P007

First-in-Human Dose Selection and Safety, Tolerability, Pharmacokinetics, and Immunogenicity of ARGX-119, an Agonist Antibody for Human Muscle-Specific Kinase

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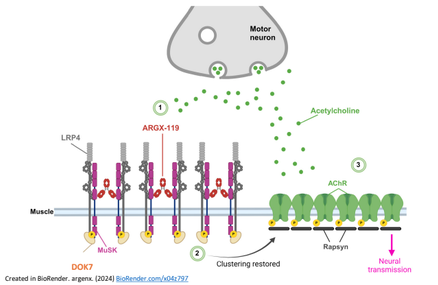
BACKGROUND

MuSK and ARGX-119

- The agrin-LRP4-MuSK signaling pathway is essential for NMJ establishment, maintenance, and function[1]
- ARGX-119 is a first-in-class humanized, agonistic mAb that specifically targets and activates MuSK[2] (**Figure 1**)

FIGURE 1 ARGX-119 Proposed Mechanism of Action



1. Agonistic binding of **ARGX-119** promotes the **dimerization and activation of MuSK**[2–4]
2. Activated **MuSK** phosphorylates downstream **DOK7**, which leads to clustering of **AChR**[2]
3. Acetylcholine binding to **AChR** initiates muscle contraction[2]

Proof-of-Concept Studies

- In nonclinical proof-of-concept studies, ARGX-119:
  - restored NMJ formation and signaling, prevented NMJ deterioration, and reversed disease relapse in mouse models of DOK7-CMS and MuSK-myasthenia gravis[2,4]
  - protected NMJs from muscle denervation in NMJ coculture models of ALS[5]
- ARGX-119 may have broad therapeutic potential for patients with diseases and disorders of the neuromuscular junction

OBJECTIVES

- To present the approach for ARGX-119 dose selection and results of a phase 1, first-in-human, randomized, double-blinded, placebo-controlled study (NCT05670704)[6] to assess the safety, tolerability, PK, and immunogenicity of single and multiple ascending doses of ARGX-119 in healthy participants

METHODS

FIGURE 2 Dose Escalation Scheme

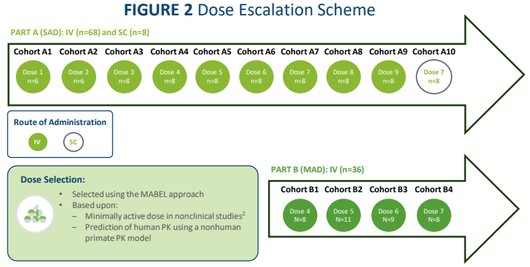
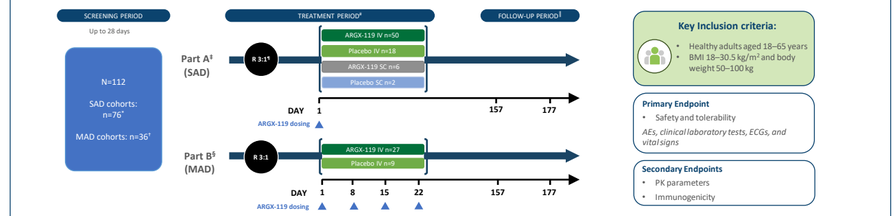


FIGURE 3 Study Design



*All participants in the SAD cohort (n=76) completed treatment and the study. †Participants receiving ARGX-119 discontinued treatment/withdrew from the study due to AEs (n=3) or participant decision (n=1). One participant receiving placebo IV withdrew due to physician decision. ‡Part A (SAD cohorts) received ARGX-119 or placebo in escalating single IV infusion doses (cohorts A1–A9) or a single SC injection (cohort A10) on Day 1. §MAD cohorts received ARGX-119 or placebo as 4 once-weekly IV infusions (Days 1, 8, 15, and 22) in escalating single doses (cohorts B1–B4). ¶With the exception of cohorts A1 and A2, which were randomized 2:1 to receive ARGX-119 IV or placebo IV, respectively. #Study cohorts received ascending ARGX-119 doses sequentially, with subsequent cohort treatment initiated following evaluation of PK and safety by the DRT. §Follow-up period up to 5 months.

RESULTS

TABLE 1 Participant Demographics and Baseline Characteristics

	Part A: SAD (n=76)	Part B: MAD (n=36)	Overall (N=112)
Age, mean (SD), years	41.2 (16.2)	43.7 (14.2)	42.0 (15.6)
Sex, male, n (%)	62 (81.6)	33 (91.7)	95 (84.8)
Race, n (%)			
American Indian/Alaska Native	1 (1.3)	1 (2.8)	2 (1.8)
Asian	3 (3.9)	2 (5.6)	5 (4.5)
Black/African American	2 (2.6)	2 (5.6)	4 (3.6)
Native Hawaiian/Other Pacific Islander	1 (1.3)	0	1 (0.9)
White	69 (90.8)	30 (83.3)	99 (88.4)
Multiple	0	1 (2.8)	1 (0.9)
Ethnicity, n (%)			
Hispanic or Latino	1 (1.3)	3 (8.3)	4 (3.6)
Not Hispanic or Latino	75 (98.7)	33 (91.7)	108 (96.4)
BMI, mean (SD), kg/m²*	24.3 (2.8)	25.4 (2.9)	24.6 (2.9)
Height, mean (SD), cm*	177.7 (10.0)	177.7 (6.8)	177.7 (9.1)
Weight, mean (SD), kg*	76.7 (10.8)	80.4 (10.0)	77.7 (10.6)

*Provided at screening.

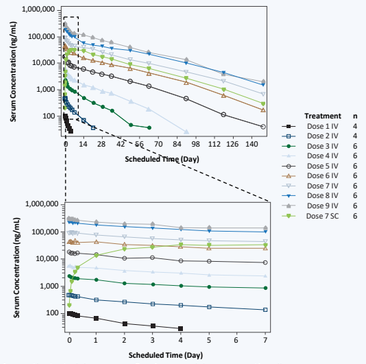
TABLE 2 Overview of Adverse Events

	Part A: SAD IV (n=68)		Part A: SAD SC (n=8)		Part B: MAD) IV (n=36)		Total (N=112) n (%) [E]
	ARGX-119 (n=50) n (%) [E]	Placebo (n=18) n (%) [E]	ARGX-119 (n=6) n (%) [E]	Placebo (n=2) n (%) [E]	ARGX-119 (n=27) n (%) [E]	Placebo (n=9) n (%) [E]	
All AEs	40 (80.0) [102]	16 (88.9) [46]	6 (100) [13]	2 (100) [6]	22 (81.5) [67]	8 (88.9) [24]	94 (83.9) [258]
Related to study drug	1 (2.0) [1]	0	0	0	0	0	1 (0.9) [1]
Not related to study drug	40 (80.0) [101]	16 (88.9) [46]	6 (100) [13]	2 (100) [6]	22 (81.5) [67]	8 (88.9) [24]	94 (83.9) [257]
Related to study procedure	12 (24.0) [14]	1 (5.6) [1]	3 (50.0) [3]	2 (100) [2]	11 (40.7) [16]	3 (33.3) [4]	32 (28.6) [40]
Leading to study discontinuation*	0	0	0	0	3 (11.1) [3]	0	3 (2.7) [3]

- The frequency and incidence of AEs were similar across the cohorts; no dose-dependent increases or trends in AEs were observed
- The majority of AEs were mild to moderate in severity, with no reported fatalities, severe AEs, serious AEs or injection/infusion site reactions
- The mean changes from baseline over time in the clinical laboratory values were similar among cohorts, and there were no clinically meaningful findings for laboratory values, vital sign measurements, physical examination parameters, or ECGs

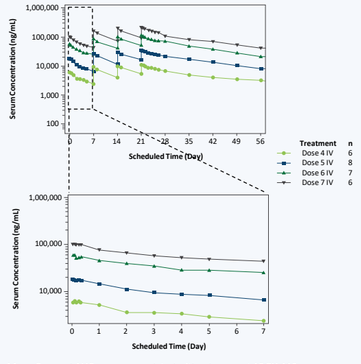
*Three grade 1 AEs led to study discontinuation in ARGX-119-treated participants in MAD cohorts B2 (COVID-19, n=1 and nasopharyngitis, n=1) and B3 (COVID-19, n=1). These were considered not related to study treatment per investigator.

FIGURE 4 Serum Concentration-Time Profiles: Part A (SAD Cohorts)



- Across the tested dose range, C_{max} increased dose-proportionally
- AUC_{0-inf} increased more than dose proportionally (~6-fold), with a mean elimination half-life of ~3 (lower doses) to 23 (higher doses) days
- The absolute bioavailability of ARGX-119 SC (Dose 7) was 63.1% (90% CI: 50.7%-78.6%), based on AUC_{0-inf}

FIGURE 5 Serum Concentration-Time Profiles: Part B (MAD Cohorts)



- Mean C_{max} and AUC_{0-168h} accumulated with subsequent ARGX-119 infusions due to the long elimination half-life
- The mean accumulation ratio for C_{max} ranged from 1.75–2.09, and for AUC_{0-168} it ranged from 2.37–2.75

Immunogenicity of ARGX-119

- No dose-dependent differences in ADA incidence or prevalence were observed among the ARGX-119 treatment groups in part A
- All participants in part B were ADA-negative

SCAN ME

For additional information on the **phase 1b clinical trial** of ARGX-119 in participants with **CMS** (NCT06436742)

For additional information on the **phase 2a clinical trial** of ARGX-119 in participants with **ALS** (NCT06441682)

KEY TAKEAWAYS

- **ARGX-119 was well tolerated with a favorable safety profile in healthy participants**
- **PK data demonstrated nonlinear elimination of ARGX-119 at low concentrations, indicative of target-mediated drug disposition and in line with nonclinical PK observations[2]**
- **No dose-dependent differences in ADA incidence/prevalence were observed among the ARGX-119 treatment groups in part A; all participants in part B were ADA-negative**
- **This FIH phase 1 study supports the development of ARGX-119 as a treatment for patients with disorders of the NMJ**
- **ARGX-119 is currently being evaluated in a phase 1b study in adult participants with DOK7-CMS (NCT06436742) and a phase 2a study in adult participants with ALS (NCT06441682)**

Presented at the American Academy of Neurology (AAN) Annual Meeting; April 5–9, 2025; San Diego, CA, USA.

ABBREVIATIONS

AChR, acetylcholine receptor; ADA, antidrug antibody; AE, adverse event; ALS, amyotrophic lateral sclerosis; AUC, area under the curve; BMI, body mass index; CI, confidence interval; CMS, congenital myasthenic syndromes; DOK7, downstream of kinase 7; DOK7-CMS, CMS caused by a mutation in the DOK7 gene; DRT, data review team; E, number of events; ECG, electrocardiogram; FIH, first-in-human; inf, infinity; IV, intravenous; LRP4, low-density lipoprotein receptor-related protein 4; mAb, monoclonal antibody; MABEL, minimum anticipated biological effect level; MAD, multiple ascending doses; MuSK, muscle-specific kinase; NMJ, neuromuscular junction; PK, pharmacokinetic; R, randomization; SAD, single ascending doses; SAE, serious adverse event; SC, subcutaneous.

DISCLOSURES AND ACKNOWLEDGMENTS

TvB: Consultant to argenx, Curare Consulting BV; **CK, SP, XL, SKP, PV, CV, RS, RV:** Employees of argenx; **RM:** Contracted to argenx, ThermoFisher Scientific Inc., United States

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SCAN ME