argenx
MEDICAL AFFAIRS

Scan for Clinical Trial Information

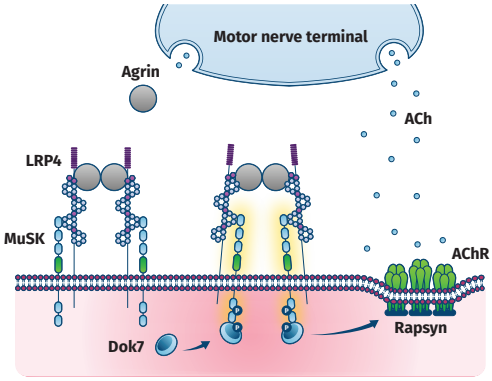
ClinicalTrials.gov identifiers: NCT07287982

Clinical Trial to Investigate Intravenous Administration of Adimanebart (ARGX-119) for the Treatment of Spinal Muscular Atrophy

Spinal Muscular Atrophy (SMA)

- SMA is a genetic neuromuscular disease caused by autosomal recessive mutations in *SMN1* gene on chromosome 5, which leads to a reduction in SMN protein that impairs motor neuron function[1,2]
- SMA is characterized by neuromuscular weakness, which varies in severity but can include motor function impairment, disability, and premature death[1,3]
- The US prevalence is 1 in 14,694 and the global prevalence is 1 to 2 per 100,000 persons[4,5]
- SMA is the most common autosomal recessive inherited disease associated with pediatric mortality[2]

Proposed Pathophysiology of SMA at the NMJ



Low levels of agrin can negatively impact the structure and function of the NMJ[6]

Glial cell dysfunction reduces myelination of motor neurons, impairing signal transduction[6]

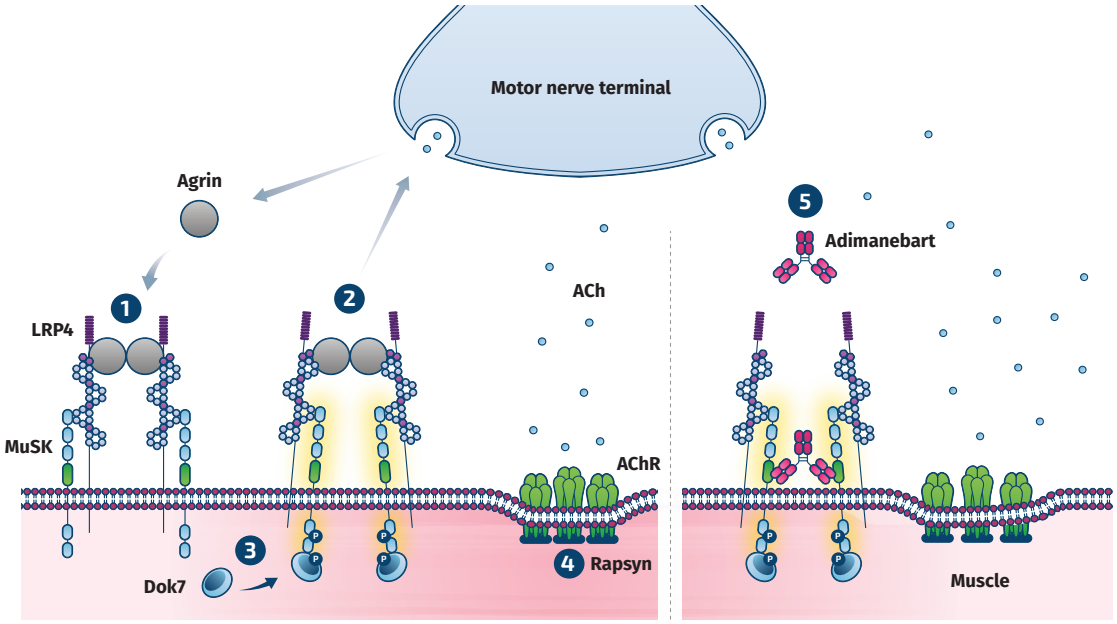
A reduction in ACh and dispersion of AChRs on the postsynaptic muscle membrance interferes with the typical functioning of the NMJ[6,7]

Abnormalities of the postsynaptic mitochondrial structure and function impact the production of adenosine triphosphate (ATP) and contribute to increased oxidative stress[6]

Reduced SMN protein levels are associated with a variety of aberrant functions at the NMJ that can contribute to neuronal dysfunction[6,7]

Adimanebart Proposed Mechanism of Action[8-11]

1. Agrin, released from motor nerve terminals, binds LRP4 and stimulates the association between LRP4 and MuSK
2. LRP4 sends retrograde signals to the motor nerve terminal to stimulate presynaptic differentiation. LRP4, when clustered by MuSK, also stimulates MuSK phosphorylation and activation
3. Dok7 is recruited to phosphorylated MuSK and further stimulates MuSK dimerization and phosphorylation
4. Downstream signaling pathways are activated, leading to rapsyn-dependent AChR clustering which enhances synaptic transmission and muscle contraction



5 **Independent of agrin binding, adimanebart binds MuSK to promote dimerization, which stimulates phosphorylation and subsequent AChR clustering. This is believed to enhance synaptic transmission which may support the restoration of some muscle function in patients with neuromuscular disease**

argenx
MEDICAL AFFAIRS

Scan for Clinical Trial Information

ClinicalTrials.gov identifiers: NCT07287982

SPARKLE Clinical Trial, Now Enrolling

SPARKLE (ARGX-119-24-SMA-2001): A Phase 2, Double-Blinded, Randomized, Placebo-Controlled Study to Assess the Safety, Tolerability, Efficacy, Pharmacokinetics, and Immunogenicity of Intravenous Administration of ARGX-119 in Pediatric Participants Aged 5 to Less Than 18 Years With Spinal Muscular Atrophy[12]

Sparkle
spinal muscular atrophy study

Key Inclusion Criteria[12,13]

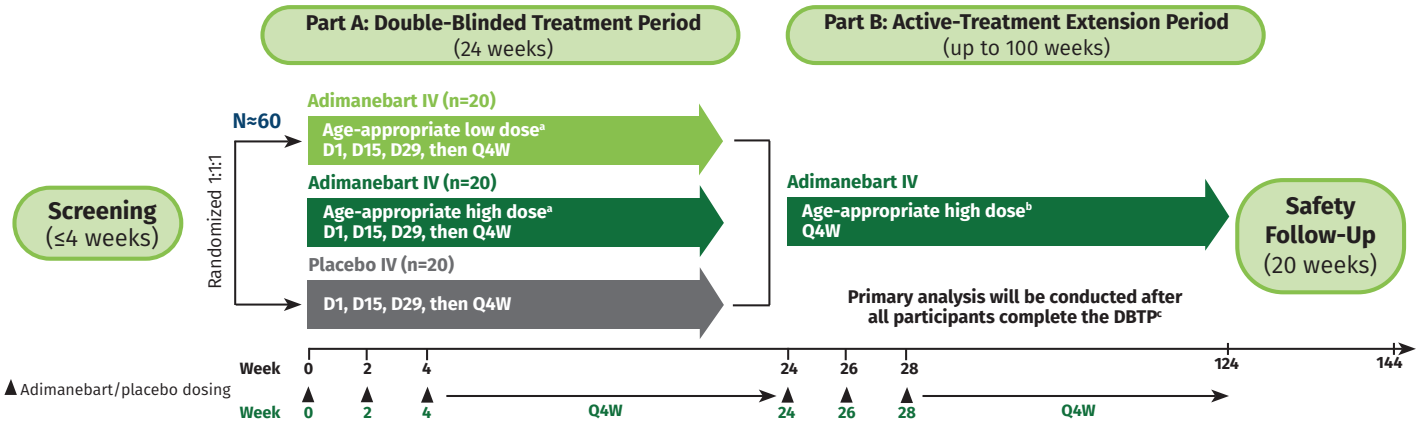
- ≥5 to <18 years of age
- Confirmed genetic diagnosis of 5q-SMA
- Receiving treatment with a SMN-upregulating therapy
  - A stable regimen of nusinersen or risdiplam for 1 year before baseline and continuing throughout the study
  - A single dose of onasemnogene abeparvovec received ≥2 years before baseline
- Ambulant: 6MWT ≥50 meters unaided
- RHS score >15 and <50 at screening

Key Exclusion Criteria[12,13]

- Known medical condition that would interfere with the accurate assessment of SMA, confound the results of the study, or put the participant at undue risk
- Recent major surgery within 3 months of screening or planned major surgery during the study
- History of spinal fusion within 6 months before screening or planned during the study
- Severe scoliosis (curvature >40 degrees) and/or contractures at screening
- Respiratory insufficiency (medical necessity for invasive or noninvasive ventilation for daytime treatment while awake)
- Current or previous antimyostatin therapy in the past 6 months

Additional inclusion and exclusion criteria apply.[12,13]

SPARKLE Study Design[12,13]



Primary safety and tolerability endpoints:
- Incidence and severity of AEs and SAEs
- Change in ECG results, vital signs, and clinical laboratory test results

Primary efficacy endpoint:
- Change in RHS total score from baseline to week 24 of the DBTP

~~This clinical trial investigating adimanebart for the treatment of SMA is now enrolling.~~

Adimanebart (ARGX-119) is not approved by any regulatory body for the treatment of patients with SMA as safety and efficacy have not been established.

Abbreviations: **5Q-SMA,** Spinal muscular atrophy linked to chromosome 5q; **6MWT,** 6-minute walk time; **ACh,** acetylcholine; **AChR,** acetylcholine receptor; **AE,** adverse event; **D,** day; **DBTP,** double-blind treatment period; **Dok7,** docking protein 7; **ECG,** electrocardiogram; **IMP,** investigational medicinal product; **IV,** intravenous; **LRP4,** low-density lipoprotein receptor-related protein 4; **MuSK,** muscle-specific tyrosine kinase; **NMJ,** neuromuscular junction; **Q4W,** every 4 weeks; **RHS,** Revised Hammersmith Scale; **SAE,** serious adverse event; **SMA,** spinal muscular atrophy; **SMN,** survival motor neuron; **SMN1,** human survival motor neuron 1 gene; **US,** United States.

[a]Age-appropriate doses based on age for participants aged ≥12 to <18, ≥7 to <12, and ≥5 to <7, respectively: low dose (6, 7, or 8 mg/kg), high dose (12, 14, or 16 mg/kg).[13] [b]All participants in the active-treatment extension period will receive adimanebart high dose as administered in the double-blind treatment period. The adimanebart low dose may be selected following primary analysis of the double-blind treatment period, in which case all of the participants in the active-treatment extension period will change to adimanebart low dose and will continue receiving it for the remainder of the study.[13] [c]Or discontinued IMP early.[13]

References

1. Mercuri E, et al. *Nat Rev Dis Primers.* 2022;8(1):52. **2.** Jablonka S, et al. *Neurol Res Pract.* 2022;4(1):2. **3.** Lunn MR, Wang CH. *Lancet.* 2008;371(9630):2120-2133. **4.** Belter L, et al. *JAMA Pediatr.* 2024:e241911. **5.** Verhaart IEC, et al. *Orphanet J Rare Dis.* 2017;12(1):124. **6.** Torri F, et al. *Int J Mol Sci.* 2024;25(13):7311. **7.** Feng Z, et al. *Int J Mol Sci.* 2021;22(15):8015. **8.** Vanhauwaert R, et al. *Sci Transl Med.* 2024;16(765):eado7189. **9.** Nicole S, et al. *J Neuromuscul Dis.* 2017;4(4):269-284. **10.** Oury J, et al. *Proc Natl Acad Sci.* 2024;121(39):e2408324121. **11.** Herbst R, et al. *Cold Spring Harb Perspect Biol.* 2024;16(5):a041490. **12.** ClinicalTrials.gov identifier: NCT07287982. Accessed March 4, 2026. https://clinicaltrials.gov/ct2/show/NCT07287982. **13.** Study ARGX-119-24-SMA-2001 Clinical Trial Protocol v1.0, 15 Sep 2025.