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Safety, Tolerability, Pharmacokinetics, Immunogenicity, and Efficacy of ARGX-119 in Participants With DOK7 Congenital Myasthenic Syndromes: Phase 1b Study in Progress

Hanns Lochmüller,[1] Steven J. Burden,[2] Javier Avendaño,[3] Tonke van Bragt,[4] Deborah Gelinas,[3] Stéphanie Dincq,[3] Anne Sumbul,[3] Roeland Vanhauwaert,[3] Rebecca Shilling,[3] Jaqueline Palace[5]

[1]Children's Hospital of Eastern Ontario Research Institute; Division of Neurology, Department of Medicine, The Ottawa Hospital; and Brain and Mind Research Institute, University of Ottawa, Ottawa, Canada; [2]Massachusetts General Hospital, Boston, MA, USA; [3]argenx, Ghent, Belgium; [4]Curare Consulting B.V., Liempde, The Netherlands; [5]Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, Oxford, UK

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INTRODUCTION

Congenital Myasthenic Syndromes (CMS)

- CMS are a rare, heterogeneous group of congenital disorders caused by impaired neuromuscular transmission and characterized by periods of muscle weakness and fatigue[1,2]
- CMS are frequently caused by mutations in the *DOK7* gene, a protein coactivator of MuSK essential for NMJ development and neurotransmission[2,3]
- Identification of targetable pathways for novel efficient therapies remains a key unmet need in CMS[1]

ARGX-119

- ARGX-119, a humanized, agonistic, monoclonal antibody that specifically targets and activates MuSK, has therapeutic potential in patients with neuromuscular disease (**Figure 1**)
- As a MuSK agonist, ARGX-119 has the potential to stabilize, mature, and improve the function of the NMJ, significantly reducing muscle weakness and fatigability, and improving QoL[4]
- ARGX-119 rescued DOK7-CMS mice from early neonatal lethality and disease relapse[4]
- Blinded interim results from an ongoing, phase 1 (NCT05670704), FIH, double-blinded, placebo-controlled study of ARGX-119 administered as single doses (IV or SC) or multiple doses (IV) to healthy participants suggested that ARGX-119 has a favorable safety profile at the doses investigated[5]

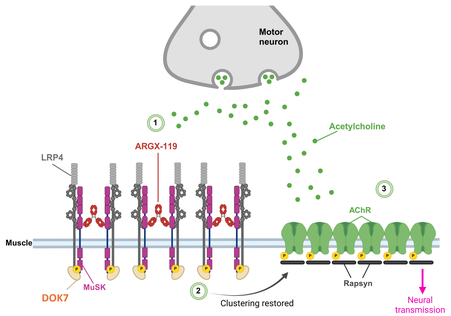
Phase 1b Study Objective

- This phase 1b study will evaluate the safety, tolerability, PK, immunogenicity, and efficacy of ARGX-119 in participants with DOK7-CMS (**Figure 2**)

FIGURE 1 ARGX-119 Proposed Mechanism of Action

In DOK7-CMS, the DOK7 protein is mutated and AChR clustering is reduced.[2]
Treatment with ARGX-119 has been shown *in vivo* to restore AChR clustering[4]

1. Agonistic binding of **ARGX-119** promotes the **dimerization and activation of MuSK,** triggering retrograde signaling to motor axons[1,4,6]
2. Activated **MuSK** phosphorylates downstream **DOK7**, which leads to clustering of **AChR**[4]
3. Acetylcholine binding to **AChR** initiates muscle contraction[4]



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STUDY DESIGN AND ENDPOINTS

FIGURE 2 Phase 1b, Double-Blinded, Randomized, Placebo-Controlled Study (NCT06436742) in Adult Participants With DOK7-CMS

Inclusion Criteria

- Adults aged ≥18 years with genetically confirmed DOK7-CMS
- Score of ≥2 on at least 3 of 5 key components of the QMG: right arm raise, left arm raise, right leg raise, left leg raise, and head tilt
- Stable dosing of oral beta agonists/other CMS medications for ≥3 months
- Agree to remain on the same stable dosing regimen until the end of the follow-up period

Exclusion Criteria

- Diagnosis of CMS due to mutation of any gene other than *DOK7*
- Presence of other medical condition(s) affecting an accurate CMS assessment
- Current participation in an interventional trial
- Receipt of any other IMP <12 weeks or <5 half-lives (whichever is longer) before screening
- Prior participation in any gene therapy or cell therapy study

Study population: 15 participants with DOK7-CMS

SCREENING	TREATMENT PERIOD	FOLLOW-UP PERIOD
Up to 4 weeks	12 weeks	28 weeks

R 4:1
- ARGX-119 IV (n=12)
- Placebo IV (n=3)

STUDY VISITS

WEEK -4 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 42

ARGX-119 or placebo dosing

1 PRIMARY ENDPOINT

Safety and tolerability of ARGX-119
- *AEs*
- *Clinical laboratory tests*
- *ECGs and vital signs*

2 SECONDARY ENDPOINTS
- PK parameters
- Incidence/prevalence of ADA against ARGX-119
- Efficacy measures
  - *Change from baseline for QMG score key components, MG-ADL score, and PROMIS Global Health score*

3 EXPLORATORY ENDPOINTS

Additional clinical outcome measures
- *Mobility, QoL and dyspnea*
- *Home physical activity*
- *Patient/physician global assessments of disease activity*

STUDY DESIGN FEATURES

Evaluating proof-of-biology for ARGX-119
- To assess whether ARGX-119 can increase muscle strength and function in patients with DOK7-CMS
- Objective assessment of ARGX-119 proof-of-biology using key components of the QMG related to limb-girdle muscle weakness and fatigability

The selected dose regimen allows for evaluation of the exposure-response relationship of ARGX-119 across a broad concentration range in a small population, given the rarity of patients with DOK7-CMS

Duration of follow-up period allows for evaluation of the duration of effect and characterization of the PK profile after stopping treatment

KEY TAKEAWAYS

ARGX-119 is a humanized, agonistic monoclonal antibody that specifically targets and activates MuSK, and has the potential to stabilize and improve the function of the NMJ[4]

Interim results from the ongoing, phase 1, FIH study suggest that ARGX-119 has a favorable safety profile in healthy participants at the doses investigated in single- and multiple-dose cohorts[5]

This phase 1b study will assess the safety, tolerability, PK, immunogenicity, and activity of ARGX-119 in 12 participants with DOK7-CMS, and will evaluate the exposure/response relationship for ARGX-119 across a broad dose range

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ABBREVIATIONS

AChR, acetylcholine receptor; ADA, antidrug antibody; AE, adverse event; CMS, congenital myasthenic syndromes; DOK7, downstream of kinase 7; DOK7-CMS, CMS caused by a mutation in the *DOK7* gene; ECG, electrocardiogram; FIH, first-in-human; IMP, investigational medicinal product; IV, intravenous; LRP4, low-density lipoprotein receptor-related protein 4; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MuSK, muscle-specific kinase; NMJ, neuromuscular junction; PK, pharmacokinetic; PROMIS, Patient-Reported Outcomes Measurement Information System; QMG, Quantitative Myasthenia Gravis; QoL, quality of life; SC, subcutaneous; R, randomization.

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