjects will be asked to place 9 pegs in 9 holes on a board and then remove them as quickly as possible, using their

dominant hand. Two trials will be performed. The time to complete each trial in seconds will be recorded. The fastest (minimum) time and the average time across the two trials will be summarized separately.

5.7.10. Myotonia Video Hand Opening Time (vHOT)

Myotonia will be assessed by video hand open time (vHOT) trials. The subject will be asked to squeeze their dominant hand for three seconds then open as quickly as possible. Two vHOT trials will be performed at the planned visit of assessment. Hand opening time, middle finger opening time and thumb opening time, measured in seconds, will be determined from the reviewers. Hand opening time for a trial is defined as the maximum opening time for the thumb and middle finger. Each trial will be reviewed by two independent, blinded reviewers. If a rater is unable to set an opening time for a trial or differences between opening times determined from the two independent raters exceeds a predefined threshold, the video is reviewed at a panel meeting that includes a third lead rater where consensus is met.

For a given trial, opening time is the average of the two raters opening time if the video is not sent to panel meeting, and the consensus time if sent to panel. If the panel is not able to determine a finger opening time, it will be imputed to the worst opening time for the study. The mean opening time from the two trials performed at the visit will be summarized.

5.7.11. Spirometry

Spirometry will be performed in the sitting and supine positions using standardized, calibrated equipment. Pulmonary parameters including forced vital capacity (FVC), peak expiratory flow and forced inspiratory vital capacity after expiration will be assessed and reviewed by central readers. Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) will also be assessed but will not have overreads. The best of 3 values for MIP and MEP will be entered into the spirometry device.

5.8. Efficacy Assessments – Assessments by Clinicians

5.8.1. Clinical Global Impression of Severity (CGIS)

The investigator or designee will evaluate the subject for his/her global severity. The scores and responses to the question ‘Please describe the Severity of DM1 based on your clinical assessment of the patient today’ are as follows: 0 = ‘None’, 1 = ‘Mild’, 2 = ‘Moderate’, 3 = ‘Severe’ and 4 = ‘Extremely Severe’.

5.8.2. Clinical Global Impression of Change (CGIC)

The investigator or designee will evaluate the subject for his/her rate of change. The scores and responses to the question ‘Please describe the change from baseline in DM1 severity based on your clinical assessment of the patient today’ are as follows: 3 = ‘Very much better’, 2 = ‘Moderately better’, 1 = ‘A little better’, 0 = ‘No change’, -1 = ‘A little worse’, -2 = ‘Moderately worse’ and -3 = ‘Very much worse’.

5.9. Efficacy Assessments – Assessments by Subjects

5.9.1. DM1 Neuromuscular Severity Measure (DM1-NSM)

The DM1-NSM comprises 25 questions on severity of neuromuscular impairment and evaluation of the weakness of certain body parts, and consists of two domains, Difficulties and Symptoms. The questionnaire should be completed by the subject daily for at least 7 days prior to Day 1) then daily for 14 consecutive days prior to the Day 43, 92, and 183 visits. Responses are 0 = not difficult/none, 1 = mildly difficult/mild, 2 = moderately difficult/moderate, 3 = difficult and 4 = too difficult to do/too difficult to do unaided/severe or for breathing difficulty 'I use an assistive breathing device during the daytime'. Subjects are also asked to rate muscle discomfort on scale of 0 (none) to 10 (as bad as you can imagine).

DM1-NSM total, domain and individual question weekly scores are calculated for baseline and Days 36, 43, 85, 92, 176 and 183. A DM1-NSM question score is the average response to the question over the week period. The DM1-NSM total score is the average of the weekly DM1-NSM question score to Questions 1-25a and the DM1-NSM domain score is the average of the weekly DM1-NSM question scores for those questions that define the domain. An average DM1-NSM score for a given question over a 7 day assessment period will be computed if the subject had assessments on at least 4/7 of the days, else it will be missing. The total or domain score will not be computed if any of the average question scores are missing.

5.9.2. DM1-NSM Patient Global Impression of Severity (DM1-NSM-PGIS)

The DM1-NSM-PGIS will evaluate global severity for both symptoms and activity impact. The questionnaire is completed by the patient on Day -1, then at the end of each week after DM1-NSM is performed (Day 7 of each week). The DM1-NSM-PGIS has three items to assess muscle-related DM1 symptoms, the impact of DM1 on daily activities and severity of DM1 over the period of a week. The items are scored as 0 = No impact/None, 1 = Mild impact/Mild, 2 = Moderate impact/Moderate, 3 = Moderately severe impact/Moderately severe and 4 = Severe impact/Severe. Responses to the individual DM1-NSM-PGIS items will be summarized for baseline and Days 36, 43, 85, 92, 176 and 183.

5.9.3. DM1-NSM Patient Global Impression of Change (DM1-NSM-PGIC)

The DM1-NSM-PGIC will evaluate rate of change for both symptoms and activity impact. The questionnaire is completed by the subject after DM1-NSM-PGIS on the last day of each assessment period after baseline (Days 43, 92, and 183). The DM1-NSM-PGIC has three items which assess changes in muscle-related DM1 symptoms, the impact of DM1 on daily activities, and the severity of DM1. The items are scored on a 7 point scale from 3 = 'Very much better' to -3 = 'Very much worse'. Responses to the individual DM1-NSM-PGIC items will be summarized for Days 43, 92 and 183.

5.9.4. Fatigue and Daytime Sleepiness Scale (FDSS)

The 12-item Fatigue Severity Scale and Daytime Sleepiness Scale (FDSS) is a combined scale designed and validated for subjects with DM1 (Hermans et al., 2013). The scale was shown to measure a single construct combining aspects of sleep propensity as well as behavioral consequences of fatigue within the DM1 population. FDSS is assessed at the Baseline, Day 92,

and 183/EOPT (Part A) or 183/EOT/EOPT (Part B) visits. Each item is scored as: 0 ('Seldom or never'), 1 ('Sometimes') or 2 ('Almost always'). After completion of FDSS, the items are added and a raw sum score (RSS) is obtained. The RSS will be translated to a centile metric score ranging from 0 to 100 using a scoring table (Appendix Section 11.1.5). Higher centile scores correspond to higher levels of sleep propensity and behavioral consequence of fatigue.

5.9.5. DM1-Activ

DM1-Activ is composed of 25 items to assess the impact of DM1 on daily life (Hermans et al., 2015). DM1-Activ is assessed at the Baseline, Day 92, and 183/EOPT (Part A) or 183/EOT/EOPT (Part B) visits. Each item is scored as: 0 ('Not possible to perform'), 1 ('Possible, but with some difficulty') or 2 ('Possible, without any difficulty'). After completion of DM1-Activ, the items are added and a total sum score is obtained. This score is referred to as the RSS. The RSS will be translated to a centile metric score ranging from 0 to100 using scoring tables (Appendix Section 11.1.6). There are two scoring tables; one table is to be used for subjects < 30 years of age at baseline and the other for subjects ≥ 30 years of age at baseline. Higher centile scores correspond to higher ability to perform activities of daily living. The subject's score for analysis will be the centile metric score.

5.9.6. EQ-5D-5L

The EQ-5D-5L (EuroQol Research Foundation, 2009) is a brief questionnaire to assess overall health and impairment and consists of the EQ-5D descriptive element and the EQ visual analogue scale (EQ VAS). EQ-5D-5L is assessed at the Baseline, Day 92, and 183/EOPT (Part A) or 183/EOT/EOPT (Part B) visits. The EQ-5D-5L includes five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and each dimension has five levels (responses). The digits for the 5 dimensions will be combined into a 5-digit code that describes the subject's health state that will be transformed into EQ-5D-5L index values using the EQ-5D-5L_Crosswalk_Index_Value_Calculator_v2 (Euroqol, 2019). Index values range from < 0 to 1, where 1 represents full health. The EQ VAS is scored from 0 (the worst health you can imagine) to 100 (the best health you can imagine).

5.9.7. Myotonic Dystrophy Health Index (MDHI)

MDHI is a standardized questionnaire to quantify DM1 related symptoms and disease severity. It is assessed at the Baseline, and 183/EOPT (Part A) or 183/EOT/EOPT (Part B) visits. The MDHI consists of the 17 subscales that measure 17 individual areas of disease health. The subscales measure a subject's perception on their mobility, upper extremity function, ability to do activities, communication, social satisfaction, social performance, fatigue, pain, myotonia, gastrointestinal issues, swallowing, vision, emotional issues, sleep, cognitive impairment, hearing, and breathing. The MDHI questionnaire consists of 114 questions. Each question is scored as 0 ('I don't experience this' or 'I experience this but it does not affect my life'), 1 ('It affects my life a little'), 2 ('It affects my life moderately'), 3 ('It affects my life very much'), 4 ('It affects my life severely'). The score for each subscale and the total MDHI ranges from 0 to 100, with 100 representing highest disease burden and a score of 0 representing no disease burden.

A MDHI subscale score is derived by multiplying the response (0-4) to a question in the subscale by the question's weight; the weighted responses for all questions in the subscale are then summed. The MDHI total score is derived by multiplication of the response to a question by the question's weight; the weighted responses for all questions in the MDHI are then summed. The

weights to define each MDHI subscale and the MDHI total score are provided in Appendix Section 11.1.7.

For missing data, if a subject leaves a question blank, the average response (0-4) to the other questions in the subscale is used for that item. If every question in a subscale is left black, then the average response (0-4) to the other questions in the total MDHI is used for that item. If a subject marks more than one box, the score from the highest box is utilized.

5.10. Pharmacodynamic Analyses (PD)

Muscle needle biopsy sample from the tibialis anterior at each time point (per SOA) will be used to determine levels of DMPK mRNA and levels of spliceopathy. Samples with a RNA integrity number score less than 4 will be excluded due to poor RNA extraction quality.

5.10.1. DMPK mRNA Levels in Muscle

DMPK mRNA relative expression level and percent of baseline will be summarized. Percent change from baseline, derived from percent of baseline (percent of baseline-100), will also be summarized. Relative expression is calculated via normalization of expression levels of DMPK to that of housekeeping genes. Percent of baseline can be expressed as the ratio of relative expression values.

5.10.2. Spliceopathy in Muscle

Spliceopathy will be quantified based on the Percent Spliced-in (PSI) of exons. PSI is calculated as the percent of amplicons that include the specific exon relative to the total amplicons for the parental gene (Tanner et. al. 2021) and allows us to assess the levels of mis-splicing in muscles from DM1 subjects.

Spliceopathy analysis will be based on 22 exons, listed in the table below. Scaled PSI will also be presented. Scaled PSI is derived using the reference range for each gene generated from 25 healthy volunteers and 172 DM1 patients. For a given gene, a scaled PSI value of 1 equates to the 5th percentile of PSI in DM1 patients (or 95th percentile for select genes that show elevated PSI in DM1 subject vs. healthy subjects) and a 0 equates to the median PSI in healthy volunteers. Reference data set is generated and provided by Dr. Charles Thornton. Scaled PSI for a given gene will be calculated as:

$$Scaled\ PSI = 100 \times \frac{(PSI - PSI_{healthy})}{(PSI_{DM} - PSI_{healthy})}$$

where PSI is the observed PSI value, $PSI_{healthy}$ is the median PSI from the 25 healthy individuals and PSI_{DM} is the gene appropriate percentile PSI (5th or 95th percentile) in 172 first-time biopsies from DM1 patients. $PSI_{healthy}$ and PSI_{DM} values are provided in Table 6.

A spliceopathy score will be computed as the mean of the scaled PSI values across the 22 exons. A 4- and 12-gene panel spliceopathy score will also be computed as the mean scaled PSI value from the following genes:

- 4-gene (muscle-specific) panel: CLCN1, CACNA1S, ATP2A1, BIN1

- 12-gene panel: ANK2, ATP2A1, BIN1, CACNA1S, CLCN1, DMD, GFPT1, GOLGA4, MBNL1, MBNL2, NFIX, OPA1.

Alternative spliceopathy scores based on a subset of the 22 exons may be explored.

Table 6: Spliceopathy Reference Data

Gene	Gene (Chromosome coordinates)	Median PSI in 25 healthy individuals	172 DM1 patients	
			Reference percentile	PSI percentile value
ANK2	chr4:113372533:113372625	97.2	5th	48.8
ATP2A1	chr16:28903700:28903741	99.9	5th	1.8
BEST3	chr12:69694370:69694464	84.6	5th	5.7
BIN1	chr2:127060596:127060640	99.7	5th	67.6
CACNA1S	chr1:201054505:201054561	95.2	5th	25.4
CAMK2B	chr7:44239589:44239663	65	5th	1.8
CAPZB	chr1:19342752:19342864	82.1	5th	7.1
CCPG1	chr15:55374155:55374250	33	5th	0.3
CLASP1	chr2:121445449:121445496	91.5	5th	3.6
CLCN1	chr7:143323819:143323897	5.4	95th	99.9
DMD	chrX:31126642:31126673	94.1	5th	61.2
GFPT1	chr2:69354259:69354312	83.8	5th	29.2
GOLGA4	chr3:37361243:37361305	5.9	95th	55.2
INSR	chr19:7150497:7150532	75.4	5th	1.0
KIF13A	chr6:17821786:17821905	54.3	5th	0.4
MBNL1	chr3:152446704:152446757	7.1	95th	80.2
MBNL2	chr13:97366459:97366553	14.6	95th	75.8
NFIX	chr19:13078613:13078735	19.7	95th	92.8
OPA1	chr3:193617784:193617837	48.6	5th	6.2
RYR1	chr19:38523915:38523929	41.8	5th	2.8
SOS1	chr2:38989270:38989314	98	5th	14.0
VPS39	chr15:42192066:42192098	84.9	5th	3.1

6. ANALYSIS SETS

6.1. Randomized Analysis Set

The Randomized Analysis Set will include all randomized subjects. Subjects will be grouped as randomized.

6.2. Safety Analysis Set

The Safety Analysis Set will include all subjects who received at least one dose of study drug. Subjects will be grouped according to the dose level they received. The Safety Analysis Set will be used for all safety analyses.

6.3. Full Analysis Set

The Full Analysis Set is defined as all subjects who were randomized and have received any amount of study drug and had a baseline efficacy measurement and at least 1 post-baseline efficacy assessment. Subjects will be grouped as randomized. The Full Analysis Set is the primary analysis set for efficacy analyses. Additional analysis subset(s) may be formed based on different outcome measures as appropriate.

6.4. Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis (PK) Analysis Set will include all subjects who receive any amount of study drug and provide a sufficient number of plasma sample(s) for PK analysis. Subjects will be grouped according to the dose level they received.

The Pharmacokinetic Analysis Set is the primary analysis set for PK analyses.

6.5. Pharmacodynamic Analysis Set

The Pharmacodynamic (PD) Analysis Set will include all subjects who receive any amount of study drug and had a baseline PD assessment and at least 1 post-baseline PD assessment. Subjects will be grouped according to the dose they received.

The Pharmacodynamic Analysis Set is the primary analysis set for PD analyses.

7. DATA SCREENING AND ACCEPTANCE

7.1. Handling of Missing and Incomplete Data

Subjects may have missing data points for a variety of reasons, including a missed visit, premature study discontinuation or non-evaluability of a measurement. Unless otherwise stated, there will be no imputation to accommodate missing data points. The missing or incomplete values (e.g., dates) will be displayed in the data listings as reported on the eCRF rather than the imputed values.

7.1.1. Missing or Incomplete Date Imputation for Medical History

Missing or incomplete dates will not be imputed for medical history.

7.1.2. Missing or Incomplete Date Imputation for Myotonic Dystrophy Type 1 Disease History

Incomplete dates for symptom onset and diagnosis will be imputed according to the rules in Table 7. Dates that are missing entirely will not be imputed.

Table 7: Date Imputation for Myotonic Dystrophy Type 1 Disease History

	Missing	Impute
Onset/Diagnosis Date	Day	01
	Day/Month	01Jan
	Month	Jan

7.1.3. Missing or Incomplete Date Imputation for Concomitant Medications

Missing or incomplete medication start date will be imputed for the purpose of determining whether the medication is defined as prior, baseline or concomitant.

For medications with completely missing start dates, no imputation will be performed.

For a medication with incomplete start date:

- If “day” is the only missing field, impute the “day” as the first of the month.
- If “day” and “month” are the missing fields, impute the “day” and “month” to January 1.
- If only day is missing, and month and year are the same as first dose date then consider as concomitant.

For a medication that is not checked as ongoing, the start date is completely missing and the end date is either complete, incomplete or completely missing:

- If the end date can be deduced as prior to the first dose date of study drug, then consider as prior medication.
- Otherwise, consider as concomitant medication.

For a medication with completely missing end dates but with complete start date and ongoing is not checked:

- End date will not be imputed, furthermore:
  - If start date is on or after Study Day 1, then consider as concomitant medication
  - If start date is prior to Study Day 1 then consider as prior medication.

For a medication with incomplete end dates:

- If “day” is the only missing field, and if month and year are the same as the start date and ongoing is not checked, then impute “day” as the start date “day”; otherwise impute as the last day of the month.
- If “day” and “month” are the missing fields, and if year is the same as the start date and ongoing is not checked, then impute “day” and “month” as the start date day and start date month; otherwise impute as December 31.

For medications that have both completely missing start dates and end dates, no imputation will be made; these medications will be assumed to be prior.

7.1.4. Missing or Incomplete Date Imputation for Adverse Events

Missing or incomplete adverse event start dates will be imputed for the purpose of determining whether the adverse event is treatment emergent. No imputation will be done on missing or incomplete stop dates. Missing or incomplete start dates for an adverse event will be imputed according to the rules in Table 8.

Table 8: Imputation for Adverse Events

	Missing	Impute	Exception
Start Date	Day	01	Default to study day 1 date if the event started in the same year and month as study day 1
	Day / Month	01Jan	Default to study day 1 date if the event started in the same year as study day 1
	Month	Jan	Default to study day 1 date if the event started in the same year as study day 1
	Day / Month / Year	First dose date	

7.1.5. Missing Severity Assessment for Adverse Events

If the severity is missing for an adverse event, severity status will not be imputed.

7.1.6. Missing Casual Relationship to Study Drug for Adverse Events

Any treatment emergent adverse event with missing casual relation to the study drug or study procedure, the casual relationship will be considered "Related". The imputed relationship will be used for summary tables.

7.1.7. Missing Data for Efficacy Endpoints

In general, there will be no imputation made to accommodate missing data points. All data recorded on the case report form will be included in data listings that will accompany the CSR.

For multi-item scoring algorithms, missing data for the purpose of subscore and total score calculations will follow guidance outlined in the questionnaire.

7.2. Visit Time Windows

7.2.1. Visit Windows

The following post-baseline assessments will be summarized using nominal visits:

- Assessments measured only once during the study post baseline: body weight, echocardiogram
- Study drug administration, muscle PK
- Assessments measured as specified in Protocol Table 2 and Table 4: 12-lead ECG (triplicate), PK, ADA, spot urine and 24-hr urine
- Remote hand grip strength, DM1-NSM daily, DM1-NSM-PGIS and DM1-NSM-PGIC

Other post-baseline assessments will be summarized using analysis visit windows, based on the measurement frequency:

- More frequently measured assessments: chemistry, hematology, urinalysis, thyroid panel, HbA1c, coagulation, vital signs, TSAT, TIBC, iron, ferritin and cardiac troponin, and C-SSRS (Table 9).
- Less frequently measured assessments: MMT, QMT, Pinch Strength, 10MWRT, TUG, Timed 4 stair climb, Timed 4 stair descend, 9HPT, spirometry, vHOT, MIRS, FDSS, DM1-Activ, MDHI, EQ-5D-5L, CGIS, CGIC and PD (Spliceopathy and DMPK mRNA) (Table 10).

Note: Vital signs collected in Part B during or post infusion on D1, D43, or D93 will not be summarized in the by visit analysis. Any spirometry values with a "Repeat" label will not be considered for analysis windowing.

Sensitivity analyses using nominal visits or alternative window analysis strategies for select less frequently measured assessments may be performed.

Table 9: Analysis Visit Windows for More Frequently Measured Assessments

Analysis Visit	Study Part A		Study Part B	
	Target Day	Study Day Interval	Target Day	Study Day Interval
Day 1	1	1	1	1
Day 2	2	2 to 4	2	2 to 4
Day 8	8	5 to 11	8	5 to 11
Day 15	15	12 to 22	15	12 to 22
Day 29	29	23 to 36	29	23 to 36
Day 43	43	37 to 58	43	37 to 46
Day 50†	-	-	50	47 to 58
Day 71	71	59 to 84	71	59 to 84
Day 92	92	85 to 105	92	85 to 95
Day 99†	-	-	99	96 to 105
Day 120	120	106 to 131	120	106 to 131
Day 141	141	132 to 153	141	132 to 153
Day 162	162	154 to 175	162	154 to 175
Day 183	183	176 to 197	183	176 to 197

†There is no Day 50 or Day 99 visit in Study Part A.

Table 10: Analysis Visit Windows for Less Frequently Measured Assessments

Analysis Visit	Target Day	Study Day Interval
Day 43	43	28 to 72
Day 92	92	73 to 161
Day 183	183	>=162

7.2.2. Multiple Measurements within Visit Window

In the event that there is more than one assessment assigned to an analysis visit, the measurement that is closest to the target study day will be selected for the by-visit analyses. If two eligible assessments are equidistant from the target day, then the chronologically last assessment will be used.

For analyses where the most extreme values should be selected (e.g., post-baseline maximum), all non-missing post-baseline values should be considered, regardless of whether the value is selected for the by-visit summaries.

7.2.3. Unscheduled Assessments

For measurements summarized using nominal visit, unscheduled assessments will not be summarized in by-visit tables. For measurements summarized using analysis visits, unscheduled visits will be mapped into the analysis visit accordingly. Only the planned visit for the assessments will be presented in the summary tables.

7.3. Testing/Validation Plan

All dataset specifications, dataset analysis programs, and programmed outputs will be required to pass the quality control and statistical review processes.

7.4. Software

All statistical analyses will be performed using SAS statistical software Version 9.4 (or newer), unless otherwise stated. Pharmacokinetic calculations will be performed using relevant software e.g., WinNonlin Phoenix (Certara Corporation).

8. STATISTICAL METHODS OF ANALYSES

8.1. General Principles

This study is primarily descriptive in nature; therefore, there are no formal statistical hypothesis tests planned.

In general, data summaries will be presented separately for Part A and Part B. Summary tables will be presented according to the specifications below.

- Baseline data (including demographics and baseline characteristics, disposition, medical history, and prior and baseline medications) will include groups for Part A placebo, pooled Part B placebo, pooled placebo (Part A and Part B), separate AOC 1001 dose levels (1 mg/kg, 2 mg/kg, 4 mg/kg, 8 mg/kg by siRNA component weight), pooled AOC 1001 dose levels from Part B, and total (placebo or AOC 1001).

- Safety and efficacy data will include groups for Part A placebo, pooled Part B placebo, pooled placebo, separate AOC 1001 dose levels and pooled Part B AOC 1001 dose levels.

- PD data will include groups for Part A placebo, pooled Part B placebo, pooled placebo, separate AOC 1001 dose levels.

- PK data will include groups for the separate AOC 1001 dose levels.

Unless otherwise stated for categorical variables, the number and percentage of subjects within each category of the parameter will be presented. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the analysis population for the treatment group, unless otherwise specified. Unless otherwise stated for continuous variables, the number of subjects, mean, median, standard deviation (SD), standard error of the mean (SE), minimum, and maximum values will be presented. The standard error of the mean (SE) and 95% confidence intervals (CIs) will be reported for PD and efficacy data; for Part A placebo the SE and CI will be reported for PD measures only. For change and percent change from baseline, the mean difference between AOC 1001 and placebo, standard error and 95% CI will be presented for PD and efficacy endpoints. The placebo group used for the comparison is detailed in the Table below.

AOC 1001 Group	**A1**	**B1**	**B2**	**B3**	**Pooled B**
Comparator	A1 PBO	Pooled B PBO	Pooled B PBO	Pooled B PBO	Pooled B PBO
Measure Type	PD only	PD, Efficacy	PD, Efficacy	PD, Efficacy	PD, Efficacy

PBO = Placebo

Descriptive p-values from two-sample t-test or Fisher's exact test may be reported for select PD and efficacy measures. Alternative statistical testing methods may be considered depending on the data distribution assumptions.

For statistical summary of PK concentration values, assessments that are below the lower limit of quantification (LLOQ) will be set to zero prior to summarization. For graphical presentation of

individual concentrations vs. time plot, concentrations below LLOQ will be set to half of LLOQ and LLOQ will be displayed on the graph. PD results that are either below or above the limit of quantification will not be imputed. For non-PK/PD measures, results that are below LLOQ will be set to half of LLOQ prior to summarization or graphing. Results that are above the upper limit of quantification (ULOQ) will be imputed to the ULOQ for summarization or graphing.

All data collected will be listed by study part, dose level and subject, unless noted otherwise.

8.2. Subject Disposition

The number of subjects screened, screen failed, randomized, and treated will be tabulated.

For subjects who participate in the screening phase and are screen failures, screen-failure reason, and inclusion criteria not met and/or exclusion criteria not met will be listed. Reason for screen failure, inclusion criteria not met, and exclusion criteria met will be tabulated.

Subject disposition for the Randomized Analysis Set will be summarized. The number and percentage of subjects who completed the study, discontinued from the study early, completed treatment and discontinued treatment early (Part B only) will be summarized. The primary reason for early study discontinuation and early treatment discontinuation (Part B only) will be tabulated.

8.3. Protocol Deviations

Protocol deviations will be reviewed periodically over the course of the study. The review process, definition of deviation categories, and the classification of a deviation as Major or Minor are detailed in the Protocol Deviation Plan.

Protocol deviations will be summarized for the Randomized Analysis Set. The number and percentage of subjects with any (major or minor) protocol deviations overall and for each deviation category will be presented. Major protocol deviations will also be summarized.

A listing of protocol deviations will be presented.

8.4. Extent of Exposure and Study Drug Administration

Extent of exposure and study drug administration will be summarized for the Safety Analysis Set.

The number of infusions will be summarized as both a continuous and categorical variable. Duration of exposure, duration of on-study follow-up and the number and percentage of subjects with at least one study drug infusion with modification (i.e., infusion rate change, interruption, or re-start) will be descriptively summarized. The number and percentage of subjects in Part B that had a dose adjustment will also be tabulated.

The amount of siRNA component and total weight of AOC 1001 administered in mg and mg/kg will be descriptively summarized overall and by nominal study day, where overall is based on the sum across all administered infusions. Percentage of study drug administered by nominal study visit and the average percentage of study drug administered across planned administrations will be descriptively summarized.

8.5. Demographics and Baseline Characteristics

Demographic variables will be summarized using descriptive statistics for the Safety Analysis Set. Demographic variables include age (years), sex, race (a subject can select multiple race categories), ethnicity, weight (kg), height (cm) and body mass index (kg/m^2). Subjects who select multiple race categories will be classified as "multiple" and subjects who only select one race category will be counted in that respective category.

Baseline data will be summarized for the following variables: hand grip strength from QMT, ankle dorsiflexion strength from QMT, MIRS both as a continuous and categorical variable, hand, thumb, and middle finger opening time (vHOT), and 10MWRT. Additional baseline characteristics will be summarized.

8.5.1. DM1 History

DM1 history will be summarized using descriptive statistics for the Safety Analysis Set. DM1 history variables that will be presented as continuous variables include age at symptom onset (years), time since symptom onset (years), age at DM1 diagnosis (years), and time since DM1 diagnosis (years). The following variables will be presented as categorical variables: dominant hand (right, left, or not applicable), device use/therapy history, how the subject was diagnosed, DM1 natural history study participation, participation in END-DM1, education level and employment status.

DMPK CTG repeat length will be summarized both as a continuous and a categorical variable (< 100, ≥ 100 to < 500, ≥ 500 to < 1000, ≥ 1000). The maximum repeat length from allele 1 and allele 2 from the AOC 1001-CS1 Central Laboratory will be summarized

All DM1 History and DMPK CTG repeat length data will be provided in a by-subject data listing.

8.5.2. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or newer. Medical history will be summarized for the Safety Analysis Set by system organ class (SOC) and preferred term. A subject will only be counted once per SOC or per preferred term for the summary. Medical history where DM1 contributes to the event will also be summarized.

8.6. Efficacy Analyses

Efficacy analyses will be summarized using the Full Analysis Set. Graphical display of subject response data may be prepared.

8.6.1. Myotonia Video Hand Opening Time (vHOT)

Opening time (secs), change from baseline, and percent change from baseline for middle finger and thumb will be summarized, by visit, using descriptive statistics. Mean (± SE) results and change from baseline over time will be plotted.

The impact of starting anti-myotonia medication during the study on opening time may be assessed. A sensitivity analysis excluding assessments performed on the non-dominant hand may be considered.

Data from the vHOT trials will be provided in a by-subject data listing.

8.6.2. Percentage of Subjects Needing Myotonia Medications after Dosing

The number and percentage of subjects that had prior myotonia medication (i.e. anti-myotonia agent) will be tabulated. The number and percentage of subjects that initiated myotonia medications after first dose of study drug will also be tabulated. Myotonia medication use status will be identified from the "anti-myotonia agent" category recorded on the concomitant medication eCRF. The number for days from the date of first dose to restarting myotonia medication will be descriptively summarized for those that restarted.

8.6.3. Quantitative Myometry Test (QMT)

The observed force, change from baseline, and percent change from baseline will be summarized, by visit, using descriptive statistics for each muscle group

Observed value and change from baseline for percent of predicted normal will be summarized, by visit, using descriptive statistics for:

- Each muscle group score (ankle dorsiflexion, knee flexion, knee extension, elbow flexion, elbow extension, and hand grip)
- Total composite QMT score
- Upper extremity muscle group composite QMT score
- Lower extremity muscle group composite QMT score.

Responder analysis based on percent of predicted normal for each muscle group or composite QMT scores (total, lower extremity, upper extremity) may be defined and performed.

A sensitivity analysis excluding assessments performed on the non-dominant sided may be considered.

All QMT data will be provided in a by-subject data listing.

8.6.4. Pinch Strength by Dynamometer

Pinch strength, change from baseline, and percent change from baseline will be summarized, by visit, using descriptive statistics.

A sensitivity analysis excluding assessments performed on the non-dominant hand may be considered.

Data from pinch strength trials will be provided in a by-subject data listing.

8.6.5. 10-Meter Walk/Run Test (10MWRT)

For first and average 10MWRT trial results, observed value and change from baseline for the time (secs) and velocity (m/sec) will be summarized, by visit, using descriptive statistics. Mean (± SE) results and change from baseline over time will be plotted.

10MWRT times may be summarized by walk/run status at baseline and by assistive device use at baseline (yes, no). Change in walk/run status and assistive devices use may be explored. Subject performance relative to normative data may also be investigated.

Data from 10MWRT trials will be provided in a by-subject data listing.

8.6.6. DM1 Neuromuscular Severity Measures (DM1-NSM)

There are three DM1-NSM questionnaires:

1. For DM1-NSM (daily), the observed value, change from baseline, and percent change from baseline for each individual question, domain and total score will be summarized by visit (baseline, Days 36, 43, 85, 92, 176, and 183).

2. For DM1-NSM-PGIS, the observed value for each question and change from baseline will be summarized, by visit (baseline, Days 36, 43, 85, 92, 176, 183), using descriptive statistics. Responses for each question will also be tabulated.

   If sample size permits, an anchor analysis will be performed for Part B subjects based on the change from baseline to Day 183 on the PGIS question: 'Describe the severity of your DM1 over the past week' ('Severity'). Subjects will be categorized as follows:

   - 'Decrease PGIS' if Baseline > Day 183
   - 'No Decrease PGIS' if Baseline ≤ Day 183

   Day 183 results will be summarized by category ('Decrease PGIS', 'No Decrease PGIS') for the following variables: 10MWRT, Remote Hand Grip Strength, Pinch Strength, vHOT, Ankle Dorsiflexion from the QMT, Supine FVC and Sitting FVC.

3. For DM1-NSM-PGIC the observed value for each question will be summarized descriptively for post-baseline visits (Days 43, 92 and 183) and responses will be tabulated.

All DM1-NSM data will be provided in a by-subject data listing.

8.6.7. Timed Up and Go (TUG)

TUG time (secs), change from baseline, and percent change from baseline will be summarized, by visit, using descriptive statistics for the comfortable pace and maximum pace. The number and percent of subjects with TUG time < 10 seconds will be tabulated for baseline and by visit. A TUG time >= 10 seconds indicates reduced physical capacity when compared with healthy elders or young adults attending a primary care visit (Kear et al., 2017). Mean (± SE) results and change from baseline over time will be plotted.

The relationship between time to complete the task and assisted device use, and timing to complete the task under a comfortable and maximum pace may be explored. The time to complete the task by assistive device use at baseline (yes, no) and change in assistive devices use throughout the study may be explored. Subject performance relative to normative data may also be investigated.

Data from the TUG evaluations will be provided in a by-subject data listing.

8.6.8. Timed 4-Stair Climb and Timed 4-Stair Descend

Observed value, change from baseline, and percent change from baseline for 4-stair climb and 4-stair descend times (seconds) and velocity (steps/second) will be summarized, by visit, using descriptive statistics. Mean (± SE) results and change from baseline over time will be plotted.

Relationships between railing use and manner of ascent and time to complete the task may be explored. Subject performance relative to normative data may also be investigated.

Data from the 4-stair ascent and descent trials will be provided in a by-subject data listing.

8.6.9. Spirometry

The observed value, change from baseline, and percent change from baseline values will be summarized, for best result and by visit, using descriptive statistics for the following parameters:

- PFT sitting and supine: FVC (L), percent predicted FVC (%), FIVC after Ex (L)
- Peak cough flow sitting and supine: peak expiratory flow (L/s)
- MIP (cmH_20)
- MEP (cmH_20)

where PFT = Pulmonary function testing; FVC = Forced Vital Capacity, MEP = Maximal Expiratory Pressure, MIP = Maximal Inspiratory Pressure, FIVC after Ex = Forced Inspiratory Vital Capacity after Expiration.

The number and percentage of subjects with a percent predicted FVC value > 80% will be tabulated at baseline and by visit.

Data from the spirometry assessments will be provided in a by-subject data listing.

8.6.10. Manual Muscle Testing (MMT)

The observed value, change from baseline, and percent change from baseline for the individual MMT tests and MMT composite scores (total, total muscle, upper extremity, lower extremity) will be summarized, by visit, using descriptive statistics.

All MMT data will be provided in a by-subject data listing

8.6.11. 9-Hole Peg Test (9HPT)

9HPT time (secs), change from baseline, and percent change from baseline for average and fastest times will be summarized, by visit, using descriptive statistics. Subject performance relative to normative data may also be investigated.

A sensitivity analysis excluding assessments performed on the non-dominant hand may be considered.

All 9HPT data will be provided in a by-subject data listing.

8.6.12. Muscular Impairment Rating Scale (MIRS)

The MIRS score and change from baseline will be summarized, by visit, using descriptive statistics. MIRS scores will also be tabulated.

All MIRS data will be provided in a by-subject data listing.

8.6.13. Remote Hand Grip Strength

Hand grip strength, change from baseline, and percent change from baseline will be summarized, by visit, using descriptive statistics. Observed value and change from baseline for % of predicted normal will be descriptively summarized by visit.

A sensitivity analysis excluding assessments performed on the non-dominant hand may be considered.

Data from remote hand grip strength trials will be provided in a by-subject data listing.

Relationship between hand grip strength from QMT and remote hand grip strength may be explored.

8.6.14. Myotonic Dystrophy Health Index (MDHI)

The observed values, change from baseline, and percent change from baseline for the total MDHI score and MDHI subscale scores will be summarized, by visit, using descriptive statistics.

All MDHI data will be provided in a by-subject data listing.

8.6.15. DM1-Activ

The DM1-Activ centile metric score, change from baseline, and percent change from baseline will be summarized, by visit, using descriptive statistics.

All DM1-Activ data will be provided in a by-subject data listing.

8.6.16. Fatigue and Daytime Sleepiness Scale (FDSS)

The FDSS centile metric score, change from baseline, and percent change from baseline will be summarized, by visit, using descriptive statistics.

All FDSS data will be provided in a by-subject data listing.

8.6.17. Clinician Global Impression of Severity (CGIS) and Clinical Global Impression of Change (CGIC)

CGIS score will be summarized, by visit, using descriptive statistics. Responses will also be tabulated by visit. CGIC score will be tabulated and summarized using descriptive statistics by post-baseline visit.

An anchor analysis will be performed for Part B subjects using CGIC. Subjects will be categorized into one of two groups (Better CGIC or Not Better CGIC) based on their CGIC result at Day 183. The Better CGIC group will include subjects with result of 'Very much better' or 'moderately better'. The Not Better CGIC group will include subjects with a non-missing result that was not 'Very much better' or 'moderately better'. Day 183 results by CGIC categories will be summarized for the following variables: 10MWRT, hand grip strength, pinch strength, vHOT, ankle dorsiflexion from QMT, Supine FVC, Sitting FVC. A sensitivity analysis using alternative category definitions may be considered.

A sensitivity analysis that excludes assessments where the evaluator is different from the evaluator at baseline may be considered.

All CGIS and CGIC data will be provided in a by-subject data listing.

8.6.18. EuroQol 5 Dimension 5 Level Quality of Life Scale (EQ-5D-5L)

Observed values, change from baseline, and percent change from baseline for EQ-5D-5L index values and EQ VAS will be summarized, by visit, using descriptive statistics. Responses for each EQ-5D-5L dimension will be tabulated by visit.

All EQ-5D-5L data will be provided in a by-subject data listing.

8.7. Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed using the PK Analysis Set with siDMPK.19 levels in plasma, urine, and muscle as the primary analyte. For intact AOC 1001 and total AV01mAb, available concentrations will be listed. Analyses without outliers may be performed. Unless noted otherwise, the following unit convention for concentration data will be used:

- Muscle: nM and ng/g (nM for figures)
- Plasma: nM and ng/mL (ng/mL for figures)
- Urine: nM and ng/mL

The pharmacokinetic parameters in Table 12 will be calculated by non-compartmental analysis. Additional PK parameters may be derived.

Table 11: Pharmacokinetic Parameters

Part A

Matrix/ Analyte	Dose	Infusion Day	PK Parameter*	Unit	Definition
Plasma (siDMP K.19)	Single (Part A)	D1	C_{max}	ng/mL	Maximum observed plasma concentration
			t_{max}	hr	Time of maximum observed plasma concentration
			$AUC_{0\text{-last}}$	ng*hr/mL	Area under the plasma concentration-time curve from dosing to the last quantifiable concentration following post infusion, calculated using the linear-up/log-down trapezoidal method
			$AUC_{0\text{-inf}}$	ng*hr/mL	Area under the plasma concentration-time curve from dosing to infinity, following post infusion, calculated using the linear-up/log-down trapezoidal method
			$t_{1/2}$	hr	elimination half-life
			V	mL/kg	Volume of distribution
			CL	mL/hr/kg	Systemic clearance

Part B

Matrix /Analyte	Dose	Infusion Day	PK Parameter*		Definition
Plasma (siDMP K.19)	Single	D1	C_{maxd1}	ng/mL	Maximum observed plasma concentration
			$\mathbf{t_{maxd1}}$	hr	Time of maximum observed plasma concentration
			$AUC_{0\text{-lastd1}}$	ng*hr/mL	Area under the plasma concentration-time curve from dosing to the last quantifiable concentration following post infusion, calculated using the linear-up/log-down trapezoidal method
			$AUC_{0\text{-infd1}}$	ng*hr/mL	Area under the plasma concentration-time curve from dosing to infinity, following post infusion, calculated using the linear-up/log-down trapezoidal method
			$t_{1/2}$	hr	elimination half-life
Plasma	Multiple	D43	C_{maxd43}	ng/mL	Maximum observed plasma concentration
			t_{maxd43}	hr	Time of maximum observed plasma concentration

Plasma	Multiple	D92	C_{maxd92}	ng/mL	Maximum observed plasma concentration
			t_{maxd92}	hr	Time of maximum observed plasma concentration
			$AUC_{0\text{-}lastd92}$	ng*hr/mL	Area under the plasma concentration-time curve from dosing to the last quantifiable concentration following post infusion, calculated using the linear-up/log-down trapezoidal method, D1
			$AUC_{0\text{-}infd92}$	ng*hr/mL	Area under the plasma concentration-time curve from dosing to infinity, following post infusion, calculated using the linear-up/log-down trapezoidal method, D1
			$t_{1/2}$	hr	elimination half-life
			V_{ss}	mL/kg	Volume of distribution at steady state
			CL_{ss}	mL/hr/kg	Systemic clearance at steady state
			RA		Accumulation index based on appropriate PK parameter (i.e., C_{max}, AUC) derived after first (D1) and third (D92) doses
Urine	Single (Parts A and B)	D1	Ae_{24}	Mg	Amount excreted in urine over 0-24 hours
			Fe_{24}	%	Percent of administered dose excreted unchanged un urine during the time interval 0 to 24 hours; calculated as (Ae24/dose)*100

*Plasma and urine PK parameters will be derived for total siRNA component of AOC 1001.

Concentration data (siDMPK.19) for plasma, urine and muscle will be descriptively summarized by nominal time and dose level. Individual plasma (siDMPK.19) and mean concentrations (±SD) versus nominal time will be plotted on linear and semi-logarithmic scales by dose level. Box plots of muscle concentration data (concentration at Day 43 for AOC 1001 1 mg/kg and Day 92 for AOC 1001 2 mg/kg and 4 mg/kg) versus dose level will be presented. Mean (±SD) plasma concentration over time for all 3 analytes (siDMPK.19, intact AOC 1001 and total AV01mAb) (nM) will be presented.

Summary statistics (number of observations, arithmetic mean, median, standard deviation, standard error of the mean, minimum, maximum, geometric mean and coefficient of variation) will be presented for all relevant PK parameters. The relationship between PK parameters and dose level will be explored. All concentration data and PK parameters will be listed.

Dose proportionality of relevant plasma PK parameters following single dose will be assessed using a power model at Day 1 (only Day 1). A statistical linear relationship between ln-transformed PK parameters (AUC and C_{max}) and ln-transformed dose will be evaluated using the following equation, where Y represents the PK parameter of interest, β0 represents the intercept, β1 represents the slope, and ε represents the error:

$$Ln(Y) = \beta 0 + \beta 1 \, Ln \, (Dose) + \varepsilon$$

Regression parameter estimates and associated 90% CIs from the dose proportionality analysis will be reported.

8.8. Pharmacodynamic Analyses (PD)

PD analyses will be performed using the PD Analysis Set in muscle biopsy samples according to schedules outlined in the current protocol.

8.8.1. DMPK mRNA Levels in Muscle

The observed value for DMPK mRNA relative expression level, percent of baseline) and percent change from baseline will be descriptively summarized by visit. Individual and mean DMPK mRNA level (% of baseline, percent change from baseline, and relative expression) will be graphed by visit and dose level. All DMPK mRNA data will be provided in a by-subject data listing.

8.8.2. Spliceopathy in Muscle

For the spliceopathy scores (22-, 12- and 4-gene panels) and scaled PSI and PSI for each gene, the observed value and change from baseline will be summarized using descriptive statistics by visit. Individual and mean PSI and scaled PSI for each gene, and the spliceopathy score will be graphed by visit and dose level.

Individual and mean results across genes may be presented. The relationship between baseline and post-baseline PD biomarkers may be explored. Subgroup analyses based on baseline levels of PD biomarkers may be explored. All spliceopathy data will be provided in a by-subject data listing.

8.9. Safety Analyses

Safety analyses will be summarized using the Safety Analysis Set, unless otherwise stated.

8.9.1. Adverse Events

Adverse Events (AEs) will be coded using MedDRA version 24.0 or newer. An AE (classified by preferred term) will be considered a treatment emergent adverse event (TEAE) if the onset date/time was on or after the date/time of the first dose of study drug. AEs reported on study day 1 without an onset time will be considered as TEAEs.

The number of TEAE and number and percentage of subjects reporting a TEAE will be summarized. TEAEs will be tabulated by SOC and preferred term; by preferred term; and by SOC, preferred term and severity. A subject will only be counted once per SOC or per preferred term for the summary, or once per severity per SOC or preferred term for summary tables by severity.

The following will be summarized by SOC and preferred term:

- TEAEs

- TEAEs related to study drug
- TEAEs related to study procedure
- Severe TEAEs
- Severe TEAEs related to study drug
- Severe TEAEs related to study procedure
- Serious TEAEs
- Serious TEAEs related to study drug
- Serious TEAEs related to study procedure
- TEAEs leading to discontinuation of study drug
- TEAEs with a fatal outcome

An overall summary of TEAEs with the above AE categories will be provided.

The number and percentage of subjects reporting an infusion-related reaction (IRR), hypersensitivity reaction, and cutaneous involvement will be tabulated along with the associated preferred term.

All AEs will be listed. Separate listings will be presented for AEs with a fatal outcome, AEs leading to treatment discontinuation and serious AEs.

8.9.2. Prior, Baseline and Concomitant Medication

Medications will be coded using the WHO Drug Dictionary March 2021 B3 Global or later. Results will be tabulated by anatomical therapeutic chemical (ATC) class level 4 and preferred term. The number and percentage of subjects taking each drug class and medication preferred term will be tabulated. A subject will be counted once per drug class or per medication preferred term. Prior, baseline and concomitant medications will be summarized separately.

All reported medications will be provided in a by-subject data listing.

8.9.3. Concomitant Procedures

Concomitant procedures will be coded using MedDRA version 24.0 or newer. All reported concomitant procedures will be listed.

8.9.4. Clinical Laboratory Parameters

Clinical laboratory values will be presented in conventional units. Laboratory test results from the central laboratory are eligible for summarization; results from local laboratories will not be used for summarization.

Observed value and change from baseline by visit will be summarized for clinical laboratory parameters for chemistry, hematology, and urinalysis. Mean (± SE) results and change from baseline over time will be plotted.

The number and percentage of subjects meeting the following criteria, for any post-baseline visit, will be summarized:

- Bilirubin > 2 x ULN
- ALP > 3 x ULN
- Hemoglobin > 2 g/dL decrease from baseline
- Hemoglobin < 8.5 g/dL
- ALT or AST > 3 x ULN (or > 3x baseline or > 300 U/L [whichever is lower] in subjects with elevated baseline)
- ALT or AST > 5 x ULN (or > 5x baseline in subjects with elevated baseline)
- ALT or AST > 8 x ULN (or > 8x baseline or > 500 U/L [whichever is lower] in subjects with elevated baseline)
- ALT or AST > 3 x ULN (or > 3x baseline or > 300 U/L [whichever is lower] in subjects with elevated baseline) and INR > 1.5 x ULN
- ALT or AST > 3 x ULN (or > 3x baseline or > 300 U/L [whichever is lower] in subjects with elevated baseline) and bilirubin > 1.5 x ULN
- ALT or AST > 3 x ULN (or > 3x baseline or > 300 U/L [whichever is lower] in subjects with elevated baseline) and bilirubin > 2 x ULN
- ALT or AST > 3 x ULN (or > 3x baseline or > 300 U/L [whichever is lower] in subjects with elevated baseline) and bilirubin > 2.5 x ULN
- ALT or AST > 3 x ULN (or > 3x baseline or > 300 U/L [whichever is lower] in subjects with elevated baseline) and a TEAE with preferred term in (nausea, pyrexia, rash, vomiting, decreased appetite, abdominal pain, fatigue)
- ALT or AST > 3 x ULN (or > 3x baseline or > 300 U/L [whichever is lower] in subjects with elevated baseline) and elevated bilirubin to > 2x ULN or INR > 1.5x ULN
- GLDH ≥ 2.5x ULN and bilirubin ≥ 2x ULN
- Hemoglobin < 10 g/dL and > 1 g/dL decrease from baseline
- Hemoglobin > 2 g/dL decrease from baseline, and MCV < LLN
- Hemoglobin < 8.5 g/dL, and MCV < LLN

Evaluation of drug-induced serious hepatotoxicity (eDISH) plots will be prepared, with bilirubin [/ ULN] plotted on the y-axis (log scale) and ALT [/ ULN] on the x-axis (log scale).

Profile plots for select laboratory parameters may be generated.

Pregnancy-related laboratory values will not be tabulated.

All clinical laboratory data including results from local laboratories will be provided in a by-subject data listing.

8.9.5. Vital Signs, Height, and Weight

Observed value and change from baseline by visit will be summarized for height (cm), weight (kg), derived BMI, pulse (beats/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), respiratory rate (breaths/min), and temperature (Celsius). All vital sign data will be listed.

8.9.6. Electrocardiogram

Triplicate 12-lead ECGs will be performed at time-points described in the SOA; the mean of triplicate readings will be used for descriptive summaries. All ECGs will be centrally read.

ECG parameters of PR interval (ms), QRS duration (ms), RR interval (ms), Q-T interval (ms), QTcF, QTcB and Heart Rate (HR; bpm) will be summarized using descriptive statistics for the observed value and change from baseline. QTcB is QT corrected for HR using Bazett's method i.e., $QTcB=QT/RR^{1/2}$ and QTcF is QT corrected for HR using Fridericia's method, i.e., $QTcF=QT/RR^{1/3}$.

A categorical analysis of QTcF data will be presented. The number and percentage of subjects with QTcF results meeting the criteria below will be tabulated.

Absolute QTcF interval prolongation

- Pre-Dose QTcF interval > 500 ms
- Pre-Dose QTcF interval > 480 ms
- Pre-Dose QTcF interval > 450 ms
- Post-Dose QTcF interval > 500 ms
- Post-Dose QTcF interval > 480 ms
- Post-Dose QTcF interval > 450 ms

Change from baseline in QTcF interval

- QTcF interval increase from baseline > 60 ms
- QTcF interval increase from baseline > 30 ms

Shift tables may be presented for changes from baseline to post-baseline maximum and post-baseline minimum. Mean (± SE) result and change from baseline over time for QTcF, PR interval and QRS duration will be plotted by dose level.

All ECG data will be provided in a by-subject data listing.

Relationship between AOC 1001 exposure, plasma total siRNA concentration, and QTc analysis will be explored and results will be summarized in a separate report.

8.9.7. Echocardiogram

Echocardiogram will be centrally read. The observed value and change from baseline will be summarized, by visit, using descriptive statistics for the following echocardiogram parameters from the central cardiac imaging lab:

- LV Ejection Fraction 2D (%)
- Deceleration time (sec)
- E/A Ratio (n/a)
- LA Volume (ml)

Additional echocardiogram parameters may be summarized.

All echocardiogram data will be provided in a by-subject data listing.

8.9.8. Columbia-Suicide Severity Rating Scale (C-SSRS)

The number of subjects answering 'yes' to any suicidal ideation questions at baseline, at any post-baseline visit, and by visit will be summarized. Shift tables from baseline to worst post-baseline in ideation severity will be presented.

All C-SSRS data will be provided in a by-subject data listing.

8.9.9. Anti-drug Antibodies

Analyses of the anti-AOC 1001 antibodies will be conducted using the Safety Analysis Set.

ADA titers for subjects with a positive confirmatory assay, will be summarized by visit using descriptive statistics. The number and percentage of subjects with positive pre-dose ADA response and with positive post-dose ADA response will be provided.

All ADA data will be provided in a by-subject data listing.

9. CHANGES TO ANALYSES SPECIFIED IN THE PROTOCOL

Percent change from baseline for spliceopathy is listed as a secondary endpoint but will not be derived. Observed and change from baseline in spliceopathy will be summarized

A listing of AEs leading to study drug discontinuation will be provided, not AEs leading to study discontinuation.

10. REFERENCES

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11. APPENDICES

11.1. Appendix

11.1.1. Schedule of Assessment (Part A; Study AOC 1001-CS1 Protocol Version 5.0)

Part A Study Period	Screening	Baseline[a]	Dosing	Post-Treatment (26 Weeks)											Extended Follow-up[c]
Study Day	D-42 to D-8	D-14 to D-1	D 1	D 2	D 8	D 15	D 29	D 43	D 71	D 92	D 120	D 141	D 162	D 183/EOPT[b]	
Visit Window (+/-days)	0	0	0	0	±1	±2	±3	±3	±5	±5	±7	±7	±7	±7	
Clinic Visit	X	X	X	X	X		X	X		X				X	
Clinic Visit or Home Visit[d]						X			X		X				
Home Visit via Telehealth												X	X		X
Pre-Screening Informed Consent[e]	No time limit														
Main Informed Consent	X														
Overnight Clinic Stay			X												
Inclusion/Exclusion Criteria	X	X													
Demographics, Disease History	X														
Medical History[f]	X	X	X[1]												
Randomization[g]			X[1]												
Study drug administration			X												
Clinical Safety Assessments															
Height	X														
Body Weight	X	X												X	
Physical Exam[h]	X		X[1]	X	X		X	X						X	
Vital Signs[i]	X		X[1]	X	X	X	X	X		X	X			X	
12-lead ECG (triplicate)[j]	X	X	Table 2		X		X	X		X				X	
Echocardiogram[k]		X												X	
Adverse Events Monitoring[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments															
HIV, Hepatitis B & C	X														
Pregnancy Test[m]	X	X	X[1]				X			X				X	X
FSH[n]	X														
DMPK genetic test[o]	X														
Chemistry, hematology, and urinalysis	X		X[1]	X[2]	X	X	X	X	X	X	X			X	
Thyroid panel, HbA1c, coagulation	X													X	
TSAT, TIBC, Iron, Ferritin	X		X[1]		X	X	X	X		X	X			X	
Cardiac Troponin			X[1]					X		X				X	

Part A Study Period	Screening	Baseline[a]	Dosing	Post-Treatment (26 Weeks)											Extended Follow-up[c]
Study Day	D-42 to D-8	D-14 to D-1	D 1	D 2	D 8	D 15	D 29	D 43	D 71	D 92	D 120	D 141	D 162	D 183/EOPT[b]	
Visit Window (+/-days)	0	0	0	0	±1	±2	±3	±3	±5	±5	±7	±7	±7	±7	
Archived Blood			X[1]		X			X		X				X	
Archived Blood for DNA (Optional)[p]			X[1]												
Pharmacokinetic and ADA Assessments															
Plasma and Urine Sampling			Table 2		X	X[q]	X			X				X	
Exploratory Efficacy Assessments															
DM1-NSM (daily)[r]		X						X		X				X	
DM1-NSM-PGIS (weekly)[r]		X						X		X				X	
DM1-NSM-PGIC[r]								X		X				X	
FDSS[s]		X								X				X	
DM1-Activ[s]		X								X				X	
EQ-5D-5L[s]		X								X				X	
MDHI[s]		X												X	
C-SSRS[s]		X	X[1]		X		X	X		X				X	
Measures of function and strength[t]	X	X								X				X	
Myotonia (vHOT)	X	X						X		X				X	
Remote Hand Grip Strength[u]		X					X		X		X				
MIRS	X	X								X				X	
CGIS, CGIC		X[v]								X				X	
Tissue Pharmacokinetic, Pharmacodynamic, and Secondary Endpoint Assessments															
Muscle Needle Biopsy[w]		X						X		X					

ADA = anti-drug antibodies; CGIC =clinical global impression of change; CGIS = clinical global impression of severity; C-SSRS= Columbia-Suicide Severity Rating Scale; D=Day
EOPT = End of Post-Treatment; EQ-5D-5L = EuroQol 5 Dimension 5 Level quality of life scale; FDSS= fatigue and daytime sleepiness scale; HbA1c = hemoglobin A1c; MDHI = Myotonic Dystrophy Health Index; DM1-NSM= DM1 neuromuscular severity measure; TIBC =Total iron binding capacity; TSAT = Transferrin Saturation; vHOT = Video Hand Opening Time

Part A Footnotes:

(a) **Baseline:** These assessments can be performed over multiple days or at the same visit (anytime between Day -14 to Day -1). Baseline visit should not be performed until participant has met eligibility criteria. All assessments must be completed prior to start of Day 1 infusion.

(b) **Day 92 and 183 (EOPT) Visits – Endpoint Scheduling Flexibility:** Day 92 and 183 (or EOPT) may be performed over multiple days for scheduling flexibility to allow collection of exploratory efficacy endpoints. If participant discontinues any time prior to Day 183, the EOPT visit should be performed and the medical monitor (or designee) should be informed as soon as possible and be involved in the planning of subsequent follow up to ensure patient safety. All assessments indicated should be performed when possible, unless an alternate follow-up schedule is discussed with medical monitor (or designee).

(c) **Extended follow-up:** For participants that discontinue before Day 183 or do not proceed to OLE, site staff will monitor participants for safety every 3 months (quarterly) (+/- 7 days) for a total of 9 months from the last dose of study drug. Data including AEs and Concomitant Medications/Procedures will be collected. Follow-up may be in the form of routine clinic visits, or via telephone/telehealth or e-mail with the patients/caregivers. See footnote (m) re: pregnancy testing at the last visit.

(d) **Clinic Visit or Home Visit:** Visits may be performed in clinic or remotely. Remote visits may utilize telemedicine with site personnel in conjunction with mobile home nurse contracted by sponsor. If a clinic visit cannot occur due to unforeseen circumstances (e.g., pandemic travel restrictions), a home health visit or local lab collection may be scheduled to obtain laboratory samples per discussion with Sponsor.

(e) **Pre-screening Informed Consent (Optional):** Can be used for *DMPK* genetic testing and/or to remote pre-screen participants in advance of 1st in-clinic visit to reduce patient burden and time requirements for preliminary eligibility confirmation.
(f) **Medical History:** Changes from Screening to Randomization to be collected unless an event fulfills the criteria of an SAE.
(g) **Randomization:** May be performed on Day -1 to allow scheduling flexibility for muscle needle biopsy and unblinded pharmacy preparation of study drug. Dose will be calculated based on body weight recorded at Baseline.
(h) **Physical Exam:** Full physical exam to be given at Screening. At all other specified visits, an abbreviated physical exam (assessment of heart, lungs, abdomen, and symptom directed examination, if any symptoms) to be given as indicated to assess changes from Screening.
(i) **Vital Signs:** BP, HR, RR, temperature
(j) **12-lead ECG (triplicate):** All ECGs are 12-lead in triplicate using study provided equipment. Timing of assessments is shown in Table 2. When ECG and blood sample collection occur at the same time for PK, ECGs should be performed prior to drawing of blood samples.
(k) **Echocardiogram:** Baseline may be performed up to one month prior to Day 1 after confirmation of eligibility. Day 183 (or EOPT) may be performed up to one month prior to Day 183.
(l) **AE Monitoring:** SAEs should be reported starting at time of informed consent. AEs should be reported starting at time of study drug administration (Day 1), or if related to protocol-mandated assessments prior to start of study drug administration.
(m) **Pregnancy Test:** For women who are not post-menopausal and/or surgically sterile. Serum pregnancy test is performed at Screening and all other non-dosing visits after Day 1. Urine pregnancy test is performed on Baseline visit and the day of dosing. During Extended Follow Up period, a urine pregnancy test should be performed ONLY at the last visit either in-clinic or remotely by home visit.
(n) **FSH:** For post-menopausal women to confirm post-menopausal status.
(o) ***DMPK* Genetic Test**: All participants will have a blood sample analyzed by the AOC 1001-CS1 genetic testing lab to determine DMPK CTG repeat length and the sample may be collected at any time throughout the study. The sample may be collected via home health or in-clinic. For eligibility, historical genetic test results may be used after discussion with the medical monitor. The sample may be collected prior to screening, after signing a prescreening consent form.
(p) **Archive for DNA:** Participants who give additional consent (optional) consent will have an archived blood sample collected any time on trial after randomization for DNA isolation. Future potential analyses will be limited to further characterizing the disease (DM1), the drug (AOC 1001), and/or their interactions.
(q) **Day 15 PK sampling**: Only collected if participant attends the visit in-clinic.
(r) **DM1-NSM (daily) and DM1-NSM-PGIS (weekly) and DM1-NSM-PGIC:** Completed between 6:00-10:00pm at home. There are 4 assessment periods: before Day 1, 43, 92, and 183. DM1-NSM must be completed daily for at least 7 days prior to Day 1 (Day -7 to Day -1). DM1-NSM-PGIS is performed on Day -1. DM1-NSM will be completed daily for 14 consecutive days prior to the visits on Day 43, 92, and 183. DM1-NSM-PGIS will be completed at the end of each week after DM1-NSM is performed (Day 7 of each week). DM1-NSM-PGIC is completed after DM1-NSM-PGIS on the last day of each assessment period after baseline.
(s) **PROs (in-clinic):** Perform in the same order each time and before all other clinic procedures on the same day.
(t) **Measures of function and strength**: Assessments will be performed once at Screening and once at Baseline and cannot be performed on the same day. The following assessments will be collected in the order specified in Section 7.4, including: MMT of selected muscle groups, QMT of selected muscle groups, Pinch Strength, 10-meter walk/run test (10MWRT), Timed up and go (TUG), Timed 4 stair climb, Timed 4 stair descend, 9-hole peg test, spirometry, and myotonia. Measures of function and strength should be performed after PROs but before laboratory and biopsy procedures on the same day.
(u) **Remote hand grip strength:** To be performed during baseline via remote visit, Day 29 by patient reporting, Day 71 by remote visit, Day 120 by patient reporting. Windows for the procedure on Day 29, 71, and 120 are ± 4 days.
(v) **CGIC:** Change scale not to be assessed at Baseline.
(w) **Muscle needle biopsy:** If multiple assessments are performed on a single day, biopsy should be performed as the last assessment of the day. Time of day for biopsies should be kept similar across successive biopsies for each patient.

Time-points:
(1) Predose
(2) 24 hours after start of infusion

11.1.2. Schedule of Part A Pharmacokinetic, ECG, ADA and Urine Collection (Study AOC 1001-CS1 Protocol Version 5.0)

Study Day	Time	Window	Triplicate ECG	PK	ADA	Spot Urine[a]	24-hr Urine[b]
D1	-1.5 hr prior to start of D1 infusion	± 15 mins	X			X	
D1	-1 hr prior to start of D1 infusion	± 15 mins	X				
D1	-0.5 hr prior to start of D1 infusion	± 10 mins	X	X	X		
D1	start of D1 infusion						X Samples pooled 0-6 hr, 6-12 hr, 12-24 hr
D1	at end of D1 infusion	± 10 mins	X	X			
D1	1 hr after end of D1 infusion	± 10 mins	X	X			
D1	2 hr after end of D1 infusion	± 20 mins	X	X			
D1	6 hr after end of D1 infusion	± 20 mins	X	X			
D2	24 hr after start of D1 infusion	± 2 hrs	X	X			
D8	7 days after start of D1 infusion	± 1 day	X	X			
D15	14 days after D1 infusion	± 2 days		X if in clinic[c]			
D29	28 days after D1 infusion	± 3 days	X	X	X	X	
D43	42 days after D1 infusion	±3 days	X	X			
D92	91 days after D1 infusion	±5 days	X	X			
D183 / EOPT	182 days after D1 infusion or at EOPT visit	±7 days	X	X	X		

[a] Spot urine: anytime
[b] 24-hr urine: Void prior to start of D1 infusion.
[c] PK sampling: Only collected if patient attends the visit in-clinic (not to be collected if performing visit by home health).

11.1.3. Schedule of Assessment (Part B; Study AOC 1001-CS1 Protocol Version 5.0)

Part B Study Period	Screening	Baseline[a]	Treatment (13 Weeks)									Post-Treatment (13 Weeks)[b]					Extended Follow-up[c]
Study Day	D-42 to D-8	D-14 to D-1	D 1	D 2	D 8	D 15	D 29	D 43	D 50	D 71	D 92[d]	D 99	D 120	D 141	D 162	D 183/ EOT/EOPT[b, d]	
Visit Window (+/-days)	0	0	0	0	±1	±2	±3	±3	±3[e]	±5	±5	±5[e]	±7	±7	±7	±7	
Archived Blood for DNA (Optional)[z]			X[1]														
Pharmacokinetic and ADA Assessments																	
Plasma and Urine Sampling			Table 4		X	X[t]	X	Table 4			Table 4		X			X	
Exploratory Efficacy Assessments																	
DM1-NSM (daily for 2 wks)[u]		X						X			X					X	
DM1-NSM-PGIS[u]		X						X			X					X	
DM1-NSM-PGIC[u]								X			X					X	
FDSS[v]		X									X[1]					X	
DM1-Activ[v]		X									X[1]					X	
EQ-5D-5L[v]		X									X[1]					X	
MDHI[v]		X														X	
C-SSRS[v]		X	X[1]		X		X	X[1]	X		X[1]	X				X	
Measures of function and strength[w]	X	X									X[1]					X	
Myotonia (vHOT)	X	X						X[1]			X[1]					X	
Remote Hand Grip Strength[x]		X					X			X			X				
MIRS	X	X									X[1]					X	
CGIS, CGIC		X[y]						X[1]			X[1]					X	
Tissue Pharmacokinetic, Pharmacodynamic, and Secondary Endpoint Assessments																	
Muscle Needle Biopsy[z]		X									X[1]					X	

ADA = anti-drug antibodies; CGIC =clinical global impression of change; CGIS = clinical global impression of severity; C-SSRS= Columbia-Suicide Severity Rating Scale; D=Day
EOPT = End of Post-Treatment; EQ-5D-5L = EuroQol 5 Dimension 5 Level quality of life scale; FDSS= fatigue and daytime sleepiness scale; HbA1c = hemoglobin A1c;
MDHI = Myotonic Dystrophy Health Index; DM1-NSM= DM1 neuromuscular severity measure; TIBC =Total iron binding capacity; TSAT = Transferrin Saturation; vHOT = Video Hand Opening Time

Part B Footnotes:

(a) **Baseline:** These assessments can be performed over multiple days or at the same visit (anytime between Day -14 to Day -1). Baseline visit should not be performed until participant has met eligibility criteria. All assessments must be completed prior to start of Day 1 infusion.

(b) **EOT/ EOPT and 13-week Post-Treatment Follow-Up:** If participant discontinues prior to Day 92, the EOT visit should be performed followed by the 13-week post-treatment follow up period (Refer to study schema above). If participant discontinues during the post-treatment period prior to Day 183, the EOPT visit should be performed. In these situations, medical monitor (or designee) should be informed as soon as possible and be involved in the planning of subsequent follow up to ensure patient safety. All assessments indicated should be performed at end of treatment (EOT) and at the end of post-treatment (EOPT) when possible, unless an alternate follow-up schedule is discussed with medical monitor (or designee). Per discussion with MM for participants who completed an EOT, select assessments at EOPT can be skipped.

(c) **Extended follow-up:** For participants that do not proceed to OLE, site staff will monitor participants for safety every 3 months (quarterly) (+/- 7 days), for a total of 9 months from the last dose of study drug. Data including AEs and Concomitant Medications/Procedures will be collected. Follow-up may be in the form of routine clinic visits, or via telephone/telehealth or e-mail with the patients/caregivers. See footnote (o) re: pregnancy testing at the last visit.

(d) **Day 92 and 183 (EOT/EOPT) Visits – Endpoint Scheduling Flexibility:** Day 92 and 183 (or EOT/EOPT) may be performed over multiple days for scheduling flexibility to allow collection of exploratory efficacy endpoints. All assessments, except for post-dose PK sample collection must be completed prior to start of infusion.

(e) **Day 50 and Day 99 Visit Windows for PK:** For PK purposes, Day 50 and Day 99 visits must be 7 days (+/-1 day window) from the infusion day the previous week. As an example: if -3 day window is utilized for D43 infusion, the D50 visit should also utilize -3 day window (+/- 1 day) so PK is collected 6-8 days after the previous infusion.
(f) **Clinic Visit or Remote Visit:** Visits may be performed in clinic or remotely. Remote visits may utilize telemedicine with site personnel in conjunction with mobile home nurse contracted by sponsor. If a clinic visit cannot occur due to unforeseen circumstances (e.g., pandemic travel restrictions), a home health visit or local lab collection may be scheduled to obtain laboratory samples per discussion with Sponsor.
(g) **Pre-screening Informed Consent:** Optional, can be used for *DMPK* genetic testing and/or to remote pre-screen participants in advance of 1st in-clinic visit to reduce patient burden and time requirements for preliminary eligibility confirmation.
(h) **Medical History:** Changes from Screening to Randomization to be collected unless an event fulfills the criteria of an SAE.
(i) **Randomization:** May be performed on Day -1 to allow scheduling flexibility for muscle needle biopsy and unblinded pharmacy preparation of study drug. Dose will be calculated based on body weight recorded at Baseline.
(j) **Physical Exam (Abbreviated or Full):** Full physical exam to be given at Screening. At all other specified visits, an abbreviated physical exam (assessment of heart, lungs, abdomen and symptom directed examination, if any symptoms) to be given as indicated to assess changes from Screening.
(k) **Vital Signs:** BP, HR, RR, temperature. Blood pressure should initially be measured on both arms. The arm with the higher systolic measurement should be used at all future visits. VS should be collected every 15 minutes from start of infusion until 2 hours after the end of infusion. Participants should also be asked "how do you feel?" whenever vital signs are collected during and after the infusion and any newly emergent neurological symptoms should be assessed by a clinician.
(l) **12-lead ECG (triplicate):** All ECGs are 12-lead in triplicate using study provided equipment. Timing of assessments is shown in Table 4. When ECG and blood sample collection occur at the same time for PK, ECGs should be performed prior to drawing of blood samples.
(m) **Echocardiogram:** Baseline may be performed up to one month prior to Day 1 after confirmation of eligibility. Day 183 (or EOPT) may be performed up to one month prior to Day 183. Echo not required at EOPT if performed at EOT.
(n) **AE Monitoring:** SAEs should be reported starting at time of informed consent. AEs should be reported starting at time of study drug administration (Day 1), or if related to protocol-mandated assessments prior to start of study drug administration.
(o) **MRI of brain and MRA of brain and neck and full Neurological exam:** To be performed prior to first dose for new participants and as soon as possible for current participants. See Section 7.1.8 for more detail.
(p) **Pregnancy Test:** For women who are not post-menopausal and/or surgically sterile. Serum pregnancy test is performed at Screening and all other non-dosing visits after Day 1. Urine pregnancy test is performed on Baseline visit and dosing days (Days 1, 43 and 92). During Extended Follow Up period, a urine pregnancy test should be performed ONLY at the last visit either in-clinic or remotely by home visit
(q) **FSH:** For post-menopausal women to confirm post-menopausal status
(r) ***DMPK* Genetic Test:** All participants will have a blood sample analyzed by the AOC 1001-CS1 genetic testing lab to determine DMPK CTG repeat length and the sample may be collected at any time throughout the study. The sample may be collected via home health or in-clinic. For eligibility, historical genetic test results may be used after discussion with the medical monitor. The sample may be collected prior to screening, after signing a prescreening consent form.
(s) **Archive for DNA:** Participants who give additional consent (optional) consent will have an archived blood sample collected any time on trial after randomization for DNA isolation. Future potential analyses will be limited to further characterizing the disease (DM1), the drug (AOC 1001), and/or their interactions.
(t) **Day 15 PK/ADA sampling**: Only collected if participant attends the visit in-clinic.
(u) **DM1-NSM and DM1-NSM-PGIS and DM1-NSM-PGIC:** Completed between 6:00-10:00pm at home. There are 4 assessment periods: before Day 1, 43, 92, and 183. DM1-NSM must be completed daily for at least 7 days prior to Day 1 (Day -7 to Day -1). DM1-NSM-PGIS is performed on Day -1. DM1-NSM will be completed daily for 14 consecutive days prior to the visits on Day 43, 92, and 183. DM1-NSM-PGIS will be completed at the end of each week after DM1-NSM is performed (Day 7 of each week). DM1-NSM-PGIC is completed after DM1-NSM-PGIS on the last day of each assessment period after baseline.
(v) **PROs (in-clinic):** Perform in the same order each time and before all other clinic procedures on the same day.
(w) **Measures of function and strength**: Assessments will be performed once at Screening and once at Baseline and cannot be performed on the same day. The following assessments will be collected in the order specified in Section 7.1 including: MMT of selected muscle groups, QMT of selected muscle groups, Pinch Strength, 10-meter walk/run test (10MWRT), Timed up and go (TUG), Timed 4 stair climb, Timed 4 stair descend, 9-hole peg test, spirometry, and myotonia. Measures of function and strength should be performed after PROs but before laboratory and biopsy procedures on the same day.

(x) **Remote hand grip strength:** To be performed during baseline via remote visit, Day 29 by patient reporting, Day 71 by remote visit, Day 120 by patient reporting. Windows for the procedure on Day 29, 71, and 120 are ± 4 days.
(y) **CGIC:** Change scale not to be assessed at Baseline.
(z) **Muscle needle biopsy:** If multiple assessments are performed on a single day, biopsy should be performed as the last assessment of the day. For Day 92 assessments when both dosing and muscle biopsy are scheduled, muscle biopsy should be performed on the day prior to dosing. Time of day for biopsies should be kept similar across successive biopsies for each patient.

Time-points:
(1) Predose
(2) 24 hours after start of infusion
(3) Predose; From start of infusion through 2 hours post end of infusion every 15 minutes; After infusion at 4, and 6 hours post end of infusion.
(4) Predose; From start of infusion through 2 hours post end of infusion every 15 minutes.

11.1.4. Schedule of Part B Pharmacokinetic, ECG, VS, ADA and Urine Collection (Study AOC 1001-CS1 Protocol Version 5.0)

Study Day	Time	Window	Triplicate ECG*	VS*	PK*	ADA	Spot Urine[a]	24-hr Urine[b]
D1	-1 hr prior to start of D1 infusion	***	X	X			X	
D1	-0.5 hr prior to start of D1 infusion	***	X		X	X		
D1	start of D1 infusion			X[d]				X Samples pooled 0-6 hr, 6-12 hr, 12-24 hr
D1	at end of D1 infusion	± 10 mins	X		X			
D1	1 hr after end of D1 infusion	± 10 mins	X		X			
D1	2 hr after end of D1 infusion	± 20 mins	X		X			
D1	4 hr after end of D1 infusion	± 20 mins		X				
D1	6 hr after end of D1 infusion	± 20 mins	X	X	X			
D2	24 hr after start of D1 infusion	± 2 hrs	X	X	X			
D8	7 days after start of D1 infusion	± 1 day	X	X	X			
D15	14 days after start of D1 infusion	± 2 days		X	X if in clinic[c]	X if in clinic[c]		
D29	28 days after start of D1 infusion	± 3 days	X	X	X	X	X	
D43	-0.5 hr prior to start of D43 infusion	- 2 hrs	X	X	X	X		
D43	start of D43 infusion			X[d]				
D43	at end of D43 infusion	± 10 mins	X		X			
D43	1 hr after end of D43 infusion	± 10 mins	X		X			
D43	2 hr after end of D43 infusion	± 20 mins	X		X			
D50**	**7 days after start of D43 infusion	± 1 day	X	X	X			
D92	-0.5 hr prior to start of D92 infusion	- 2 hrs	X	X	X	X		
D92	start of D92 infusion			X[d]				
D92	at end of D92 infusion	± 10 mins	X		X			
D92	1 hr after end of D92 infusion	± 10 mins	X		X			
D92	2 hr after end of D92 infusion	± 20 mins	X		X			
D92	24 hr after start of D92 infusion	± 2 hrs	X	X	X			
D99**	**7 days after D92 infusion	**± 1 day	X	X	X			
D120**	**28 days after D92 infusion	**± 3 days	X	X	X	X		
D183 or EOT/EOPT**	**3 months after D92 infusion or at EOT/EOPT visit	**± 5 days	X	X	X	X		

[a] Spot urine: anytime
[b] 24-hr urine: Void prior to start of D1 infusion.
[c] PK and ADA sampling: Only collected if patient attends the visit in-clinic (not to be collected if performing visit by home health).

11.1.5. Fatigue and Daytime Sleepiness Scale Scoring Table

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Sources: MDHIsubscoresscoringfinal.xlsx, MDHItotalscoreweighting.xlsx