

Phase 1 Study of a PROTAC PolyQ-AR Degradar (ARV-027) in Healthy Participants and Participants With Spinal and Bulbar Muscular Atrophy

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Objective

This first-in-human, single-center, randomized, double-blind, placebo-controlled phase 1 study is evaluating the safety, tolerability, PK, and pharmacodynamics of ARV-027, a PROTAC polyQ-AR degrader, in healthy participants and participants with SBMA

Background

- SBMA is an X-linked disease caused by a CAG repeat expansion in the *AR* gene that introduces an expanded polyglutamine (polyQ) tract
- Upon androgen binding, polyQ-AR misfolds, accumulates, and causes a toxic gain-of-function, resulting in disrupted proteostasis and transcription, mitochondrial stress, and progressive degeneration¹
- In skeletal muscle, polyQ-AR impairs contractility and oxidative metabolism, driving atrophy and muscle weakness^{2,3}
- ARV-027 is an orally bioavailable PROTAC degrader that drives ubiquitin–proteasome mediated degradation of polyQ-AR in the periphery, including skeletal muscle (**Figure 1**)⁴
- Preclinically, ARV-027 induced potent degradation of WT AR and polyQ-AR in vitro and in vivo and rescued premature lethality and muscle function in SBMA models (**Figure 2**)⁴

Figure 1: Mechanism of action of ARV-027

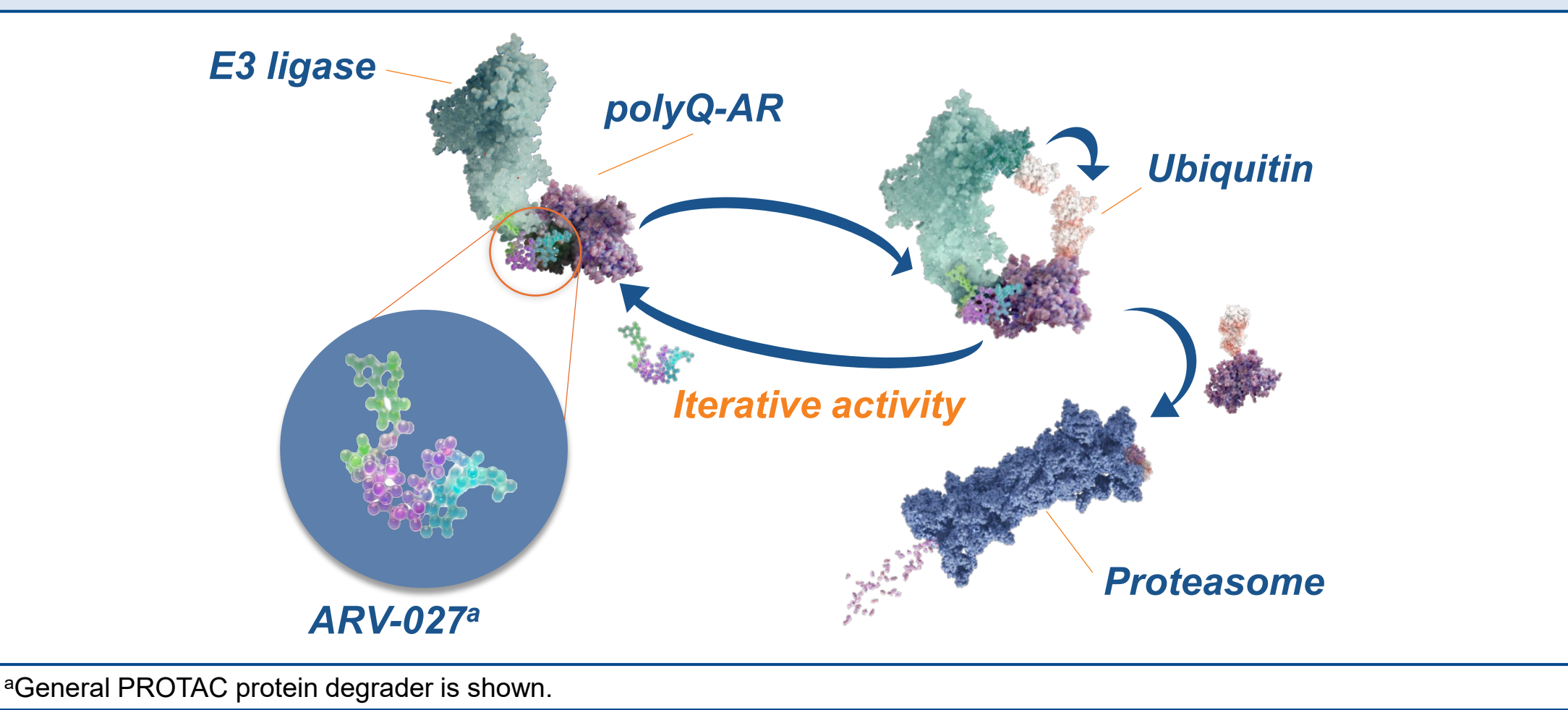
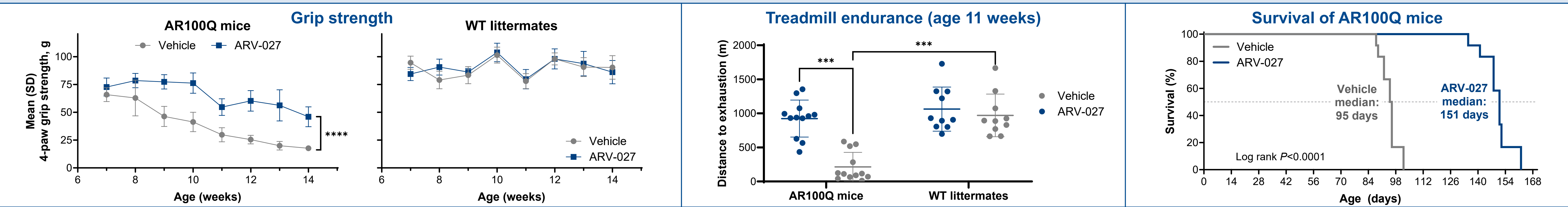


Figure 2: ARV-027 improved muscle strength, endurance, and survival in AR100Q mice⁴



Study Design

- This first-in-human, single-center, randomized, double-blind, placebo-controlled study (EU CT 2025-523469-79-00) is evaluating ARV-027 in healthy participants and participants with SBMA
- The study has 3 parts: (A) SAD and (B) MAD portions in healthy participants and (C) a multiple-dose portion in participants with SBMA (**Figure 3**)
- Key eligibility criteria are listed in **Table 1**
- Participants will receive a single dose of placebo or ARV-027 (part A) or multiple doses for 14 days (part B)
- In part C, a single dose level, selected based on part B, or placebo will be administered QD for 28 days
- Primary, secondary, and exploratory outcome measures are listed in **Table 2**
- Up to 96 healthy participants and 10–16 participants with SBMA will be enrolled

Figure 3: Study design

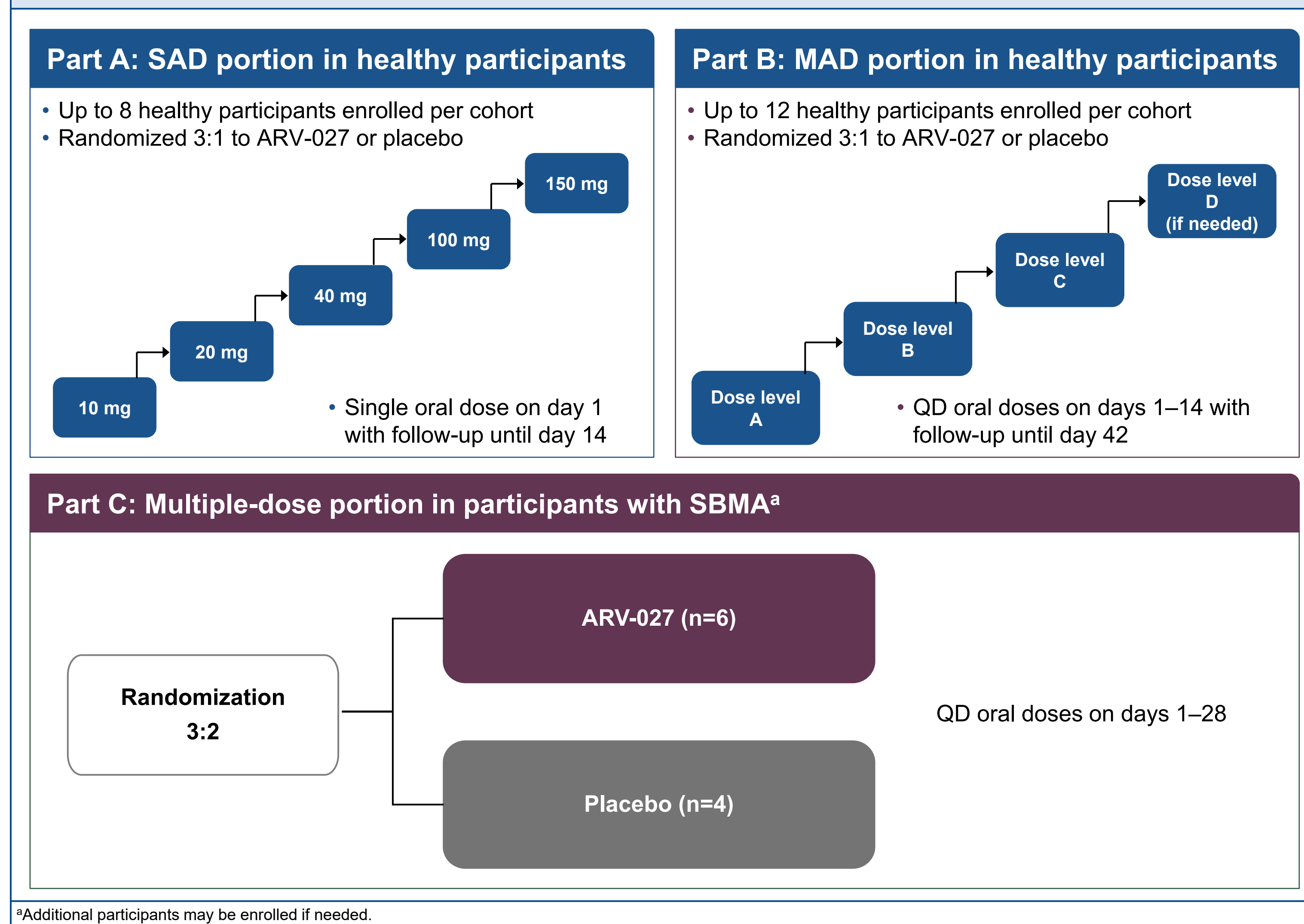


Table 1: Key eligibility criteria^a

Parts A and B: Healthy participants

- Healthy, nonsmoking males aged 18–55 years
- BMI 18.0–<32.0 kg/m²; body weight 50–115 kg
- Fitzpatrick skin type I–III
- Generally healthy with normal vital signs and laboratory values
- No concomitant medications or supplements (except as-needed acetaminophen)

Part C: Participants with SBMA

Inclusion criteria

- Males aged ≥18 years
- Genetically confirmed SBMA, defined by presence of ≥38 polyQ repeats in the *AR* gene
- Neurological signs and symptoms of SBMA
- Participants must be ambulatory; use of a cane or other walking device is permitted

Exclusion criteria

- Contraindications to muscle or skin biopsy, including clinically significant bleeding risk
- Major cardiovascular/cerebrovascular or thromboembolic event within 12 months
- Clinically significant arrhythmias or conduction abnormalities within 6 months
- Uncontrolled hypertension (>150/90 mmHg) despite treatment
- Clinically significant gastrointestinal disease or prior gastrointestinal surgery
- Unstable or ≥10 mg/day prednisone, prednisolone, or its equivalent use
- Anti-androgen or anti-AR therapy in the 3 months prior to screening
- Inadequate bone marrow, renal, or liver function

^aThis is not the complete list of inclusion/exclusion criteria.

Table 2: Outcome measures

Primary

- Incidence, severity, and nature of AEs, SAEs, and AEs leading to discontinuation, dose reduction, or dose interruption in healthy participants and participants with SBMA
- Clinically significant abnormalities in laboratory parameters, vital signs, ECGs, psychiatric assessments, and semen parameters^a in healthy participants and participants with SBMA

Secondary

- Plasma PK parameters of ARV-027 in the single-dose and multiple-dose parts of the study in healthy participants and participants with SBMA

Exploratory

- Changes from baseline in pharmacodynamic biomarkers, including AR protein levels in muscle and skin, and blood biomarkers in healthy participants and in participants with SBMA
- Change in 4-β hydroxycholesterol following multiple doses of ARV-027 in healthy participants
- Concentration ratios of ARV-027 isomers
- Concentration of ARV-027 in urine

^aSemen parameters assessed in healthy participants in Part B only.

Abbreviations

AE=adverse event; ANOVA=analysis of variance; AR=androgen receptor; BMI=body mass index; ECG=electrocardiogram; MAD=multiple ascending dose; PK=pharmacokinetic; polyQ-AR=polyglutamine-expanded androgen receptor; PROTAC=PROteolysis TArgeting Chimera; QD=once daily; SAD=single ascending dose; SAE=serious adverse event; SBMA=spinal and bulbar muscular atrophy; SD=standard deviation; WT=wild type.

References

- Gruneich C, Fischbeck KH. Curr Opin Neurol. 2020;33(5):629-34.
- Gromova A, et al. Acta Neuropathol Commun. 2023;11(1):90.
- Marchioretto C, et al. Curr Opin Pharmacol. 2023;71:102394.
- Gregory J, et al. Poster at Annual International Congress of the World Muscle Society (WMS); 2025.

Acknowledgments

This research was funded by Arvinas, Inc. Medical writing support was provided by Lela Creutz of Arvinas Operations, Inc.

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Study Status

Enrollment is currently ongoing



Scan to view the euclinicaltrials.eu webpage for this study