[redacted]

Sponsor Project No.: [redacted]

US IND No.: [redacted]

Safety and tolerability of S 48168 (ARM 210) for the treatment of *RYR1*-related myopathies (*RYR1*-RM)

GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

1 PROTOCOL REVISION HISTORY

Amendment 1:

Page(s)	Summary of change
20, 52	Schedule of activites: Timeframe of screening tests changed to "Within 28 days prior to the first dose of study drug with the exeption of HIV, HCV, HbsAg, and *CYP2C8* tests"
20, 58	Schedule of activities: Clarification that FSH and HbA1C tests are only required at baseline "FSH and HbA1c are only required at screening."
18	Schedule of activities: Added pulse oximetry to vital signs measurements of d28 to make consistent with prior visits
31	Dose Justification: Description of dose for Figure 2 corrected to state "240 mg" and Figure numbering changed to reflect "Figure 2".
36, 37, 40, 45, 53, 73,	Language pertaining to local blood draws (screening and follow-up): Language specifying local "facility" was removed and replaced with flexible language to allow for in-home blood draws. Example: "The blood sample for *CYP2C8* analysis will be collected locally to the participant".
52	Screening: Reference to appendices 19 and 20 were corrected.
60	AE severity: Clarified the severity rating based on CTCAE v5 here to make consistent with the remainder of the protocol
61	SAE reporting: Language was amended to refer to the Medical Monitoring Plan for SAE reporting: "All SAEs will be reported to the Sponsor per the medical monitoring plan (Appendix # 17)"
63	Blood Sampling and Processing: Language was amended to reflect use of -80 freezer, rather than a -20 freezer. "The plasma aliquots will be frozen at -80 ± 10°C within 30 minutes maximum from the end of centrifugation".

Amendment 2:

Page(s)	Summary of change
6	Additional key contacts for the study: Genelex has been replaced with ARUP Laboratories as the CLIA-certified vendor of choice for *CYP2C8* genotyping
13	Precis: The term "seven" in reference to the second dose group has been removed. The approximate number of participants has been changed from 10 to 8-20.
14	Synopsis:

	The phrase "clinically significant" has been removed.
16	Synopsis (continued): Target accrual number has been revised to " approximately 8-20 completers (pre-screening accrual ceiling n= 50)". Randomization is no longer applicable and has been removed from Figure 1 (study design). The n for the dose group 2 has been left undefined.
17	Synopsis (continued - dose regimen): The term "seven" in reference to the second dose group has been removed.
31	Dose justification: The term "seven" in reference to the second dose group has been removed.
32	Dose justification (continued): The term "seven" in reference to the second dose group has been removed.
38	Investigational Plan: Number of individuals was changed to "8 individuals with *RYR1*-RM completing the study." The study design in Figure 1 has been updated (removal of randomization and n for dose group 2 left undefined). The phrase "up to 14 participants with *RYR1*-RM" has been removed.
39	Investigational Plan (continued): The pre-screening accrual ceiling and target number of completers have been clarified as n= 50 and n= 8-20, respectively.
49	Treatments administered: The term "seven" in reference to the second dose group has been removed.
50	Method of assigning subjects to treatment: The following language has been removed: (1): "Once 8-20 individuals are identified who meet the telephone and genotyping screen criteria, randomization will be conducted. This randomization will dictate the order in which these 8-20 individuals are invited to the NIH to finish screening procedures". (2): The following language has been removed "individuals from the originally screened 8-20 subjects" and "per the randomized order". (3): The following language has been removed "Dosing will continue until 10 patients complete the study or the study is terminated".
51	Interim analysis (PK): The phrase "if this is the case, then" has been replaced with "subsequently".
53	Recruitment: Expected number of participants to be recruited within 6-12 months has been changed from 10 to approximately 8-20.
55	CYP2C8 genotyping: The phrase "sample submission form" has been removed.
56	Safety assessments: The phrase "clinically significant" has been removed.

57	Safety assessments continued: The phrase "by telephone" has been removed.
59	Cannulation and Phlebotomy: Number of participants has been updated from 10 to 8.
65	Blood sampling and processing: The term "lithium" has been removed.
68	Determination of Sample Size: Sample size changed from 10 to 8.
71	Subject information and consent: The first paragraph has been revised to clarify that blood obtained under the telephone consent will be used to test for CYP2C8 and serology.
72-73	Management of data and samples: NINR Tissue Injury Branch has been added as a location for sample storage. The following language has been removed: (1): "De-identified, unlinked skeletal muscle tissue samples will be collected and transported to the NINDS Neurogenetics Branch (building 35) for storage, ahead of analyses described in the biopsy manual" (2): "after the completion of the first 5 patients and after the completion of the 5 last patients". (3): "and/or submitted to NIH designated repositories and databases" (4): "repositories receiving data and/or samples from this protocol may be open-access or restricted access" (5): "Submissions to NIH-sponsored or supported databases and repositories will be reported at the time of Continuing Review. Submission to non-NIH sponsored or supported databases and repositories will be submitted for prospective IRB approval."
Amendment 3 (expedited)	
4, 12-16, 21, 30-31, 35, 37, 48-49, 55-57, 64, 67, 69	Dosing period was changed from "28 days" to "28 not to exceed 30 days" throughout the protocol
Amendment 4	
12, 16, 41-43, 51, 66	Muscle biopsy RyR1-calstabin1 assay (inclusion criterion) was deleted and reference to this removed throughout the protocol
Amendment 5	
17, 41, 43-44, 51, 56	Removal of skeletal muscle needle biopsy procedure for subject 0007 and subsequent participants, including all reference to this
47	Muscle biopsy-specific inclusion/exclusion criteria removed

15, 18, 40, 41, 65	Removal of 24hour PK study for subjects who have been previously dosed and are therefore not drug naïve
15, 17, 23, 39-41	Switch in-person study visit on Day 14 to remote assessments and labs
19, 33	Removal of Day 14 EKG
67	Anticipated blood draw volumes added for re-enrolled subjects
17, 21, 22, 39 41	Switch Day 42 remote follow-up to an in-person study visit with efficacy assessments. Schedule of activities was updated accordingly
15, 20, 22, 37, 43	Addition of quantitative muscle assessment (QMA) to the battery of physical therapy tests
54, 55	Updated description of consent process for re-enrolled subjects
17, 39	Updated Figure 1 to reflect Amendment 5 changes
30, 31, 59	Updated reference to the IB to 2020 version
20	Schedule of activities updated to reflect 8 rather than 11 PK timepoints
46	Inclusion criterion added: Evidence of functional deficit (defined by MFM-32 $\leq$ 80% maximum score) or demonstratable deficits in at least one of the baseline muscle/motor function assessments

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

Safety and tolerability of S 48168 (ARM 210) for the treatment of *RYR1*-related myopathies (*RYR1*-RM)

SPONSOR: ARMGO Pharma Inc.
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SPONSOR'S REPRESENTATIVE: [redacted]

Signature Date

PRINCIPAL INVESTIGATOR AND CLINICAL SITE: [redacted]

Signature Date

3 ADDITIONAL KEY CONTACTS FOR THE STUDY

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5 PRÉCIS

Ryanodine receptor isoform 1-related congenital myopathies (*RYR1*-RM) comprise a group of rare neuromuscular diseases estimated to affect at least 1/90,000 pediatric individuals in the United States (Amburgey et al. 2011). Affected individuals generally present with delayed motor milestones, muscle weakness, impaired ambulation, and, in severe cases, scoliosis, ophthalmoplegia, and respiratory distress all due to skeletal muscle weakness (Witherspoon and Meilleur, 2016). Causative variants in *RYR1*, which encodes the major calcium (Ca^{2+}) release channel in skeletal muscle, RyR1, exert different effects on the RyR1 channel. They generally disrupt the normal Ca^{2+} flow between the sarcoplasmic reticulum (SR) and muscle cell cytosol and commonly result in excessive Ca^{2+} leak into the cytosol. Persistent Ca^{2+} leaks reduce its availability in the SR that is necessary for excitation-contraction coupling. Additionally, chronic SR Ca^{2+} leak results in elevated cytosolic Ca^{2+} concentration, and mitochondrial-related oxidative stress and cellular injury (Görlach et al. 2015). The oxidative stress, in turn, can further contribute to RyR1 Ca^{2+} leak by channel oxidation and nitrosylation. Although *RYR1*-RM have been associated with significant morbidities and early mortality, there remains no FDA-approved treatment.

A new class of Ca^{2+} channel stabilizers, Rycals®, were developed by Dr. Andrew Marks at Columbia University. Under normal physiological conditions, Calstabin1 binds and stabilizes the RyR1 closed state. Rycals function as Ca^{2+} channel stabilizers by restoring RyR1-Calstabin1 binding when it is deficient, thereby stabilizing the RyR1 closed state. To date, Dr. Marks laboratory has tested Rycals pre-clinically in at least 20 *RYR1*-RM patient muscle biopsies *in vitro*, including ten obtained during a previous clinical trial (NCT02362425). All untreated samples initially showed decreased RyR1-Calstabin1 binding (<10- 40% of healthy control muscle), which improved to 70-90% of control levels upon treatment with Rycals *ex vivo*. This work has demonstrated that Rycal treatment can restore RyR1-Calstabin1 binding and rescue leaky RyR1 channels in human biopsies *ex vivo*. In addition, a few muscle disease mouse models demonstrated that Rycal treatment improved muscle strength and muscle cell survival and may therefore offer a promising treatment for *RYR1*-RM (Andersson and Marks, 2010; Capogrosso et al. 2018; Waning et al. 2015). S 48168 may also have benefit for malignant hyperthermia susceptibility, a condition allelic to *RYR1*-RM, by restoring the conformational integrity of mutant RyR1 channels. The lead Rycal, S 48168 (ARM210), has completed Phase I clinical studies in healthy volunteers. In those studies, S 48168 (ARM210) was safe and well tolerated in single and multiple dose studies and has now been tested in six (6) patients with *RYR1*-RM. This study continues to test S 48168 (ARM210) in a Phase I trial in *RYR1*-RM patients.

The objectives of this study are to explore the safety and tolerability, pharmacokinetics (PK), pharmacodynamics (PD)/target engagement (TE) of S 48168 (ARM210), as well as effects on muscle/motor function, and fatigue in adult *RYR1*-RM patients. The open-label study design consists of approximately 8-20 participants and two dose groups. The first three participants received 120 mg S 48168 (ARM210) daily for approximately 28 (not to exceed 30) days. Three participants have been enrolled in the second group and received 200 mg S 48168 (ARM210) daily for approximately 28 (not to exceed 30) days. The decision to escalate to a top dose of 200 mg daily was made by an independent Data and Safety Monitoring Board (DSMB) after

review of safety, tolerability and PK of the 120 mg daily dose. Interim data analysis suggested improvement in hand grip and pinch strength and improvement in manual muscle strength testing. Participants in the high dose group also reported decreased fatigue based on the patient reported outcome measure standardized tool (PROMIS-fatigue). Based on these findings and in preparation for the planned phase II trial, for the remainder of the trial, the post-intervention efficacy measures will be repeated after drug withdrawal to better assess the durability of observed benefits in participants. In addition, to maximize equitability and potential for maximum benefit, participants previously enrolled at the low dose will be invited to re-enroll at the high dose with the modified post-intervention and pharmacokinetic schedule. Safety and tolerability will remain the primary objective in this study. Exploratory objectives, including PK, PD/TE as well as measures of muscle/motor function and fatigue are being modified based on interim analysis.

6 SYNOPSIS

Compound:	S 48168 (ARM210)
Clinical Indication:	Ryanodine receptor 1-related congenital myopathy (*RYR1*-RM)
Study Phase and Type:	Phase 1– Safety and Tolerability, pharmacokinetic (PK), and pharmacodynamic/target engagement (PD/TE)
Primary objective:	**To determine safety and tolerability of S 48168 (ARM210) treatment in *RYR1*-RM affected individuals.** **Hypothesis:** S 48168 (ARM210) treatment will have no safety concerns that limit further development and will be generally well tolerated in *RYR1*-RM patients. **Primary endpoint:** Composite safety and tolerability profile (Frequencies of the following: TEAEs ≥ grade 2 in severity (CTCAE version 5), all SAEs, and all AESIs). **Methods:** Safety and tolerability of S 48168 (ARM210) will be determined by monitoring Adverse Events (AEs) over approximately 28 (not to exceed 30) days of treatment via patient interviews, patient diary reviews, physical examinations, echocardiograms, electrocardiograms (ECGs), vital signs, and laboratory safety tests. A reference dataset of AEs/SAEs obtained from a natural history study of *RYR1*-RM will also be available to assist in interpretation of safety events. The Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered pre- and post-intervention. The frequency and severity of AEs will be compared between treatment and historical controls including a previously conducted natural history study at the NIH.
Exploratory objectives:	**1. To determine PK of a 28 day (not to exceed 30-day) administration of S 48168 (ARM210) in *RYR1*-RM affected individuals.**

	Hypothesis: There will be no clinically meaningful difference in S 48168 (ARM210) exposure at steady state in *RYR1*-RM affected individuals when compared to existing data established in healthy volunteers. **Endpoints:** S 48168 (ARM210) pharmacokinetics Day 1 composite PK profile (drug naïve individuals only) (Comprised of the following: AUC0-t, AUC0-inf, Cmax, Tmax, and t½). Day 28 (not to exceed Day 30) composite PK profile (Comprised of the following: AUCtau, Cmax, Tmax, Cmin, RAAUC, and RACmax). **Methods:** For participants who have not been dosed previously (i.e., drug naïve individuals), bloods for PK assessments will be drawn at study visit one (Day 0, 24h PK), study visit two (Day 28; not to exceed Day 30, 24h PK),. For individuals who have been dosed previously, a 24hr PK assessment at Day 0 will not be required. Whole blood will be processed, and the plasma fraction stored for PK analyses. **2. To explore if S 48168 (ARM210) treatment increases RyR1-calstabin1 binding in skeletal muscle of *RYR1*-RM affected individuals.** **Hypothesis:** S 48168 (ARM210) treatment will increase RyR1-calstabin1 binding, compared to baseline, as determined by co-immunoprecipitation of RyR1 and calstabin1 and decrease relative Fluo-4 signal compared to baseline. **Endpoints:** Change from baseline in relative RyR1-calstabin1 binding (AU) and (pending sufficient tissue yield) change from baseline in relative Fluo-4 signal (AU). **Methods:** Skeletal muscle tissue was obtained from the first six participants by needle biopsy. This tissue has been assessed for RyR1-calstabin1 binding by co-immunoprecipitation followed by protein detection. Additional biopsies are not needed. **3. To explore if S 48168 (ARM210) treatment improves muscle function, motor activity, and fatigue in *RYR1*-RM affected individuals.** **Hypothesis:** Treatment with S 48168 (ARM210) will increase grip and pinch strength, increase strength as determined by quantitative muscle assessment, decrease the time it takes to complete graded functional tests, increase the total MFM-32 % maximum score, and decrease the PROMIS-fatigue subscale score, when compared to baseline. **Endpoints:** Grip strength (kg), pinch strength (kg), quantitative muscle strength assessment (kg), time taken to complete each of the following (seconds): walk 10-meters, supine to stand, ascend 4 stairs, and descend 4 stairs, MFM-32 score for domains 1, 2, 3, and total (% of maximum score), PROMIS-fatigue subscale score (t-score). **Methods:**

	Grip and pinch strength: Participants will be seated comfortably with his/her elbow flexed to 90 degrees, with the forearm and wrist in neutral position. Participants will then be asked to squeeze the dynamometer and pinch the gauge. This process will be repeated three times with the best effort used for final analyses. A physical therapist will administer these study procedures. Quantitative muscle strength assessment: Participants will undergo assessment of muscle strength in standardized seated and supine positions. Participants will be asked to exert force against an elastic strap-based force transducer. A physical therapist will administer this study procedure. Graded Functional Tests: Participants will complete a timed 10-meter walk test, supine to stand, ascend 4 stairs, descend 4 stairs, pre- and post- intervention. A physical therapist will administer these study procedures. MFM-32: The MFM-32 scale, a validated measure of motor function, will be administered pre- and post-intervention by a physical therapist. The participant is asked to roll, sit, lift head from prone and supine position, get up from a lying position, prop on arms, kneel, crawl, stand and step. Fatigue Questionnaire: The validated PROMIS-fatigue subscale will be administered using the NIH toolbox app on an iPad. Participants will be asked to enter responses for fatigue-related quality of life questions pre- and post-intervention.
Summary of Trial Design:	**Trial phase and type:** Phase 1 safety and tolerability, PK, and PD/TE **Sites:** Single site (NIH/NINDS, Bethesda MD, USA) **Randomization:** Not applicable **Study population**: *RYR1*-related myopathy **Target participant accrual number:** approximately 8-20 completers (pre-screening accrual ceiling n= 50) **Investigational drug:** S 48168 (ARM210) **Dose and duration:** ≤ 200 mg/day for approximately 28 days (not to exceed 30 days) **Sponsor:** ARMGO Pharma Inc.

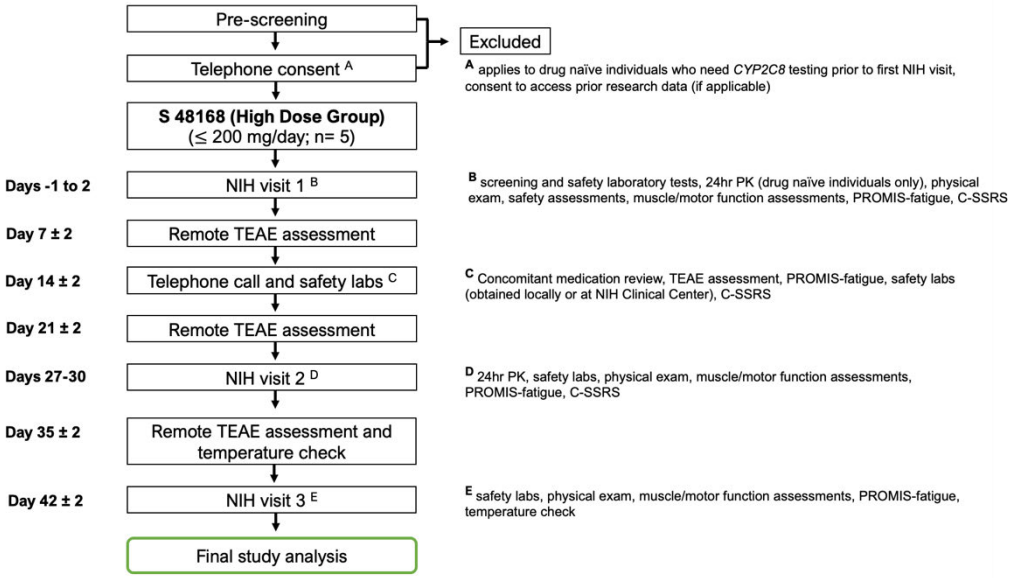

Figure 1: Overview of trial design

For each participant, the study duration will be approximately 2 months from enrollment to completion. Overall there will be three visits to the NIH Clinical Center (NIH CC), Bethesda, MD; one prior to the first dose, one at the end of the dosing period, and one approximately two weeks after the cessation of S 48168 (ARM210). Study participants will be contacted by phone/ secured email approximately weekly for follow-up regarding AEs and can describe daily any symptoms in a participant diary. Follow-ups will also serve to encourage study compliance. The dosing interval will be approximately 28 days (not to exceed 30 days). The day 42 follow-up assessment will be conducted in-person and include safety labs, , and the full battery of exploratory efficacy assessments.

Participants local to the study site will have the option of completing all weekly AE assessments at the NIH.

Study Population:	This study will be conducted in adult (≥18 years) male and female *RYR1*-RM affected individuals. Dropouts/withdrawals may be replaced.
Dosage, Dosage Form, Route, and Dose Regimen:	The first three participants were dosed with 120 mg S 48168 (ARM210) (6 x 20 mg tablets) daily for approximately 28 days (not to exceed 30 days). These participants will be provided an opportunity to re-enroll and receive the high dose. The second group was dosed with 200 mg S 48168 (ARM210) (10 x 20 mg tablets) daily for approximately 28 days (not to exceed 30 days). Study investigators will administer S 48168 (ARM210) during the time the participant is confined to the NIH CC for 24h PK assessments. Baseline (Day 0) 24hr PK assessments will not be conducted in participants who already received the low dose. Dosing was staggered for the first three participants at each dose level, starting each participant on drug after the previous participant had finished 14 days of dosing. Study investigators will instruct the

	participant in the proper dosing instructions for home administration when drug supplies are dispensed. Study drug (S 48168 [ARM210]) tablets will be provided to the participant in a bottle. All participants will be instructed to self-administer the study medication daily with water in the morning. Compliance will be assessed during each phone/e-mail contact. Compliance will be verified at in-person visits for residual pill counts and by a participant diary.

7 STUDY EVENTS FLOW CHART

Study Procedures [a]	Pre-screening	Screening [b]	Study Days																	
Days →			-1	1										2	3-5	6	7	8	9-12	13	14
Hours →			C-I	0	0.5	1	2	3	4	5	6	8	12	24							
Administrative Procedures																					
Telephone Informed Consent		X																			
In-person Informed Consent			X																		
Inclusion/Exclusion Criteria	X	X	X																		
Medical History		X																			
Safety Evaluations																					
Full Physical Examination [c]		X																			
Height		X																			
Weight		X																			
Suicidality Assessment		X																			X
12-Lead Electrocardiogram		X																			
Echocardiogram		X																			
Pulmonary Function Tests		X																			
Vital Signs (heart rate and blood pressure)		X		X [f]																	
Vital Signs (respiratory rate, temperature, pulse oximetry)		X																			
Hematology, Serum Chem, [d] and Urinalysis		X																			X
Pregnancy Test (females only)		X																			X
Serum FSH (postmenopausal females only)		X																			
Urine Drug and Alcohol Screen		X																			X
HIV/Hepatitis Screen		X																			
TEAE Monitoring[e]			X----------											----------X			X				X

Study Procedures [a]	Pre-screening	Screening [b]	Study Days																	
Days →			-1	1										2	3-5	6	7	8	9-12	13	14
Hours →			C-1	0	0.5	1	2	3	4	5	6	8	12	24							
Diary[e]															X	X	X	X	X	X	
Phone/e-mail[e]																	X				X
Concomitant Medication Monitoring		X	X														X				X
Study Drug Admin / PK																					
S 48168 (ARM210) Admin				X										X	X	X	X	X	X	X	X
Blood for S 48168 (ARM210) PK[g]				X[h]		X	X		X		X	X	X	X[h]							
Other Procedures																					
CYP2C8 Genotyping		X																			
Graded Functional Testing			X																		
Motor Function Measure 32			X																		
Grip/pinch Strength Dynamometry			X																		
Quantitative Muscle Assessment			X																		
Quality of Life Assessment			X																		X
Confinement in the NIH CC			X----------											----------X							
Visit		X																			

STUDY EVENTS FLOW CHART (cont.)

Study Procedures [a]	Study Days																		FU	FU[j]
Days →	15	16-19	20	21	22	23-26	27[i]	28[i]										29[i]	35	42
Hours →								0	0.5	1	2	3	4	5	6	8	12	24		
Administrative Procedures																				
Telephone Informed Consent																				
In-person Informed Consent																				
Inclusion/Exclusion Criteria																				
Medical History																				
Safety Evaluations																				
Suicidality assessment							X													
Full Physical Examination [c]							X													
Height																				
Weight							X													
12-Lead Electrocardiogram								X[f]												
Pulmonary Function Tests																				
Temperature check																			X	X
Vital Signs (heart rate and blood pressure)								X[f]												X
Vital Signs (respiratory rate, temperature, pulse oximetry)								X[f]												X
Hematology, Serum Chem, [d] and Urinalysis							X													X
Pregnancy Test (females only)							X													X
Serum FSH (postmenopausal females only)																				
Urine Drug and Alcohol Screen							X													
HIV/Hepatitis Screen																				
TEAE Monitoring [e]				X			X----------X												X	X
Diary [e]	X	X	X	X	X	X														
Phone/e-mail [e]				X															X	
Concomitant Medication Monitoring				X			X												X	X

Study Procedures [a]	Study Days																	FU	FU[j]
Days →	15	16-19	20	21	22	23-26	27[i]	28[i]									29[i]	35	42
Hours →								0	0.5	1	2	3	4	5	6	8	12	24		
Study Drug Admin / PK																			
S 48168 (ARM210) Admin	X	X	X	X	X	X	X	X											
Blood for S 48168 (ARM210) PK								X[g]		X	X		X		X	X	X	X		
Other Procedures																			
CYP2C8 Genotyping																			
Graded Functional Testing							X												X
Motor Function Measure 32							X												X
Grip/pinch Strength Dynamometry							X												X
Quantitative Muscle Assessment							X												X
Quality of Life Assessment							X												X
Confinement in the NIH CC							X----------										----------X		

a: For details on Procedures, refer to Section 12.

b: Within 28 days prior to the first dose of study drug with the exeption of HIV, HCV, HbsAg, and *CYP2C8* tests. Screening safety evaluations will occur during the first visit and will be within 24-48 hours of first dose, therefore not repeated unless deemed necessary by the PI pre-dose Day1.

c: Symptom-driven physical examination may be performed at other times, at the PI or designee's discretion.

d: Samples for serum chemistry will be obtained following a fast of at least 10 hours, however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample is taken. FSH and HbA1c are only required at screening.

e: AE's will be monitored throughout the study. Study Investigators will attempt to contact all subjects who received at least one dose of study drug (including subjects who terminate the study early) using their standard procedures on Days 7 and 21 (± 2 days) whilst on study drug and on Days 35 ± 2 and 42± 2 (Follow-up) to determine if any AE has occurred since the last study visit. A compliance assessment will be conducted as a part of the Day 7 and Day 21 contact. Subjects will enter daily log of symptoms as well as study drug intake in a diary for the days when direct communication is not done.

f: To be performed within 24 hours prior to dosing.

g: Baseline 24hr PK will only be conducted on study drug naïve individuals.

h: Prior to dosing.

i: Participants will return to NIH CC on Day 27 for scheduled events. Participants will be observed and examined one day post cessation of dosing, for any withdrawal effects. Administration of the final dose and 24 hour PK will occur following approximately 28 days dosing (not to exceed 30 days).

j: Approximately 14 days (± 2 days) following cessation of S 48168 (ARM210), participants will have follow-up safety laboratory tests.

Abbreviations: Admin = Administration, AE = Adverse event(s), C-I = Check-in, Chem = Chemistry, CYP = Cytochrome P450, FU = Follow-up, HIV = Human immunodeficiency virus, NIH CC = National Institutes of Health Clinical Center, PI = Principal Investigator, PK = Pharmacokinetics.

8 ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC%extrap	Percent of AUC0-inf extrapolated
AUC0-t	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration (t)
AUC0-inf	Area under the concentration-time curve, from time 0 extrapolated to infinity
AUCtau	The area under the concentration-time curve during a dosing interval (tau) at steady state
BCRP	breast cancer resistance protein
BMD	Becker Muscular Dystrophy
BMI	Body mass index
°C	Degrees Celsius
Ca^{2+}	Calcium ion(s)
CD	Clinical Director NINDS
CDM	Clinical Data Management
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
Cm	Centimeter
Cmax	Maximum observed concentration
Cmax,u	Maximum plasma unbound concentration
Cmin	Minimum concentration at steady state
CNS	Central nervous system
CRF	Case report form
Ctrough	Concentration observed at the end of the dosing interval
CV	Coefficient of variation
CYP	Cytochrome P450
D	Day
DICR	depolarization-induced Ca^{2+} release

DMD	Duchenne Muscular Dystrophy
DSMB	Data and Safety Monitoring Board
ECC	Excitation-contraction coupling
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDL	Extensor Digitorum Longus
FKBP12	12 kDa FK506-binding protein-Calstabin1
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume at 1 second
FIM	First-in-man
FWA	Federal Wide Assurance
G	Gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GR	Gastro-resistant
H	Hour
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPLC-MS-MS	High performance liquid chromatography with tandem mass spectrometry
HRPP	Human Research Protection Program
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
Kel	Apparent terminal elimination rate constant
Kg	Kilogram
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
MFM	Motor Function Measure 32

mIU	Milli-international units
Mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
N	Sample size
NCA	Non-compartmental analysis
NIH	National Institute of Health
NIH CC	NIH Clinical Center
NINDS	National Institute of Neurological Disorders and Stroke
NMD	Neuromuscular diseases
No.	Number
NOEL	No observed effect level
Oz	Ounce
PD	Pharmacodynamics(s)
PFT	Pulmonary Function Tests
PI	Principal Investigator
PII	Personally identifiable information
PK	Pharmacokinetic(s)
QA	Quality assurance
RAAUC	Ratio of accumulation for AUC
RACmax	Ratio of accumulation for Cmax
RyR	Ryanodine receptor
RYR1	Ryanodine receptor isoform-1
RYR1-RM	RYR1-related myopathies
RYR2	Ryanodine receptor isoform-2
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Plan
SERCA	Sarco/endoplasmic reticulum calcium-ATPase
SR	Sarcoplasmic reticulum
t½	Apparent terminal elimination half-life
Tau	Dosing interval

TE	Target engagement
TEAE	Treatment Emergent Adverse Events
Tlag	Lag time
Tmax	Time to reach maximum observed concentration
Tmin	Time to Cmin
ULN	Upper limit of normal
US	United States
USA	United States of America
VC	Vital capacity
WHO	World Health Organization

9 INTRODUCTION AND BACKGROUND

9.1 Introduction

Ryanodine receptor isoform 1-related congenital myopathies (*RYR1*-RM) are rare, slowly progressive neuromuscular diseases estimated to affect at least 1/90,000 pediatric individuals in the United States (Amburgey et al. 2011). Causative *RYR1* variants lead to a spectrum of *RYR1*-RM histopathological subtypes and clinical phenotypes. The most common clinical phenotype of *RYR1*-RM is a congenital myopathy. Affected individuals usually present with delayed motor milestones, proximal muscle weakness, impaired ambulation, and, in severe cases, scoliosis, ophthalmoplegia, and respiratory distress (Witherspoon and Meilleur, 2016). *RYR1*-RM may also cause rhabdomyolysis or atypical periodic paralysis and is associated with malignant hyperthermia. Histopathological subtypes include central core disease, multi-minicore disease, congenital fiber-type disproportion, centro-nuclear myopathy and core-rod myopathy. Although *RYR1*-RM have been associated with significant morbidities and early mortality, there remains no FDA-approved treatment.

Ryanodine receptor isoform-1 (RyR1) is the major skeletal muscle Ca^{2+} release channel. RyR1 is embedded within the sarcoplasmic reticulum (SR) membrane and is a principal component of skeletal muscle excitation-contraction coupling (ECC). Causative *RYR1* variants can have different effects on the RyR1 channel function. Some of these mutations result in chronic SR Ca^{2+} leak while others primarily impair ECC. Chronic Ca^{2+} leak into the sarcoplasm may result in increased mitochondrial-related oxidative stress, RyR1 channel oxidation, and cellular injury (Görlach et al. 2015).

9.2 Study Rationale

Under typical physiological conditions, SR Ca^{2+} flux is tightly regulated to facilitate effective ECC. RyR1 interacting proteins contribute to this regulation. In particular, Calstabin1 (also referred to as FKBP12) modulates SR Ca^{2+} release by stabilizing the RyR1 closed state (Zalk, Lehnart et al. 2007). In those with *RYR1*-RM, there is evidence of decreased RyR1-Calstabin1 binding and increased RyR1 Ca^{2+} leak (unpublished data) supporting the concept of a drug trial that targets this pathomechanism in the aforementioned population.

9.3 Scientific Basis

Excitation-Contraction Coupling

ECC is initiated when depolarization of the skeletal myocyte plasma membrane causes activation of L-type Ca^{2+} channels on the transverse T-tubule, which then activates the juxtaposed ryanodine receptors (RyR) through a direct interaction between both ion channels (Marty, Robert et al. 1994). This interaction induces Ca^{2+} release from the sarcoplasmic reticulum (SR) to the sarcoplasm, a phenomenon also called depolarization-induced Ca^{2+} release (DICR) (Murayama and Kurebayashi 2011). DICR enables the actin-myosin cross-bridge formation and sarcomere shortening that results in muscle contraction. During skeletal muscle relaxation, Ca^{2+} is sequestered in the SR by an ATP-dependent Ca^{2+} pump

(sarco/endoplasmic reticulum calcium-ATPase, SERCA), thus lowering the sarcoplasmic Ca^{2+} concentration and removing Ca^{2+} from the troponin complex. RyR1, the main RyR isoform in skeletal muscle, forms a large sarcoplasmic membrane complex, consisting of four monomers that constitute a Ca^{2+} release channel associated with several proteins, such as Calstabin1, kinases, phosphatases, phosphodiesterases, and other regulatory subunits (Marx, Reiken et al. 2000, Lehnart 2007). This assembly allows for tight regulation and gating of intracellular Ca^{2+} release for the control of skeletal muscle function. In *RYR1*-RM, this process can be disrupted owing to chronic SR Ca^{2+} leak, excitation-contraction uncoupling, and decreased RyR1 expression (Lawal *et al.* 2018).

Calstabin1 Binding

The 12 kDa FK506-binding protein, Calstabin1 (also known as FKBP12) is encoded by *FKBP1A* and is located in the sarcoplasm. There are four Calstabin1 subunits that bind to the homotetrameric RyR1 protein in a 1:1 manner. Calstabin1 prevents leaky RyR1 signaling under sub-optimal ligand concentrations, and therefore serves as a molecular gradient reader. Calstabins are suggested to have a stabilizing effect on RyR1 channel function by lowering open probability and preventing sub-conductance state gating, which leads to fewer leaky RyR1 channels and fewer aberrant Ca^{2+} release events (Venturi et al. 2014).

Decreased Calstabin1 binding is in part caused by pathologic RyR1 post-translational modifications such as excessive PKA-phosphorylation (Marx, Reiken et al. 2000; Reiken, Lacampagne et al. 2003) and/or hypernitrosylation (Bellinger, Reiken et al. 2009; Gonzalez, Treuer et al. 2010). The resulting dissociation of Calstabin1 from RyR1 may exacerbate the deleterious increase in RyR1 open probability under resting conditions in *RYR1*-RM affected individuals.

The *RYR1*-RM (dyspedic) mouse model has a low survival rate and other knock-in *RYR1*-RM mouse models either more closely reflect a malignant hyperthermia (Y522S) phenotype or have a severe phenotype (I4895T) that may not reflect *RYR1*-RM as a slowly progressive myopathy. In part due to this limitation, the majority of preclinical Rycals research has been conducted in the Duchenne Muscular Dystrophy (DMD) mouse model (*mdx* mice). RyR1 channels isolated from *mdx* mice were shown to be hypernitrosylated as a potential consequence of altered nitric oxide signaling downstream of dystrophin loss resulting in increased SR Ca^{2+} leak. Hypernitrosylation of RyR1 coupled to depletion of Calstabin1 from RyR1 in *mdx* mice, increased spontaneous RyR1 openings, as determined by Ca^{2+} sparks, and reduced specific muscle force (Bellinger, Reiken et al. 2009). Preventing Calstabin1 depletion from RyR1 with Rycals treatment inhibited SR Ca^{2+} leak, decreased biochemical and histological evidence of muscle damage, improved muscle function, and increased exercise performance in *mdx* mice (Bellinger, Reiken et al. 2009).

Hypernitrosylation of RyR1 has also been observed in muscle biopsies from Becker Muscular Dystrophy (BMD) patients, disrupting the RyR1/Calstabin1 complex (Gentil, Leturcq et al. 2012). Moreover, elevated intracellular Ca^{2+} was found sufficient to cause a dystrophic phenotype even when dystrophin remained intact suggesting that some of the muscle damage observed in dystrophin–glycoprotein complex (DGC)-related muscular dystrophies may be

attributed to downstream defects in Ca^{2+} homeostasis (Millay, Goonasekera et al. 2009; Gumerson and Michele 2011).

9.4 S 48168 (ARM210) – Research Drug

Overview

S 48168 (ARM210) is the lead compound in a new pharmacological class of specific calcium release channel stabilizers, termed Rycals. Rycals are thought to stabilize leaky RyR channels through restoration of Calstabin binding. S 48168 (ARM210) is proposed for the treatment of genetically determined diseases of muscle including DMD and *RYR1*-RM. S 48168 (ARM210) acts on both skeletal and cardiac RyRs (RyR1 and RyR2, respectively) if dysfunctional, and correct channel dysfunction due to Calstabin dissociation. This may in turn restore Ca^{2+} homeostasis at the sarcoplasmic and cytosolic levels, improving muscle fiber survival and function. S 48168 (ARM210) repairs dysfunctional RyRs but should have no effect on normal RyRs (Liu et al., 2012). Thus, in muscle diseases such as DMD where RyR1 and RyR2 are affected, S 48168 (ARM210) would repair both types of the channel. In *RYR1*-RM, where only RyR1 is affected, the therapeutic effect would be on RyR1 in skeletal muscle only. The new therapeutic approach embodied by Rycals targets a pathophysiological mechanism that is implicated in the skeletal muscle function dysfunction observed in muscular degenerative diseases. S 48168 (ARM210) is being manufactured and formulated under cGMP conditions by Servier Laboratories, France.

Refer to the Investigator's Brochure (IB) for more background information on S 48168 (ARM210) [redacted]

Formulation

S 48168 (ARM210) Phase I formulations are oral gastro-resistant (GR) tablets dosed at 5 mg, 20 mg, 40 mg or 200 mg of S 48168 (ARM210) (as hemifumarate salt). Two formulations have been developed: the adult First-In-Man (FIM) study formulation dosed at 20, 40 and 200 mg (adult formulation A) and the formulation suitable for pediatric administration, at, 5 mg and 20 mg (pediatric/adult formulation B). These two formulations have been shown to be equivalent in exposure in a clinical study [redacted] . The latter formulation will be used for this study. The formulations contain no excipients with known effect.

Pharmacodynamics

In *mdx* mice, S 48168 (ARM210) was administered daily for 3 or 4 weeks in drinking water (*ad lib.*). This treatment was shown to have a beneficial effect: (i) on *in vivo* muscular function (*i.e.*, significant improvement of voluntary wheel activity at 10 and 50 mg/kg/day after 3 weeks of treatment, no decline in treadmill exhaustion test performance compared to vehicle-treated mice); (ii) on *in vivo* muscle force (*i.e.*, improvement of forelimb grip strength); and (iii) on *ex vivo* Extensor Digitorum Longus (EDL) specific force (3-week treatment) and diaphragm specific tetanic force at 50 mg/kg/day (4-week treatment) (Capogrosso et al., 2018). Two *in*

vitro parameters of intracellular Ca^{2+} homeostasis (*i.e.*, mechanical threshold and resting cytosolic Ca^{2+} level) were improved by a 4-week treatment of S 48168 (ARM210) at 50 mg/kg/day. [redacted]

Pharmacokinetics

After single oral administration in young healthy males of 20, 40, 80, 160, 240 and 400 mg of S 48168 (ARM210), rapid absorption was observed, after a lag time consistent with the GR properties of the tablet administered. There was no evidence of non-linearity with the dose. After 14-days of repeated once daily oral administrations of 20 mg of S 48168 (ARM210), the Cmax was reached with a median Tmax between 3 and 3.5 hours. Steady-state was attained after 3-7 days of daily treatment with S 48168 (ARM210). After 14-days of repeated administration of 20, 60,120 and 240 mg of S 48168 (ARM210), accumulation ratios are around 1.5-1.8 for Cmax and AUC24, consistent with the half-life (20 hours) of S 48168 (ARM210) and its dose regimen.

The effect of food on the absorption of S 48168 (ARM210) has been tested in a three-period crossover study, comparing fasted with administration with a high fat breakfast, and with administration of a light breakfast [redacted]. The results showed that there is minimal effect on the exposure of S 48168 (ARM210) when administered with food when compared to fasted. The inclusion of food can delay the Tmax and blunt the Cmax so when PK is to be measured in the trial, S 48168 (ARM210) should be given fasted. However, on all other days S 48168 (ARM210) can be given without regard to food, i.e. fasted or with food.

In human liver microsomes, S 48168 (ARM210) did not inhibit the metabolism of selective substrates for CYP1A1/2, 2A6, 2B6, 2C9, 2C19, 2E1, 2D6 and 3A4 iso-enzymes. However, S 48168 (ARM210) showed an inhibitory potential towards CYP2C8 and a low inducer potential towards CYP3A4. The involvement of the CYP2C8 as one of the main metabolic pathway of S 48168 (ARM210) metabolism has been confirmed *in vivo* via an interaction study with the CYP2C8 inhibitor gemfibrozil [redacted].

Toxicology

A complete safety pharmacology program was performed. No major safety concern was raised. S 48168 (ARM210) was devoid of genotoxic potential in the three regulatory genotoxicity studies. [redacted]

Overall, non-clinical safety studies showed potential dose limiting findings with respect to:

- **Central Nervous System (CNS) toxicity** with tremors in isolated animals at the highest tested doses of 540 and 250 mg/kg/day in the regulatory 4-week rat study and in the regulatory 39-week dog study, respectively, and convulsions after single administration at 500 mg/kg in the exploratory (non-regulatory) intra-duodeno-jejunal administration study in dog and in one dog at the high dose of 250 mg/kg/day in the

regulatory 39-week dog study. In the regulatory 26-week rat study, CNS signs were limited to decreased activity at the highest tested dose of 540 mg/kg/day.

- **Testicular toxicity** [characterized by decreased testis weights associated to depletion/sloughing of germ cells leading to aspermia or increased hypospermatogenesis (correlated to low sperm counts) and minimal germ cells degeneration and/or cellular debris in the epididymides] observed in the exploratory 8-week (+10-week recovery) study at the highest dose of 250 mg/kg/day in sexually mature dogs and in the regulatory 13- and 39-week (+10-week recovery period) studies at the highest dose of 250 mg/kg/day or from the mid-dose of 50 mg/kg/day, respectively, where the dogs were not sexually mature at the start of dosing (maturation under treatment). Following the 10-week recovery period in both studies, these changes were no longer apparent and considered to be reversible.

- **Gastric toxicity (**minimal neck cell hyperplasia in the fundic mucosa) observed at the highest dose of 100 mg/kg/day in the regulatory 4-week dog study but not in any S 48168 (ARM210) dosed-animals in the regulatory 13- and 39-week dog studies, the risk for human is considered to be low since the gastro-resistant formulation developed for the overall clinical development program would limit the contact with stomach.

9.5 Dose Justification

The initial proposed dose for this study was 120 mg S 48168 (ARM210) daily for approximately 28 days (not to exceed 30 days) for the first three participants (6 x 20 mg tablets) (see details outlining dose modification in Section 9.6). An additional three participants were dosed with 200 mg S 48168 (ARM210) (10 x 20 mg tablets) daily for approximately 28 days (not to exceed 30 days) after DSMB evaluation of the interim safety and PK data. The remainder of participants will be dosed at the same high dose ≤ 200 mg S 48168 (ARM210) (10 x 20 mg tablets) daily for approximately 28 days. The projected exposure at 200 mg/day dose remains below preclinical safety margins (Cmax<35 ug/ml), as well as below the highest dose tested in healthy volunteers (240 mg/day for 14 days). Preclinically, the one finding that is not monitorable in humans is the proconvulsant risk, with convulsions rarely observed at highest dose level in dogs in the 39-week study. The convulsions occurred at the high dose of 250 mg/kg/day in the 39-week GLP chronic study. The Cmax of that dose for both genders is 374 ug/ml. This concentration range is associated with an *in vivo* unbound fraction of 3.5%, which is greater than 20-fold higher than the *in vivo* fraction unbound (0.16%) in the human at 240 mg. It is likely that this high unbound fraction, which is able to penetrate tissues, including the brain, was responsible for the rare convulsions seen in 1 of 20 dogs (i.e. 1/12 dogs from the 39-week study and 0/8 dogs from the 13-week study, both studies at 250 mg/kg/day). The FDA has determined that the high dose (250 mg/kg/day from 13-week dog study) sets the NOEL for convulsions for this trial. The Cmax at the NOEL (from the 250 mg/kg high dose) from the 13-week dog study is a mean of 320 ug/ml for both sexes. In consultation with the FDA, the current dose cap is at 35 ug/ml for Cmax to provide a significant margin to the NOEL Cmax from the dog.

In the first in man study [redacted] 40 male healthy volunteers (5 groups, approximately 8 participants p : placebo) completed the study part I (single escalating dose). Five dose levels were tested successively: 20 mg, 60 mg, 120 mg, 240 mg and 400 mg. In part II, a four dose levels were studied with daily doses for 14 days (20 mg/day, 60 mg/day, 120 mg/day and 240 mg/day) all of which were well tolerated.

Using total PK to determine the safety margin, the Cmax should be limited to 35 ug/ml per the FDA partial clinical hold comments. This limit is based on a 10-fold safety margin to the Cmax of the high dose of the 13-week dog toxicology study. We propose to dose the first three participants at 120 mg/ day. The mean Cmax for healthy volunteers at this dose was 17 ug/ml. Assuming the safety, tolerability and PK are acceptable [redacted] to the DSMB, a top dose of ≤ (not to exceed 30 days) is proposed for the remaining participants. Preliminary human PK of 14 days of dosing at 240 mg/day S48168 (ARM210) shows a mean Cmax of 35 ug/ml [redacted]). The Cmax at steady state has been dose proportional, with no evidence of non-linearity, with low variability (13.5%). The projected Cmax for 200 mg/day at steady state is 28 ug/ml. Assuming that the PK at 120 mg/day dose is similar to the previous numbers seen in heathy volunteers, then a dose ≤ 200 mg/day should remain below the dose cap of 35 ug/ml.

Staggered dosing was implemented for the first three participants at the low dose level, starting each participant on drug after the previous participant had finished 14 days of dosing. At the high dose level (200 mg/day), Cmax at steady state of each participant was measured before dosing the next participant. S48168 (ARM210) reaches steady state typically after five days of dosing, consistent with its terminal half life. PK profiles have been established in *RYR1*-RM trial participants at both low and high dose levels and are consistent with healthy volunteer studies. In addition, none of the subjects tested so far have exceeded the FDA Cmax limit of 35 ug/ml at steady state and no clear safety signals have been observed to date in safety labs, EKG, or other safety related assessments.

Although testes toxicity was observed in dogs (see above), it was not seen in the 4-week dog study, which is the duration of dosing in this protocol. In the 13-week dog studies in mature dogs the NOEL = 50 mg/kg/day with an expected safety margin of 22-fold in terms of unbound plasma exposure (AUC). Thus, high safety margins are expected in adult population for a 28-day (not to exceed 30-day) treatment duration as in this study. These findings in the dogs were reversible with cessation of treatment. Furthermore, no clinically meaningful effects on sperm counts numbers have been observed to date in the ongoing 14-day multiple dose studies in young healthy males.

The gastric toxicity observed in animals is mitigated by a gastric-resistant formulation, which will not undergo dissolution at pH below 5. In order to avoid chronic increases in gastric pH, which may allow gastric dissolution, proton pump inhibitors and histamine 2 receptor blockers are not allowed in the study. Antacids may be used only at night, with S 48168 (ARM210) dosed in the morning. Numerous studies have shown that antacids only affect gastric pH for 1-2 hours after administration (Decktor et al., 1995). Antacids cannot be dosed at the same time as S 48168 (ARM210).

The target exposure at the level of the muscle can be estimated from a number of sources. The measured level of unbound muscle exposure of the 120 mg/day dose in healthy volunteers at steady state from muscle biopsies ranges from 1.15-3.59 µg.h/mL, which overlaps with the target unbound AUC in *mdx* mouse muscle, estimated to be 2.47 µg.h/mL. There was efficacy in 4 weeks seen in the *mdx* mouse model, at these concentrations (Capogrosso et al., 2018). The ≤ 200 mg daily dose is likely to ensure that the muscle concentration in all patients will be similar or higher than the efficacious level in *mdx* mice.

S 48168 (ARM210) has orphan designation for *RYR1*-RM and a phase II clinical trial is in the planning stages. Preliminary analysis of the exploratory outcome measures of the trial so far suggests improvement in hand grip and pinch strength and improvement in manual proximal muscle strength. Participants in the high dose group also reported decreased fatigue as assessed by the standardized patient reported outcome measure (PROMIS-fatigue), consistent with the efficacy expectations at the high dose of 200 mg daily.

The PK profile of the 240 mg dose at steady state in healthy volunteers shows a slow decline over several days at the end of drug administration (Figure 2). This gradual decline in exposure reduces the risk of a sudden effect at the end of the dosing period due to withdrawal.

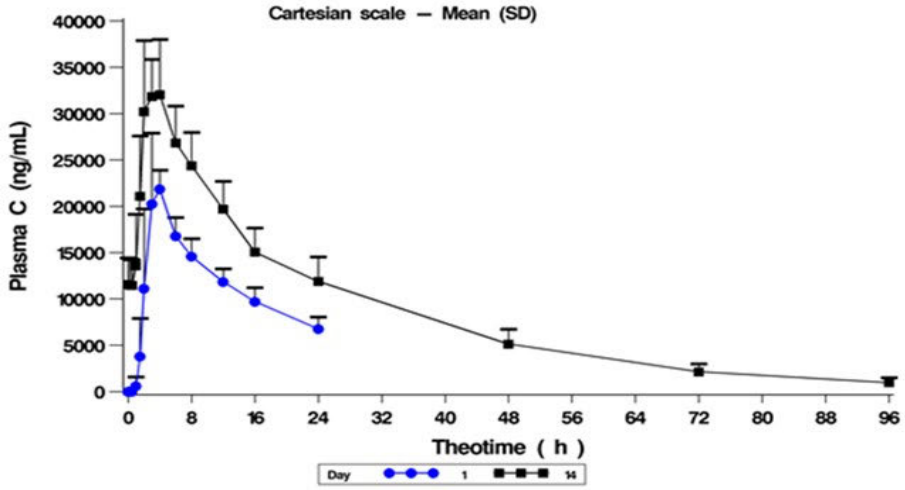

Figure 2. PK profile of S 48168 (ARM210) at day 1 and day 14 in healthy volunteers dosed at 240mg/day.

Modification of the Dose and/or Dosing Regimen

This protocol is written with some flexibility to accommodate the inherent dynamic nature of early clinical trials. Modifications to the dose and dosing regimen currently outlined below may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects.

As such, lowering the currently outlined dose may be permitted based on newly available data, but the dose may not exceed 200 mg per day.

- Decrease in the dose of the trial drug administered during the study

The current top dose of ≤ 200 mg/day (10 X 20 mg tablets) is not expected to exceed the Cmax limit of 35 ug/ml (projected mean from healthy volunteer data of 28 ug/ml) However if PK monitoring reveals that the limit could be exceeded, then 180 mg/day will be given (9 X 20 mg tablets). This dose would be projected to have a Cmax of 25.75 ug/ml.

- Decrease in the duration of trial drug administration (*e.g.*, number of days) in the study
- Addition of a pharmacokinetic data review

9.6 S 48168 (ARM210) Research Studies to Date (including potential interactions)

9.6.1 S 48168 (ARM210) Pre-Clinical Studies in *RYR1*-RM

To date, we have utilized extra skeletal muscle tissue collected from *RYR1*-RM patients at the NIH CC for testing Rycals preclinically in this population. Skeletal muscle tissue was obtained *via* needle biopsy in a previous *RYR1*-RM clinical trial (NCT02362425). Skeletal muscle samples were tested in Dr. Marks' lab for RyR1-Calstabin1 binding. All biopsies demonstrated decreased Calstabin1 binding, which was rescued with Rycal treatment *ex vivo*. Seven samples had sufficient material to evaluate channel function in a Ca^{2+} leak assay as well. All seven samples exhibited increased leakiness compared with control muscle RyR1, and decreased channel leakiness upon Rycal treatment *ex vivo*.

9.6.2 S 48168 (ARM210) Clinical Studies

To date, unblinded data are available for a total of 107 adult subjects that participated in Phase I clinical studies (including single and multiple dose-escalation) where 90 participants were exposed to S 48168 (ARM210) treatment. S 48168 (ARM210) has been safe and well-tolerated in single doses (up to 240 mg) and in 14 days of multiple dosing up to 240 mg daily. The study drug has been well tolerated. No serious AEs were reported. There were no clinically significant, dose dependent changes in vital signs, physical examination, laboratory data, ECG and telemetric data.

S 48168 (ARM210) has been used in four Phase I clinical studies, [redacted] with two further described below. All studies to date have been in adult healthy male Caucasian volunteers aged 18- 45 years. The FIH study [redacted] was divided into two parts; part 1 is a randomized placebo-controlled blind [redacted] ose escalation study where 5 dose levels were tested (40 mg, 80 mg, 160 mg, 240 mg and 400 mg), and part 2 is a four-panel rising multiple dose study (20 mg/day, 60 mg/day, 120 mg/day and 240 mg/day) for 14 days of dosing. The single dose level of 400 mg and the repeated dose level of 240 mg/day for 14 days of S 48168 (ARM210) were tested in a second step with a study amendment. The data are unblinded for all dose levels. S 48168 (ARM210) has been safe and

well-tolerated in part 1 and part 2. No serious AEs were reported. All AEs were of mild intensity including an increase in transaminases which occurred 14 days after cessation of drug in the 20 mg dose panel at the post study follow up visit. These elevations were considered not related to the study drug by the investigator and were not related to any signs and symptoms. There were no elevations in the dosing period. There were no clinically significant changes in vital signs, physical examination, ECG and telemetric data. No other laboratory changes apart from this mild increase in transaminases was observed.

In this study, additional monitoring was performed for two theoretical risks, based on prior animal studies. First, pre- and post-dose sperm levels were measured in all panels and there were no clinically significant changes seen in sperm numbers. Secondly, gastroscopies were performed to ensure that the gastric restrictive formulation was protective for the transient gastric toxicity **(**minimal neck cell hyperplasia in the fundic mucosa) seen in the four-week (but not 13-week) dog toxicology studies. Here, two minor erosions reported as mild adverse events not considered as related to the product by the investigator were seen in the 60 mg/day cohort, which resolved at 8 weeks. No erosions were seen at the 20 or 120 mg dose level in any subjects.

The IND opening study [redacted] is complete. A total of 18 subjects received single doses of 40 mg of S 48168 (ARM210). This was an open-label, 2-cohort study. Cohort 1 was a randomized, 3-period, 3-way crossover study in extensive CYP2C8 metabolizers to examine the effect of food on the rate and extent of absorption of S 48168 (ARM210). Administration of S 48168 (ARM210) 40 mg was compared between fasted, high fat meal and a light meal after a brief delay. The lighter meal was meant to be a "real world" assessment, as patients in future clinical studies, are likely to eat a lighter meal than the high-fat meal, a worst-case scenario.

As described above, there is no clinically meaningful difference in AUC when S 48168 (ARM210) is given fasted or fed.

Cohort 2 is a 1-period study in intermediate CYP2C8 metabolizers. All studies to date have been conducted in CYP2C8 extensive metabolizers. Approximately 1/3 of the population is likely to be intermediate metabolizers. These levels of metabolism have been classified on the basis of *in vitro* assays. Subjects who are poor CYP2C8 metabolizers are expected to exhibit a similar S 48168 (ARM210) PK profile as observed in the presence of a CYP2C8 inhibitor in CYP2C8 extensive metabolizers. Surprisingly, several CYP2C8 sensitive substrates (*i.e.* increased by gemfibrozil treatment), when examined *in vivo* for their clearance with extensive versus intermediate metabolizers have had the opposite results; namely that intermediate metabolizers had higher clearance and therefore lower exposure than their wild type counterparts. It is therefore possible that these classifications, based on *in vitro* data, are not meaningful. This study examined the single-dose PK in extensive versus intermediate metabolizers. The results showed that intermediate metabolizers did not have higher levels of Cmax or AUC than extensive metabolizers and are therefore safe to include. In the current protocol rare (~1% of the population) poor CYP2C8 metabolizers are excluded as a precaution.

No serious AEs were reported in this study. All AEs were of mild intensity and resolved. There were no clinically significant changes in vital signs, physical examination, laboratory and ECG data.

10 STUDY OBJECTIVES AND ENDPOINTS

10.1 Study Objectives

Primary objective: To determine safety and tolerability of S 48168 (ARM210) treatment in *RYR1*-RM affected individuals.

Hypothesis: S 48168 (ARM210) treatment will have no safety concerns limiting further development and will be generally well tolerated in *RYR1*-RM patients.

Exploratory objectives:

1. To determine PK of a 28-day (not to exceed 30-day) administration of S 48168 (ARM210) in *RYR1*-RM affected individuals.

Hypothesis: There will be no clinically meaningful difference in S 48168 (ARM210) exposure at steady state in *RYR1*-RM affected individuals when compared to existing data established in healthy volunteers.

2. To explore if S 48168 (ARM210) treatment increases RyR1-calstabin1 binding in skeletal muscle of *RYR1*-RM affected individuals.

Hypothesis: S 48168 (ARM210) treatment will increase RyR1-calstabin1 binding, compared to baseline, as determined by co-immunoprecipitation of RyR1 and calstabin 1, and decrease relative Fluo-4 signal compared to baseline

3. To explore if S 48168 (ARM210) treatment improves muscle function, motor activity, and fatigue in *RYR1*-RM affected individuals.

Hypothesis: Treatment with S 48168 (ARM210) will increase hand grip, pinch, and quantitative muscle assessment strength, decrease the time to complete graded functional tests, increase the total MFM-32 % maximum score, and decrease the PROMIS-fatigue subscale score, when compared to baseline.

10.2 Study Endpoints

Primary endpoint:

Composite safety and tolerability profile

(Frequencies of the following: TEAEs ≥ grade 2 in severity (CTCAE version 5), all SAEs, and all AESIs).

Exploratory Endpoints:

S 48168 (ARM210) pharmacokinetics

Day 1 composite PK profile (for study drug naïve participants only)

(Comprised of the following: AUC0-t, AUC0-inf, Cmax, Tmax, and t½).

Day 28 (not to exceed Day 30) composite PK profile

(Comprised of the following: AUCtau, Cmax, Tmax, Cmin, RAAUC, and RACmax).

S 48168 (ARM210) pharmacodynamics

RyR1-calstabin1 binding

(Change from baseline in RyR1-calstabin1 binding (arbitrary units)).

RyR1 channel integrity

(Change from baseline in RyR1-mediated Ca^{2+} leak (arbitrary units)).

Muscle/motor function and fatigue

Hand grip strength (kg), pinch strength (kg).

Time taken to complete each of the following (seconds): walk 10-meters, supine to stand, ascend 4 stairs, and descend 4 stairs.

MFM-32 score for domains 1, 2, 3, and total (% of maximum score).

PROMIS-fatigue subscale score (t-score).

Quantitative muscle strength (kg)

11 INVESTIGATIONAL PLAN

11.1 Overall Study Design and Plan

This is a Phase 1, single-site, open label, safety and tolerability, PK, and PD trial of S 48168 (ARM210) with approximately 8-20 individuals with *RYR1*-RM completing the study. Participants will be dosed for approximately 28 days (not to exceed 30 days) at 120 mg or 200 mg daily of S 48168 (ARM210). To date, three participants have been dose at 120 mg and three have been dosed at 200 mg. This study is being conducted in the US at the National Institutes of Health (NIH) in the Neurogenetics Branch of NINDS in collaboration with ARMGO Pharma Inc (the Sponsor), and Les Laboratoires Servier.

The overall design of the study is shown below (Figure1)

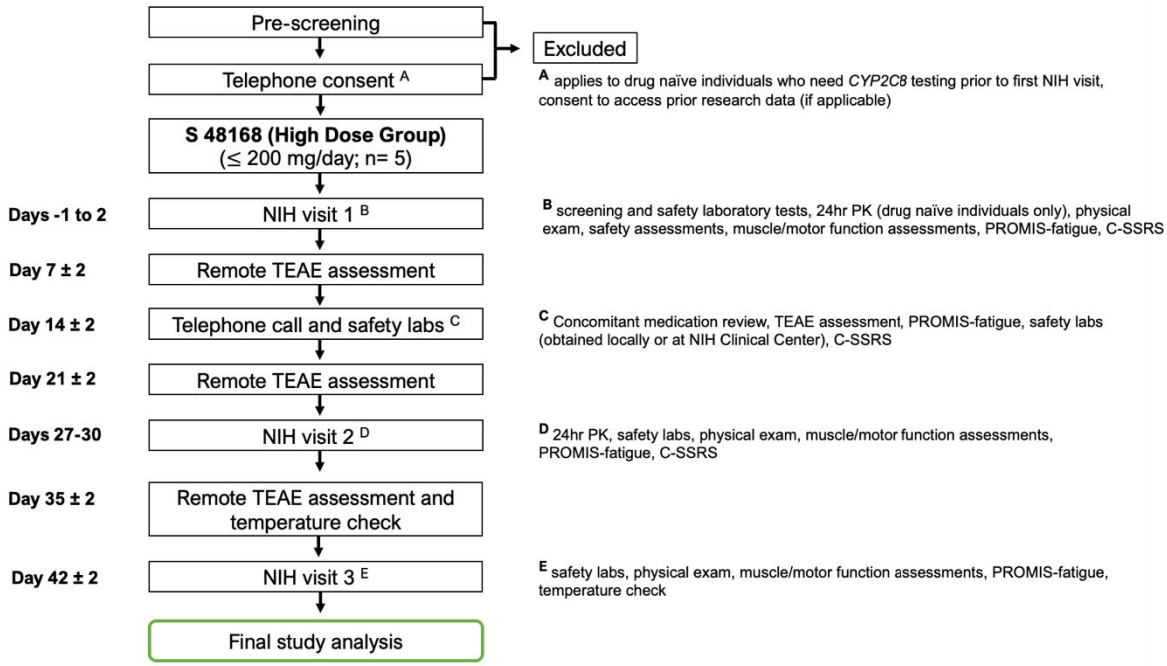

Figure 1: Study Design

For each participant, the study duration will be approximately 2 months from enrollment to completion. Overall there will be three visits at the NIH CC, Bethesda, MD; one prior to the first dose, one at the end of the dosing period, and one approximately 2 weeks after cessation of S 48168 (ARM210). The last visit will include a blood draw for safety labs, and the full battery of exploratory efficacy assessments. Study participants are contacted by telephone/ secured email approximately weekly for a follow-up regarding AEs and can also describe daily any symptoms in a subject diary. Follow-ups will serve to encourage study compliance. The dosing interval for S 48168 (ARM210) will be approximately 28 days (not to exceed 30 days). A study investigator will contact participants by telephone to remind them of upcoming, scheduled local phlebotomy appointments if relevant.

Safety will be monitored throughout the study by repeated clinical and laboratory evaluations.

Discontinued subjects may be replaced at the discretion of the Sponsor in consultation with the PI and DSMB. The pre-screening accrual ceiling will be up to 50 subjects with a target number of approximately 8-20 completers.

Overview of study visits:

Pre-screening of individuals will be conducted by the study coordinator who will use prior medical records and biospecimen data and/or an IRB-approved script (Appendix # 2). During pre-screening, interested individuals may be asked pre-specified questions pertaining to the inclusion and exclusion criteria if needed.

Informed consent will be obtained before any study procedures begin, including formal screening procedures. Formal screening will initiate remotely, upon completion of a telephone consent form for a blood draw. Remote analysis of CYP2C8 genotype will be done at this initial stage of consent to avoid unnecessary burden for the particants who do not meet this inclusion criterion.

The first study visit will begin with the completion of an in-person consent form, covering screening procedures to be conducted at the NIH Clinical Center (e.g. PE, safety laboratory assessments, PFT, ECG) and all remaining study procedures. Participants that complete the study screening assessments at NIH and meet all the eligibility criteria (per an IRB-approved eligibility checklist, Appendix # 3) will receive an allocation number. This number will be distinct from the participant's baseline number. Next, participants will undergo muscle/motor function assessments. They will fast overnight. The following morning, administration of the first dose will begin and participants will remain at the NIH CC for at least 24 hours for single-dose PK (baseline 24hr PK for drug naïve participants only), safety labs, ECG, vital signs and physical examination. Participants will then be discharged, provided with a lifestyle recommendations sheet (Appendix # 4) and contacted approximately one week later for AE assessment (Appendix # 5) by a study investigator (Day 7 ± 2 days). Re-enrolled participants will be assigned a new allocation number. Re-enrolled participants will not undergo baseline 24hr PK studies and will be discharged and instructed to take the study drug after all baseline safety assessments (safety labs, ECG, vital signs and physical examination) are completed.

Participants will attend a phone call on Day 14 (± 2 days). This will include review of any concomittant medication, TEAE assessment, and C-SSRS and PROMIS-fatigue questionaires. Safety labs will be obtained remotely or at NIH CC if the participant is local to the study site.

Participants will return to the NIH CC on Day 28 (± 2 day) for repeat safety labs, ECG, vital signs, physical examination, and 24hr PK. In addition, participants will be observed and examined one day post cessation of dosing, for any withdrawal effects, although none are expected.

A study investigator will contact participants by telephone weekly when not on site to remind them of upcoming, scheduled local phlebotomy appointments and perform remote TEAE assessments, if applicable.

The final onsite study visit (Day 42 ± 2 Days) will consist of muscle/motor function assessments, PROMIS-fatigue questionnaire, AE assessment, vital signs, physical examination, safety labs, and a blood draw.

Daily subject diaries will be used to capture both time of dose administered as well as any symptoms they may feel in between remote TEAE assessments.

Confinement, Return Visits, and Follow-Up

Participants will be admitted to the NIH CC on the evening of Day -1 for drug administration. Drug naïve participants will undergo baseline 24hr PK sample collection the next morning.

Participants will attend a phone call on Day 14 (± 2 days). This will include review of any concomittant medication, TEAE assessment, and C-SSRS and PROMIS-fatigue questionaires. Safety labs will be obtained remotely or at NIH CC if the participant is local to the study site.

Participants will return to the NIH CC on Day 28 (± 1 day) for repeat safety labs, PE, ECG, vital signs, and a 24hr PK sample collection.

Participants will return to the NIH CC for Day 42 ± 2 days for vital signs, AE assessment, exploratory efficacy assessments, safety labs, and a blood draw.

At all times, a subject may be required to remain at the NIH CC for longer at the discretion of the Principal Investigator (PI) or designee (e.g. when deemed necessary for safety reasons).

Participants will be contacted by telephone/secured email for a follow up regarding TEAEs approximately weekly when not on site and will also have a blood draw for safety clinical laboratory tests at day 14. This will include participants who terminate the study early. Participants local to the study site will have the option of completing AE assessments and safety clinical laboratory tests at the NIH.

Participants will also be able to enter any symptoms they experience in a participant diary (Appendix # 6).

11.2 Risks and Discomforts

Medical History

There may be some psychological distress associated with providing medical and family history. Frequent breaks may be taken to decrease the risk of distress.

Suicidality assessment

There may be some psychological distress associated with completing the suicidality assessment. Frequent breaks may be taken to decrease the risk of distress. There is a risk that

the suicidality assessment will be positive. If positive, we will take steps to assure the participant's safety and well-being.

Physical Examination
There is minimal medical risk and discomfort from the physical examination.

Videotaping
Risks are minimal. The patient may be identified if a face is featured. When possible, the patient's face and other identifying marks will not be included in the recording or photograph in order to protect confidentiality.

Pulmonary Function Tests
There are minimal risks. Participants may feel tired after the procedures.

Cardiac assessment (ECG and Echocardiogram)
Patients may experience slight discomfort from laying still. These are minimal risk procedures however patients may experience discomfort with removal of the electrodes or a topical reaction to the adhesive on the electrodes.

Cannulation and phlebotomy
Participants may have some discomfort and bruising at the site of cannulation/needle entry. There is a minimal risk of fainting. Infection in the area of the cannulation/needle insertion is rare. To address this risk cannulation and phlebotomy will be conducted by clinicians / phlebotomists.

Pregnancy testing
There is a risk that a pregnancy test will be positive. This may be upsetting to the participant. A clinician will be present the results to the participant and be available for any questions.

Urine collection
There is minimal risk associated with urine collection.

Motor Function Measure 32
Participant self-limiting tests with minimal risk and discomfort. Participants may become fatigued.

Graded Functional Tests
These are patient self-limiting tests with minimal risk and discomfort. Participants may become fatigued.

Grip/Pinch Strength: These are patient self-limiting tests with minimal risk and discomfort. Participants may become fatigued.

Quantitative Muscle Assessment: Participant self-limiting test with minimal risk and discomfort. Participants may become fatigued.

PROMIS-fatigue:

This is a minimal risk procedure.

Remote TEAE reporting
There may be some psychological distress associated with recalling adverse events. A clinician will conduct remote TEAE reporting data collection and be available for any questions the participant may have relating to their responses. Participants local to the study site will have the option of completing TEAE assessments at the NIH.

Post-study follow-up blood draw
The risks associated with phlebotomy (detailed above) apply. A study investigator will contact participants by telephone to remind them of upcoming, scheduled local phlebotomy appointments.

Administration of study drug
As this is a phase 1 study, and the first time S 48168 will be administered to a patient population, we consider administration of study drug to be greater than minimal risk. To date however, data are available for a total of 107 adult healthy male Caucasian participants aged 18- 45 years that participated in Phase 1 clinical studies. Of these participants, 90 were exposed to S 48168 (ARM210) treatment. S 48168 (ARM210) has been safe and well-tolerated in single doses up to 240 mg and in 14 days of multiple dosing up to 240 mg daily (un-blind data), and in single dose of 400 mg and 14 days of multiple dosing of 240 mg daily (blinded data). No serious AEs were reported. There were no clinically significant, dose dependent changes in vital signs, physical examination, laboratory data, ECG and telemetric data.

Risk to the participant from study drug administration will be minimized through 24h inpatient monitoring following administration of the first dose and AE monitoring scheduled throughout the intervention phase as well as 1 day, 7 ± 2 days, and 14 ± 2 days post-intervention. As a precaution, all participants will be provided with a malignant hyperthermia alert bracelet and asked to wear this throughout the study and two-week follow-up.

11.3 Human Subjects Protection

11.3.1 Subject Selection

Subject selection will be equitable considering the rarity of *RYR1*-RM. Pediatric *RYR1*-RM affected individuals are not being considered for this trial since clinical trials of S 48168 (ARM210) have only been completed in adult healthy volunteers to date. All ages within the specified range, races, and both sexes will be accepted. Individuals over 65 years of age will be excluded from participation in this study to avoid potential increased risks due to pre-existing conditions or confounding factors (e.g. from concomitant medication use and age-related muscle weakness (sarcopenia)).

11.3.2 Justification for Exclusion of Children

Children (individuals below 18 years of age) will be excluded from participating in this trial since clinical trials of S 48168 (ARM210) have only been completed in adult healthy volunteers to date.

11.3.3 Justification for Exclusion of Other Vulnerable Subjects

Those unable to provide consent due to cognitive issues will be excluded, due to the requirement to be able to respond to remote TEAE reporting.

11.3.4 Safeguards for Vulnerable Populations and Sensitive Procedures

For women of childbearing age, we will do pregnancy testing to exclude those who are pregnant at the beginning of the study. We will also exclude women who are breastfeeding. Women who are sexually active will require contraception. Acceptable contraception includes hormonal methods (oral contraceptives, the patch, shot/injection, and vaginal ring), implantable devices (implantable rods and intrauterine devices), and permanent birth control methods (sterilization implant and surgical sterilization).

11.4 Anticipated Benefit/Classification of Risk

Anticipated Benefits: This study may offer a temporary direct benefit to participants allocated to receive S 48168 (ARM210), such as improved skeletal muscle function owing to enhanced RyR1-Calstabin1 binding and, in turn, improved excitation-contraction coupling. The short nature of this study may limit these benefits.

Overall Risk and Benefit Ratio: The risks are reasonable in relation to the anticipated benefit in this adult patient population.

11.5 Alternative to Participation

As this study is a clinical trial to determine the effects of S 48168 (ARM210) on patients with *RYR1*-RM, it is necessary for participants in the trial to take S 48168 (ARM210). S 48168 (ARM210) is used under an IND. For patients who do not wish to take S 48168 (ARM210) the alternative is to not participate in the trial. There are no approved therapeutic alternatives.

11.6 Selection of Study Population

11.6.1 Inclusion Criteria

Patients must meet all the following conditions to be eligible for enrollment into the study:

1. Adult males and females, 18 – 65 years of age, inclusive, at screening.

2. Body mass index (BMI) $\geq$ 18.0 and $\leq$ 36.0 kg/m^2 at screening.

3. Confirmed genetic diagnosis of *RYR1*-RM and supporting clinical phenotype with demonstrable deficits on at least one of the baseline study assessments.

4. Evidence of functional deficit (defined by MFM-32 ≤ 80% maximum score) or demonstratable deficits in at least one of the baseline muscle/motor function assessments.

5. Ambulatory. Able to walk ten meters (with or without assistance e.g. with a cane).

6. Must have a CYP2C8 extensive or intermediate metabolizer genotype.

7. Daily use of medicines and dietary supplements need to be approved by the PI and Sponsor, or a drug/supplement-dependent wash-out prior to inclusion.

8. For male subjects: is sterile or agrees to use an appropriate method of contraception, including a condom with spermicide, from study drug administration on the first day of dosing until 5 half-lives plus 90 days (approximately 94 days) after the last dose of study drug administration. No restrictions are required for a vasectomized male subject provided the subject is at least 1-year post–bilateral vasectomy procedure prior to study drug administration on first day of the first dose. A male subject whose vasectomy procedure was performed less than 1 year prior to study drug administration on the first day of dosing must follow the same restrictions as a non-vasectomized male. Appropriate documentation of surgical procedure should be provided.

9. For male subjects: agrees to not donate sperm from study drug administration on the first day of dosing until 5 half-lives plus 90 days (approximately 94 days) after the last dose of study drug.

10. For female subjects of childbearing potential: uses one of the following highly effective birth control methods (from the first dose until 5 half-lives plus 90 days (approximately 94 days):

    - Prescribed hormonal oral contraceptives, vaginal ring, or transdermal patch.
    - Intrauterine device (IUD).
    - Intrauterine hormone-releasing system (IUS).
    - Depot/implantable hormone (e.g., Depo-provera®, Implanon).
    - Bilateral tubal occlusion/ligation.
    - Sexual abstinence:
        - Refraining from heterosexual intercourse during the entire period of risk associated with the study requirements.
        - If the participant decides to become sexually active during the study, then one of the highly effective birth control methods must be used.

11. For female subjects of non-childbearing potential; defined by at least 1 of the following criteria:

- Postmenopausal defined as 12 months of spontaneous amenorrhea and follicle-stimulating hormone (FSH) serum level > 40mIU/mL. Appropriated documentation of FSH levels is required.
- Surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.
- Has a congenital condition resulting in no uterus.

12. Willingness and ability to comply with scheduled visits, drug administration plan, laboratory tests, study restrictions, and study procedures

13. Able to provide written informed consent and understands the study procedures in the informed consent form (ICF).

11.6.2 Exclusion Criteria

The presence of any of the following conditions will exclude a patient from study enrollment:

1. Patient is mentally or legally incapacitated at the time of the screening visit or during the conduct of the study.

2. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dose of study drug.

3. History or presence of hypersensitivity or idiosyncratic reaction to the study drug, related compounds, or inactive ingredients.

4. Positive urine drug or alcohol results at screening.

5. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).

6. Patients with baseline ALT levels three times above the upper limits of normal (ULN) or baseline AST levels five times the ULN (isolated elevations of total bilirubin <2 X ULN with direct bilirubin below the ULN will be included).

7. Patients with severe pulmonary dysfunction at screening (Forced Vital Capacity (FVC) < 50% predicted) or evidence of pulmonary exacerbation. Pulmonary exacerbations refer to an acute worsening of respiratory symptoms that result from a decline in lung function.

8. Patients with a history of a seizure.

9. Subject has a history of cancer (malignancy) Exceptions: (1) Subjects with adequately treated non-melanomatous carcinoma or carcinoma in situ of the cervix may participate in the trial (2) Subjects with other malignancies who have been successfully treated > 10 years prior to the screening where in the judgment of the investigator has revealed no evidence of recurrence from the time of treatment through the time of the screening except those identified at the beginning of the exclusion criterion or (3) Subjects who in the

opinion of the investigator are highly unlikely to sustain a recurrence for the duration of the trial.

10. Patients with uncontrolled diabetes defined as HbA1c > 7% or diabetic neuropathy.

11. Estimated creatinine clearance <40 mL/minute at screening, which may be calculated using the Chronic Kidney Disease Epidemiology Collaborative method (CKD-EPI), due to reduced muscle mass often seen in *RYR1*-RM patients.

12. Patients with a clinically significant abnormality on their ECG other than hypertensive related, or heart failure (ejection fraction <30%) or other clinically significant structural heart disease on echocardiogram.

13. Patients with a history of myocardial infarction in the last five years, or evidence of congestive heart failure.

14. Pregnant and breastfeeding women.

15. Unable to refrain from or anticipates the use of:

    - Any non-approved medicines and/or dietary supplements beginning 14 days prior to the first dose of study drug and throughout the study. Thyroid hormone replacement medication may be permitted if subject has been on same stable dose for the last 3 months prior to the first dose of study drug.

    - Any drugs known to be significant inducers or inhibitors of CYP2C8 enzymes for 28 days prior to the first dose of study drug and throughout the study. Any substrates of breast cancer resistance protein (BCRP).

16. Is currently taking any drug which raises gastric pH, including proton pump inhibitors or H2 antagonists. Antacids may be used if taken at night.

17. Donation of blood or significant blood loss within 56 days prior to the first dose of study drug.

18. Plasma donation within 7 days prior to the first dose of study drug.

19. Participation in clinical trials for other therapeutic investigational drugs simultaneously or within the 4 weeks prior to the first dose of study drug.

20. Ongoing medical condition that is deemed by the Principal Investigator to interfere with the conduct or assessments of the study or safety of the subject.

21. Is an NIH employee who is a subordinate/relative/coworker of a study investigator.

11.6.3 Early Termination of Subjects from the Study

All participants have the right to withdraw from the study at any time.

In addition, subjects may be withdrawn from the study by the PI or designee for the following reasons:

- AEs.
- Subject has a positive urine drug or alcohol result.
- Difficulties in blood collection.
- Pregnancy.
- Disease progression which requires discontinuation of the study intervention.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

The PI, in consultation with the Medical Monitor, may withdraw any subject from the study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue. A subject may be withdrawn by the PI (or designee) or the Sponsor/Medical Monitor if enrollment into the study is inappropriate, the study plan is violated, or for safety reasons.

If withdrawn from the study, participants will be required to return all remaining study drug. A mailing address will be provided to the participant upon withdrawal. If withdrawn, the participant will still need to provide a blood sample locally and have a remote TEAE assessment 7 ± 2 days post-withdrawal from the study. A study investigator will contact participants by telephone to remind them of upcoming, scheduled local phlebotomy appointments. The participant will also need to have a remote TEAE assessment 14 ± 2 days post-withdrawal from the study. Participants local to the study site will have the option of completing AE assessments at the NIH. If a participant is withdrawn for a safety reason(s), more intensive safety monitoring may be undertaken as clinically indicated.

11.7 Study Restrictions

11.7.1 Prohibitions and Concomitant Medications

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/Caffeine: 24 hours before administration of the first and final S 48168 doses continuing through the last PK sample collection for that day (small amounts of caffeine derived from normal foodstuffs e.g., 250 mL/8 oz./1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz. chocolate bar, per day, would not be considered a deviation to this restriction);

- Alcohol: 48 hours before administration of the first and final S 48168 doses continuing through the last PK sample collection for that day;

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 11.6.2. Once the subject has been dosed, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI or designee.

If deviations occur, the PI or designee will decide on a case-by-case basis whether the subject may continue participation in the study and may consult the Sponsor if needed.

All medications taken by subjects during the course of the study will be recorded.

11.7.2 Meals

Water and other fluids (except water provided with each dosing) will be restricted 1 hour prior to and 1 hour after their first and final S 48168 dose administrations but will be allowed ad libitum at all other times.

Subjects will fast overnight for at least 10 hours prior to their first and final S 48168 dose administrations and will continue the fast for at least 4 hours post-dose.

When confined in the NIH CC, meals and snacks will be provided at appropriate times, except when subjects are required to fast.

During confinement, each meal and/or snacks served at the NIH CC will be similar in caloric content and composition and will be taken at approximately the same time for all participants.

11.7.3 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours following S 48168 (ARM210) dosing, except when they are supine or semi-reclined for study procedures.

However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down.

Depending on the NIH CC rules and regulations, subjects may be prohibited from smoking during their confinement or during portions of their confinement.

11.8 Treatments

11.8.1 Treatments Administered

Research with an investigational drug

S 48168 (ARM210) requires an IND, and the FDA approved IND number is: [redacted] (See Appendix # 7). The company manufacturing S 48168 (ARM210) is Laboratoires Servier. Study drug will be shipped by Laboratoires Servier directly to the NIH Pharmacy as therapeutic units. The study sponsor is ARMGO Pharma Inc.

S 48168 (ARM210) will be supplied as 20 mg gastro-resistant tablets.

Study visits will be scheduled such that no more than two participants receive their initial dose in the same week (See Section 12.11.10 of this protocol for details). The first three participants were dosed with 120 mg S 48168 (ARM210) (6 x 20 mg tablets) daily for approximately 28 days (not to exceed 30 days). After DSMB review of the safety, tolerability and PK of the 120 mg dose, the remaining participants were dosed with 200 mg S 48168 (ARM210) (10 x 20 mg tablets) daily for approximately 28 days (not to exceed 30 days). All subsequent participants are planned to be dosed with ≤ 200 mg S 48168 (ARM210) (10 x 20 mg tablets) daily for approximately 28 days (not to exceed 30 days). The tablets are small in size (5 mm diameter).

Study investigators will administer S 48168 (ARM210) during the time the participant is confined to the NIH CC for 24h PK assessments (first and final dose administrations). S 48168 (ARM210) should be administered orally following an overnight fast (at least 10 hours) with approximately 240 mL of water on all PK days. A mouth check will be performed by the qualified designee to ensure that the subjects have swallowed the study drug. The exact clock time of dosing will be recorded using a standardized network clock.

Study investigators will instruct the participant in the proper dosing instructions for home administration when drug supplies are dispensed (Appendix # 8). Study drug (S 48168 [ARM210]) will be provided in tablet form. All participants will be instructed to self-administer the study medication daily with water in the morning. Compliance will be assessed during each phone/e-mail contact. Compliance will be verified at in-person visits for residual pill counts as well as with diary. Adequate compliance will be defined as taking 80% of the study drug. If a participant completely misses a dose (e.g. missed one day of drug), we will have them take the next dose and contact the site.

11.8.2 Method of Assigning Subjects to Treatment

Individuals who have expressed an interest in participating and meet the pre-screening eligibility criteria will be contacted for telephone screening as detailed in Appendix # 2. Each individual will be assigned a unique identification number (baseline number) at this time.

The individuals who complete the study screening assessments at NIH and meet all the eligibility criteria (Appendix # 3) will receive an allocation number. The allocation number will be different from the baseline number. If replacement subjects are used, the replacement subject number will be 100 more than the original (e.g., Subject No. 101 will replace Subject No. 1). Eligible participants will be started on ≤ 200 mg/day dose.

11.8.3 Blinding

This is an open label study.

11.8.4 Interim Analysis (PK)

Interim PK analysis was conducted by Nuvisan (contract vendor) as follows:

First dose group (120 mg/day): Full PK analysis once the first three participants completed dosing for approximately 28 days (not to exceed 30 days). This allowed verification that the observed PK results from these *RYR1*-RM affected individuals agreed with PK results from previous studies in healthy volunteers and that the Cmax limit of 35 ug/mL was not exceeded. At this stage of drug development, a PK value that would not require a dose adjustment would be considered as similar. This would mean 50% lower or 200% higher than that of healthy volunteers.

Based on PK results and safety data from the first dose group, the dose to be administered in subsequent participants was increased to 200 mg/day. This was based on DSMB recommendations and investigator and sponsor's joint decision.

Second dose group (200 mg/day): PK analysis for Cmax once the first three participants have completed dosing for approximately 28 days (not to exceed 30 days). This will allow verification that the Cmax limit of 35 ug/mL was not exceeded. Subsequently, all remaining samples will be shipped to the contract laboratory for analysis at the end of the study, when full PK analysis beyond the Cmax measurement will occur for all of the samples obtained from this group

11.8.5 Stopping Rules

A decision to stop dose administration or terminate the study will be made jointly by the Sponsor, Medical Monitor, Data and Safety Monitoring Board (DSMB), and the PI following the review of all pertinent safety/tolerability data and PK data (if available). However, the DSMB may independently decide to pause, halt, or terminate the study. In addition, the DSMB may independently decide to pause or stop dose administration in an individual.

To stop or temporarily halt dose administration in any subject:

- Participant has a SAE that is possibly or definitely related to drug.
- Participant has a non-serious adverse event that is possibly or definitely related to drug and is severe (on a scale of mild, moderate, or severe) per the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
- Participant has an AE special interest (AESI) that is considered serious as defined by 21 CFR 312.32. AESIs for this study are as follows:

  Large increases in transaminases, Aspartate aminotransferase or Alanine aminotransferase. If the subject's baseline transaminases were within normal limits, then a change of 3X ULN is the criteria. If the subject's baseline transaminases are above the ULN at baseline, then 5X ULN would be the criteria. Baseline elevations in transaminases have been known to occur in some patients with *RYR1*-RM, likely due to muscle injury as a consequence of the disease and normal activity.

  CNS toxicity (tremors/convulsions seen in safety assessment animals) - consider tremors and any symptoms of seizure as the events to monitor for.

Gastric toxicity - severe gastric or epigastric pain or severe vomiting.

Plasma Cmax (S 48168) >35 µg/mL.

Dosing may be temporarily halted in any subject for medically important non-serious AE that is possibly or definitely related to drug and requires medical intervention. Dosing may be halted until the AE resolves and then may be resumed with careful observation for reoccurrence. The PI, IRB, CD, the Sponsor (ARMGO Pharma Inc.), DSMB, or the FDA may pause, halt, or terminate the study at any time following review of any safety concerns.

The study will be terminated if:

- ≥ 2 subjects have a SAE that is possibly, probably, or definitely related to drug.
- ≥ 2 subjects have a medically important non-serious TEAE that is probably or definitely related to drug and is severe (on a scale of mild, moderate, or severe) per the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
- ≥ 3 subjects have a medically important non-serious TEAE that is possibly related to drug and is severe (on a scale of mild, moderate, or severe) per the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

12 STUDY ACTIVITIES AND PROCEDURES

The Study Events Flow Chart (Section 7) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. **All procedures in this protocol are for research purposes.** Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to individual subject safety. If required for all subjects, such procedures will be added to the protocol via amendment.

For this study, the blood collection for S 48168 (ARM210) is the critical parameter and needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible but can be performed prior or after the prescribed/scheduled time.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

12.1 Recruitment

Although *RYR1*-RM constitute a rare disease, investigators on the protocol work closely with this patient population and with advocacy groups such as the Muscular Dystrophy Association, the RYR-1 Foundation and Cure CMD. The *RYR1*-RM population is highly motivated and there is significant interest surrounding S48168 (ARM210) as a potential therapy. As such, we expect to recruit approximately 8-20 participants within six to twelve months of opening the study with an accrual ceiling of up to 50 to allow for dropouts.

We will implement a strategy that promotes equitable subject recruitment as follows:

- IRB-approved letters providing an overview of the study will be emailed to staff at neuromuscular disease clinics (Appendix # 10). In particular, clinics that are known to have previously sent tissue for RyR1-Calstabin1 binding assay or referred patients to NCT02362425. This will be provided with the abovementioned study advertisement for distribution to patients at the clinician's discretion.
- An IRB-approved letter and study advertisement will be provided to patient advocacy groups, such as the RYR-1 Foundation, for circulation (e.g. via email or posting online). The advertisement includes contact details for the study coordinator as well as key inclusion and exclusion criteria (Appendix # 9).

12.2 Screening

Pre-screening

Interested participants will contact the study team directly or may be referred by their physicians. Pre-screening of individuals will be conducted by the study coordinator who will use prior medical and research records and biospecimen data in accordance with the revised

common rule and/or an IRB-approved script (Appendix # 2). During pre-screening, interested individuals may be asked pre-specified questions pertaining to the inclusion and exclusion criteria, if needed. The study coordinator will then contact the potentially eligible individuals to initiate the telephone consent process as detailed below and in Section 14.1.3.

Formal screening procedures

Formal screening will be conducted in two parts.

Part 1: Telephone consent for blood draw and tests.

Participants will be required to have a local blood draw for CYP2C8, HIV and hepatitis testing (inclusion criteria) prior to attending the NIH. A telephone consent (Appendix # 19) will be used to cover this procedure. A study investigator will contact participants by telephone to remind them of upcoming, scheduled local phlebotomy appointments.

CYP2C8 genotyping will be performed at a contract laboratory. Individuals that are deemed to be rare (1% of the population) poor CYP2C8 metabolizers will be excluded. To assess eligibility criteria, informed consent will also be obtained to access additional medical and research records, if applicable.

Part 1 continued: Telephone consent for blood draw and tests (re-enrolled subjects)

Participants who are re-enrolling from the low dose cohort to the high dose, will not require re-assessment of CYP2C8 metabolizer genotype since this is a non-modifiable factor. Thus, re-enrolled subjects will not have to complete a separate telephone consent and instead will be able to provide samples for HIV and hepatitis screening at their first study visit under the study consent form (Appendix #20).

Part 2: In-person consent (for final screening procedures and for the trial).

Clinical Laboratory Assessments, Echocardiogram, ECGs, PFTs, general medical history, and physical exams will be done at the first study visit. Part 2 procedures will be completed within 28 days of the first dose administration.

The second consent form (Appendix # 20) will be sent to the participant prior to the NIH study visit to give the participant sufficient time to read the information. This consent form will cover the remaining screening procedures (e.g. PFTS, ECG, echocardiogram) as well as all other study-related procedures.

Prior to the first dose of study drug, several tests and procedures will be performed to assess and mitigate the risk to participants with pre-existing medical conditions. Medical history and demographic data, including name, age, body weight (kg), height (cm), BMI (kg/m^2), and tobacco use (including number of cigarettes smoked per day) will be reported. Each subject will also have a physical examination, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), 12-lead ECG, echocardiogram, PFTs, and the clinical laboratory tests of hematological, hepatic and renal function. Additional research blood

samples (e.g. serum, plasma, DNA, and PAX tubes) will also be obtained. These samples are all noted in Section 12.11.6 and Table 1.

Part 2 continued: In-person consent (process for re-enrolled subjects).

Individuals interested in re-enrolling to receive the high dose will be reconsented to the most recent study consent and must meet all inclusion and exlusion crtieria prior to dosing. For re-enrolled participants, an interim medical history will be performed and a subset of research blood samples obtained (e.g., plasma only).

12.3 CYP2C8 Genotyping

A blood sample (1 × 4 mL polypropylene K_2EDTA Vacutainers® tubes) for CYP2C8 genotyping will be collected from all subjects as outlined in the Study Events Flow Chart (Section 7), to confirm subject eligibility for the study. The blood sample for CYP2C8 analysis will be collected locally to the participant.

These samples will only be used for CYP2C8 genotyping and will be discarded after subject eligibility has been confirmed.

Each sample must be labeled with a unique identifier that is present on the sample container. Good Laboratory Practice (GLP) requires a chain-of-custody that is traceable to the sample donor. Labels must be legible and waterproof.

On the same day as collection, samples will be packaged and shipped at ambient temperature (fresh sample) or on dry ice (stored sample), as per the clinical site's standard operating procedures, to the appropriate laboratory (listed in Section 3) for analysis.

12.4 Medical History

Study physicians or nurses will obtain medical history information.

12.5 Quality of Life Assessment

Participants will complete a PROMIS-fatigue questionnaire at each study visit following screening (Appendix # 11).

12.6 Review of Inclusion/Exclusion Criteria

For each study visit following screening, the study staff will review the inclusion and exclusion criteria with each participant to affirm that the inclusion and exclusion criteria have not been violated since the last study visit.

12.7 Concomitant Medications

Use of concomitant medications will be documented throughout the study at the time of each study visit including the follow-up visit and at the time of each phone/e-mail contact during the study.

12.8 Videotaping and/or Photography

Videotaping or photography will be performed during portions of the physical examination to accurately document the condition. When possible, the patient's face and other identifying marks will not be included in the recording or photograph in order to protect confidentiality.

12.9 Motor Function Measure 32 (MFM)

The MFM is a generic scale which provides a measurement of the effects of muscle weakness in neuromuscular diseases (NMD) (Appendix # 14). Assessments are based on posture and movements of the whole body. It is applicable to both ambulant and non-ambulant patients with a wide range of disease severity. The patient is asked to roll, sit, lift head from prone and supine position, get up from a lying position, prop on arms, kneel, crawl, stand and step. This test will be combined with timed tests (floor to stand, ascend/descend 4 steps). Time to complete both tests: approximately 60 minutes.

12.10 Safety Assessments

Safety and tolerability of S 48168 (ARM210) will be determined by monitoring Adverse Events (AEs) over approximately 28 days (not to exceed 30 days) of treatment via physical examinations, electrocardiograms (ECGs), vital signs, and laboratory safety tests. A reference dataset of AEs/SAEs obtained from a natural history study of *RYR1*-RM will also be available to assist in interpretation of safety events. Per FDA requirements for a drug with a novel mechanism that has not been evaluated in patients, the Columbia-Suicide Severity Rating Scale (C-SSRS) (Appendix # 15) will be administered pre- and post-intervention. The frequency and severity of AEs will be compared between treatment and historical controls including a previously conducted natural history study at the NIH.

The aggregate review of AEs, discontinuations and other safety findings from diaries and AE monitoring, will determine participant tolerability. A participant will be considered to have tolerated a dose if the participant experiences no clinically significant drug-related AE or laboratory abnormality. Conversely, a participant will not be considered to have tolerated the dose if he/she experiences a clinically significant drug-related AE or laboratory abnormality during the study drug administration or post-administration follow-up period. Clinically meaningful changes in vital signs (heart rate, blood pressure, and breathing rate) and cardiac function tests (ECGs and echocardiography) will be assessed by the medical monitor in conjunction with investigators. Further interpretation of such tests by a specialist (e.g. cardiologist) may be requested if deemed necessary by the medical monitor and PI.

S 48168 (ARM210) has been safe and well tolerated to date. However, in normal healthy volunteers, there is not likely to be an effect on muscle function. In patients with *RYR1*-RM,

even in this short study, there may be improvement in muscle function and strength with approximately 28 days (not to exceed 30 days) of dosing with S 48168 (ARM210). Although there are no mechanistic reasons to assume that removal of the drug after the proposed dosing period would have any consequences other than a return to baseline function, post-dose monitoring has been included in the study. These measures include observation and examination after 24 hours off drug, as well as remote TEAE monitoring and a blood draw for safety labs on day 35 ± 2 days, approximately one week off drug and a remote TEAE assessment on day 42 ± 2 days, approximately two weeks off drug. A study investigator will contact participants to remind them of upcoming, scheduled local phlebotomy appointments. Participants local to the study site will have the option of completing AE assessments and safety laboratory tests at the NIH.

12.10.1.1 Physical Examination

A full physical examination will be performed as outlined in the Study Events Flow Chart (Section 7). Symptom-driven physical examinations may be performed at other times, if deemed necessary by the PI or designee.

Height, weight, and BMI will be obtained by trained staff (including study investigators, nurses, nurse practitioners, and physicians). Study physicians or nurse practitioners will perform a physical examination including the evaluation of cranial nerves, reflexes, sensation, strength, gait, movement, motor function and coordination.

12.10.1.2 Pulmonary Function Tests

Each participant will perform pulmonary function testing (PFTs) to assess vital capacity (VC) at screening. To measure VC the participant will be asked to take the deepest breath they can, and then exhale into a flow sensor. During the test, soft nose clips may be used to prevent air escaping through the nose (patients will use their own flow sensors, so filters will not be needed). Measures to be obtained include VC (both forced and slow) and forced expiratory volume at 1 second (FEV_1).

12.10.1.3 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate, will be measured as outlined in the Study Events Flow Chart (Section 7). Additional vital signs may be taken at any other times, if deemed necessary.

Blood pressure and heart rate measurements will be performed with subjects in a seated position, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g. nausea, dizziness) or if deemed necessary by the PI or designee.

Blood pressure and heart rate will be measured within 24 hours prior to first and final S 48168 dose administrations.

12.10.2Cardiac Monitoring

Cardiac evaluations will be performed in an effort to identify cardiac conditions or abnormalities which may preclude the participant from being able to participate in the study. It will also monitor them for any adverse reactions to the investigational drug, although cardiac specific side effects are not anticipated. These assessments will include ECGs and echocardiograms.

ECG: Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 7). Additional ECGs may be taken at any other times, if deemed necessary by the PI or designee. ECGs will be performed with subjects in a supine position. ECGs take 10 minutes or less to perform and will be reviewed and interpreted by a cardiologist. ECGs will be measured within 24 hours prior to the first and final S 48168 dose administrations.

Echocardiogram: Screening echocardiography will be performed as outlined in the Study Events Flow Chart. Particular focus will be given to overall ventricular systolic function (ejection fraction) and major structural heart and valve abnormalities. Echocardiogram is expected to be performed in 30-45 minutes.

Abnormal cardiac test results may be followed by cardiology consultation and/or additional cardiac testing such as event monitoring or cardiac MRI, if clinically indicated.

12.10.3 Cannulation and Phlebotomy

Cannulation will be performed by the phlebotomy service or nurses at the NIH CC. Clinicians will obtain blood samples for clinical laboratory tests as well as PK throughout the study.

Bloods for PK assessments will be drawn at baseline (Day 1, 24h PK; drug naïve participants only), at the second in-person study visit (Day 28 – not to exceed Day 30, 24h PK). Whole blood will be processed, and the plasma fraction stored for PK analyses.

Although there is not a specific hypothesis for the comparison of the PK of *RYR1*-RM patients with that of normal healthy volunteers, the expectation is that the difference should not be clinically meaningful. At this stage of the development of S 48168 (ARM210) the program bounds for exposure are not clear until efficacy is established. However, an increase of roughly two-fold in exposure or a decrease of approximately 50% in exposure would be considered clinically meaningful. Given the very low variability in Phase 1 to date for S 48168 (ARM210) (coefficient of variability- %CV ~15%) it is likely that 8 participants would be sufficient for this comparison since six subjects were sufficient to provide 80% power in a parallel design comparison in healthy volunteers (Study CL1-210-01 described in the IB 2020).

12.10.4 Temperature Check

Participants will be instructed on how to take their temperature using a thermometer for the follow-up assessment at approximately 7 days post-drug withdrawal. Participants will record

their temperature the morning of their remote TEAE assessment and report the result to the study team. Participants local to the study site will have the option of completing their temperature check at the NIH.

12.10.5 The Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a suicidal ideation and behavior assessment instrument. The FDA recommends assessment of suicidal ideation and behavior for all clinical trials where the drug has central nervous system activity per Guidance for Industry Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials. Although S 48168 (ARM210) at this dose will have minimal brain penetration, the requirement extends to novel mechanisms that have not previously been evaluated in patients.

The C-SSRS is a detailed interview, but the full interview is needed only if the initial screening questions about suicidal ideation and behavior are positive. Although the screening questions should be completed at baseline and at every visit for every patient, they are not by themselves burdensome, typically taking only 1 to 2 minutes for patients who have no positive findings. Even for a patient with multiple positive findings, the full interview typically takes less than 10 minutes. Investigators administering the C-SSRS will be required to have completed training provided by The Columbia Lighthouse Project: http://cssrs.columbia.edu/training/training-research-setting/.

Management of participants positive for suicidal ideation and behavior:

- Result of C-SSRS is positive for suicidal ideation and behavior
- Principal Investigator is informed of the positive C-SSRS
- NIH Psychiatry Service is consulted
- Participant is managed in accordance with standard clinical care and suicide risk assessment. This may include social work consultation, referral to local psychiatric care, or psychiatric admission when clinically indicated.

12.10.6 Clinical Laboratory Tests

All tests listed below will be performed as per Study Events Flow Chart (Section 7). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or designee.

Hematology

- Hemoglobin
- Hematocrit
- Total and differential leukocyte count
- Red blood cell count
- Platelet count
- HbA1C (screening only)

Serum Chemistry*

- Blood Urea Nitrogen
- Bilirubin (total and direct)
- Alkaline phosphatase
- Aspartate aminotransferase
- Alanine aminotransferase
- Gamma-glutamyl transferase
- Creatine Kinase
- Albumin
- Sodium
- Potassium
- Chloride
- Glucose (fasting)
- Creatinine**
- Cystatin C

Urinalysis

- pH
- Specific gravity
- Protein***
- Glucose
- Ketones
- Bilirubin
- Blood***
- Nitrite***
- Urobilinogen
- Leukocyte esterase***

Additional Tests

- HIV test
- HBsAg
- HCV
- Urine drug screen
  - Opiates
  - Amphetamines
  - Cocaine
  - Cannabinoids
- Urine alcohol screen
- Serum pregnancy test****
  (for females only)
- FSH (for postmenopausal females at screening only)

* Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample is taken. Participants will be encouraged to drink water as usual during the fast.

** At screening, creatinine clearance will be calculated using the CKD-EPI formula.

*** If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

**** Pregnancy tests must be confirmed as negative prior to administering the first dose. Contraception will be required for women of childbearing potential who are sexually active. If a pregnancy test is positive, the study participant will be notified of the results. Women who become pregnant during the study will be withdrawn and followed through their pregnancy and birth.

12.10.7 Adverse Events

12.10.7.1 Adverse Event Definition and Grading

Adverse events (as defined per 21 CFR 312.32) will be tracked and submitted to the IRB as outlined NIH Policy 801.

All adverse events will be reviewed by a safety monitor and graded in accordance with CTCAE version 5 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm)

12.10.7.2 Expected Adverse Events

Previous adverse events include stomach pain, diarrhea, vomiting, constipation, nausea, dry mouth, loss of taste, catheter site pain, fatigue, nose and throat pain, muscle stiffness, lower back pain, dizziness, headache, local numbness, and excessive sweating. A complete list of previous adverse events, which may be expected in this trial, are provided in the Investigator's Brochure.

12.10.7.3 Monitoring

Data and safety monitoring for this study will be conducted in accordance with the "NINDS Guidelines for Monitoring in Clinical Trials". Safety will be monitored on a weekly basis during the intervention phase of the study either at study visits or via remote TEAE assessments. Moreover, safety will be assessed approximately one-week post-intervention by a remote TEAE assessment and safety labs. A study investigator will contact participants by telephone to remind them of upcoming, scheduled local phlebotomy appointments. An additional remote TEAE assessment will also be made approximately two-weeks post-intervention. For remote TEAE assessments, if study investigators are unable to make contact with the participant on the first attempt, at least two further attempts will be made. Participants local to the study site will have the option of completing TEAE assessments and safety laboratory tests at the NIH.

A DSMB will be established and provide independent medical oversight for this study. The DSMB will act in an advisory capacity to the study Principal Investigator (PI) and the NINDS Clinical Director (CD) and Medical Monitor to monitor participant safety, data quality and evaluate the progress of the study. This will also include deciding if stopping rules should be triggered. To ensure oversight, the DSMB may independently pause, halt, or terminate the study. The DSMB may also pause or stop dose administration in an individual. DSMB activities will be governed as detailed in the DSMB Charter (Appendix # 16). There will be four DSMB members with expertise in neurology, clinical trials, clinical pharmacology, and biostatistics. The DSMB will meet monthly after the first subject is dosed and acutely if a significant safety concern is raised by the PI or medical monitor. Additional meetings may be scheduled when necessary for adequate monitoring. Any member of the DSMB may request a meeting if they believe data provided within interim reports warrant an additional meeting.

Subjects will be monitored throughout the study and during confinement for adverse reactions to the study drug and/or procedures. Prior to release from confinement, subjects will be asked how they are feeling. At each subsequent visit, subjects will be queried with an open-ended

question such as: 'How have you been feeling since your visit or last telephone and/or email contact?'

Participants will be contacted by a study investigator by telephone and/or e-mail four times during the study for AE assessments. The investigator will ask a series of open-ended and focused questions relating to safety and tolerability of S 48168 (ARM210). On rare occasions, additional participant contact may be made by telephone or secure email to ensure comprehensive monitoring. Examples include contacting participants to inform them of important new safety-related information, changes in key study personnel, and clarification of medical information.

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI or designee and treated and/or followed up until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI or designee.

Treatment of SAEs will be performed by a licensed independent provider, either at NIH CC or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up).

12.10.7.4 Reporting

All AEs that occurred during this clinical study will be recorded on the AE CRF using a recognized medical term or diagnosis that accurately reflects the event. For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The PI or designee will review each event and assess its relationship to drug treatment (likely, probably, possibly, unlikely or unrelated). Each sign or symptom reported will be graded in accordance with CTCAE (version 5), and the date of onset, time of onset, and outcome of each event will be noted. To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular AE is "listed" (i.e. known side effect of the drug or not). Medical judgment should be used to determine the causal relationship of adverse event, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Serious AEs that are considered related to S48168 will be considered a suspected unexpected serious adverse reaction (SUSAR). Assessment of causal relationship must also be recorded on the CRF. If an AE has not resolved at the end of the study reporting period it will be documented as ongoing on the corresponding CRF.

Prompt reporting of adverse events is the responsibility of the PI or designee. The reporting period for AEs is the period immediately following each study administration through 28 days after each dose. AEs must be followed until resolution or stabilization, the subject is lost to follow-up, even if this extends beyond the 28-day post-dosing reporting period (for the purpose of obtaining a stop date for the event).

If an AE has not resolved at the end of the study reporting period it will be documented as ongoing on the corresponding CRF.

Each AE will be reviewed with the medical monitor, [redacted] and discussed with the PI. AEs will be reported to the DSMB, regardless of PI classification for review.

The AE severity definitions of CTCAE version 5 will be used for rating the severity of all AEs (Grade 1-5).

12.10.7.5 Serious Adverse Event

If any AEs are serious, as defined by the FDA Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All SAEs will be reported to the Sponsor per the medical monitoring plan (Appendix # 17) and adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012 (FDA 2012). Reporting of SAEs to the IRB will be consistent with NIH Policy 801.

A SAE is any AE or suspected adverse reaction that in the view of either the PI (or designee) or Sponsor, results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the PI (or designee) or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the IB or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

12.10.7.6 Reporting of Unanticipated Problems, Adverse Events, and Protocol Deviations

The Principal Investigator is responsible for detecting, documenting, and reporting unanticipated problems, AEs, including SAEs, and deviations in accordance with NIH policy, IRB requirements, and federal regulations. Relatedness to the research of all serious adverse events will be determined by the PI in consultation with the medical monitor.

Reporting of unanticipated problems, adverse events, and protocol deviations will be reported to the IRB as detailed in NIH Policy 801.

Within 24 hours of identifying a SAE, regardless of the presumed relationship to the study product, the PI must complete the serious adverse event (SAE) case report form and email it to [redacted] as ARMGO representative according to the requirements of 21 CFR 312.64(b) and as agreed upon with the sponsor.

The PI will record nonserious AEs and report them to the Sponsor as agreed upon in the Medical Monitoring Plan (Appendix # 17). All expedited AE reports will be processed by ARMGO with Celerion.

12.10.7.7 AE's of Special Interest

An AE of Special Interest (serious or nonserious) is one of scientific and medical concern specific to the compound or program, [redacted]

AEs of special interest in this trial include:

- Large increases in transaminases, Aspartate aminotransferase or Alanine aminotransferase. If the subject's baseline transaminases were within normal limits, then a change of 3X ULN is the criteria. If the subject's baseline transaminases are above the ULN at baseline, then 5X ULN would be the criteria. Baseline elevations in transaminases have been known to occur in some patients with *RYR1*-RM, likely due to muscle injury as a consequence of the disease and normal activity.

- CNS toxicity (tremors/convulsions seen in safety assessment animals) - consider tremors and any symptoms of seizure as the events to monitor for.

- Gastric toxicity - severe gastric or epigastric pain or severe vomiting.

- Plasma Cmax (S 48168) >35 µg/mL.

12.10.7.8 End of Participation

Participants will remain under the care of their local clinicians and/or primary neurologists while in this study. Participants will be informed of any clinically relevant findings identified during the study via secure e-mail. Participants will also be provided with a letter to give to their primary care provider detailing such findings. Participation in this study will be considered to have ended once the participant has completed the Day 42 post-intervention TEAE assessment (exceptions to this may be made on a case-by-case basis e.g. if an individual has an ongoing AE/SAE at Day 42).

12.10.8 Pharmacokinetic Assessments

12.10.9 Blood Sampling and Processing

For all subjects, blood samples for the determination of S 48168 (ARM210) will be collected into polypropylene heparinized tubes at scheduled time points as delineated in the Study Events Flow Chart (Section 7). All attempts will be made to collect the blood samples at, or within ± 15 minutes of the scheduled time point. Actual sample times will be recorded.

Within 30 minutes from collection, PK blood samples will be centrifuged at approximately 2000 g for 10 minutes, at approximately 4°C.

After centrifugation, plasma will be transferred into aliquots (polypropylene tubes) containing approximately 0.3 mL/tube. The plasma aliquots will be frozen at -80 ± 10°C within 30 minutes maximum from the end of centrifugation. Samples will be stored at this temperature until shipped to the bioanalytical laboratory.

12.10.10 Interim PK Analysis

Interim PK analysis was conducted by the contract vendor (Nuvisan) as follows:

Full PK once the first dose group (120 mg/day) have completed dosing for approximately 28 days (not to exceed 30 days) (Section 13.1).

Interim analysis of Cmax once the first 3 participants in the second dose group (≤ 200 mg/day) have completed dosing for approximately 28 days (not to exceed 30 days).

Provided that the Cmax limit of 35 ug/mL is not exceeded in the above samples, all remaining PK analyses will be conducted upon study completion.

12.10.11 Analytical Method

Samples will be assayed for plasma S 48168 (ARM210) using a validated HPLC-MS-MS bioanalytical method. The subjects to include in the analysis are specified in Section 13.2.2.

This analysis will be conducted by the contract vendor, Nuvisan. Since this is the first study of S 48168 (ARM210) in the *RYR1*-RM population, and profiling of S 48168 (ARM210) metabolism is currently ongoing in healthy volunteers, the remaining portions of plasma samples collected for PK analysis may be preserved for S 48168 (ARM210) metabolite analysis.

12.11 Blood Volume Drawn for Study Assessments

Table 1: Approximate Blood Volume During the Study (drug naïve participants)

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, serology) FSH (for postmenopausal female subjects only), and serum pregnancy (for female subjects only)	1	12.5	12.5
Screening CYP2C8 genotyping	1	4	4
On-study (including follow-up) hematology, serum chemistry, and serum pregnancy (as scheduled for female subjects only)	3	12.5	37.5
Blood for S 48168 (ARM210)	16	2	32
Baseline blood (future research use)	1	50.0	50.0
Post-intervention blood (future research use)	1	10.0	10.0
		Total Blood Volume (mL)→	146.0**

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

** If additional safety or PK analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained (up to a maximum of 50 mL).

Table 2: Approximate Blood Volume During the Study (re-enrolled participants)

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, serology) FSH (for postmenopausal female subjects only), and serum pregnancy (for female subjects only)	1	12.5	12.5
Screening CYP2C8 genotyping	0	0	0
On-study (including follow-up) hematology, serum chemistry, and serum pregnancy (as scheduled for female subjects only)	3	12.5	37.5
Blood for S 48168 (ARM210)	8	2	16
Blood for future research use	2	10.0	20.0
		Total Blood Volume (mL)→	86.0**

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

** If additional safety or PK analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained (up to a maximum of 50 mL).

13 DATA ANALYSIS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCP.

13.1 Pharmacokinetic Parameters

The following PK parameters for plasma S 48168 (ARM210) will be calculated, as appropriate:

Day 1

AUC0-24:	The area under the concentration-time curve, from time 0 to the 24 hours post dose, as calculated by the linear trapezoidal method.
AUC0-t:	The area under the concentration-time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.
AUC0-inf:	The area under the concentration-time curve from time 0 extrapolated to infinity. AUC0-inf is calculated as the sum of AUC0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.
AUC%extrap:	Percent of AUC0-inf extrapolated, represented as (1 - AUC0-t/AUC0-inf)*100.
Cmax:	Maximum observed concentration.
Tmax:	Time to reach Cmax. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.
Kel:	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g., three or more non-zero plasma concentrations).
t½:	Apparent first-order terminal elimination half-life will be calculated as 0.693/Kel.
Tlag:	Lag time – the time delay between drug administration and the onset of absorption; where onset of absorption can be defined as: the time point prior to the first observed/measured non-zero plasma concentration.

Day 28 (not to exceed Day 30)

AUCtau	The area under the concentration-time curve during a dosing interval (tau) at steady state.
Cmax:	Maximum observed concentration.
Tmax:	Time to reach Cmax. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.
Cmin	Minimum observed concentration.
Tmin	Time to reach Cmin.
RAAUC	The ratio of accumulation for AUC calculated as the ratio of the AUCtau Day 28 (not to exceed Day 30)/AUC0-24 Day 1.
RACmax	The ratio of accumulation for Cmax calculated as the ratio of the Cmax Day 28 (not to exceed Day 30)/Cmax Day 1.

Concentration observed at the end of the dosing interval on Day 13 Ctrough (associated with Day 14 pre-dose) will be ascertained for the first six subjects. Additional parameters may be calculated as appropriate.

No value for Kel, AUC0-inf, AUC%extrap, or t½ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile.

No PK parameters will be calculated for subjects with 2 or fewer consecutive time points with detectable concentrations.

Individual and mean plasma concentration time curves (both linear and log-linear) will be included in the final report.

13.2 Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP) (Appendix # 18). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

13.2.1 Determination of Sample Size

The sample size (n= 8) was determined based on the number of *RYR1*-RM affected individuals expected to have loss of RyR1-calstabin1 binding. This sample size is expected to be sufficient for analysis of the primary endpoint (safety and tolerability). The accrual ceiling for this study is n = 50 subjects to allow for dropout.

13.2.2 Subjects to Analyze

Safety Population: All subjects who received at least one dose of the study drug will be included in the safety evaluations.

PK Population: All subjects who comply sufficiently with the protocol (see Section 11.8.1) and display an evaluable PK profile (e.g., exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the statistical analyses.

Pharmacodynamic/Target Engagement: All subjects who complete the study will be included in the pharmacodynamics/target engagement analysis.

Muscle/Motor Function (Grade Functional Tests and MFM32): All subjects who complete the study will be included in the muscle/motor function assessments.

Quality of Life: All subjects who complete the study will be included in the quality of life assessments.

13.2.3 Descriptive Statistics

Values will be calculated for the plasma concentrations and the PK parameters listed in Section 13.1 using appropriate summary statistics to be fully outlined in the SAP.

PK data from [redacted] will be utilized for comparisons between healthy subjects and *RYR1*-RM patients.

13.3 Safety Evaluation

All safety data will be populated in the individual CRFs. All safety data will be listed by subjects.

Dosing dates and times will be listed by subject in their diary when not confined to the NIH CC.

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion and summarized by cohort and treatment for the number of subjects reporting the Treatment Emergent Adverse Events (TEAE) and the number of TEAEs reported. A by-subject AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

Safety data including ECGs, vital signs assessments, clinical laboratory evaluations, will be summarized by treatment and point of time of collection.

Descriptive statistics using appropriate summary statistics will be calculated for quantitative safety data as well as for the difference to baseline, when appropriate.

Concomitant medications will be listed by subject and coded using the most current version of WHO drug dictionary available at Celerion. Medical history will be listed by subject.

13.4 Pharmacodynamic/Target Engagement

% RyR1-Calstabin1 binding of normal control muscle will be listed by subject and compared between pre- and post-treatment biopsies. If there is sufficient remaining tissue, % RyR1-mediated Ca^{2+} leak may be determined, using muscle membrane preparations, and listed by subject and compared between pre- and post-treatment biopsies.

13.5 Muscle/Motor Function

A physical therapist will administer these study procedures.

Graded functional tests will be completed by participants at each in-person study visit. These will include 10-meter walk test, supine to stand, ascend 4 stairs, descend 4 stairs. The recorded time will be listed by subject and summarized descriptively for each test to compare between pre- and post-treatment results.

Day 1 versus Day 28 (not to exceed Day 30) motor function will be documented and listed for each subject quantitatively (% of maximum score) using the scoring of the MFM32 for the following: total score, domain 1 (standing and transfers), domain 2 (axial and proximal motor function), and domain 3 (distal motor function). The resulting scores will be listed by subject and summarized descriptively to compare between pre- and post-treatments results.

Grip and pinch strength: Participants will be seated comfortably with his/her elbow flexed to 90 degrees, with the forearm and wrist in neutral position. Participants will then be asked to squeeze the dynamometer and pinch the gauge. This process will be repeated three times with the best effort used for final analyses.

Quantitative muscle strength assessment: Participants will undergo assessment of muscle strength in standardized seated and supine positions. Muscle strength testing will focus on each participant's dominant side for shoulder abductors, elbow flexors/extensors, hip flexors and knee extensors/flexors. Participants will be asked to exert force against an elastic strap-based force transducer. A physical therapist will administer this study procedure and the best of multiple efforts used for final analyses.

13.6 Quality of Life Assessment

The PROMIS-fatigue subscale (questionnaire) will be completed during each study visit. Results (t-scores) for each individual (Day 1 and Day 28 – not to exceed Day 30) will be summarized descriptively.

14 STUDY ADMINISTRATION

14.1 Ethics

14.1.1 Institutional Review Board

This protocol will be reviewed by the NIH Intramural Institutional Review Board, and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The IRB is compliant to International Council for Harmonisation (ICH) guidelines.

14.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

14.1.3 Subject Information and Consent

Two consent forms (Appendix # 19 and Appendix # 20) will be used in this study (1) telephone consent form that will cover a blood draw for CYP2C8 genotyping and serology (inclusion criteria), and informed consent to obtain prior research data and PII for participants in NCT02362425 and (2) in-person consent form that will cover all screening procedures that will be conducted at the NIH Clinical Center. The in-person consent form will also cover all additional procedures associated with the study.

Telephone (screening) consent: Only adults (greater than 18 years of age) are being considered for this study. Participants will be mailed a telephone consent form for completion during a scheduled telephone appointment with an investigator authorized to obtain consent. A pre-paid return label will be included so the participant can return the signed form.

In-person consent: this consent form will be completed upon arrival of each participant at the NIH Clinical Center.

All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review both consent forms and ask questions regarding this study prior to signing. The investigator obtaining consent will document the consent process in the participant's medical record. A copy of the completed signed screening and, if applicable, study consent forms will be provided to the participant.

For individuals who are not fluent in English, both blood draw and study consent documents will be translated to the individual's native language with an interpreter present throughout the consenting process.

The consent forms contain all required elements.

14.2 Termination of the Study

NIH reserves the right to terminate the study in the interest of subject welfare.

Sponsor reserves the right to suspend or terminate the study at any time.

Termination of the Study shall be governed by Section 11.8.5 [redacted]

14.3 Management of Data and Samples

14.3.1 Storage

Biological samples obtained during this study will be appropriately stored in a locked freezer at -20 ± 10°C or -80 ± 10°C located in the laboratory of the NINDS [redacted] or NINR [redacted]. Although the majority of biological samples will be shipped to contract laboratories for analyses, muscle biopsies, whole blood and blood products (serum/plasma) may be retained at the aforementioned locations for future use, if permitted by the participant as per their consent documentation. Contract laboratories will be instructed to dispose of samples once all analyses have been completed. Data obtained during this study will be stored in the Celerion's EDC system, with full access granted to the NIH Investigators. Only listed study investigators will have the permissions required to access data. Paperwork relating to this study will be kept in a locked cabinet in the office of the NINDS [redacted]). Loss of samples and/or data will be reported to the IRB.

14.3.2 Data and Sample Sharing Plan

This protocol will not generate large-scale human or non-human genomic data, as defined by the NIH Genomic Data Sharing Policy, and is therefore not subject to this policy. Biological samples and data will not be submitted to a repository. There will be controlled access to study data (i.e. only listed study investigators will have access via a secure system).

PD analyses will be conducted on a fee-for-service basis.. For S 48168 (ARM210) PK analyses, whole blood and blood product samples (serum/plasma) will be shipped to Nuvisan Pharma Services, Neu-Ulm, Germany. PK analyses will be conducted on a fee-for service basis. Coded data will be shared with ARMGO Pharma Inc.

Data and samples may also be shared with collaborating laboratories at NIH or outside of NIH if consent for sharing was obtained.

Samples and data will be stripped of identifiers and may be coded ("de-identified") or unlinked from an identifying code ("anonymized"). When coded data is shared, the key to the code will not be provided to collaborators but will remain at NIH. Data and samples may be shared with investigators and institutions with a Federal Wide Assurance (FWA) or operating under the

Declaration of Helsinki (DoH) and reported at the time of continuing review. Sharing with investigators without an FWA or not operating under the DoH will be submitted for prospective IRB approval.

Required approvals from the collaborating institution will be obtained and materials will be shipped in accordance with NIH and federal regulations.

14.4 Data Collection

Electronic CRFs will be supplied by Celerion. The investigators' authorized site personnel must enter the information required by the protocol on the CRF, which will be housed within Celerion's Electronic Data Capture (EDC) system. A study monitor will visit the site in accordance with the clinical monitoring plan (Appendix # 21) and review the CRF data against the source data (e.g. Rehabilitation Medicine Department paper CRF) for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel in accordance with GCP. When a data discrepancy warrants correction, the correction will be made by authorized site personnel.

CRFs are printed off directly from the database. Each CRF is reviewed and signed by the PI.

14.5 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion relevant to the quality of this study. Designated personnel of Celerion will be responsible for implementing and maintaining quality assurance (QA) and quality control systems to ensure that the study is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and GLP requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study. A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

The Clinical Study Report will be audited by the QA department (Sponsor's CRO) and the QA audit certificate will be included in the study report.

All clinical data will be entered by the site or uploaded into the EDC electronically. Edit checks are built into the EDC. Clinical Data Management (CDM) will resolve all queries with the site via the EDC.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® or comparable statistical program to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to database lock.

14.6 Direct Access to Source Data/Documents

NIH/Celerion will ensure that the Sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). In the event that other study-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained by the site (i.e. PI may need to request previous medical records or transfer records). Current medical records must be available. For eCRFs all data must be derived from source documents.

14.7 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of S 48168 (ARM210) tablets to allow completion of this study. The lot numbers and expiration dates of the study drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drugs will be retained by the pharmacy, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

14.8 Record Keeping

All raw data generated in connection with this study, together with the original copy of the final report, will be retained until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the Sponsor to inform the PI/Institution as to when these documents no longer need to be retained.

14.9 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

14.10 Publication Policy

All unpublished information given to Celerion by the Sponsor shall not be published or

disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor or the NIH [redacted]

14.11 Research and Travel Compensation

Research subjects will be reimbursed for travel. If coming from outside the US, travel to the port of entry will be reimbursed by non-NIH sources. NIH will cover the costs of travel to and from the Clinical Center within the U.S., lodging and meals, per the NIH policy for Reimbursement of Travel and Subsistence Expenses for NIH Clinical Research Protocol Participants. If within the United States, the NIH will also cover the cost of the local blood draws. This will be paid directly by the NIH. If research subjects elect to have local blood draws outside the U.S., the cost of this will be reimbursed by non-NIH sources.

15 PRIVACY AND CONFIDENTIALITY

Only investigators listed on the protocol will have access to records, data, and samples. If sponsors, monitors or auditors outside of study investigators require access, they will have access to coded data. Deidentified study results will be posted on clinicaltrials.gov.

All research activities will be conducted in as private a setting as possible.

15.1 Research Data and Investigator Medical Records

Medical records will be stored in CRIS behind the NIH firewall. All electronic data will be stored on encrypted, password protected servers only accessible by authorized NIH associate investigators. For photographs and videos, when possible, the patient's face and other identifying marks will not be included in the recording or photograph in order to protect confidentiality. Biological samples sent to contract laboratories for analyses will be de-identified.

15.2 Stored Samples

Stored samples will be kept behind a double lock or will be coded and kept behind a single lock. Samples will be stored indefinitely and may be used for future research. However, this is contingent upon each participant's consent and a MTA being in place if future research is to be conducted outside of NINDS. Any loss or destruction of samples will be reported to the IRB.

15.3 Special Precautions

Samples and data will be stored using codes that are assigned. Data will be kept in password-protected computers. Samples will be kept in locked storage. Only study investigators will have access to the samples and data.

15.3.1 Hard Copy Data/Records

Hard copies of data will be kept in locked file cabinets in locked offices at NINDS. All participant data will be coded for the purpose of data analysis and sharing between listed investigators.

15.3.2 Samples without identifiers (coded or unlinked)

A single lock will be used for samples without identifiers.

16 CONFLICT OF INTEREST AND TECHNOLOGY TRANSFER

NIH guidelines on conflict of interest have been distributed to all investigators. There are no conflicts-of-interest to report for NIH investigators. Non-NIH investigators will abide by the conflict-of-interest policies of their own institutions.

[redacted]

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18 APPENDICES

1. Investigator's brochure
2. Pre-screening script
3. Eligibility checklist
4. Lifestyle recommendations
5. Script for remote/in-person TEAE assessments
6. Participant diary
7. IND documentation
8. Guide to taking study medications
9. Study advertisement
10. Neuromuscular clinic recruitment letters
11. PROMIS-fatigue questionnaire
12. Needle Aspiration Muscle Biopsy Procedure Information Sheet
13. Skeletal muscle biopsy manual
14. MFM-32
15. Columbia suicidality scale
16. DSMB charter
17. Medical monitoring plan
18. Statistical analysis plan
19. Blood draw consent form
20. Study consent form
21. Clinical monitoring plan
22. [redacted]
23. Data access and sharing plan