Clinical Trial Protocol

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) Patients

AVIDITY PROTOCOL NUMBER: AOC 1001-CS1
STUDY NAME: MARINA™
EUDRACT NUMBER 2021-000368-31
PROTOCOL VERSION: 5.0
PROTOCOL DATE: 21 OCTOBER 2022

SPONSOR: AVIDITY BIOSCIENCES
10578 Science Center Drive
Suite 125
San Diego, CA 92121

Sponsor Signatory:

DocuSigned by:
[redacted]

SPONSOR CONTACT
[redacted]

PROTOCOL SIGNATURE

I hereby acknowledge that I have read and agree to conduct the study as described in the clinical protocol titled below:

Protocol Number:	AOC 1001-CS1
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) Patients
Study Name:	MARINA™
Protocol Version:	Version 5.0
Date:	21 October 2022

I agree to comply with the International Council on Harmonization Tripartite Guideline on Good Clinical Practice (ICHE6(R2)), and in accordance with the ethical principles that originated from the Declaration of Helsinki, and applicable national and/or regional regulations/guidelines. I agree to conduct this trial according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub-investigators (including, if applicable, their spouses [or legal partners] and dependent children) at the start of the study and for up to one year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Avidity Biosciences.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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STUDY GLOSSARY

Abbreviation	Definition
10MWRT	10-Meter Walk/Run Test
9HPT	9-Hole Peg Test
ADA	anti-drug antibodies
AE	adverse event
AL	light chain amyloidosis
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
ANA	antinuclear antibody
AOC	antibody oligo conjugate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (SGOT)
AUC	area under the curve
βhCG	beta-subunit of human chorionic gonadotropin (pregnancy test)
Bb	complement factor Bb (activated complement split product)
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
C5a	complement factor C5a (activated complement split product)
CBC	complete blood count
CCG	CRF Completion Guide
cDM1	congenital myotonic dystrophy type 1
CELF1	CUGBP Elav-like family member 1
CGIC	clinical global impression of change
CGIS	clinical global impression of severity
CGG	cytosine-guanine-guanine
CIOMS	Council for International Organizations for Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum peak observed concentration
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTG	trinucleotide composed of cytosine, thymine, and guanine nucleotides in sequence
CUG	trinucleotide composed of cytosine, uracil, and guanine nucleotides in sequence
DILI	drug-induced liver injury
DM1	myotonic dystrophy type 1
DM1-Activ	DM1 activity and participation scale for clinical use
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
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study
EOT	end of treatment
EOPT	end of post treatment

Abbreviation	Definition
EQ-5D-5L	EuroQol 5 Dimension 5 Level quality of life scale
FAS	Full Analysis Set
FDSS	fatigue and daytime sleepiness scale
FEV1	Forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FT4	free thyroxine
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GI	Gastrointestinal
GLDH	Glutamate dehydrogenase
HAV	hepatitis A virus
Hb	hemoglobin
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HED	human equivalent dose
HIV	human immunodeficiency virus
HR	heart rate
Hs-cTnT	highly sensitivity cardiac troponin T
IA	interim analysis
IB	Investigator Brochure
ICD	implantable cardioverter defibrillator
ICF	informed consent form
ICH	International Council on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IRR	Infusion related reaction
IRT	interactive response technology
IV	intravenous(ly)
LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of normal
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
MIP	maximal inspiratory pressure
MIRS	muscular impairment rating scale
MM	medical monitor
MMP	Medical Monitoring Plan
MMT	Manual Muscle Testing

Abbreviation	Definition
MRC	Medical Research Council Scale
mRNA	messenger ribonucleic acid
MRSD	maximum recommended starting dose
NCS	not clinically significant
NOAEL	no observed adverse effect level
OLE	open-label extension
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PRO	patient reported outcome
PT	prothrombin time
QMA	Quantitative Muscle Assessment
QMT	Quantitative Myometry Testing
QoL	quality of life
QTL	Quality tolerance limit
RBC	red blood cell
RDW	red cell distribution width
RISC	RNA-induced silencing complex
RR	respiratory rate
RSI	Reference Safety Information
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SC	subcutaneous(ly)
siRNA	small interfering ribonucleic acid
SNP	single nucleotide polymorphisms
SOA	Schedule of Assessments
SOC	System Organ Class
SOM	Study Operations Manual
SOP	standard operating procedure
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
TB	total bilirubin
TEAE	treatment-emergent adverse event
Tf	transferrin
TfR1	transferrin receptor 1
TIBC	Total iron binding capacity
t_{max}	time to maximum peak observed concentration
TSAT	Transferrin Saturation
TSH	thyroid stimulating hormone
TT3	total triiodothyronine
TUG	Timed up and Go
ULN	upper limit of normal
UPCR	urine protein : creatinine ratio
US	United States
vHOT	Video Hand Opening Time
WBC	white blood cell

Abbreviation	Definition
WFI	water for injection
WNCBP	woman of non-childbearing potential
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Name of Sponsor/Company	Avidity Biosciences
Name of Investigational Product	AOC 1001
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) Patients
Short Title	A Phase 1/2 Study to Evaluate AOC 1001 in Adult Patients with DM1
Study Sites(s)	Study will be conducted at 8 study sites in the USA
Study Phase	1/2

Objectives	**Endpoints**
Primary Objective • To evaluate the safety and tolerability of single and multiple ascending doses of AOC 1001 in DM1 patients	**Primary Endpoint** • Frequency of treatment emergent adverse events (TEAEs)
Secondary Objectives • To evaluate the pharmacokinetic profile of single dose and multiple doses of AOC 1001 in DM1 patients • To evaluate the pharmacodynamic profile of single dose and multiple doses of AOC 1001 in muscle biopsies in DM1 patients • To evaluate the efficacy of multiple doses of AOC 1001 in DM1 patients as measured by spliceopathy	**Secondary Endpoints** • AOC 1001 levels in plasma, urine, and muscle tissue • Estimation of PK parameters, including C_{max}, t_{max}, $t_{1/2}$, AUC, and fraction excreted in urine • Change and percentage change from baseline in *DMPK* mRNA levels • Change and percentage change from baseline in spliceopathy
Exploratory Objectives • To evaluate the exploratory efficacy of multiple doses of AOC 1001 in DM1 patients on measures of mobility, muscle strength, muscle function, and patient-reported outcomes • To evaluate immunogenicity and metabolite PK of AOC 1001	**Exploratory Endpoints** Change from Baseline in: • Myotonia • Ankle dorsiflexion strength by QMT • Multiple Muscle Strength by Quantitative Myometry Test (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 • % of participants needing myotonia medications after dosing • Muscular Impairment Rating Scale • DM1-Neuromuscular Severity Measure (DM1-NSM) • Myotonic Dystrophy Health Index (MDHI) • DM1-Activ

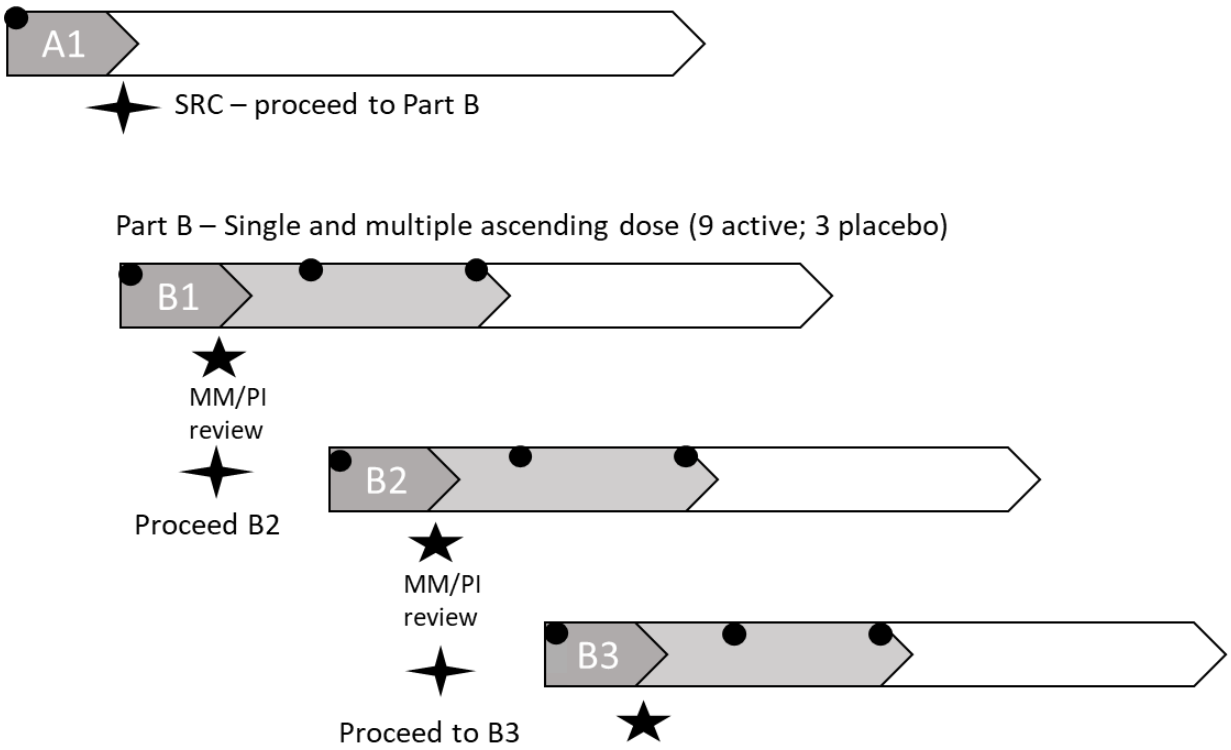
	• DM1-NSM Patient Global Impression of Severity (DM1-NSM-PGIS) • DM1-NSM Patient Global Impression of Change (DM1-NSM-PGIC) • Fatigue and Daytime Sleepiness Scale • Clinician Global Impression of Severity (CGIS) • Clinician Global Impression of Change (CGIC) • EQ-5D-5L • Columbia-Suicide Severity Rating Scale **PK endpoints:** • Measurement of ADA • Measurement of potential metabolites
Additional Safety Objectives • To further characterize the safety and tolerability profile of AOC 1001	• Laboratory parameters • Vital signs • Infusion related reactions (IRR) • Electrocardiographic measures • Echocardiographic measures
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 patients 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** – 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 of 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. Participants 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), participants will enter the multiple-dose treatment period and receive 2 additional doses on Days 43 and 92. After the third dose, participants 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. **Extended Follow-Up** –Eligible participants will have the option to enroll into an open label extension (OLE) trial following completion of this study. However, participants who are not eligible or decline to participate in the OLE will be monitored for safety by quarterly telehealth visits for a total of 9 months from the last dose of study drug, which corresponds to 5 half-lives of AOC 1001 in tissue. **Dose Escalation and Safety Review –** From initiation of the study up through protocol version 4.0 a Safety Review Committee (SRC) was involved in the decision to dose escalate between successive cohorts and trial continuation and ad hoc evaluation of AEs meeting criteria for safety management (Section 4.2). After AOC 1001-CS1

	protocol version 5.0 is implemented, this responsibility will transition to an Independent Data Monitoring Committee. The SRC will continue to fulfill their oversight role until the IDMC is in place.
Number of Participants	Part A will enroll 8 participants in one single dose cohort. Part B consists of 3 nested single and multiple ascending dose cohorts with 12 participants planned per dose level and the option to expand enrollment in one or more cohorts to obtain additional data. The maximum enrollment for the trial will be limited to 52 participants. Dose escalation between cohorts will not exceed a two-fold increase over the previous cohort. Maximum dose will not exceed 8 mg/kg by siRNA component weight of AOC 1001 (see below). This protocol will refer to those enrolled in this trial as participants.
Study Population	The study will include adult patients 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 Section 5.1.
Treatment Groups	Doses of AOC 1001 are presented in terms of the siRNA component of AOC 1001. For conversion into total AOC 1001 weight, please see Section 6.1. **Part A: Single Dose** There is 1 planned dose level in Part A that will evaluate a single dose in 8 participants (Cohort A1). Participants will be randomized 3:1 (6 active and 2 placebo). A sentinel group will be randomized 1:1 active: placebo, then remaining participants are randomized to 5:1 active: placebo. Participants will receive a single dose of study drug (AOC 1001 or placebo) by IV infusion on Day 1 and will be monitored for at least 24 hours in clinic or on an inpatient basis and then enter the 6-month post-treatment period. **Part B: Nested Single and Multiple Ascending Dose** There are 3 planned dose levels in Part B. Participants in each cohort will be randomized at a planned ratio of 3:1. Each cohort will include a sentinel group which is randomized 1:1 active: placebo. Participants will receive a total of three doses of study drug (AOC 1001 or placebo) by IV infusion on Day 1, 43, and 92. On Day 1 participants will be monitored for at least 24 hours in clinic or on an inpatient basis. Enrollment in Part B cohorts will proceed once the Day 29 safety and tolerability data for at least 75% of the preceding cohorts has been reviewed by either the SRC or IDMC, with decisions to escalate to 2 mg/kg and 4 mg/kg being made by the SRC and the decision to escalate above 4 mg/kg being made by the IDMC. For each participant, the 2nd dose on Day 43 for an individual can only proceed after the sponsor MM (or designee) and PI have reviewed the participant's accumulated AE and safety lab data through Day 29. After the 3rd dose on Day 92, participants will enter a 13-week post-treatment period. **Part A and B Sentinel Groups** For each dose cohort in Parts A and B there will be 2 sentinel participants (one treated with AOC 1001 and one treated with placebo) and a period of at least 1 day is required between administering the first dose of study drug to the sentinel participants and the remaining participants in the cohort. The decision to initiate dosing for the rest of the cohort will be made based on the review of the safety data through the first 24 hours by the sponsor medical monitor (or designee), with the PIs of each of the two participants.

<table>
<tr><td>Study Drug Dosage and Administration</td><td>The study drug includes AOC 1001 and placebo (saline). Detailed storage, preparation, accountability, and administration instructions are outlined in the Pharmacy Manual. All doses will be administered by IV infusion based on body weight (see Section 6.1).

The doses planned are as follows:
<table>
<tr><th>Cohort</th><th>Number of Doses</th><th>Dose Level by SiRNA Component of AOC 1001</th></tr>
<tr><td>Cohort A1</td><td>1</td><td>1 mg/kg</td></tr>
<tr><td>Cohort B1</td><td>3</td><td>2 mg/kg</td></tr>
<tr><td>Cohort B2</td><td>3</td><td>4 mg/kg</td></tr>
<tr><td>Cohort B3</td><td>3</td><td>8 mg/kg</td></tr>
</table></td></tr>
<tr><td>Statistical Considerations</td><td>The sample size is based on practical considerations and is consistent with this type of early phase study.
Statistical analyses will be primarily descriptive in nature. Descriptive statistics (e.g., mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables. Frequencies and percentages will be presented for categorical and ordinal variables.
The populations (analysis sets) are defined as follows:
Safety Analysis Set: The Safety Analysis Set will include all participants who received at least one dose of study drug. Participants will be grouped according to the dose level they received. The Safety Analysis Set will be used for all safety analyses.
Full Analysis Set (FAS): All participants who were randomized and have received any amount of study drug and had a baseline measurement and at least 1 post-baseline assessment. Participants will be grouped as randomized.
Pharmacokinetic (PK) Analysis Set: The PK Analysis Set will include all participants who receive any amount of study drug and provide a sufficient number of plasma sample(s) for PK analysis. Participants will be grouped according to the dose level they received.
Pharmacodynamic (PD) Analysis Set: The PD Analysis Set will include all participants who receive any amount of study drug and had a baseline pharmacodynamic assessment and at least 1 post-baseline pharmacodynamic assessment. Participants will be grouped according to the dose level they received.
Safety, the primary endpoint, will be analyzed using the Safety Analysis Set. The PK, and PD Analysis Sets will be used to conduct PK and PD analyses, respectively. Efficacy analysis performed will be executed on the Full Analysis Set with additional supportive sensitivity analyses to be specified in the study SAP.</td></tr>
</table>

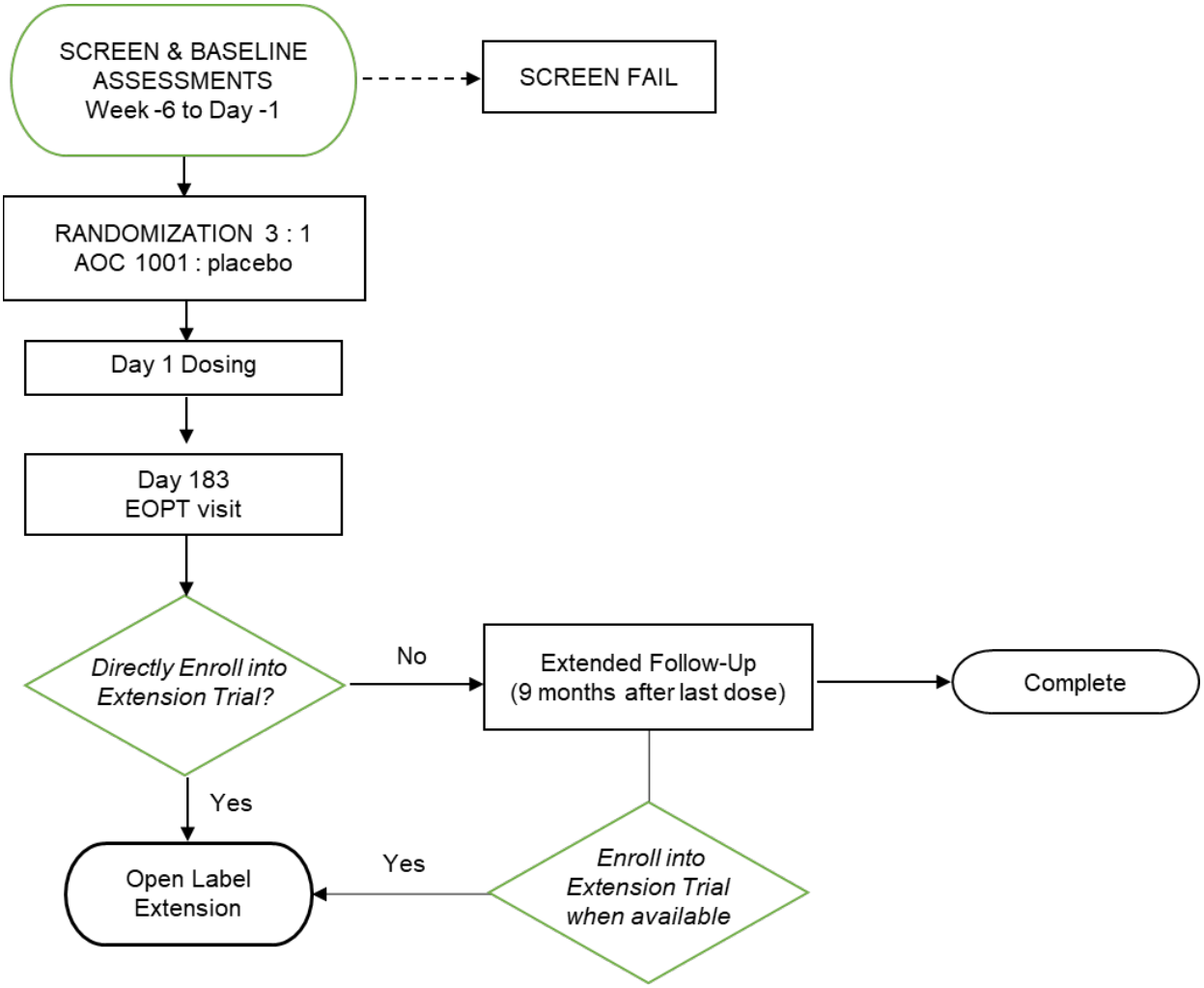
1.2. Study Design and Treatment Schema



- Dosing of Study Drug is indicated by black dots. Part A: Day 1; Part B: Days 1, 43 and 92.
- Part A will consist of a single dose treatment period (dark grey) and a post-treatment period (white). The SRC will review data through Day 29 to determine if it is safe to proceed to Cohort B1.
- Part B will consist of a single dose treatment period (dark grey), a multiple dose treatment period (light grey) and a post-treatment period. The decision to continue from the single to multiple dose period for each participant in Part B will be made after reviewing data through Day 29 for each participant (indicated by stars).
- The SRC or IDMC (indicated by crosses) will review all safety data through Day 29 for Cohort B1 and B2 in at least 9 participants to determine if dose escalation is acceptable.
- For each cohort, safety data through 24 hours after dosing from two sentinel participants will be reviewed to allow dosing for the rest of the cohort.
- Randomization for the planned 12 participants per Part B cohort will be 9 active:3 placebo. If additional participants are enrolled in a cohort, the same randomization scheme will be implemented.

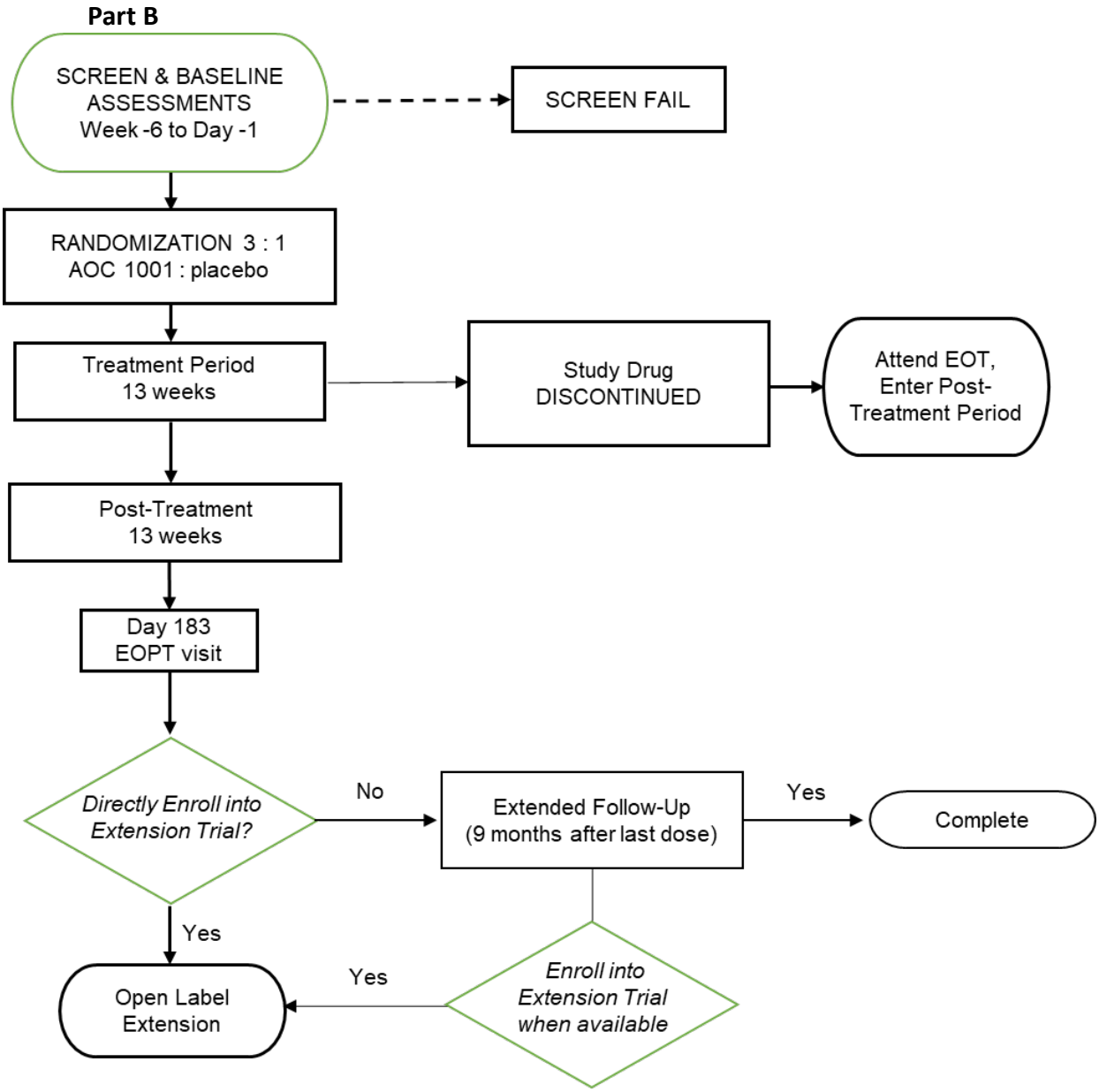
TREATMENT SCHEMA

Part A



EOT = End of Treatment; EOPT = End of Post-Treatment

- Extended follow up will continue until 9 months after the last dose.



EOT = End of Treatment; EOPT = End of Post-Treatment

- Extended follow up will continue until 9 months after the last dose.

1.3. Schedule of Assessments – Part A

Table 1: Part A Schedule of Assessments (SOA)

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

Table 2: Part A Pharmacokinetic, ECG, ADA and Urine Collection

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).

1.4. Schedule of Assessments – Part B

Table 3: Part B Schedule of Assessments (SOA)

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	
Clinic Visit	X	X	X	X	X		X	X	X		X	X	X			X	
Clinic Visit or Remote Visit[f]						X				X							
Home Visit via Telehealth														X	X		X
Pre-Screening Informed Consent[g]	No time limit																
Main Informed Consent	X																
Overnight Stay			X														
Inclusion/Exclusion Criteria	X	X															
Demographics, Disease History	X																
Medical History[h]	X	X	X[1]														
Randomization[i]			X[1]														
Study Drug Administration			X					X			X						
Clinical Safety Assessments																	
Height	X																
Body Weight	X	X														X	
Physical Exam (Abbreviated or Full)[j]	X		X[1]	X	X		X	X[1]			X[1]					X	
Vital Signs[k]	X		X[3]	X	X	X	X	X[4]	X		X[4]	X	X			X	
12-lead ECG (triplicate)[l]	X	X	Table 4		X		X	Table 4			Table 4		X			X	
Echocardiogram[m]		X														X	
Adverse Events Monitoring[n]	X	X	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	X	X
MRI and MRA and Neurological exam[o]		X – See footnote and Sections 7.1.4 and 7.1.8															
Laboratory Assessments																	
HIV, Hepatitis B & C	X																
Pregnancy Test[p]	X	X	X[1]				X	X[1]	X		X[1]	X				X	X
FSH[q]	X																
DMPK genetic test[r]	X																
Chemistry, hematology, and urinalysis	X		X[1]	X[2]	X	X	X	X[1]	X	X	X[1]	X	X			X	
Thyroid panel, HbA1c, coagulation	X										X[1]					X	
TSAT, TIBC, Iron, Ferritin	X		X[1]		X	X	X	X[1]	X	X	X[1]	X	X			X	
Cardiac Troponin			X[1]					X[1]			X[1]					X	
Archived Blood			X[1]					X[1]			X[1]					X	

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)[s]			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.

Table 4: Part B Pharmacokinetic, ECG, VS, ADA and Urine collection

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).

[d] 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.

*When ECG, VS and PK are collected at the same time point, ECG should be conducted first, followed by VS, and PK draw last

**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. The same logic should be applied to other similar visits as outlined.

*** Two pre-dose triplicate ECGs are required. The first should be approximately 0.5 hours pre-dose but timing can be adjusted as long as the measurements are separated by at least 10 minutes

2. BACKGROUND AND RATIONALE

2.1. Disease Overview

DM1 is a rare, monogenic, autosomal dominant, trinucleotide repeat expansion disorder that affects between 40,000 and 156,000 patients in the US (Udd 2012, Johnson 2019, Johnson 2021). It is a progressive disorder that affects multiple organ systems including skeletal and smooth muscle, heart, eye, and the endocrine and central nervous systems (Bird 2019). DM1 is typically characterized by myotonia and muscle weakness leading to immobility, respiratory insufficiency, dysarthria, and dysphagia (Udd 2012, Meola 2015). Other common manifestations include cardiac conduction defects, extreme fatigue, excessive daytime sleepiness, and gastrointestinal (GI) disturbances (includes irritable bowel syndrome, acid reflux, abdominal pain and constipation (Hilbert 2017). The congenital and childhood forms include intellectual disabilities and psychosocial problems.

DM1 patients often present with abnormal laboratory values (Heatwole 2006), including elevated hemoglobin A1c and triglyceride consistent with insulin resistance, elevated FSH and LH due to hypogonadism, abnormal lactate dehydrogenase and creatinine kinase due to muscular dysfunction, and both elevated or decreased hemoglobin values. In addition, up to 44% of DM1 patients have elevated transaminases. Out of these, 87% can be attributed to nonalcoholic fatty liver disease (Shieh 2010). Other liver enzymes detected in the blood, including gamma-glutamyltransferase and alkaline phosphatase, are also found to be elevated. Interestingly, these abnormalities are not thought to be progressive, and are not correlated to muscle weakness nor CTG repeat size (Achiron 1998). In fact, the consensus statement for DM1 adults states that chronic liver enzyme elevation is typical and does not necessarily indicate the need for obtaining a liver biopsy (Ashizawa 2018).

Disease manifestations are highly variable with respect to disease severity, presentation, and age of onset. It shows anticipation, such that successive generations present with increased disease severity and earlier age of onset. Severity can range from lethal effects in infancy to mild symptoms in late-onset adults. As with other triplet repeat disorders, severity of disease is correlated with the extent of the repeat expansion, with a higher number of repeats correlating with more severe disease. Based on age of onset and severity of symptoms, DM1 is often categorized into four overlapping phenotypes: late-onset, classical (or adult-onset), childhood and congenital DM1 (cDM1). The classical form accounts for approximately 75% of diagnosed DM1 patients and the cDM1 form accounts for approximately 15% (Thornton 2014).

DM1 is associated with high disease burden and premature mortality. Excluding neonatal deaths, life expectancy ranges from 45-60 years with 70% of early mortality caused by cardiorespiratory complications. Respiratory failure due to muscle weakness (especially diaphragmatic weakness), causes at least 40% of early mortality and cardiac abnormalities including conduction defect (~40% of patients with DM1) (Kaminsky 2013), cardiomyopathy, and sudden death which accounts for approximately 30% of the deaths (Turner 2014). Due to the multisystemic disease manifestations, DM1 leads to significant decreases in quality of life as a consequence of physical impairment, activity limitations, loss of independence, and decreased participation in social activities and work (Landfeldt 2019, Hermans 2010). Common challenges to daily life activities reported by DM1 patients include handling objects, performing

housework, preparing meals, going up and down stairs and standing (Hagerman 2019). There is also a significant impact on caregivers who report providing "moderate" or "major" assistance on a daily basis. Most common forms of support are emotional, household tasks, attending doctor appointments, and financial (Hagerman 2019). A large proportion (47%) of DM1 patients do not work as a consequence of their disease (Landfeldt 2019). The family burden is amplified due to the anticipation component of the disease where successive generations manifest symptoms at progressively earlier ages and with more severity. Thus, it is common for several members of the same family to be affected, with the older DM1 patients also serving as the caregiver for the younger generation.

The pathogenesis of DM1 is thought to include the following steps. In patients with DM1, one of the alleles encoding the *DMPK* gene contains an expansion of the CTG triplet repeat in the 3' non-coding region. The expansion ranges from <35 in healthy people to many thousands in DM1 patients and correlates to the severity of disease at a population level. When the mutant *DMPK* gene containing the CTG expansion is transcribed into mRNA, the self-complementary CUG repeats fold into large hairpin loops and form discrete foci in the nucleus. Although this leads to the mutant mRNA not being translated into protein (Furling 2003), the decrease in DMPK protein level (or haploinsufficiency) is not thought to be the pathogenic driver of DM1 (Brook 1992, Lee 2009, Salvatori 2005). Although mutant mRNA is not expressed in an elevated level, the CUG-repeat containing RNA binds to RNA-binding proteins such as muscleblind-like protein (MBNL) family members and CELF1 (CUGBP Elav-like family member 1) and sequester them into the foci. MBNL and CELF1 physiologically play important roles in regulating mRNA processing (Lee 2009, Chau 2015). However, when bound to the CUG repeats within the nuclear-retained *DMPK* mRNA, MBNL exhibits a loss of function whereas CELF1 activity is abnormally upregulated. This leads to a downstream mis-splicing of hundreds of mRNAs which translate into altered proteins with abnormal functions. This spliceopathy profile represents the molecular hallmark of DM1. The resulting atypical proteins are the ultimate cause of the disease manifestations (Gourdon 2017). As examples, some of the abnormal proteins include the skeletal muscle chloride channel, the insulin receptor, Troponin T, and the sodium channel, contributing to myotonia, insulin resistance, cardiac dysfunction, and conduction defects respectively (Pang 2018).

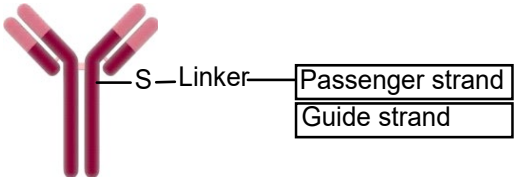
The pathogenesis of DM1 described above is supported by the following evidence. 1) Another clinically similar disease, DM2 (myotonic dystrophy type 2), is caused by tetra-nucleotide expansion within a different gene, *ZNF9* (zinc finger 9), a transcription factor. Thus, both types of myotonic dystrophy are caused by mutant RNA transcripts located in two different genes which aberrantly cause spliceopathy of the same downstream targets (Meola 2015). 2) Loss of function of *DMPK* or neighboring genes do not manifest features of DM1 (Berul 1999, Carrell 2016). 3) Expanded CTG repeats by themselves aggregate in nuclear foci and inhibit myogenesis (Orengo 2008). 4) Compound heterozygote MBNL1 and MBNL2 mice manifest features of DM1 (Lee 2013). Taken together, mutant CTG repeats, independent of the rest of the *DMPK* gene causes sequestration of key RNA regulating proteins such as MBNLs into discrete nucleus foci and prevent their proper function which then lead to downstream spliceopathy.

2.2. AOC 1001 Background

AOC 1001 is an antibody oligonucleotide conjugate (AOC).

It is composed of a human transferrin receptor 1 (TfR1) targeting, effector function-null, humanized IgG1 antibody (AV01mAb) conjugated via a linker to a double stranded small interfering ribonucleic acid (siRNA) oligonucleotide against *DMPK* (siDMPK.19, referred to hereafter as the siRNA component of AOC 1001).

Figure 1: Design of AOC 1001



Antibody-siRNA conjugate

The AV01mAb facilitates delivery of AOC 1001 to muscle and cardiac tissue through TfR1-mediated endocytosis. Although the TfR1 protein is widely expressed, Avidity's nonclinical studies demonstrate that the primary site of activity of siRNAs delivered using AV01Ab is in skeletal and cardiac muscle. Once AOC 1001 is inside the endolysosomal compartment, the antibody is degraded, and the siRNA is released into the cytosol and distributes to the nucleus. The pharmacological activity of AOC 1001 is derived from the guide strand of the siRNA which is loaded into the RNA-induced silencing complex (RISC) and results in the hydrolysis of *DMPK* mRNA located in both the cytosol and nuclear compartments. The guide strand is complementary to a sequence in the 3' untranslated region in exon 15 of the *DMPK* mRNA and degrades both wild-type and mutant *DMPK* mRNA transcripts.

2.3. Therapeutic Rationale

Because the disease-causing CUG repeats in the mutant *DMPK* mRNA form hairpin loops and aggregate in the nucleus, the mRNA is not translated into DMPK protein. Instead, the toxic mRNA sequesters RNA processing proteins such as MBNL and CELF1 that are crucial for proper splicing of many downstream genes. Thus, decreasing the levels of toxic *DMPK* mRNA with AOC 1001 should free the RNA processing proteins to perform their normal functions, and correct the downstream spliceopathy that is the cause of the disease manifestations. It is expected that AOC 1001 has the potential to modify the clinical course of DM1 and improve or stabilize muscle strength and performance, cardiac conduction defects and structural abnormalities, as well as respiratory function, irrespective of disease stage and CTG repeat size.

There are currently no FDA approved drug therapies to treat DM1 and current treatment is focused largely on symptom management. Hence, there remains a high unmet need for the development of disease modifying therapies to treat the underlying cause of DM1.

2.4. AOC 1001 Preclinical Experience

Clinical development of AOC 1001 is based on a robust nonclinical program. Detailed information concerning the pharmacology, pharmacokinetics, and toxicology of AOC 1001 can be found in the current Investigator's Brochure.

2.5. AOC 1001 Clinical Experience

AOC 1001 has not been evaluated in any clinical setting other than this trial and its extension trial AOC 1001-CS2.

As of 30 Sept 2022, 38 participants (8 in cohort A1 and 12 in cohort B1, 18 in cohort B2) have been dosed.

2.6. Rationale for Study Design

This is a randomized, double-blind, placebo-controlled, phase 1/2 study, including a single dose arm (Part A) and a nested single and multiple ascending dose arm (Part B), to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of AOC 1001 administered intravenously to adult DM1 patients.

Part A of the study assesses a single dose of AOC 1001 in adult DM1 patients to characterize the safety, tolerability, muscle and plasma PK and extent and time course of *DMPK* knockdown following a single dose. The safety data through Day 29 after a single dose will be reviewed to enable the initiation of the first MAD cohort in Part B.

Part B will assess single and multiple ascending doses in DM1 patients in a nested design. The first dose in Part B will be based on initial safety data from Part A, and subsequent doses for each participant will be based on review of individual safety data following the first dose. Escalation to the next cohort in Part B requires approval of the SRC (for cohorts B1 and B2, per protocol versions 2.0 and 3.0) or IDMC (for cohort B3, per protocol version 5.0.) In addition to the primary objectives of safety and tolerability, secondary and exploratory objectives will include assessments of the correction of spliceopathy in muscle tissues to evaluate the downstream pharmacologic effect of AOC 1001, as well as measures of mobility, muscle strength, and muscle function in DM1 patients.

Eligible participants from both parts will have the option to enroll into an open label extension (OLE) trial after regulatory approval(s), to enable long term follow-up both for safety and efficacy. For those patients unable to participate in the OLE, the duration of extended follow-up period after the last dose will be 9 months. This assumes appropriate tissue washout of AOC 1001 after five half-lives in humans as predicted from nonclinical studies.

This trial design is based on the current published scientific understanding of the DM1 disease pathogenesis, manifestation, and progression as discussed in Section 2.1, input from clinician experts specialized in DM1 on clinical endpoint assessments, regulatory authority guidance, and DM1 patient feedback. In addition to individual patient interviews, a patient advisory board was convened on 10 December 2020 with six patients, ages ranging from 21 to 60 years old, with various stages of ambulation.

Key lessons from this meeting were incorporated into our design, including incorporation of patient reported outcome (PRO) and creation of a DM1 specific PRO to characterize the symptom severity and impact on function, and logistic planning to decrease in person clinic visits where appropriate and to utilize tele-health and home-health visits.

The use of strategic muscle biopsies allows for AOC 1001 PK/PD profiles and subsequent analysis of molecular mechanism and clinical manifestations. A survey was conducted at University of Rochester in 60 DM1 patients regarding their experience with muscle biopsies (Dr Charles Thornton, unpublished data). Ninety-five percent of the patients had previously had a needle biopsy taken in the lower leg in the tibialis anterior muscle. Eighty percent of the patients rated the pain of muscle biopsy after a couple of days as 2 out of 10 (10 being most severe). Over 97% of the patients rated the needle biopsy experience as “not bad at all” or “bother me a little”, and <2% rated it as “horrible”. Over 96% of the patients were willing to undergo another muscle biopsy to allow follow up of their disease or as part of a clinical trial. In summary, patients did not find the muscle biopsy procedure to be overly burdensome and appreciated the importance of comprehensive characterization of the individual’s clinical presentations and molecular profile due to the inherent variability of the disease.

2.7. Dose Rationale

Study drug doses mentioned in this section are referred to by siRNA component weight, not the total AOC 1001 weight given that the siRNA component is the pharmacologic moiety of AOC 1001. To translate into total AOC 1001 weight, please see Section 6.1.

2.7.1. Starting Dose in Part A

The strategy for selecting the first in human starting dose (1 mg/kg per siRNA component weight) was based on the safety margin relative to the NOAEL in animal toxicity studies, as well as ensuring that this dose level was on the low end of the pharmacologically active range for DM1 patients. Safety margins were calculated using multiple approaches.

The NOAEL of 45 mg/kg based on siDMPK.19 component weight is derived from the cynomolgus monkey GLP toxicity study. Thus, the starting dose of 1 mg/kg is 15-fold below the human equivalent dose of 15 mg/kg (per siRNA component weight) based on a conservative estimate of a safety margin assuming body surface area (BSA; mg/m^2) scaling from animals to humans (Table 5). This approach of selecting a human starting dose at least 10-fold below the monkey toxicity study NOAEL in the most sensitive species is consistent with FDA guidance on maximum recommended starting dose (MRSD) selection (FDA 2005).

Based on predicted plasma PK exposures for a 70 kg patient, a safety margin of > 50-fold exists for C_{max} and >100-fold for AUC (Table 5) relative to the NOAEL (45 mg/kg based on siRNA component weight).

The toxicity of oligonucleotide drugs translates to humans on a body weight (mg/kg) basis (FDA 2005, Geary 1997); therefore, this yields a safety margin of 45-fold for the starting dose of 1 mg/kg (per siRNA component weight).

Thus, a starting dose of 1 mg/kg provides adequate safety margins.

Table 5: Estimated NOAEL and Starting Dose Safety Margins

Species	NOAEL (siDMPK.19 / AOC 1001)[a, c]	Estimated Safety Margin (First-in-human dose, 1 mg/kg siDMPK.19 (12 mg/kg AOC 1001)[c]			
		BSA	Weight-based	C_{max}-based[b]	AUC-based[b]
Cynomolgus Monkey	45 / 537.4 mg/kg	~15X	~45X	~57X	~142X

AUC = area under the drug concentration versus time curve; BSA = body surface area; C_{max} = maximum plasma concentration; FIH = first in human; NOAEL = no-observed-adverse-effect-level; source for HED calculation: FDA 2005.

[a] The NOAEL was determined from the 13-week GLP toxicity study in cynomolgus monkeys.

[b] The cumulative systemic exposure (plasma cumulative AUC) after 3 doses total was used to project the exposure margin. The C_{max} and cumulative AUC following IV infusion in the cynomolgus monkey were approximately 80,000 nM and 355,600 nM*d, respectively. For a typical 70 kg patient, predicted human systemic C_{max} and plasma AUC values following single IV dosing of AOC 1001 at 1 mg/kg are approximately 1400 nM and 2500 nM*d, respectively.

[c] NOAEL and the FIH starting dose are expressed as siDMPK.19 component and total AOC 1001 dose

2.7.2. Dose Escalation and Maximal Dose

The strategy for selecting the doses of 2, 4 and 8 mg/kg (based on siRNA component weight) in Part B is based on achieving robust mutant *DMPK* mRNA reduction in muscle tissue while maintaining a 2-fold dose escalation schema. Although preclinical data shows that substantial knockdown of wild-type *DMPK* mRNA may occur at lower doses, modeling suggests that dose-dependent reduction of mutant *DMPK* mRNA is expected between 2 mg/kg and 8 mg/kg in patients with DM1.

The selection of the maximal dose of 8 mg/kg is based on preclinical data that suggests higher doses may be required to achieve optimal mutant *DMPK* mRNA reduction relative to wild-type DMPK mRNA, in part, because the mutant form is sequestered in the nucleus. This is supported by data that show higher siRNA doses were required to achieve mutant *DMPK* mRNA knockdown in *in vitro* studies utilizing DM1 patient-derived myotubes relative to wild-type *DMPK* mRNA, and that higher doses of a mouse surrogate siRNA targeting *DMPK* (mTfR1Ab-siDMPK.45) were required to achieve comparable reduction of mutant *DMPK* mRNA compared to wild-type *DMPK* mRNA in a mouse model. Please see the Investigator's Brochure for a detailed summary. Thus, dose levels of 2 to 8 mg/kg will be tested in Part B as these doses are predicted to result in graded mutant *DMPK* mRNA reductions that are anticipated to lead to potential clinical benefit.

A sufficient margin of safety is predicted for the high dose of 8 mg/kg relative to the NOAEL (45 mg/kg; maximal feasible dose) in the cynomolgus monkey toxicity study: ~2-fold margin of safety is predicted based on BSA scaling while a >5-fold margin is predicted based on body-weight-based scaling. Further, a 3-fold margin is predicted based on plasma PK exposures in a 70 kg subject after 3 doses.

The quarterly (administration every 3-months) regimen proposed for MAD part is supported by observed durable *DMPK* mRNA lowering following a single dose in cynomolgus monkeys. Predictions from PK/PD modeling indicate that, at a quarterly dose regimen, AOC 1001 dose levels of ≥ 2 mg/kg will achieve the targeted PD in skeletal muscle tissues. However, time to steady state is predicted to be up to 9 months after quarterly dose administration. To

accelerate attainment of steady state levels, a single booster dose at Day 43 is planned in the MAD portion of the study. The quarterly regimen with a booster at Day 43 is supported by the animal toxicity studies that tested an every 6-week dosing regimen (3 doses total in 13 weeks).

The anticipated half-life of AOC 1001 in human tissue is approximately 50 days, allometrically scaled from observed tissue half-life in cynomolgus monkey. The siDMPK.19 tissue levels are expected to be cleared in approximately 9 months (five tissue half-lives), which is the proposed length of safety follow-up for participants not entering the OLE.

2.8. Benefit-Risk Assessment

Due to limited human experience with AOC 1001, there are no identified risks associated with AOC 1001 administration to date. This section summarizes the potential benefits, potential risks, and risk mitigation of AOC 1001. More information may be found in the Investigator's Brochure.

2.8.1. Benefit Assessment

AOC 1001 has the potential to decrease the accumulation of the disease-causing mRNA of mutant *DMPK* gene and modify the disease progression of DM1.

It is anticipated that AOC 1001 will knockdown the mutant *DMPK* mRNA in DM1 patients, potentially leading to correction of spliceopathy, improving or stabilizing muscle strength and performance, cardiac conduction defects and structural abnormalities, as well as respiratory function. However, DM1 patients in this study may not benefit from the study drug, due to either the short duration of the trial, receiving a lower than optimal dose, or being in the placebo arm. Patients completing this study may be able to enroll in the open-label extension trial during which long term effects of AOC 1001 will be assessed.

2.8.2. Risk Evaluation

The potential risks associated with participation in this trial include infusion related reactions and hypersensitivity reaction as have been observed with other monoclonal antibodies, changes to iron homeostasis through interaction with Tfr1, and risk from the muscle biopsy procedure. In addition, one participant in the 4 mg/kg dose cohort (siRNA component weight) in Study AOC 1001-CS1 has experienced a suspected unexpected serious adverse reaction (SUSAR) with the verbatim term of "bilateral hemorrhagic lesions in the thalamus." Symptoms from this event include memory loss and sever blurred vision which began approximately 20 minutes after the end of the first infusion of study drug.

Appropriate risk mitigation measures have been put in place including addition of exclusion criteria related to iron deficiency, guidance for safety monitoring during infusions, guidance for managing infusion related reactions, incorporation of safety monitoring and stopping rules related to hemoglobin levels, and additional monitoring for neurologic complications. These potential risks are considered monitorable and manageable. Details of each risk and corresponding mitigations are provided in Section 6.6 Risk Summary and Recommended Mitigation of the Investigator Brochure.

Other mechanistic risks listed below are described in more detail in the Investigator Brochure:

- AOC 1001 binds to both wild-type and mutant *DMPK* mRNA, leading to their degradation. However, knockdown of the DMPK wildtype protein is expected to have an acceptable safety profile.
- The potential off-target risk of AOC 1001 is low based on the platform experience in siRNA therapeutics and humanized monoclonal antibodies.
- Off-target hybridization by the siRNA has been minimized and confirmed in preclinical studies. Drug-drug interactions are not expected for the siRNA platform.

Safety will be monitored throughout the trial with both in clinic visits and remote visits with home health care and/or telehealth support. Study assessments and visit schedules have been designed with the goal to minimize the burden of the study on participants without risking safety. Safety will be monitored and reviewed by the investigator(s), the sponsor medical monitor and designees, as well as an SRC/IDMC (as applicable). From initiation of the study through protocol version 4.0, SRC was responsible for dose escalation decisions, review of ongoing safety data and reviewing any cases meeting predefined safety monitoring and stopping rules throughout both Part A and Part B of the trial (see Section 4.3, Section 8). After AOC 1001-CS1 protocol version 5.0 is implemented, these responsibilities will transition to the IDMC. The SRC will continue to fulfill the oversight role until the IDMC has been implemented.

The following safety processes are built into this trial:

- Participants will be monitored closely during and after the first dosing for at least 24 hours.
- Brain imaging and neurologic exam will be completed for all participants as soon as possible to allow comparison in situations when neurologic symptoms manifest and work up required.
- Sentinel dosing is employed for all cohorts. The safety data through 24 hours after the first dose in the first two participants of each cohort will be reviewed by site PI and sponsor medical monitor (or designee) to allow dosing of subsequent participants in the same cohort.
- Dose escalation decisions will be made after reviewing Day 29 safety and tolerability data of at least 75% of the participants in the prior cohort. The 29-day monitoring period provides sufficient time to monitor for acute safety events (such as immune reaction) during and after first dose administration. In monkeys, rapid *DMPK* mRNA lowering was observed in tissues, with near maximal reduction observed within 4 weeks post first dose. Thus, the Day 29 evaluation period between cohorts will allow for safety assessment at maximal *DMPK* mRNA lowering.
- In multiple ascending dose cohorts, nested SAD/MAD design is employed in that safety and tolerability data through Day 29 for each participant after the first dose will be reviewed by the site PI and sponsor medical monitor (or designee) to allow subsequent dosing for each individual.

- In addition to collecting triplicate ECGs during this period when AOC 1001 plasma C_{max} is expected to be the highest, triplicate ECGs will be collected throughout the trial to examine the relationship of PK, PD, and electrocardiographic parameters when AOC 1001 is expected to be in cardiomyocytes. Because patients with DM1 often have electrical and structural cardiac changes, echocardiogram and highly sensitive cardiac troponin will be monitored as well.
- Because AOC 1001 is expected to knockdown *DMPK* mRNA in muscles, serum levels of muscle proteins that are considered biochemical markers of muscular injury will be monitored throughout the duration of the trial, including creatine kinase, aspartate aminotransferase, and myoglobin.
- In preclinical studies, the distribution of AOC 1001 is observed in liver, kidney, and bone marrow, in addition to muscle containing organs. Eligibility criteria have been placed to exclude participants with baseline abnormalities to reduced potential risks while taking into consideration the ranges of lab abnormalities expected in the DM1 population. Additionally, safety monitoring rules are designed to provide guidance related to the potential risks described below.
- Although siDMPK.19 is distributed to reproductive organs, reproductive effects are not expected given the lack of meaningful *DMPK* mRNA reduction in these tissues and lack of any histopathology findings in the 13-week monkey GLP toxicity study. To limit embryofetal risk, female participants of child-bearing potential are required to have a negative pregnancy test, cannot be breast feeding, and must be willing to use a highly effective method of contraception as specified in Section 6.4. Exposure level in the partners of male participants is expected to be negligible for the following reasons. First, AOC 1001 is not genotoxic per standard battery of nonclinical studies conducted and described in the IB. Second, AOC 1001 is a relatively large molecule to be able to cross the blood-testis barrier and administered infrequently with short duration of meaningful plasma concentration. Third, the amount of unconjugated siRNA in the circulation is expected to be very low and are likely to be renally cleared rapidly. Fourth after AOC 1001 is internalized through transferrin receptor mediated endocytosis, the antibody portion of the molecule is degraded, leaving only the unconjugated siRNA. Unconjugated siRNAs are highly polar and, they do not readily cross cell membranes without receptor-mediated endocytosis. This means any unconjugated siRNAs present in the seminal fluid would be unable to be taken up by cells of the female partner. Fifth, it is unlikely that AOC 1001 would be exposed to the placenta and for those drugs actually in contact with the placenta, it would be unlikely to cross the placenta due to its large size. Sixth, negligible amount of the unconjugated siRNAs is expected to be in the sperm and whatever present is not expected to lead to meaningful *DMPK* reduction in maternal tissues or in the conceptus. Nonetheless, male participants and their female partners of child-bearing potential, will be required to use contraception as specified in Section 6.4.
- Any participant who does not enroll in the OLE will be followed for at least 9 months after the last dose, which is predicted to be at least 5 tissue half-lives.

2.8.3. Risks and Mitigation Due to the COVID-19 Pandemic

This study has been designed to reduce the likelihood of COVID-19 spread for participants and healthcare personnel, to maintain safe and continuous study conduct, and to analyze the data for potential effects of COVID-19 illness on results.

Study participants will be tested for COVID-19 per site and local regulatory requirements. Participants with a history of COVID-19 based on clinical presentation and/or COVID-requiring medical management within 1 week of Day 1; or presence of clinically relevant post-COVID symptoms/conditions after discussion with medical monitor are also excluded. It is possible that this process may lead to more screen failures, but overall, the pandemic is not expected to significantly impact recruitment.

Recent or future vaccination is not excluded or prohibited as patients with DM1 are at high risk for severe COVID-19 and poor outcome (Dhont 2020) and have a high priority for vaccination due to cardiorespiratory risk factors. Previous clinical trials with siRNA therapeutics have not excluded vaccine administration to trial participants in general. It is believed that there COVID-19 vaccines would have minimal impact on the effect of AOC 1001. COVID-19 illness or vaccination status will not affect the length of follow-up.

The impact of COVID-19 on concomitant medications and clinical monitoring should not be significantly different in this study. It is not known if there are any treatments for COVID-19 (e.g., remdesevir or monoclonal antibody infusions) that would affect DM1 patients differently than the general population, nor of any interaction between these medications and AOC 1001. To assess the potential for virus/drug interactions, participants enrolled in the trial who contract COVID-19 will be monitored per standard of care, and per trial schedule as well as per investigator judgment. It is not expected that AOC 1001 would affect COVID-19 disease progression. It is possible that AOC 1001 could improve muscular strength of the DM1 patients, in which case it may improve respiratory function in DM1 patients.

Careful risk mitigation steps have been instituted at the clinical sites to decrease the risk of participants and healthcare providers contracting COVID-19 during the study, per local and institution regulation and guidance. Risk mitigation will include working closely with sites and rearranging schedules if site personnel require isolation. These measures will be agreed in advance between the sponsor and clinical trial site. Telehealth visits are allowed if travel is restricted. The schedule of assessments and visit windows have been designed to allow flexibility for trial conduct. Use of remote and telehealth visits and home health lab collections have been built in, as well as telephone visits for patient monitoring. Protocol deviations due to COVID-19 will be recorded to allow analysis of impact due to COVID-19. Similarly, screen failure and treatment discontinuation due to COVID-19 will be recorded and monitored. These will be reviewed to assess for the need for a protocol amendment.

Should the overall duration of the study be extended, this should not affect the availability of study drug as stability testing is ongoing.

Overall, the risk benefit balance of conducting the trial during the COVID-19 pandemic is considered to be positive, due to the ability to mitigate risks and conduct the study safely, and to provide potential benefit to a vulnerable population.

2.8.4. Overall Assessment of Benefit: Risk

Based on preclinical results and analysis, it is predicted that the dose range tested will exhibit acceptable safety and tolerability profile in adult DM1 patients, and knockdown of the mutant *DMPK* mRNA may potentially lead to correction of spliceopathy in DM1 patients.

The potential safety concerns associated with AOC 1001 treatment can be monitored by clinical signs and/or lab tests, and this study has been designed with appropriate exclusion criteria, dose escalation, safety monitoring and review to minimize potential risks to study participants. The information obtained during this study is critical to further development of AOC 1001 for DM1, a rare disease with high unmet need for an effective treatment. Key opinion leaders in the field of DM1 were consulted and agreed that, given the high unmet need, the trial has a favorable risk/benefit profile. Thus, exposure of participants in this study is justified by the anticipated benefits that may be afforded to the wider population of patients by continued development of AOC 1001.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Objective • To evaluate the safety and tolerability of single and multiple ascending doses of AOC 1001 in DM1 patients	**Primary Endpoint** • Frequency of treatment emergent adverse events (TEAEs)
Secondary Objectives • To evaluate the pharmacokinetic profile of single dose and multiple doses of AOC 1001 in DM1 patients • To evaluate the pharmacodynamic profile of single dose and multiple doses of AOC 1001 in muscle biopsies in DM1 patients • To evaluate the efficacy of multiple doses of AOC 1001 in DM1 patients as measured by spliceopathy	**Secondary Endpoints** • AOC 1001 levels in plasma, urine, and muscle tissue • Estimation of PK parameters, including C_{max}, t_{max}, t1/2, AUC, and fraction excreted in urine • Change and percentage change from baseline in *DMPK* mRNA levels • Change and percentage change from baseline in spliceopathy

Exploratory Objectives • To evaluate the exploratory efficacy of multiple doses of AOC 1001 in DM1 patients on measures of mobility, muscle strength, muscle function, and patient-reported outcomes • To evaluate immunogenicity and metabolite PK of AOC 1001	**Exploratory Endpoints** Change from Baseline in: • Myotonia • Ankle dorsiflexion strength by QMT • Multiple Muscle Strength by Quantitative Myometry Test (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 • % of participants needing to start myotonia medications after dosing • Muscular Impairment Rating Scale • DM1-Neuromuscular Severity Measure (DM1-NSM) • Myotonic Dystrophy Health Index (MDHI) • 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) • EQ-5D-5L • Columbia-Suicide Severity Rating Scale **PK Endpoints:** • Measurement of ADA • Measurement of potential metabolites
Additional Safety Objectives • To further characterize the safety and tolerability profile of AOC 1001	• Laboratory parameters • Vital signs • Infusion related reactions (IRR) • Electrocardiographic measures • Echocardiographic measures

4. INVESTIGATIONAL PLAN

4.1. Study Design

AOC 1001-CS1 is a first in human, double-blind (participant and trial site personnel), placebo-controlled multicenter study in two parts. Part A is a single dose design, enrolling approximately 8 adult DM1 patients, whereas part B is a nested single and multiple ascending dose (MAD) design enrolling up to 44 adult DM1 participants.

For participants who withdraw from the study prematurely, additional participants may be enrolled at sponsor discretion so that minimal evaluable participants are achieved for dose escalation. The maximum enrollment will be limited to 52 participants, including replacement participants.

Consistent with the pathogenesis of DM1 and the mechanism of action of AOC 1001, one of the pharmacodynamic parameters for this study will be the knockdown of the *DMPK* mRNA. The safety of AOC 1001 will be monitored in an ongoing fashion throughout the study including safety labs from blood/urine samples, ECGs, physical examinations, vital signs, and adverse events. Exploratory efficacy endpoints to measure participants' mobility, muscle strength, muscle function, and patient-reported outcomes will be assessed.

Detailed information regarding study procedures is outlined in the Schedules of Assessments (SOA) (Table 1, Table 2, Table 3, and Table 4).

The end of study is defined as the last participant last visit.

The study will continue until all treated participants have completed the last study visit.

4.1.1. Part A

The minimum 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, and a 6-month post-treatment period. The duration of the study is designed to capture the maximal *DMPK* mRNA knockdown, and to follow the duration of the knockdown as well as safety profile associated with the drug action.

Baseline assessments will be collected after participant is deemed eligible for Part A prior to Day 1. Participants will receive study drug by IV infusion on the morning of Day 1 and will be monitored overnight. After at least 24 hours of observation, they will be discharged on Day 2 after completing the Day 2 study assessments. The participant will return to the trial site for additional safety evaluations during the 6-month post-treatment period per Table 1.

At the end of the 6-month post-treatment period, eligible participants may directly enroll into an open label extension trial (OLE). Participants not willing or eligible to enroll in the OLE will be followed in the extended follow-up period for an additional 3 months, for a total of 9 months post-dose, which is estimated to be 5 tissue half-lives of the drug. The extended follow up will consist of communication between the site and participant via telephone, telehealth or other applicable means.

A muscle needle biopsy from the tibialis anterior will be obtained at Baseline, on Days 43, and 92.

If a participant discontinues prior to completing the required assessments, perform the Day 183/End of Post-Treatment (EOPT) assessments, if possible (Table 1 and Table 2).

4.1.2. 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. Pending approval by the regulatory agencies, all eligible participants will have the option to enroll into the OLE.

Baseline assessments will be collected after participant is deemed eligible for Part B prior to Day 1. Participants will receive study drug by IV infusion on the morning of Day 1 and will be monitored overnight. After at least 24 hours of observation, they will be discharged on Day 2 after completing the Day 2 study assessments. The participant will return to the trial site for additional safety evaluations during the 3-month treatment period per Table 3. They will receive IV infusions on Day 43 and 92 and will be followed for an additional 13 weeks in the post-treatment period after the 3rd dose.

For each participant in Part B, continuation of the second dose will require the review of Day 29 safety and tolerability data by the participant's PI, and the sponsor medical monitor or designee. The decision will be documented on the Dose Continuation Approval form.

A muscle needle biopsy from the tibialis anterior will be obtained at Baseline, on Days 92, and 183.

If a participant discontinues prior to completing Day 92 (3rd infusion), every effort should be made to complete End of Treatment (EOT) assessments, then have the participant begin the 13-week post-treatment period. See Section 5.3, Section 5.4, and Section 5.5. Detailed information regarding study procedures is outlined in Table 3 and Table 4.

For participants who terminate treatment early and/or do not enroll into the OLE trial, participants will be followed in the extended follow-up period to be monitored for safety every 3 months until they have been followed for 9 months from the last dose.

4.2. Safety Oversight

4.2.1. Safety Review Committee (SRC)

An SRC will perform ongoing blinded reviews of safety, tolerability data collected in all study parts (Parts A and B) with the primary purpose of protecting the safety of participants.

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. SRC may also participate in ad hoc meetings for decisions related to AEs meeting criteria listed in Section 4.3. After the 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 the SRC charter.

4.2.2. Independent Data Monitoring Committee (IDMC)

An IDMC will be responsible for recommending the decision to dose escalate from cohort B2 to cohort B3 (upon implementation as of protocol version 5.0). The IDMC will also conduct regular meetings to review the safety and tolerability. The IDMC will also approve resumptions in dosing as described in Table 6.

The details regarding membership, responsibilities, meeting frequency, data to be reviewed, and process for communication with the Sponsor are included in the IDMC charter.

4.3. Cohort Safety Management Rules

Individual participant, dosing cohort, and study dose suspension and stopping rules are presented in Table 6.

AE severity and seriousness are assessed independently, according to the definitions listed in Section 8.2 and Section 8.4.1, but are considered together for the purpose of applying the suspension and stopping rules described here.

Abnormal laboratory and other test results should always be repeated at a central laboratory, if possible, before evaluating clinical relevance and grading AEs to ensure consistency and to exclude technical errors. If applicable, diurnal variations in laboratory parameters and other measurements as well as baseline status should be considered when grading AEs and assessing whether abnormal laboratory values constitute a drug-related AE.

Participants who discontinue dosing because they have met a stopping rule will be asked to undergo scheduled study assessments until completion of the study or until resolution or stabilization of the AE, whichever is later. Participants who meet stopping rules will be managed as clinically indicated, with appropriate consultation and referral to their primary physicians, as necessary.

Table 6: Safety Management Rules for Related AEs

Related AE Severity/ Seriousness	Action for Individual Patient	Effect on Cohort and Study
Mild	No action required.	• No effect.
Moderate	If considered related to AOC 1001, study drug administration may continue at the same or a lower (intermediate) dose if the investigator considers it safe for the participant.	• No effect.
Severe	If related to study drug, the next AOC 1001 administration may proceed at the same or a lower (intermediate) dose if the IDMC* considers it safe for the participant.	• If similar AEs (as defined in the Medical Monitoring Plan [MMP]) related to AOC 1001 occurs in ≥2 participants: o Suspend dosing in cohort and higher dose cohorts. o A lower dose level or an intermediate (but lower) dose level may be administered in the next cohort. o Approval by IDMC* required to resume dosing at same and higher dose level.
Serious not life-threatening/ non-fatal	If related to AOC 1001, stop dosing.	• If the SAE related to AOC 1001 occurs in ≥1 participants: o Suspend dosing in cohort and any higher dose cohorts. o A lower dose level or an intermediate (but lower) dose level may be administered in the next cohort. o Approval by IDMC* required to resume dosing at same and higher dose level.
Serious life-threatening/ fatal	If related to AOC 1001, stop dosing.	• If the SAE related to AOC 1001 occurs in ≥1 participants: o Stop all dosing on study. o Approval by IDMC*, IEC/IRB, and regulatory authority, as applicable, required to resume dosing at any dose level.

Abbreviations: AE=adverse event; IEC=Independent Ethics Committee; IRB=Institutional Review Board; MD=multiple dose; SRC=Safety Review Committee, IDMC = Independent Data Monitoring Committee.
Note: If more than 1 condition in this column applies, the higher severity/seriousness level will be used.
*Until the IDMC is implemented, SRC will fulfill this role

Additionally, please refer to Section 8.10 for management of hypersensitivity reaction for individual participants, Section 8.12.2 for management of liver function test abnormality, and Section 8.13.2 for guidance relating to iron homeostasis.

5. SELECTION AND WITHDRAWAL OF PARTICIPANTS

5.1. Inclusion and Exclusion Criteria

5.1.1. Inclusion Criteria

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be willing and able to comply with all study requirements
2. Males or females aged 18 to 65 years (inclusive) at the time of informed consent
3. Genetic diagnosis of DM1 with *DMPK* CTG repeat length ≥ 100 during screening, if not done prior
4. Ability to walk independently (orthoses and ankle braces allowed but not cane or walker) for at least 10 meters at screening
5. 10mWRT velocity at Screening
   a. Part A: 10mWRT velocity 0.7 -3.3 m/sec (3-14 seconds)
   b. Part B: 10mWRT velocity 0.7 -2.63 m/sec (3.8-14 seconds)
6. Muscular Impairment Rating Scale (MIRS) score
   a. Part A: MIRS score ≥2
   b. Part B: MIRS score ≥3

5.1.2. Exclusion Criteria

1. Females who are pregnant, planning a pregnancy, or breast-feeding
2. Males or Females not willing to comply with contraceptive requirements as described in Section 6.4.
3. Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that would render a participant unsuitable for inclusion.
   a. ALT, AST >2.5x ULN, alkaline phosphatase >2x ULN
   b. Total bilirubin > 1.5 mg/dL. Total bilirubin between 1.5 and ≤ 3 mg/dL with clinical diagnosis of Gilbert's syndrome as determined by the investigator may also be eligible if approved by sponsor medical monitor or designee
   c. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation
   d. Platelet count < 100x10^9/L
   e. Hemoglobin < 10 g/dL
   f. TSH outside reference range and thyroid panel including reflexive TT3 and FT4 consistent with clinically significant abnormalities per investigator judgment
   g. HbA1c > 9%
4. Diabetes that is not, in the opinion of the investigator, adequately controlled with diet and/or antidiabetic medication(s)
5. PR interval >240 milliseconds at screening (except those with appropriately programmed cardiac rhythm management devices after discussion with the medical monitor) or planned pacemaker procedure during study period. Clinically significant and unstable heart disease including decompensated heart failure within 3 months of screening (such as New York Heart Association (NYHA) Classification III or more), atrial flutter, atrial fibrillation, ventricular arrhythmias, or receiving medication for the treatment of a cardiac arrhythmia, in the opinion of the investigator. (Patients

presenting with Stable ventricular dysfunction without congestive heart failure, pre-existing pacemaker or ICD are not excluded from this study.)

6. Uncontrolled hypertension (BP > 160/100 mm Hg)
7. BMI > 35 kg/m^2
8. Congenital DM1
9. Have unstable medical conditions that affect the musculoskeletal system (other than DM1) that could affect interpretability of the outcome measures
10. History of tibialis anterior biopsy 3 months within the first biopsy of the trial or planning to undergo tibialis anterior biopsies over the duration of the trial. History of bleeding disorders, significant keloid or other skin or muscle conditions (eg. Severe muscle wasting) that in the opinion of the investigator make the participant unsuitable for serial muscle biopsy.
11. Anticipated survival less than 2 years
12. Evidence of current active or chronic infection with hepatitis C, hepatitis B, or HIV (including chronic infection requiring ongoing treatment to maintain viral suppression)
13. Malignancy within 5 years, except for basal or squamous cell carcinoma, melanoma in situ of the skin, or carcinoma in situ of the cervix that has been successfully treated. Participants with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by sponsor medical monitor or designee
14. Treatment with another investigational drug or biological agent within one month of screening, or 5 half-lives of the drug, whichever is longer. Participation or plan to participate in another intervention trials with investigational devices, or other types of interventional trials (including trials studying behavioral modification and/or physical therapy)
15. Treatment with an oligonucleotide within 9 months of screening
16. Treatment with anti-myotonic medication within 14 days prior to dosing. May include, but not limited to: phenytoin, carbamazepine, procainamide, disopyramide, nifedipine, acetazolamide, clomipramine, imipramine, amitriptyline, taurine, quinine, mexiletine
17. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
18. Recent history of, or current drug or alcohol abuse
19. Have any other conditions (e.g., medical concern, neuropsychiatric or intellectual disabilities), which, in the opinion of the investigator or sponsor would make the participant unsuitable for inclusion, could interfere with participating in, or completing the Study.
20. History of multiple drug allergies or history of allergic reaction to any component of, or excipient in, the study drug.
21. COVID-19 based on clinical presentation and/or COVID-requiring medical management within 1 week of Day 1; or presence of clinically relevant post-COVID symptoms/conditions after discussion with medical monitor. (Screening and Baseline periods may be extended without the need for rescreen after discussion with Sponsor medical monitor.)

22. Unwillingness to receive COVID-19 testing per local or site COVID-19 guidance.

5.2. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized due to not meeting eligibility criteria outlined in Section 5.1. Screening labs can be repeated without the need to screen fail if the investigator feels the lab results are out of range due to technical issues or mild or reversable clinical conditions.

Select information regarding screen failure is required in the EDC. Please refer to eCRF Completion Guidelines.

Participants who fail screening can be rescreened if the investigator documents that the reason for screen failure has reversed and after consultation with medical monitor. However, for 10mwrt velocity, participant should not be rescreened unless the transient medical condition affecting the performance of 10mwrt has reversed. A participant can be rescreened twice. If rescreened, the participant will keep the originally assigned screening number. Assessments performed prior to reconsent but within the current screening period may be used for eligibility upon approval from Sponsor (or designee).

5.3. Discontinuation of Study Drug

In some instances, it may be necessary for a participant to permanently discontinue study drug. If study drug is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for post-treatment visits, and the extended follow-up visits, if applicable, unless they have specifically withdrawn consent for any further involvement with the study.

The reason for discontinuing study drug should be recorded in the EDC. Reasons could include, but are not limited to, the following:

- Withdrawal of consent
- Significant violation of the protocol (including participant unwilling or unable to comply with the protocol)
- Adverse Event
- Pregnancy
- Meets protocol specified treatment discontinuation criteria

If possible, the investigator will confer with the medical monitor or designee before discontinuing study drug administration. Medical monitor (or designee) should be involved in the planning of subsequent follow up to ensure patient safety and trial integrity.

Participants who are pregnant will be discontinued from study drug dosing immediately (see Section 8.8 for reporting and follow-up of pregnancy).

If a participant discontinues study drug due to an AE or SAE, the event should be reported as described in Section 8.4. The primary reason must be recorded in the appropriate section of the eCRF. Safety data will be captured for the entire duration of the study for participants who discontinue study drug.

A participant may also be discontinued for protocol violations or if the protocol specified treatment discontinuation criteria are met for cohort/study (see Section 4.3, Table 6).

For Part B participants who permanently discontinue study drug, they should complete End of Treatment (EOT) assessments prior to initiating post treatment visits.

5.4. Declining of Study Procedure

Participants who decline protocol assessments (e.g., muscle biopsy) should not be automatically removed from study unless the participant specifically withdraws consent for any further involvement with the study. Participants should be encouraged to continue with the remaining protocol assessments, especially safety monitoring.

If a participant declines some or all of the study assessments, the investigator must discuss with the participant options for continuing Schedule of Assessments including different levels for follow-up and collection of data, including endpoints and AEs. These options may include in person clinic or remote visits, by phone, by mail, through family or friends, or options not involving direct contact, such as communication with other treating physicians or from review of medical records. Investigator should document this decision in the participant's medical records.

Medical monitor (or designee) should be informed.

5.5. Participant Discontinuation/Withdrawal from the Study

A participant is considered to have completed the study if the participant has completed the post treatment period and complete either of the following:

- Enroll in the OLE, or
- Extended Follow-up through 9 months after the last dose

A participant may withdraw from the study at any time. However, study integrity and interpretation are optimal if all randomized participants continue study assessments and follow-up. Participants considering withdrawing from the study should be informed that they can discontinue study drug administration and complete the remaining scheduled study visits or agree to alternative follow-up processes as described in Section 5.4.

If a participant still chooses to withdraw consent from study participation, every effort should be made to conduct the assessments performed at the EOPT visit prior to the withdraw of consent.

After withdrawal of consent from further participation in the study, participants will have no additional study procedures performed and no additional data collected. The information and samples that he or she has provided prior to withdrawal may be kept and continue to be used, transferred, and processed.

The investigator should notify the medical monitor or designee of all discontinuations of participants from the study, preferable before the discontinuation. Medical monitor (or designee) should be involved as applicable in the planning of subsequent follow up to ensure

patient safety and trial integrity. In addition, the investigator should follow the following guidance's:

- Discontinuation due to AE should occur AFTER proper follow up of the AE.
- If a participant withdraws due to a serious adverse event (SAE), the SAE should be followed as described in Section 8.5. See SOA for data to be collected at the time of study discontinuation (Table 1, Table 3).

If the participant withdraws from the study, the information and samples that he or she has provided prior to withdrawal may be kept and may continue to be used, transferred and processed.

5.6. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Medical monitor (or designee) should be informed.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

6. STUDY INTERVENTIONS AND OTHER REQUIREMENTS

6.1. Study Drug Description, Administration, and Storage

The study drug used includes AOC 1001 and placebo. Detailed storage, preparation, accountability, and administration instructions are outlined in the Pharmacy Manual.

IMP	AOC 1001	Placebo/Sterile Saline
Dosage Form	Lyophilized powder	Solution for Injection
Supplied Form	175 mg AOC 1001	Saline (0.9% sodium chloride w/v)
Preparation	Resuspension in 8.2 mL sterile WFI would lead to a concentration of 21.9 mg/mL AOC 1001 and a total volume per vial of 8.6 mL. From each vial 8.0 mL is extractable for further dilution in saline for IV infusion.	N/A
IV infusion Concentration and rate	≤ 10 mg/mL AOC 1001 at ≤ 250 mL/hr IV	≤ 250 mL/hr IV
Physical Description	Colorless, free of particulate	Clear, colorless solution

AOC 1001 for intravenous (IV) infusion is provided as sterile lyophilized powder in a sealed colorless glass vial.

The AOC 1001 drug product is formulated in 50 mM sodium citrate, 60 mM NaCl, 10 mM L-methionine, 120 mM sucrose, 0.03% polysorbate 80, pH 5.5. Sodium citrate is the buffer salt present to maintain the pH of the solution. Sodium chloride is a stabilizing salt. L-methionine is present as an antioxidant. Sucrose serves as a cryoprotectant, and polysorbate is a stabilizing surfactant.

Throughout the protocol, AOC 1001 is presented based on the weight of the siRNA component, in addition to the weight of the entire molecule. This is provided because the preclinical findings refer to AOC 1001 by the siRNA component weight, and to enable translation into human doses which are based on the weight of the entire molecule. The siRNA component weight accounts for ~8.4% of the total weight of AOC 1001, i.e. a 4 mg/kg dose of siRNA would correspond to ~48 mg/kg dose of AOC 1001.

The placebo for this study is saline for IV administration and will be provided by the trial site. An unblinded pharmacist and staff (who will not participate in any other aspect of the study) will perform accountability, dose preparation, and dispensation of the study drug.

All study drug must be stored in a secure, temperature-controlled location and may be dispensed only by a staff member specifically authorized by the investigator, or by a pharmacist, as appropriate. All study drug will be stored upright and refrigerated at 2-8°C. Any deviation from the recommended storage conditions must be reported to the sponsor or designee.

All doses will be administered based on body weight. The duration of infusion may be increased with approval from the sponsor medical monitor or designee on a case-by-case basis for safety, or cohort wide if an unacceptable proportion of participants are experiencing infusion related

reactions (IRRs) in the opinion of the IDMC (or SRC until the IDMC is implemented). See Section 8.9.2.

6.1.1. Packaging and Labeling

The sponsor will provide the investigator with packaged AOC 1001 labeled in accordance with specific country regulatory requirements. Placebo will be provided by the study site.

6.1.2. Study Drug Accountability

The unblinded pharmacist will maintain accurate records of receipt and the condition of AOC 1001 including dates of receipt. In addition, accurate records will be kept of the participants' baseline weights used to calculate each dispensed dose, and when and how much AOC 1001 is dispensed and used by each participant in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded. Please refer to Pharmacy Manual for more detail.

6.2. Randomization and Blinding

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

Investigators and site personnel will remain blinded to each participant's assigned study intervention (AOC 1001 vs placebo) throughout the course of the study. The site pharmacy and the sponsor 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 participants remain blinded to the treatment.

Once assigned, randomization numbers will not be re-used.

6.2.1. Unblinding

The IRT system will be programmed with blind-breaking instructions. In case of a medical emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should contact the sponsor prior to unblinding a participant's treatment assignment, unless this could delay emergency treatment of the participant. The date, time, and reason that the blind was broken must be recorded in the source document and filed in the eTMF.

6.3. Dosing

6.3.1. Part A: Single Dose

There is 1 planned dose level in Part A with 8 participants in the cohort (Table 7). Participants will receive a single dose of study drug (AOC 1001 or placebo) by IV infusion on Day 1 and will

be monitored in clinic on an inpatient basis for approximately 24 hours. and will subsequently enter the six-month post-treatment period.

Please see Section 4 for study design, dose escalation decision making.

Table 7: Part A Cohort Dose Levels

Cohort	siRNA Component Level	Total AOC 1001 weight
Cohort A1	1 mg/kg	11.94 mg/kg

6.3.2. Part B: MAD

There are 3 planned dose levels in Part B with at least 12 participants per cohort. Cohorts may be expanded to obtain additional data, but the maximum number of participants will not exceed 44.

Please see Section 4 for study design, dose escalation decision making.

Participants in Part B will receive a total of three doses of study drug administered by IV infusion on Day 1, 43, and 92. Participants will be monitored in clinic or on an inpatient basis for approximately 24 hours following the Day 1 dose.

Table 8: Part B Cohort Dose Levels

Cohort		siRNA component Level per dose	Total AOC 1001 weight per dose
Cohort B1		2 mg/kg	23.88 mg/kg
Cohort B2		4 mg/kg	47.76 mg/kg
Cohort B3		8 mg/kg	95.54 mg/kg

6.3.3. Dose Modification

Dose modification is not planned during this trial, except when agreed to by the SRC or IDMC (upon implementation as of protocol version 5.0). Please refer to Section 4.2 for further guidance.

6.3.4. Treatment Compliance and Documentation

Amount of study drug infused, infusion rate, dosing modification and/or interruption will be recorded in the EDC.

6.3.5. Continued Access to Study Intervention after the End of the Study

An open label extension trial under a separate study protocol is planned for eligible participants pending regulatory approval.

6.4. Contraception Requirements

Participants must agree to use the following contraceptive requirements for the duration of the trial and the extended follow up period if not enrolling into the OLE:

a. Female participants of non-childbearing potential (WNCBP): Defined as either postmenopausal (evidence of menopause based on a combination of amenorrhea for at least one year and increased serum follicle-stimulating hormone (FSH) level [> 30 IU/L]), or surgical sterilization (evidence of hysterectomy and/or bilateral oophorectomy).

CONTRACEPTION REQUIRED: None

b. Female participants of childbearing potential (WOCBP) who anticipate being sexually active with a male during the trial (from one complete menstrual cycle prior to the first study drug administration until the last visit):

   CONTRACEPTION REQUIRED: Highly effective contraception must start one complete menstrual cycle prior to the first day of dosing and continue until the end of the systemic exposure of the study drug (defined as 5 tissue half-lives or 9 months from the last dose). Highly effective contraception methods for WOCBP include:
   - Combined i.e. (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
     - oral
     - intravaginal
     - transdermal
   - Progestogen-only hormonal contraception associated with inhibition of ovulation
     - oral
     - injectable
     - implantable
   - Intrauterine hormone-releasing system (IUS)
   - Intrauterine device (IUD)
   - Bilateral tubal occlusion
   - Infertile male partner (e.g., vasectomized, permanently sterile following bilateral orchidectomy, or any other documented cause of infertility)

c. WOCBP who agree to remain abstinent for the duration of the trial (from one complete menstrual cycle prior to the first study drug administration until the last visit):

   CONTRACEPTION REQUIRED: Abstinence (Note: sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Calendar, symptothermal and post-ovulation methods of contraception are not considered to be equivalent to abstinence).

d. Male participants, who agree to remain abstinent for the duration of the trial (from first study drug administration until the follow-up visit):
   CONTRACEPTION REQUIRED: Abstinence (Note: sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant).

If the situation changes after randomization during the trial, participants must use a condom with or without spermicide for the duration of the trial and for 9 months after the end of the trial.

e. Male participants, who anticipate being sexually active during the trial period (from first study drug administration until the last follow-up visit):

CONTRACEPTION REQUIRED: from start of dosing until 9 months after the last dose. Male participants should use a condom with or without spermicide. Female partners of male participants who are WOCBP should use highly effective contraception per point b above.

6.5. Disallowed Therapy

Therapies disallowed and excluded during the eligibility process are prohibited during the trial. These include:

- Participation in interventional trials with another investigational drug, biological agent, device, or other types of interventional trials (including trials studying behavioral modification and/or physical therapy)
- Treatment with an oligonucleotide other than study drug (this does not include COVID-19 RNA vaccines)
- Treatment with anti-myotonic medication which includes, but is not limited to: phenytoin, carbamazepine, procainamide, disopyramide, nifedipine, acetazolamide, clomipramine, imipramine, amitriptyline, taurine, quinine, mexiletine. They should be washed out 14 days prior to first dose of study drug. If treatment with anti-myotonic medication is started during the trial, it should be recorded as a concomitant medication (see Section 7.1.1).

6.6. Lifestyle Considerations

Energy drinks or drinks containing taurine, glucuronolactone (e.g., Red Bull), or alcohol should be withheld 24 hours before visits that include dose administration and/or muscle biopsy procedures, if possible.

If participants take a stimulant or caffeine to prepare for clinic visit, the same regimen should be maintained before each visit and recorded in source each visit.

If participants are in physical therapy or follow an exercise routine, it should be consistent throughout the trial.

Strenuous physical activity should be avoided 72 hours before visits that include dose administration, measures of functions and strength, and/or muscle biopsy procedures.

Blood and plasma donation should be avoided for 16 weeks before the planned first study drug administration and throughout the trial.

Vaccinations should not be given within 5 days before dosing and for two weeks after dosing.

Participants should refrain from starting new supplements, herbal preparations, over the counter medications, vitamins, or minerals for the length of the trial.

6.6.1. Spirometry

For spirometry to assess pulmonary function: Participants can continue taking daily medications prior to testing unless told otherwise. Participants should not smoke for at least six hours prior to testing.

For a participant who uses short-acting inhaler on a “as needed” basis: Participants should not use for eight hours prior to testing, if possible. Participants should not eat or drink for at least 30 minutes prior to spirometry testing.

7. STUDY ASSESSMENTS

7.1. General Assessments

The schedules of assessments (SOA) for Part A are provided in Table 1 and Table 2, and for Part B in Table 3 and Table 4.

No study-specific procedures or tests will be performed prior to the participant voluntarily signing the ICF. Procedures or tests performed per standard-of-care routine medical care prior to a participant signing the ICF may be used to fulfill eligibility requirements. These conditions are specified in the SOA.

Additional assessments may be performed at any point as clinically indicated for safety.

As applicable, additional details for assessments will be described in the Study Operations Manual (SOM) and instructions for entering the data into EDC are included in the eCRF Completion Guidelines.

In general, pre-dose laboratory testing and muscle biopsy should be performed after all other assessments during a clinical visit except for dosing. PROs should be the first assessments to be performed.

7.1.1. Medications

The investigator or qualified designee will review past and current medication use to assess for eligibility according to the inclusion and exclusion criteria. Current medications as well as medications taken in the two months prior to screening should be recorded in EDC.

Use of all concomitant medications and treatments will be reviewed by the investigator and recorded in the eCRF during the trial. This will include all prescription drugs (including vaccination), herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded in the EDC.

Participants are required to discontinue use of any anti-myotonic medication at least 14 days prior to dosing. However, if, in the opinion of the Investigator, start of anti-myotonic medication is clinically warranted due to symptom recurrence or worsening after dosing has started, it should be recorded as a concomitant medication.

7.1.2. Demographics

At the Screening Visit, demographic data will be collected and include gender, year of birth, age, race, and ethnicity (where allowed, per local regulations).

7.1.3. Medical History and Disease History

A complete medical (including a comprehensive neurologic history) and surgical history will be obtained by the investigator or a qualified designee.

All clinically significant medical history (including any significant surgical procedures) must be recorded in the EDC for each participant. Each participant's full medical history will be obtained through direct questioning and the medical assessment during the Screening Period and

updated prior to dosing unless they are considered Serious Adverse Events (SAE, see Section 8.3).

A structured medical/disease history will be used to capture DM1 phenotypes in the EDC as outlined in the eCRF Completion Guidelines. Data will include age of onset, presence or absence of common DM1 symptoms, such as myotonia, muscle weakness, cataracts, cognitive or sleep symptoms. Common comorbidities will be documented, including sleep apnea, use of non-invasive ventilatory support, presence of a pacemaker or ICD, history of bowel obstruction or pseudo-obstruction, and presence of thyroid disease or diabetes mellitus. Information of prior participation in any DM1 natural history study will be recorded in the EDC.

7.1.4. Physical Examinations

The physical examination performed at Screening will include an assessment of the following: general appearance, skin, eyes, ears, nose, neck, lymph nodes, throat, heart, lungs, abdomen, musculoskeletal system, extremities, and neurological/psychiatric assessments. At all other clinic visits, an abbreviated physical exam (assessment of heart, lungs, abdomen, and symptom directed examination, if any symptoms) is administered to assess changes in symptoms from last visit. For infusion reaction monitoring, see Section 8.9. For abnormalities that are deemed clinically significant by the investigator, report as AE per Section 8.4.

For new participants, a detailed neurological examination should be conducted as part of the full PE during the screening period and include assessment of mental status, cranial nerves 2-12, motor and sensory function, deep tendon reflexes, coordination, and gait/station. For ongoing participants, this examination should be done prior to or during the next visit and prior to the next dose.

During infusions, a focused neurological exam should be conducted if participants report any neurological symptoms. If neurological symptoms are reported, a focused neurological exam should be conducted prior to subsequent doses.

7.1.5. ECG

Triplicate 12-lead ECGs using trial specific machines will be recorded at the time-points described in the SOA (Section 1.3 and Section 1.4). Procedural details will be described in the central ECG manual. Participants should be resting in a supine position for at least 5 minutes, then triplicate ECGs will be performed at approximately 1-minute intervals and each ECG recording (trace) will last 10 seconds.

Participants should remain supine between ECGs. The participants will avoid postural changes during the ECG recordings and site personnel will ensure that participants are awake during the ECG recording.

Repeat ECGs will be performed until at least three 10-second ECG records per scheduled time-point meet the quality criteria outlined in the central ECG manual.

When ECG and blood sample collection occur at the same time for PK, ECGs should be performed prior to drawing of blood samples.

7.1.6. Vital Signs, Height, and Weight

Height (cm) will be recorded at screening only. Height will be measured in cm and weight in kilograms. Measurements should be taken with participants wearing light clothing and without shoes using calibrated scales for all measurements. BMI will be calculated from the height and weight.

Vital signs (body temperature, blood pressure, heart rate, respiratory rate) will be measured pre-dose and at specified post-dose times. Vital signs should be measured in the seated position after the participant has rested comfortably for 10 minutes. Heart rate will be measured for 30 seconds and the number multiplied by 2 and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute. Blood pressure should be measured using an oscillometric device and will initially be recorded in both of the participant's arms unless a concomitant condition favors the use of a particular arm. The arm with the higher systolic reading at screening will then be used for blood pressure determinations throughout the study (including for determination of eligibility) and recorded in the EDC. The appropriate size cuff should be used. Participants must rest before blood pressure measurements.

On study drug administration days in Part B vital signs should be measured:

- Pre-dose
- From start of infusion through 2 hours post end of infusion every 15 minutes
- At 4 and 6 hours post end of infusion on Day 1

In addition, qualified site staff will ask the participant "how do you feel?" along with pre-infusion vitals prior to the start of infusion, and then every 15 minutes during and for 1 hour after the infusion along with the collection of vital signs. The question should also be asked every time ad hoc vitals are collected. If a participant complains of any newly emergent neurological symptoms during an infusion, the clinician (PI or sub-Investigator) is required to assess the participant and then, per clinical judgement, determine if a dose pause and additional work up and/or monitoring is indicated. If the clinician cannot assess a participant with emerging symptoms immediately, dosing should be paused until an assessment can be made.

7.1.7. Echocardiogram

Echocardiographic parameters will be used for assessment of cardiac structure and function. Qualified personnel will be required to administer echocardiograms as specified in the echocardiogram manual. Echocardiograms will be performed at the timepoints specified, per Table 1 and Table 3 analyzed at a central cardiac imaging lab.

7.1.8. MRI

All participants are required to have one non-contrast brain magnetic resonance imaging (MRI) and one time-of-flight MR angiogram (MRA) of the head and neck collected to establish a baseline.

The MRI/MRA should include:

- MRI of the brain without contrast including T1, T2/FLAIR, diffusion-weighted (DWI), and gradient echo (GRE)/susceptibility weighted (SWI) sequences
- MRA of the head and neck

For participants who have not yet received study drug, MRI/MRA should be performed prior to the first dose. For all other participants, MRI/MRA should be performed as soon as possible, preferably before the next dose.

For participants who are unable to undergo an MRI, a CT brain with contrast and CT angiogram head and neck should be performed.

If the participant has had imaging as specified above in the 3 months prior to enrollment, this requirement may be waived by the medical monitor.

7.1.9. Telehealth Visits

During the Extended Follow-Up Period, participants will be contacted by telephone (or other adequate communication method) per SOA to remind participant of study requirements, to assess overall health status, and to proactively plan subsequent in-clinic visit details.

7.1.10. Considerations Relating to COVID-19 Pandemic

As permitted per local regulation, select study assessments may be conducted remotely if travelling is restricted. If participant cannot travel to the clinic due to the COVID-19 pandemic, the site is encouraged to modify visit schedule after discussion with medical monitor or designee.

Asymptomatic COVID-19 test positivity should be reported in the EDC per eCRF completion Guidelines.

7.2. Assessments by Clinicians

7.2.1. Muscular Impairment Rating Scale (MIRS)

The DM1-specific muscular impairment rating scale (MIRS) will be captured at screening (as part of the inclusion criterion) and per SOA (Table 1 and Table 3). It is an ordinal five-point rating scale, established in accordance with clinically recognized distal to proximal progression of the muscular involvement in DM1 (Mathieu 2001) (Table 9). It is based on manual muscle testing of 11 muscle groups (neck flexors and six proximal [shoulder abductors, elbow flexors, elbow extensors, hip flexors, knee extensors, knee flexors] and four distal muscle groups bilaterally [wrist extensors, digits flexors, ankle dorsiflexors, ankle plantar flexors]).

Table 9: Muscular Impairment Rating Scale

Grade	Description
1	No muscular impairment
2	Minimal signs Myotonia, jaw and temporal wasting, facial weakness, neck flexor weakness, ptosis, nasal speech, no distal weakness except isolated digit flexor weakness
3	Distal weakness No proximal weakness except isolated elbow extensor weakness
4	Mild to moderate proximal weakness
5	Severe (MRC scale ≤ -3/5) proximal weakness

MRC = Modified Medical Research Council Scale. According to the Modified Medical Research Council Scale, mild to moderate weakness is an MRC score between 3/5 and +4/5 and a severe weakness as an MRC score of ≤-3/5. In severe weakness, the muscle moves the joint against gravity but not through the full extent of mechanical range of the joint or is weaker than that.

7.2.2. Clinical Global Impression of Severity and Change (CGIS, CGIC)

The investigator or designee will evaluate the participant for his/her global severity and rate of change, as well as changes in specific domains. This information will be used as an anchoring procedure to evaluate responsiveness and determine minimally important clinical difference. All efforts should be made to have the same investigator assess participants at each visit. CGIC is not to be assessed at baseline.

7.3. Assessments by Participants

7.3.1. Patient Reported Outcome Measures (PRO) and Scales

The following assessments should be performed in clinic before all other trial activities during a visit with the following order.

1. Fatigue and Daytime Sleepiness Scale (FDSS)
2. DM1-Activ
3. EQ-5D-5L
4. Myotonic Dystrophy Health Index (MDHI)
5. Columbia-Suicide Severity Rating Scale (C-SSRS)

The following assessments should be completed at home between 6:00pm and 10:00pm during the required time frames in the following order:

1. DM1 Neuromuscular Severity Measure (DM1-NSM)
2. DM1-NSM Patient Global Impression of Severity (DM1-NSM-PGIS)
3. DM1-NSM Patient Global Impression of Change (DM1-NSM-PGIC).

7.3.2. DM1 Neuromuscular Severity Measure (DM1-NSM)

This is a newly developed questionnaire specifically for adult DM1 patients. The DM1-NSM will include two subdomains: symptoms and impact of symptoms on daily activities.
The DM1-NSM questionnaire will be completed will be completed daily (between 6:00pm and 10:00pm) for 14 consecutive days during 4 assessment periods:

- Baseline – Completed daily for at least 7 (or up to 14) days prior to Day 1

- Days 43, 92, 183/EOT/EOPT – During the two-week period leading up to these visits, DM1-NSM should be completed daily for 14 days prior to the planned study day/visit.
  Example:
  - *If Day 43 uses a -3 (day) visit window for a Day 40 visit, the DM1-NSM should be completed daily on Days 25-39; PGIS on Days 32 and 39; PGIC on Day 39.*
  - *If Day 43 uses a +3 (day) visit window for a Day 46 visit, the DM1-NSM should be completed daily on Days 31-45; PGIS on Days 38 and 45; PGIC on Day 45.*

7.3.3. DM1-NSM Patient Global Impression of Severity and Change (DM1-NSM-PGIS, DM1-NSM-PGIC)

These questionnaires will evaluate the global severity and rate of change for both symptoms and activity impact. This information will be used as an anchoring procedure to evaluate responsiveness and determine minimally important clinical difference. For detail instruction, see the Study Operations Manual. Generally:

- DM1-NSM-PGIS will be performed on Day 7 and 14 (every 7th day) of each DM1-NSM assessment period.
- DM1-NSM-PGIC will be performed on Day 14 (the last day) of each of the 3 post-baseline DM1-NSM assessment periods

The order of questionnaire completion should be DM1-NSM, DM1-NSM-PGIS, and lastly DM1-NSM-PGIC.

7.3.4. Fatigue and Daytime Sleepiness Scale (FDSS)

This is a combined scale of Fatigue Severity Scale and Daytime Sleepiness Scale designed and validated for patients with DM1 (Hermans 2013).

7.3.5. DM1 Activity and Participation Scale for Clinical Use (DM1-Activ)

This questionnaire will assess impact of DM1 on daily life (Hermans 2015).

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

This brief questionnaire will assess overall health and impairment.

7.3.7. Myotonic Dystrophy Health Index (MDHI)

The MDHI is a standardized questionnaire to quantify DM1-related symptoms and disease severity (Heatwole 2014).

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

The C-SSRS (*Baseline* and *Since Last Visit*) will be administered to the participant by trained study personnel in clinic visits. This is meant to guide the investigators to monitor and follow up per standard of care.

7.4. Efficacy Assessments – Measures of Function and Strength

- The following exploratory efficacy assessments will be collected. Exploratory efficacy assessments will be performed per the SOA (Table 1 and Table 3). The assessments done

during the screening period are included to decrease the impact of a learning effect and will not be included in the change from baseline efficacy analysis.

- Detailed descriptions for these assessments are outlined in the Clinical Endpoints Manual.
- For all measures of muscle strength and function, the same therapist should conduct the assessments for an individual participant throughout the study. All therapists must receive central endpoint training prior to evaluating any participants on study.
- Testing should be done at approximately the same time of day throughout the study.
- For 10-meter walk/run test, timed up and go, and timed 4 stair climb and 4 stair descend assessments, orthotics and ankle braces are allowed but should be kept consistent and documented for each test.
- For the grip strength, myotonia, 9-hole peg test, and quantitative myometry testing (QMT), testing will be done only on one side of the body which preferably should correspond to the side with the dominant hand. The same side of the body must be tested throughout the study and documented in the EDC.
- The assessments should be conducted in the following order as much as possible when performed together. If the order is altered, the same order of assessments used at baseline should be used throughout the trial.
    1. MMT
    2. QMT
    3. Grip strength
    4. Pinch strength
    5. 10 meter walk/run test (10MWRT)
    6. Timed Up and Go (TUG)
    7. Timed 4 stair climb
    8. Timed 4 stair descend
    9. 9 hole peg test (9HPT)
    10. Myotonia Video Recording (vHOT).

Spirometry assessments may be completed at any point during or after the above listed assessments, but timing relative to other assessments should be consistent across visits.

- Select assessments are done remotely per SOA.
    1. Remote Hand Grip strength

7.4.1. Manual Muscle Testing (MMT)

Both sides of the body will be used for MMT testing and will be tested throughout the trial. Each muscle group will be scored using a modified Medical Research Council Scale (MRC) scale, in accordance with a protocol that standardizes the participant's position, direction of movement, and joint angle for resistance, as well as the examiners stabilization and hand placement. MMT will be performed on the following muscle groups:

- 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
- Plantar flexors

7.4.2. Quantitative Myometry Testing (QMT)

At screening, dominant side of the body will be chosen for QMT testing and will be the side tested throughout the trial. Quantitative Myometry Testing (QMT) will be performed using a force transducer attached to an inelastic strap as previously described (Personius 1994, (Quantitative Muscle Assessment (QMA) system (Computer Source, Atlanta, GA). Standardized positions for isometric force testing will be used on the following muscle groups. These muscles were selected for showing good test-retest reliability in previous natural history studies.

- Elbow flexion
- Ankle dorsiflexion
- Elbow extension
- Knee flexion
- Knee extension
- Hand grip

7.4.3. Pinch Strength by dynamometer

Key (lateral) pinch will be measured using a standalone hand dynamometer. Three successive trials will be recorded for the dominant hand.

7.4.4. 10-Meter Walk/Run Test (10MWRT)

From a standing start, the participant will be asked to go 10 meters as quickly as possible, whether by walking or running. Timing will start at "Go" and stop when the first full foot crosses the 10-meter mark. Orthotics and ankle braces are allowed. The time in seconds to complete the task will be recorded.

7.4.5. Timed Up and Go (TUG)

Participants will be asked to rise from a chair, walk 3 meters, turn around, return to the chair and sit. The time it takes to complete the task will be recorded. The TUG will be performed twice, once at a comfortable pace and once at a maximum pace. Assistive devices, orthoses, and ankle braces will be allowed.

7.4.6. Timed 4 Stair Climb and Timed 4 Stair Descend

Participants will be asked to climb up and down (timed as separate tests) 4 stairs as quickly as possible, using steps with a six-inch rise and ten-inch run. Quality grades will be captured for this test to record the use of railings and manner of ascent (i.e., step-to or step-over-step pattern). The time it takes to complete the task will be recorded.

7.4.7. 9-Hole Peg Test (9HPT)

The 9-hole peg test is a quantitative measure of distal upper extremity function. Participants will be asked to place 9 pegs in the 9 holes on the board and then remove them as quickly as possible, using their dominant hand. Two trials will be recorded using the participant's dominant hand. The total time to complete the task will be recorded.

7.4.8. Myotonia Video Recording (vHOT)

To eliminate "warm-up" of myotonia, participants will rest the dominant hand for five minutes before each vHOT trial. The participant will be asked to squeeze their hand for three seconds then open as quickly as possible. A video recording of the procedure will be obtained showing the forearm and hand but not the face. All recordings will later be evaluated, and hand opening times determined by independent, blinded reviewers.

7.4.9. Spirometry

Spirometry will be performed in the sitting and supine positions using standardized, calibrated equipment. Pulmonary parameters including forced vital capacity (FVC), peak cough flow, maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP) will be assessed and reviewed centrally.

7.5. Muscle Needle Biopsy for Pharmacokinetic, Pharmacodynamic and Spliceopathy Evaluations

Muscle needle biopsy sample from the tibialis anterior at each time point (per SOA in Table 1 and Table 3), will be used to determine levels of *DMPK* mRNA and spliceopathy. Please refer to the Muscle Biopsy Manual for additional details. Location of biopsy should alternate between two sides of the body at each visit to allow tissue healing. Sites of prior biopsies should be avoided. The investigators will utilize a 14-gauge, 10 mm length Supercore biopsy instrument or similar device to take up to 5 passes from the same site. The muscle tissues will be homogenized, RNA will be purified from the muscle tissue and analyzed for *DMPK* mRNA levels as well as alternative exon usage across many splicing events. Change from baseline in splicing events will be quantified, and details of relevant splicing events and computation of spliceopathy will be provided in the SAP.

Additional exploratory biomarkers related to DM1 may be evaluated in tissue, blood, and urine samples.

Please refer to the Muscle Biopsy Manual and Laboratory Manual for details on preparation, location of biopsy, processing of samples, and documentation.

7.6. Pharmacokinetic and Immunogenicity Evaluations

Blood and urine samples (24-hour and spot urine samples) will be collected for assessment of PK of AOC 1001 (total AV01mAb, total siRNA component, and intact AOC 001). Select plasma PK samples are paired with triplicate ECG assessment. When ECG and blood sample collection occur at the same time, ECGs should be performed prior to drawing of blood samples.

The amount of siDMPK.19 present in muscle needle biopsies from the tibialis anterior will be evaluated.

Potential metabolites may be quantified in these samples.

The concentration of analytes will be determined using validated assays. Details for handling of these samples including processing, storage, and shipment will be provided in the Laboratory Manual. Timepoints for PK, ECG, anti-drug antibodies (ADA), 24-hour and spot urine collections are outlined on the SOA, Table 2 and Table 4.

7.7. *DMPK* Gene Analysis

Blood will be drawn and *DMPK* gene analyzed for CTG repeat size. Historical report of *DMPK* gene analysis for enrollment needs to be approved by sponsor MM or designee.

Archival DNA from blood may be used for batched genetic analysis specifically for the *DMPK* gene at the end of the trial to allow characterization including presence of *DMPK* single nucleotide polymorphisms (SNPs) and other variants such as CCG or CGG repeats within the CTG repeat tract.

7.8. Clinical Laboratory Tests

7.8.1. Guidance for Clinically Relevant Abnormal Labs

Clinically relevant abnormal laboratory values should be repeated for confirmation as soon as possible per investigator judgment for patient safety (ideally within 3 days when possible). Those meeting monitoring and/or stopping criteria (Section 8.12, Section 8.13) should be monitored with weekly or more frequent laboratory draws. Evaluation for etiology should be performed. Sponsor medical monitor or designee should be notified.

7.8.2. Pregnancy Test

A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

7.8.3. Laboratory Analyte List

Clinical Chemistry	Hematology	Urinalysis	Blood screening
• Sodium • Potassium • Chloride • Bicarbonate • Blood urea nitrogen (BUN) • Creatinine, eGFR • Glucose • Calcium • Magnesium • Phosphorus • Total protein • Albumin • Aspartate transaminase (AST) • Alanine transaminase (ALT) • Alkaline phosphatase (ALP) • Total bilirubin (TB) • Direct (conjugated) bilirubin (reflexively measured if TB > ULN) • Indirect (unconjugated) bilirubin (reflexively measured if TB > ULN)	• Hematocrit • Hemoglobin (Hb) • MCV, MCH, MCHC • Red blood cell (RBC) count • RDW • Reticulocyte count • Platelet count • White blood cell (WBC) count • Neutrophils, absolute and % • Lymphocytes, absolute and % • Monocytes, absolute and % • Eosinophil, absolute and % • Basophil, absolute and % • Mean Platelet Volume	• Color • Appearance • Specific gravity • pH • Protein • Blood • Ketones • Urobilinogen • Glucose • Bilirubin • Leukocyte esterase • Nitrate • Microscopic examination (reflexive for abnormal findings) **Urine Chemistry** • Urinary protein: creatinine ratio (UPCR)	• Hepatitis B Surface antigen • Hepatitis C antibody • HIV antibody • FSH (women only) • HbA1c **Other** • Cardiac troponin (highly sensitivity cardiac troponin T (Hs-cTnT)) • aPTT, PT, INR • Iron • Ferritin • Transferrin saturation • Transferrin • Total iron binding capacity (TIBC) • bHCG (female only) • Thyroid panel (TSH with reflexive TT3, FT4) • Haptoglobin (reflexive) • LDH (reflexive)

• Gamma glutamyl transferase (GGT) • Creatine kinase • Myoglobin • Uric acid • Glutamate Dehydrogenase (GLDH)			

Infusion-related reaction (unscheduled collection per Section 8.9.2)

Hypersensitivity assessments (as needed per Section 8.10.1)

Hepatic assessments (as needed per Section 8.12.3)

Pharmacokinetics

- AOC 1001 levels in plasma, urine, and muscle

Immunogenicity

- Anti-AOC 1001 antibodies (ADA)

Pharmacodynamics

- *DMPK* mRNA levels in muscle
- Spliceopathy in muscle

Archived Blood

- An archived blood sample will be collected for measurement of cytokine, CRP and complement testing or other analyses as needed to characterize DM1, safety and efficacy profile of AOC 1001, and /or interactions between the disease and drug as applicable.

Biomarkers, DNA Genotyping, and Biospecimen Repository

- SiRNA therapeutics permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect. More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with DM1, as well as their responses to treatment. Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, samples will be collected as part of this study to permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of AOC 1001. Biological specimens will be collected at the intervals indicated in the SOA. These specimens will be analyzed at a central lab. Potential exploratory investigations may include DNA, RNA, or biochemical metabolite assessments as they relate to disease progression, efficacy or safety. The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc.) that are obtained during the study. These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed. Details regarding the collection, processing, storage, and shipping of the samples will be provided in the laboratory manual. Exploratory analysis of these biospecimens will be performed by the sponsor or its designees. When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

8. SAFETY DATA AND ADVERSE EVENT COLLECTION AND REPORTING

The collection, evaluation and reporting of AEs arising from this clinical study will be performed in accordance with the following where applicable:

- Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') (2011/C 172/01).
- ICH harmonized tripartite guideline on clinical safety data management: "Definitions and standards for expedited reporting" E2A.
- ICH harmonized tripartite guideline on development safety update report: E2F.
- ICH guideline E2F "Note for guidance on development safety update reports (DSUR)".

8.1. Definition of Adverse Events (AE)

- An AE is defined as any untoward medical occurrence in a clinical trial participant. The event does not necessarily have a causal relationship with study treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the clinical trial whether or not considered related to the study drug.
- An AE can include intercurrent illnesses or injuries, and exacerbation or worsening of preexisting conditions. Worsening indicates that the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome.
- Clinical laboratory, vital sign, or physical examination abnormalities will only be reported as AEs if they are deemed clinically significant by the investigator (e.g., associated with signs and symptoms, require treatment or adjustment in current therapy, or require follow-up).
- Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and not the individual signs/symptoms.
- Any laboratory, physical exam, or vital sign abnormality assessed as clinically significant by the investigator during the screening period will be recorded as medical history.
- All Infusion Related Reactions (IRR) will be recorded as an AEs.
- A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.
- Medical or surgical procedure (e.g., endoscopy, appendectomy) is not an AE. The condition that leads to the procedure is an AE if new or worsening.
- Hospitalization not intended to treat an acute illness is not an adverse event.
- Participants should be encouraged to report to the trial site as soon as possible events that required medical attention or are concerning to participants.

- The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the participant are recorded in the participant's medical record.
- Symptoms and signs that are being recorded as part of PROs or functional assessments should not be additionally recorded as AEs, unless it leads to the participant's withdrawal from dosing or it is one symptom of another diagnosis.
- A worsening of symptoms due to DM1 disease progression in the scientific opinion of the investigator is not considered an AE unless more severe than expected for the participant's condition.

8.2. Definition of Serious Adverse Events (SAE)

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- Fatal. Death is an outcome of an AE and not an AE itself. All events leading to death, regardless of causality, must be reported.
- Life threatening
  - It places the participant at immediate risk of death
  - It does not refer to an event which hypothetically might have caused death if it were more severe
- Requires in-patient hospitalization or prolongation of existing hospitalization
  - Necessitated medically an admission to a health care facility
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
  - ≤ 24-hour holds in the emergency room do not meet the criteria for hospitalization. Hospital admissions for circumstance that carries no bearing on health status and requires no significant medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) are not considered SAEs
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event
  - If an AE does not meet any of the serious criteria but an investigator considers an event to be clinically important or may require an intervention to prevent one of the other outcomes listed above, the event could be classified as a serious adverse event under the criterion of "other medically important serious event".

- Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury (DILI), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

8.3. Serious Adverse Reaction and Suspected Unexpected Serious Adverse Reactions

A Serious Adverse Reaction (SAR) is any adverse event that fulfils the criteria of seriousness, as defined above and is deemed related to study drug by the investigator.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a serious adverse reaction that is unexpected. The 'expectedness' of a serious adverse reaction is assessed in the light of the reference safety information.

The expectedness of a SAR is determined by the Sponsor. The list of 'expected SARs' should be based on 'suspected' SARs that were previously observed and not on the basis of what might be anticipated from the pharmacological properties of a medicinal product or the compound class. An 'expected' SAR is therefore one that is listed in the RSI. For this protocol, the reference document for the assessment of expectedness is the Investigator's Brochure for AOC 1001; however, at the time of writing, no clinical data is available for this compound. Therefore, any serious adverse reaction will be reported as a SUSAR, until any RSI is available in the IB.

8.4. Reporting Procedures for Adverse Events (AE and SAE)

- 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.

Additionally, spontaneously reported SAEs will be collected up until 30 days after the final visit. SAEs experienced after this 30-day period will only be reported if the Investigator suspects a causal relationship with the study drug.
The investigator will evaluate all AEs. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- Dates of onset and resolution (if resolved)
- Severity and seriousness
- Assessment of relatedness to study drug
- Action taken: If dosing of study drug is modified due to an AE, this information must be submitted to the sponsor as soon as possible
- Outcome

8.4.1. Assessment of Severity

Adverse events are to be graded according to the categories below.
Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money)
Severe: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event
Please note the following:

- The severity of AEs and SAEs relating to laboratory tests, infusion related reactions and adverse events at the injection site will be graded based on the Grading Scale for Adverse Events Relating to Lab Test Abnormalities, Infusion Related Reactions and Adverse Events at the Injection Site (Appendix 1). Analytes not listed in the table should be graded based on criteria described above.
- Severity of Infusion Related Reactions should be assessed as defined in Section 8.9.1.
- Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence.
- AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

8.4.2. Assessment of Causality

- Investigator should assess the relationship of each AE to study procedure by asking "Is there a reasonable possibility that the event may have been caused by a study procedure?" A "yes" response indicates that the event is considered as related to the study procedure.
- Investigator should assess the relationship of each AE to study drug by asking: "is there a reasonable possibility that the event may have been caused by the study drug?" A "yes" response indicates that the event is considered as related to the study drug.

The investigator will use clinical judgment to determine the relationship. The investigator will also consult the Investigator's Brochure (IB) in his/her assessment. The following factors should be considered in assessing relatedness:

- Whether the AE can be explained by other causative factors or the pharmacological effect of the study drug
- Temporal relationship to study drug exposure
- Event is known to be associated with the study drug class
- Event improved on discontinuation or dose reduction of study drug
- Event reoccurred on re-challenge of study drug
- Biological plausibility
- Event attributed to concomitant medication (provide details of the concomitant medication).

- Event attributed to the concurrent disease (s) / condition(s) (provide details of the disease/condition).
- Events expected in the study indication and/or target population

The causality assessment is one of the criteria used when determining regulatory reporting requirements. Therefore,

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change his/her opinion of causality considering follow-up information and send an SAE follow-up report with the updated causality assessment.

  The investigator should also comment on the source document whether an AE is not related to the study treatment but is related to study participation (eg, study procedures, wash-out periods etc.).

8.4.3. Action Taken with Study Drug

- If dosing of study drug is modified due to an AE, this information must be submitted to the sponsor as soon as possible.
- Action taken in regards to study drug will be defined as the following. If infusion is modified, total dose given needs to be recorded in the eCRF.
  - Not applicable
  - None
  - Infusion interrupted but completed
  - Dosing incomplete
  - Infusion not done

8.4.4. Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the AE eCRF. Treatment should also be recorded on the concomitant treatment or ancillary procedures as appropriate.

8.4.5. Outcome of Adverse Events

- **AE Persists:** participant terminates from the trial and the AE continues
- **Recovered:** participant recovered completely from the AE
- **Recovered but with sequelae:** The signs/symptoms of the reported SAE have improved but not completely resolved, and a new baseline for the participant is established since full recovery is not expected

8.5. Follow up of Adverse Events

- The investigator is expected to follow reported adverse events until stabilization or resolution. If the severity of an adverse event worsens from the date of onset to the

date of resolution, record a single event for each altered level of severity on the Adverse Event eCRF.

- All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:
    - The event resolves, stabilizes, or return to baseline.
    - The event can be attributed to agents other than the study drug or to factors unrelated to study conduct.
    - It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

8.6. Reporting Procedures for Serious Adverse Events

- Investigators or designee should record any new or updated SAE case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the SAE report form and submit the report via email or fax (please refer to the SOM).
- New or updated information will be recorded in the originally submitted documents.
- SAEs that are assessed by the investigator as related to study drug and occurring after the SAE reporting period will also be reported to the sponsor or designee immediately without undue delay, under no circumstances later than 24 hours following knowledge of the event.
- Reporting of SAEs to the IRB/IEC will be done in accordance with the standard operating procedures (SOPs) and policies of the IRB/IEC. Adequate documentation must be provided to the sponsor showing that the IRB/IEC was properly notified.
- The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator all serious adverse events that are unexpected and associated with the use of the study drug.
- SUSARs will be notified to the Competent Authority by sponsor or designee and to the relevant IECs by the sponsor within 7 (for fatal and life-threatening SUSARs) or 15 days (all other SUSARs).

8.7. COVID-19 Specific Guidance

- COVID-19 symptoms, signs, sequalae should be reported as an AE per Reporting Procedures for AEs (Section 8.4)
- Medications for prevention or treatment of COVID-19 should be entered as concomitant medications
- Please refer to eCRF Completion Guidelines for further detail

8.8. Pregnancy and Lactation Reporting

- Pregnancy is not regarded as an AE, unless there is a suspicion that study drug may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs, and many may meet criteria for an SAE, such as ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly. Elective abortions without complications should not be handled as an AE.
- If a pregnancy occurs in a female participant or female partner of a male participant while the participant is taking study drug, the Pregnancy Report Form should be completed by the investigator or designee no more than 24 hours after learning of the pregnancy and submitted using the same process as for SAEs (please refer to Section 8.6). The female participant will discontinue further study treatment. Contact information of the health care provider taking care of the pregnancy should be obtained so that the outcome of the pregnancy can be followed.
- Male participants may continue in the trial if an accidental pregnancy of their female partner occurs despite adequate contraception.
- Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required for a female participant and the partner of a male participant, even if the participant terminates from the trial. The investigator will request consent from the female partner of a male participant to collect the required information. If additional follow-up of the female partner is required, the investigator will be requested to provide the information.
- If a lactation case occurs while the female participant is taking study drug, report the lactation case to the sponsor or designee within 24 hours of the investigator's knowledge of event.

8.9. Guidance for Infusion-Related Reactions (IRR)

Participants will be monitored during and after IV administration for infusion related and/or allergic reactions. The participant's infusion site should be assessed for signs of any localized reaction during the infusion and for 120 minutes after the end of the infusion. The participant will remain at the trial site for at least 24 hours for observation after first dose. In Part B, participants should remain on site for minimally 2 hours after completion of 2nd and 3rd dosing for observation. Participants will be instructed to contact the investigator if they experience symptoms such as fever, chills, myalgia, skin rash, or nausea/vomiting after discharge from the site.

Trained site personnel at the trial site should be prepared to intervene in case of any infusion reactions occurring, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. Attention to staffing should be considered when multiple participants will be dosed at the same time.

8.9.1. Categorization of Infusion-Related Reaction

IRR is defined as an adverse reaction that the investigator deems to be related to the study infusion. Adverse events deemed by the investigator to be IRR will be indicated by the Investigator checking in the 'IRR' field in the EDC.

Signs and symptoms of an IRR may include: allergic reaction / hypersensitivity (including drug fever), rigors / chills, arthralgia (joint pain), myalgia (muscle pain), bronchospasm, wheezing, cough, dizziness, dyspnea (shortness of breath), fatigue (asthenia, lethargy, malaise), headache, hypertension, hypotension, tachycardia, nausea, vomiting, pruritus / itching, rash / desquamation, sweating (diaphoresis), urticaria (hives, welts, wheals).

Investigators should avoid reporting events deemed related to infusion generically as IRR. Instead, the individual symptoms/signs should be reported as separate adverse events, with relationship and severity assessed separately for each event.

Categorization of IRRs is as follows and can also be found in Appendix 1(adapted from CTCAE version 5.0):

- **Mild:** Mild transient reaction; infusion interruption not indicated; intervention not indicated
- **Moderate:** Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs
- **Severe reaction:** Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae

8.9.2. Management of Infusion-Related Reactions

Participants who experience adverse events during the infusion must be treated according to the investigator's judgment and best clinical practice. Premedication, infusion interruption or infusion rate decrease should be considered based on the severity of symptoms. Please refer to current Study Drug Infusion Guidance. Participants should be closely monitored until resolution of the reaction. The following guidelines may apply.

- Participants may be treated with acetaminophen /paracetamol, antihistamine, or corticosteroids. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, participants may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, participants may require vasopressors.
- Vital signs and oxygen saturation should be monitored until resolution of IRR.
- Study drug administration will not be resumed for any participant following a severe IRR. Close observation for 24 h is recommended after a severe reaction. Please refer to Section 4.3 for cohort safety management rules.
- No rechallenge should be undertaken for IgE mediated anaphylaxis or for life-threatening IRRs. Aggressive symptomatic treatment should be applied. (see next section).

- If an infusion is interrupted or the infusion rate is decreased, then a longer-than-anticipated infusion time may occur. Overnight stays at the study site because of slow infusion times should not be reported as a serious adverse event. However, if the underlying cause of the delayed infusion time is an adverse event or serious adverse event, then that should be reported as such.

Cohort level safety management guidance is provided in Section 4.3. Sponsor medical monitor or designee should be notified as soon as possible and be involved in the work up and follow up of the participant. Unscheduled plasma PK, add-on labs (see Section 8.10.1), and triplicate ECG should be obtained for each infusion-related reaction. If an infusion-related reaction is observed in the current or prior cohorts, site should consider premedication, and/or starting the infusion at a reduced rate per discussion with sponsor medical monitor.

8.10. Guidance for Hypersensitivity Reactions

Participants should be closely monitored during and after study drug administration for any symptoms of anaphylaxis and other hypersensitivity reactions. Treatment should be instituted per standard of care.

Hypersensitivity reaction will be recorded in the EDC, including documentation of timing relative to start of infusion, type and duration of symptoms, timing and type of intervention, and action to study drug administration.

Study drug infusion should be stopped if there is a suspected IgE-mediated allergic event related to IP.

Study drug should be permanently discontinued if:

- Serious adverse event of hypersensitivity reaction considered related to study drug.
- Non-serious but severe in intensity, such as bronchospasm requiring medication or intravenous intervention.
- Likely IgE mediated allergic event

8.10.1. Evaluation and Reporting of Hypersensitivity Reactions

Please contact medical monitor as soon as possible.

The following add-on tests should be taken: (please use central lab as much as possible)

- Unscheduled PK sample
- Serum tryptase (alpha and beta) and histamine
  - At 30 and 120 minutes after the onset of symptoms
  - At 2-3 days after onset of symptoms
- Anti-drug antibodies (ADA) within 15 minutes to 3 hours after onset of reaction
- C3a, C5a, and CH50, SC5b-9 2-4 hours after onset of reaction
- Cytokine levels (including IL2, IL6, IL8, IL10, IL13, TNF-α, INF-Ɣ) 2-4 hours after onset of reaction
- Archive sample for additional safety labs

- Additional tests may be performed at the request of the sponsor, including consultation with an allergist

If IgE mediated anaphylaxis is thought to be the cause of IRR subsequently, the verbatim term should be revised as such.

8.11. Guidance for Adverse Events with Cutaneous Involvement

- Adverse events with cutaneous involvement of ≥ moderate severity which are obviously of allergic origin and which are deemed to be related to study drug by the investigator should be evaluated by a dermatologist as soon as possible, and preferably within one week of the site first becoming aware of the event. The investigator should evaluate the participant for possible etiologies (new medications, etc.) and extra-cutaneous symptoms and signs.
- An unscheduled laboratory assessment for hematology, chemistry, PK, and ADA should be obtained.
- If it is possible, the site will take photographs of the skin lesions in order to provide the participant with them for the dermatologist's visit. If the photos are obtained, then copies should be kept as source documents.
- In addition to photographs of the skin lesions, the investigator should provide a summary of the participant's case, reason for consultation, and information being requested to the consulting dermatologist.
- The dermatologist should be asked to generate a full consultation report to the investigator. The full report should contain, at a minimum, the following information:
    - A detailed description of the rash (such as the morphology [lesion type], shape of individual lesions, arrangement of multiple lesions [eg, scattered, grouped, linear, etc.], distribution, color, consistency, presence of pruritus or pain, and other clinical signs).
    - In case a skin biopsy (including histopathology and immunofluorescence) was done (if it was deemed necessary as per the dermatologist's or investigator's medical judgment), the results of this investigation with, if applicable, a specific diagnosis of the AE.
- The investigator will send the full dermatologist report to the sponsor medical monitor or designee within 24 hours.

8.12. Guidance for Liver Function Test Abnormality

8.12.1. Monitoring Rule

- If multiple baseline liver function test (LFT) measurements are available, baseline LFTs will be defined as the average of the 2 most recent LFT measurements prior to the first dose administered.
- ALT or AST > 3 x ULN (or > 3x baseline or > 300 U/L [whichever is lower] in participants with elevated baseline): repeat test (at a central laboratory, if possible) and obtain total bilirubin, direct and indirect bilirubin, alkaline phosphatase, INR, and GLDH weekly or more frequent depending on the clinical severity. Sponsor medical monitor or designee

should be informed within 24 hours of the site's awareness. The monitoring should continue until the values recover (Table 10) or stabilize per consultation with sponsor medical monitor or designee (Balwani 2020, FDA 2009).

- Evaluate for etiologies based on clinical presentation, including viral or autoimmune hepatitis, concurrent diseases, concomitant drugs or supplements, environmental exposure, other infectious etiology. Refer to Table 11.

8.12.2. Criteria for Withholding or Stopping Study Drug

The study drug withholding or stopping rules are designed to minimize the risk of drug-induced liver injury. Confirmatory liver function tests should be performed through the central laboratory.

Criteria for withholding and stopping study drug are as follows:

- For ALT or AST > 8x ULN (or > 8x baseline or > 500 U/L [whichever is lower] in participants with elevated baseline), which is confirmed, without alternative cause, permanently discontinue dosing.
- For ALT or AST >3× ULN (or > 3x baseline or > 300 U/L [whichever is lower] in participants with elevated baseline), which is confirmed and without alternative cause that is accompanied by clinical symptoms consistent with liver injury (e.g., nausea, right upper quadrant abdominal pain, jaundice), elevated bilirubin to >2× ULN, or international normalized ratio (INR) >1.5, permanently discontinue dosing.
- For ALT or AST elevations >3× ULN (or > 3x baseline or > 300 U/L [whichever is lower] in participants with elevated baseline), which is confirmed and without alternative cause and not accompanied by symptoms consistent with liver injury or elevated bilirubin ≥2× ULN or INR ≥1.5, see Table 10 .
- Meeting any of the liver criteria for permanent discontinuation of study drug, listed above or in Table 10 , should be considered a SAE. The rules for cohort and study dosing suspension and stopping presented in Section 4.3 should be followed.

Table 10: Monitoring and Dosing Rules for Asymptomatic Participants with Confirmed Isolated Elevations of ALT or AST >3× ULN (or > 3x Baseline or >300 U/L [Whichever is Lower] in Participants with Elevated Baseline), with No Alternative Cause Identified

ALT or AST Transaminase Level	Participants with Normal Baseline ALT or AST	Participants with Elevated Baseline ALT or AST
>3× to 5× ULN or Baseline	• Dosing may continue with monitoring • If the ALT or AST elevation persists for ≥2 months, discussion with the medical monitor is required before continuing dosing.	• Hold dosing if ALT or AST >300 U/L, until ALT or AST recovers to ≤2× baseline; may resume dosing after discussion with medical monitor • Otherwise, dosing may continue with monitoring • If the ALT or AST elevation persists for ≥2 months, discussion with the medical monitor is required before continuing dosing.
>5× to 8× ULN or Baseline	• Hold dosing until ALT or AST recovers to ≤2 ULN; may resume dosing after discussion with medical monitor • Monitor at least weekly: LFT, GLDH, and coagulation until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly • If ALT or AST rises to >5× ULN following resumption of dosing, permanently discontinue dosing	• Hold dosing if ALT or AST >5× baseline or >300 U/L (whichever is lower), until ALT or AST recovers to ≤2× baseline; may resume dosing after discussion with medical monitor • Monitor at least weekly: LFT, GLDH, and coagulation until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly • If ALT or AST rises to >5× baseline or >300 U/L (whichever is lower) following resumption of dosing, permanently discontinue dosing
>8× ULN or Baseline	Permanently discontinue dosing after confirmation of ALT or AST >8×ULN	Permanently discontinue dosing after confirmation of ALT or AST >8×baseline or >500 U/L (whichever is lower)

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; LFT=liver function test(s); ULN=upper limit of normal.
Note: In addition to these criteria, other assessments or evaluations may be performed per investigator discretion, as appropriate.

8.12.3. Additional Assessments in Participants Who Experience Elevated Transaminases

For ALT or AST elevation >3×ULN (or >3× baseline in participants with elevated baseline) or >300 U/L (whichever is lower), results should be confirmed by the central laboratory. If such ALT or AST elevations are confirmed, the additional hepatic assessments shown in Table 11 should be obtained. Other assessments or evaluations per investigator discretion may be obtained, as appropriate.

Table 11: Hepatic Assessments in Participants Who Experience Elevated Transaminases

Hematology	
CBC with differential	
Extended Hepatic Panel	
Herpes Simplex Virus 1 and 2 antibody IgG	Herpes Zoster Virus IgM, IgG
HIV 1 and 2[a]	HHV-6
Cytomegalovirus antibodies, IgM, IgG	HBs Ag, HBc antibody Total and IgM
Anti-nuclear antibodies	Epstein-Barr Virus antibodies, IgM and IgG
Anti-smooth muscle antibodies	Anti-mitochondrial antibodies
HCV antibody	HAV antibody IgM
HCV RNA PCR – qualitative and quantitative	HEV antibody IgM
CPK	
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: AAT=alpha-1 antitrypsin; anti-LKM=anti-liver-kidney microsomal antibodies; CBC=complete blood count; CPK=creatine phosphokinase; CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; HIV=human immunodeficiency virus; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; PT=prothrombin time; RNA=ribonucleic acid; SLA=soluble liver antigen; TSH=thyroid-stimulating hormone

Note:

- All assessments will be measured in central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.
- Additional samples may be collected for assessment of potential alternative causes of liver injury, which may include AAT, ceruloplasmin, acetaminophen/paracetamol levels, anti-LKM antibodies, toxicology screen, ferritin, parvovirus B19, anti-SLA antibodies, gamma-globulins (including IgE and IgG levels), and transferrin saturation, as clinically indicated.

[a] HIV testing will not be performed where prohibited by local regulations.

8.13. Guidance Relating to Iron Homeostasis

8.13.1. Monitoring Rule

- Baseline for monitoring is defined as the average of all available pre-dose values
- Confirmed Hb < 10 g/dL and > 1 g/dL decrease from baseline should be monitored by collecting CBC every month or per protocol whichever is more frequent until normalized or stabilized. Referral should be made for hematology consultation. Continue to monitor per hematologist recommendation in consultation with sponsor medical monitor or designee
- When monitoring rules are met, central lab will reflexively measure haptoglobin, LDH, ferritin, and indirect bilirubin (if the total bilirubin >ULN). Sponsor medical monitor or designee should be notified. Additional labs may be requested by the sponsor.

8.13.2. Dosing Pause Rule

Pause study drug administration and initiate workup if:

- Confirmed Hb > 2 g/dL decrease from baseline, and MCV < LLN, without alternative etiology, OR
- Confirmed Hb < 8.5 g/dL, and MCV < LLN, without alternative etiology

Resumption of dosing may occur per discussion with sponsor medical monitor or designee.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Analysis Plan

A detailed Statistical Analysis Plan (SAP) will be developed and finalized before database lock and will provide additional information surrounding all statistical considerations.

9.2. General Considerations

Data collected during the study will be presented in summary tables and graphical figures, as appropriate. In tabular presentations, continuous variables will be summarized using descriptive statistics including mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using percentages and frequency distributions. Where appropriate, confidence intervals (CI) may be presented. As the primary objective is to evaluate the safety and tolerability of single and multiple ascending doses of AOC 1001 in DM1 patients, no formal hypothesis testing will be performed. Tabulations will be produced for appropriate disposition, demographic, baseline, safety, and efficacy parameters. Data collected will be presented in by-subject data listings.

In general, data summaries will be presented separately for Part A and Part B. Summaries will be grouped by dose level and overall for AOC 1001 and a single pooled placebo group.

9.3. 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 participants while limiting unnecessary participant exposure:

- In Part A, there is 1 planned dose level with 8 participants (6 active and 2 placebo).
- In Part B, there are 3 planned dose levels with at least 12 participants planned per cohort

The maximum enrollment for the trial will be limited to 52 participants. The sample size for this study was not based on statistical power considerations.

9.4. Analysis Sets

The following analysis sets will be used in this study:

- Safety Analysis Set: The Safety Analysis Set will include all participants who received at least one dose of study drug. Participants will be grouped according to the dose level they received. The Safety Analysis Set will be used for all safety analyses.
- Full Analysis Set (FAS): All participants who were randomized and have received any amount of study drug and had a baseline measurement and at least 1 post-baseline assessment. Participants will be grouped as randomized. Additional analysis subset(s) may be formed based on different outcome measures as appropriate.
- Pharmacokinetic (PK) Analysis Set: The PK Analysis Set will include all participants who receive any amount of study drug and provide a sufficient number of plasma sample(s) for PK analysis. Participants will be grouped according to the dose level they received.
- Pharmacodynamic (PD) Analysis Set: The PD Analysis Set will include all participants who receive any amount of study drug and had a baseline PD assessment and at least one post-baseline pharmacodynamic assessment. Participants will be grouped according to the dose level they received.

All Analysis Sets will generally be maintained separately for Part A and Part B due to the different study design and treatment schedules. Analysis of Part A and Part B will primarily be executed on the Safety Analysis Set for baseline and safety parameters and PK and PD Analysis Sets, respectively for PK and PD analyses. Efficacy analysis performed will be executed on the Full Analysis Set. Additional analysis details will be specified in the SAP.

9.5. Interim Analysis (IA)

No formal interim analyses are planned within this study.

The Sponsor may perform administrative analyses while the study is ongoing.

9.6. Safety Evaluations

Safety results will be provided for adverse events, use of concomitant medications, body weight/BMI, clinical laboratory safety tests, vital sign measurements (blood pressure, heart rate, body temperature and respiratory rate), ECGs, echocardiogram, and C-SSRS.

Safety summaries will include incidence of AEs, summarized according to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). An overall summary of AEs will include the incidence of AEs, serious AEs, treatment-related AEs, and severe AEs. Summaries of AEs by system organ class and preferred term will be presented for all AEs occurring or events worsening on or after first dose, serious AEs, AEs by relationship to study drug. Listings of AEs leading to death, discontinuation from study drug, and for serious AEs will be presented.

Concomitant medications will be classified by WHO Drug Anatomic Therapeutic Chemical (ATC) and will be presented in data listings. Observed values for body weight and BMI will be summarized at each time point.

Observed values and changes from baseline in clinical laboratory parameters will be summarized at each assessment. Shift tables may be presented for changes from baseline to worst value on study and from baseline to last value recorded. Laboratory data will be presented in standard units.

Vital signs will be summarized as observed values and changes from baseline.

ECG data (PR, QRS, QT, QTcB, QTcF and HR) and overall ECG evaluation will be listed. ECG data, along with changes from baseline will be summarized using descriptive statistics and categorical data on QTc will be summarized. Relationship between plasma PK and QTc will be explored.

All safety data will be presented in by-subject data listings.

9.7. Pharmacokinetic and Immunogenicity Evaluations

Summaries of PK and ADA data will be presented separately for Part A and Part B. Non-compartmental analysis will be used for estimation of plasma PK parameters, including C_{max}, t_{max}, $t_{1/2}$, and AUC. Additional parameters may be estimated. PK measures will be reported over time and summarized using descriptive statistics. Graphical displays may be presented. Exploratory analyses of PK data and their relationship to PD and safety endpoints may be investigated.

The fraction excreted in urine will be estimated from 24-hour urine collections.

Immunogenicity analysis will be determined at baseline, during treatment and follow up. Impact of ADA on PK will be explored.

Tissue PK will be summarized and the relationship to PD endpoints will be explored.

Further details will be provided in the SAP.

9.8. Pharmacodynamic Evaluations

Summaries, including change and percentage change from baseline, of PD data (*DMPK* mRNA levels and spliceopathy) will be presented descriptively.

9.9. Efficacy Evaluations

The exploratory efficacy analysis, including clinical assessments and patient reported outcome measures, will be performed to evaluate further aspects of participant mobility, muscle function related to the extent of treatment distribution over time in descriptive summaries. Additional details will be specified in the SAP.

10. REGULATORY, LEGAL, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1. Obligations to Regulatory Authorities and Ethics Committees

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable country-specific laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) will be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The sponsor is responsible for reporting to the investigators of serious adverse events (SAEs), including SUSARs, per ICH guidelines E2A and ICH E6.

Any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

10.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study (aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail) to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.
- Participants must be informed that their participation is voluntary and that they may withdraw consent to participate at any time.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

10.4. Study Monitoring

- All aspects of the trial will be carefully monitored by the sponsor, or designee, for compliance with all applicable government regulations with respect to Good Clinical Practice (GCP) and current standard operating procedures.
- The monitoring of this trial will be performed by the sponsor's monitor(s) or a designee in accordance with the principles of GCP as laid out in the International Council on Harmonisation (ICH) Good Clinical Practice Guideline E6(R2) (2016).
- The clinical monitor, as a representative of the sponsor, has an obligation to follow the trial closely. In doing so, the monitor may visit the investigator and site periodically as well as maintain frequent telephone and email contact. The monitor will maintain current personal knowledge of the trial through observation, review of trial records and source documentation, and discussion of the conduct of the trial with the investigator and site personnel. Further details will be described in the Clinical Monitoring Plan or SOM as appropriate.

10.5. Confidentiality and Data Protection

- The investigator must ensure that the subject's confidentiality is maintained for documents submitted to the Sponsor and in compliance with applicable data privacy deprotection laws and regulations.
- Participants are to be identified by a unique subject identification number. Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- Sponsor personnel whose responsibilities require access to personal data for study-related monitoring, audit, IEC/IRB review, and regulatory inspection agree to keep the identity of participants confidential.
- This consent also addresses the transfer of the data to other entities and to other countries. The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

- Exploratory biomarker/PK/immunogenicity research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.6. Study Documentation and Data Archive

- All participant data relating to the study will be recorded in the EDC unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a sponsor-approved Delegation of Site Responsibilities Form.
- The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.
- Guidance on completion of eCRFs will be provided in eCRF Completion Guidelines.
- Source documents are original documents, data, and records from which the participant's eCRF data are obtained. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected in the eCRF. Source documents are filed at the investigator's site. These can be either paper or electronic and include but are not limited to trial assessment/activity records, hospital records, clinical and office charts, laboratory, imaging, and pharmacy records, diaries, and correspondence. Case report form trial activities may be considered source data if the case report form is the site of the original recording (i.e., there is no other written or electronic record of data).
- The investigator and site personnel are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for

inspection at any time by representatives from sponsor or designee, and/or applicable regulatory authorities. For this study, elements include:

- Participant files containing completed informed consent and any other forms, and participant identification list.
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation, and all correspondence to and from the IRB/IEC. In addition, all original source documents supporting entries in the EDC must be maintained and be readily available.
- If drug supplies are maintained at the study site, proof of receipt, study drug Accountability Record, Return of study drug for Destruction, final study drug reconciliation, and all drug-related correspondence.

- Retention of study documents will be governed by the Clinical Trial Agreement, but in general for a retention period in compliance with local regulations or institutional policies, if they require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data to ensure accuracy, consistency, completeness, and adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries will be sent to the trial site for completion and return to the sponsor or designee. Updates to eCRFs will be automatically documented through the "audit trail".

10.7. Quality Control and Quality Assurance

- In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the sites to verify that randomization/dispensing has been done accurately.
- A regulatory inspection of this trial may be carried out by regulatory agencies. Such audits/inspections can occur at any time during or after completion of the trial. If an audit or inspection occurs, the investigators for all sites agree to allow the auditor/inspector direct access to all relevant documents and to allocate their time and the time of their site personnel to the auditor/inspector to discuss any findings or relevant issues.

10.8. Record Retention

- The Investigator Site File is part of the Trial Master File (TMF) and retention of the documents within the TMF and the medical records of study participants is a legal requirement. After completion of the trial, all documents and data relating to the trial will be kept in an orderly manner and securely by the investigator in a secure file and/or

electronically. The data will be available for inspection by the sponsor or their representatives. Essential documents must be retained for 25 years after the final marketing approval in an EU region or at least 25 years have elapsed since the formal discontinuation of clinical development of AOC 1001. The PI or delegate must contact the sponsor before destroying any trial-related documentation and it is the responsibility of the sponsor to inform the investigative site of when these documents can be destroyed. In addition, all participant records and other source documentation will be kept as required by the applicable regulatory requirements.

- For trial sites in the US, an investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.
- The ultimate responsibility for the documents to be retained by the investigator or institution resides with the investigator or institution. If the investigator becomes unable to be responsible for their essential documents (eg, relocation, retirement, etc.) the sponsor should be notified in writing of this change and informed as to whom the responsibility has been transferred.
- The Investigator Site File should never be sent to the sponsor. However, where the investigator cannot meet their archiving requirements, the sponsor can arrange archiving on behalf of the investigator and their institution, subject to the following being implemented:
    - The archive arrangements are formally agreed and documented between the sponsor and investigator or institution.
    - A formal procedure is in place such that the documents are only released from the external archive with the approval of the investigator or institution. In such cases, permission from the investigator or assigned host, is required to permit access to the contents of investigator site archived materials at the archive facility.
    - The records go directly between the investigator site and an archive facility independent of the sponsor, thereby ensuring that the sponsor does not have uncontrolled access to the investigator files.
- It is important that where an organization has centralized records that may be relevant to a number of studies, for example, SOPs, staff training records or maintenance and calibration records for equipment used in the study, that these are also considered in the arrangements for archiving and retention (including superseded versions or obsolete records for example training records of personnel who have left the organization) as they may be required to be produced in addition to the TMF to demonstrate compliance.

10.9. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional exploratory research. Samples will only be used to understand profiles of study drug and/or DM1, to understand differential drug responders, and to develop tests/assays related to AOC 1001 and/or DM1. The research may begin at any time during the

study or the post-study storage period. Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research.

10.10. Compensation

Any arrangements for compensation to participants for injury or illness that arises in the study is described in the Compensation for Injury section of the Informed Consent Form.

10.11. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

10.11.1. Study Termination

The sponsor or designee reserves the right to terminate the study. The investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The investigator/sponsor or designee as appropriate should notify the IEC/IRB, in writing, as appropriate per local requirements, of the trial's completion or early termination and send a copy of the notification to the sponsor or designee.

10.11.2. Trial Site Termination

The sponsor or designee reserves the right to close the trial site or terminate the study at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon study completion. A trial site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to the following:

- For study termination: Discontinuation of the clinical study due to reasons including unacceptable risk to participants, failure to enroll at an acceptable rate, plans to modify development strategy, or recommendation by regulatory authorities.
- For site termination:
    - Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
    - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
    - Total number of participants enrolled earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.12. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors (http://www.icmje.org/) authorship requirements.

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APPENDIX 1. GRADING SCALE FOR ADVERSE EVENTS RELATING TO LAB TEST ABNORMALITIES, INFUSION-RELATED REACTIONS AND ADVERSE EVENTS AT THE INJECTION SITE

The following grading recommendations for adverse events relating to lab test abnormalities, infusion related reactions and adverse events at the injection site are based upon the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 2017, except where indicated in the footnotes.

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding
Eosinophils increased[†]	>ULN and >Baseline	-	Steroids Initiated
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 x LLN; if abnormal, ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1.2 - 1.5; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; monitoring only indicated	>2.5; >2.5 x baseline if on anticoagulation; dose adjustment indicated
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3

Adverse Event	Mild	Moderate	Severe
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline normal 2.0 - 2.5 x baseline if baseline abnormal	>2.5 - 5.0 x ULN if baseline normal >2.5 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline was abnormal
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline normal >1.0 - 1.5 x baseline if baseline abnormal	>1.5 - 3.0 x ULN if baseline normal >1.5 - 3.0 x baseline if baseline abnormal	>3.0 x ULN if baseline normal >3.0 x baseline if baseline abnormal
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
Creatinine increased**	>ULN - 1.5 x ULN if baseline normal > 1.0 - 1.5 x baseline if baseline abnormal	>1.5 - 3.0 x ULN if baseline normal >1.5 - 3.0 x baseline if baseline abnormal	>3.0 x ULN if baseline normal >3.0 x baseline if baseline abnormal
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 mmol/L; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 mmol/L; hospitalization indicated
Hyperphosphatemia	Laboratory finding only and intervention not indicated	Noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated
Hyperuricemia	>ULN without physiologic consequences	-	>ULN with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	≥54 mg/dL - <70 mg/dL ≥3.0 mmol/L - <3.9 mmol/L	<54 mg/dL (3.0 mmol/L) AND no assistance required to actively administer carbohydrates, glucagon, or take other corrective actions	Requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions
Hypokalemia	<LLN - 3.0 mmol/L	symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 mmol/L; hospitalization indicated

Adverse Event	Mild	Moderate	Severe
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms
Hypophosphatemia	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated
Urine			
Proteinuria Adults	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	2+ and 3+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs;	4+ proteinuria; Urinary protein ≥3.5 g/24 hrs;
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective invasive intervention indicated
Infusion Related Reaction			
Infusion Related Reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae
Adverse Events at the Injection Site			
Adverse events at the injection site**	An event at the injection site (e.g., erythema, tenderness, itching) that is easily tolerated by the participant and does not affect the participant's usual daily activities	- The event causes the participant discomfort that is not easily tolerated and interrupts the participant's usual daily activities; OR - Lipodystrophy, hair growth or alopecia, OR - Prolonged (>1 month) hypo/hyperpigmentation	- Ulceration or necrosis; severe tissue damage; operative intervention indicated, OR - Any event at the injection site that is incapacitating

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007
*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014
**Criteria has been adapted from the original CTCAE V5.0 scale