Phase 1 Open-Label Trial of Rycal S 48168 (ARM210) for *RYR1*-related Myopathies

P.08 J. J. Todd[1,2]; T. Lawal[2]; I. Chrismer[2]; A. Kokkinis[1]; C. Grunseich[1]; M. Jain[3]; M. Waite[3]; M. Barnes[3]; V. Biancavilla[3]; S. Pocock[2]; K. Brooks[1]; W. Reikhof[2]; M. Emile-Backer[2]; A. R., Marks[4]; Y. Webb[5]; E. E. Marcantonio[5]; A.R. Foley[1]; K. Meilleur[2]; C.G. Bönnemann[1]; P. Mohassel[1].

[1] National Institute of Neurological Disorders and Stroke, NIH, Bethesda MD, USA; [2] National Institute of Nursing Research, NIH, Bethesda MD, USA; 3 National Institutes of Health Clinical Center, Bethesda MD, USA; 4 Department of Physiology and Cellular Biophysics, Clyde and Helen Wu Center for Molecular Cardiology, Columbia University Irving Medical Center, New York, NY, USA 5 ARMGO Pharma Inc., Ardsley NY, USA.

Rationale

RYR1-related myopathies (*RYR1*-RM) are clinically diverse myopathies that are caused by pathogenic variants in the *RYR1* gene.

RyR1 is a sarcoplasmic reticulum (SR) calcium channel and essential for excitation-contraction coupling.

Disease causing variants in RyR1 can cause aberrant SR Ca^{2+} leak, block excitation contraction coupling, cause hypersensitivity to RyR1 agonists, diminish SR Ca^{2+} release, or decreased protein expression.

In preclinical models, decreased RyR1-calstabin1 association exacerbates SR Ca^{2+} leak, with detrimental downstream effects on muscle function.

Rycal® compounds bind to RyR1, result in a conformational change, and stabilize the RyR1 closed state.

Studies of muscle biopsies of individuals with *RYR1*-RM have also shown that ex vivo addition of Rycals can mitigate aberrant Ca^{2+} leak.

Rycal® S48168 (ARM 210) demonstrated a favorable safety profile in single ascending dose and multiple ascending dose male healthy volunteer studies (N~100) and was thus tested in individuals with *RYR1*-RM.

Inclusion Criteria, Endpoints, Recruitment

Key eligibility criteria

- 18-65 years of age
- Genetic confirmation of *RYR1*-RM
- Supporting clinical phenotype
- Ambulatory and FVC > 50% predicted
- No prior history of seizures

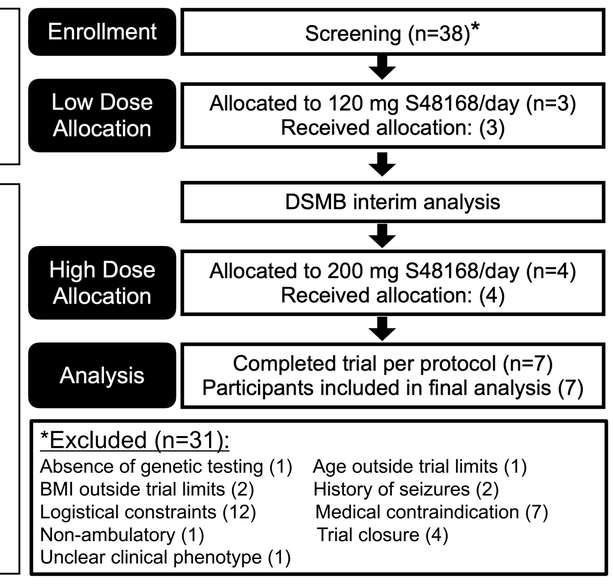
Primary endpoint (safety and tolerability)
TEAEs ≥ grade two in severity, SAEs and AESIs

Exploratory endpoints
S 48168 PK and muscle tissue concentrations

Δ in MFM-32 (% maximum score), hand grip and pinch strength (kg), timed functional tests (seconds)

Δ in PROMIS-fatigue (t-score)

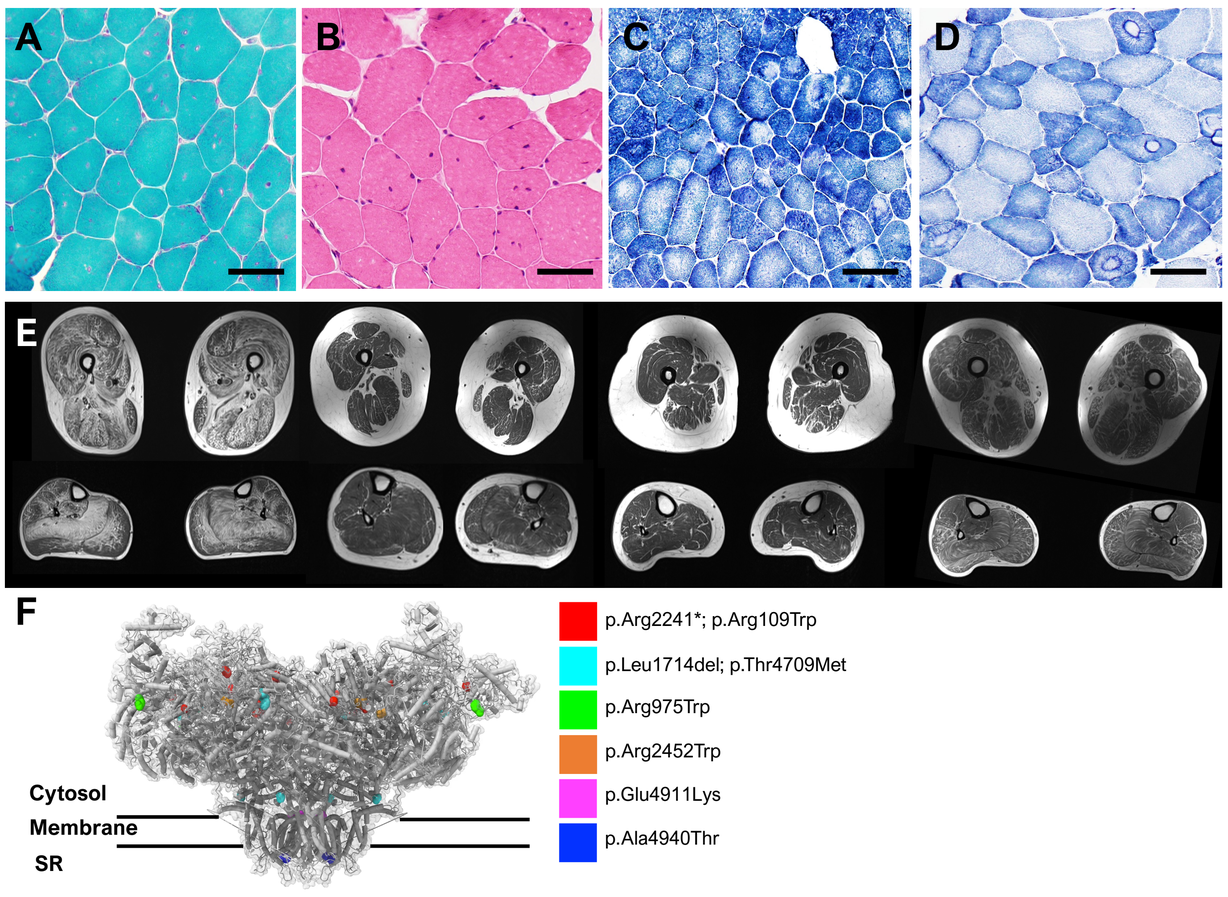
Δ in plasma 15-F2t isoprostane and protein carbonyl concentrations



Participant Characteristics

Measure	S 48168 dose group		Natural history
	120 mg/day (N= 3)	200 mg/day (N= 4)	(N= 20)
Age, years	38 ± 7	43.5 ± 5	39 ± 12
MOI, dominant	1 (33)	3 (75)	5 (33)
Sex, male	2 (67)	2 (50)	13 (65)
Height, cm	171 ± 20	171 ± 10	163 ± 12
Weight, kg	69 ± 10	88 ± 5	68 ± 18
BMI, kg/m^2	24 ± 5	30 ± 4	26 ± 7

Data are n (%) or mean ± SD; Abbreviations: BMI, body mass index; MOI, mode of inheritance



Histology analysis of trial participant muscle biopsies shows common *RYR1*-RM histotypes. Gömöri trichrome (A) and hematoxylin and eosin (B) show centronuclear myopathy. NADH stain (C and D) show core like areas and central cores. T1-weighted MRI of the lower extremities (E) showed a variable degrees of fatty infiltration, reflecting the variable phenotypic severity of *RYR1*-RM in participants in this trial. *RYR1* variants of trial participants mapped to the 3D cryo-EM channel structure (F). Scale bars = 50 µm

Safety and Tolerability

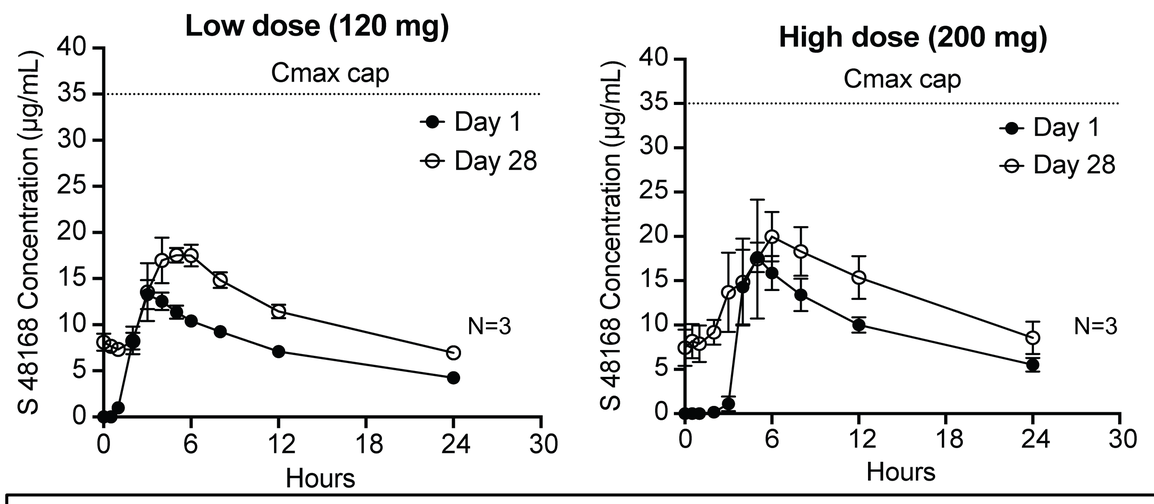
Treatment emergent adverse events (TEAEs)

Safety event	S 48168 dose group	
	120 mg/day (N= 3)	200 mg/day (N= 4)
Total TEAE	18 (100)	10 (100)
TEAE ≥ grade 2 in severity [a]	2 (11)	1 (10)
AESI	0 (0)	0 (0)
SAE	0 (0)	0 (0)
Deaths	0 (0)	0 (0)

Data are n (% total TEAEs); [a] Defined per CTCAE, V5.0

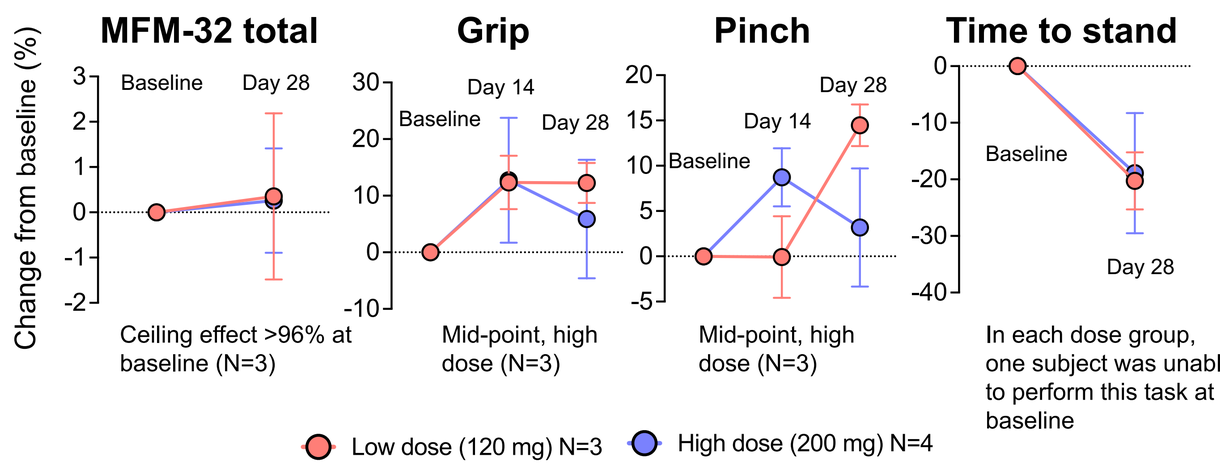
No dose limiting toxicity was observed
100% compliance was observed for both dose groups (pill count)

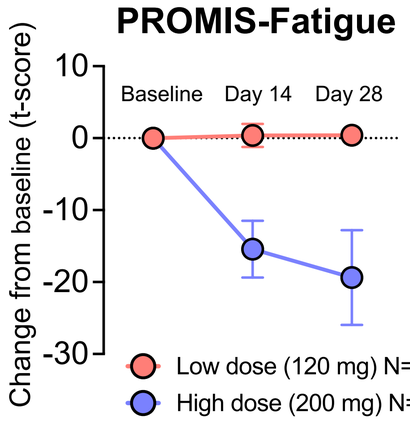
Pharmacokinetics



Consistent with prior healthy volunteer studies
No evidence of non-linearity
Range remains below the Cmax cap set by the FDA
Steady state is typically achieved after approximately 7 days of dosing

Exploratory Efficacy Outcome Measures





Subject ID	S48168 dose	Shoulder abduction MRC grade (R/L)			
		Day -1	Day 14	Day 28	Day 42**
1	120 mg	3-/3-	4-/4-	3-/3-	*N/A*
2	120 mg	4-/4-	4-/4-	4-/4-	*N/A*
3	120 mg	5/5	5/5	5/5	*N/A*
4	200 mg	4/4	4+/4+	5/5	*N/A*
5	200 mg	4/4	4+/4+	5/5	*N/A*
6	200 mg	4+/4+	5-/5-	5-/5-	4+/4
7*	200 mg	4-/4-	*N/A*	4-/4-	4-/4-

* Same as participant 2 ** Day 42 is 14 days after the last dose of S48168

Ceiling effect in some outcome measures (MFM-32)
Floor effect in some outcome measures (time to stand)
Stability or trends of improvement in some outcome measures (time to stand, MRC grade)
Notable reduction (improvement) of fatigue in the high dose group only

Conclusions

Clinical trials for rare myopathies are feasible as a collaborative endeavor between industry, academia, government, and patient advocacy (RYR-1 Foundation).

Favorable S 48168 (ARM210) safety and tolerability profile in *RYR1*-RM affected individuals.

Dose-dependent S 48168 (ARM210) PK profile consistent with healthy volunteer studies.

Positive trends in exploratory outcome measures and patient reported outcomes (fatigue) warrant further investigation in a double-blind, randomized, placebo-controlled trial.

Trial Registration | NCT04141670 **Contact Details |** pmohass1@jhmi.edu

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