Trial design and rationale for OPAL, a Phase 2, randomized, double-blind study of apitegromab in patients aged <2 years with spinal muscular atrophy

Poster #: 311

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INTRODUCTION

- Spinal muscular atrophy (SMA) is a neuromuscular disorder characterized by neuronal degeneration and muscle atrophy, leading to weakness and progressive motor function loss[1]
- Approved survival motor neuron (SMN)-targeted treatments slow disease progression and improve functional outcomes, but in many cases motor function deficits persist due to muscle atrophy[2]
- Apitegromab is an investigational, fully human monoclonal antibody that inhibits the activation of myostatin, a negative regulator of muscle mass, by selectively binding with high affinity to promyostatin and latent myostatin (**Figure 1**)[3,4]
- In the randomized, double-blind, placebo-controlled, global Phase 3 SAPPHIRE trial (NCT05156320), apitegromab treatment resulted in statistically significant and clinically meaningful improvements in motor function and was well tolerated in participants aged ≥2 years with SMA Type 2 or 3[5]
- Given the potential advantages of preventing muscle atrophy at an early age, the Phase 2 OPAL trial was designed to expand the investigation of apitegromab to a younger population

Figure 1. Apitegromab mechanism of action

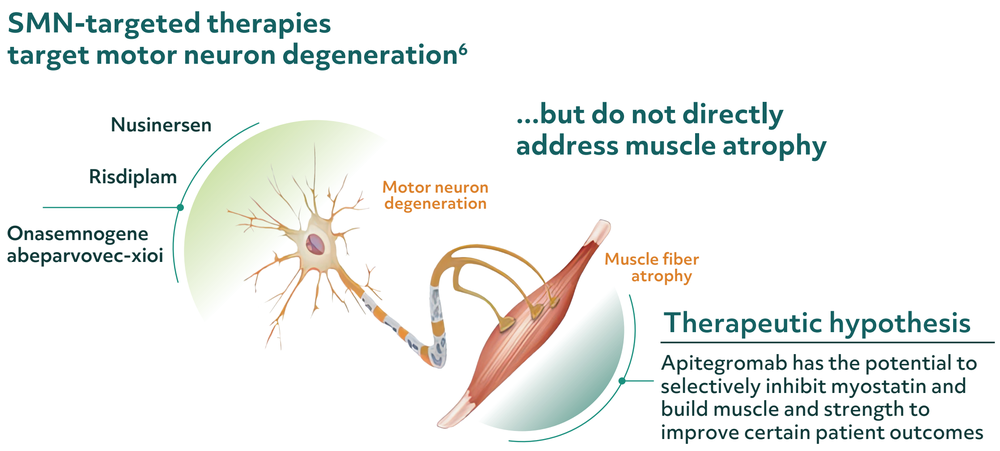


Figure adapted from: SMA Foundation Overview. Accessed Feb 11, 2025. http://www.smafoundation.org/wp-content/uploads/2012/03/SMA-Overview.pdf.
SMA, spinal muscular atrophy; SMN, survival motor neuron.

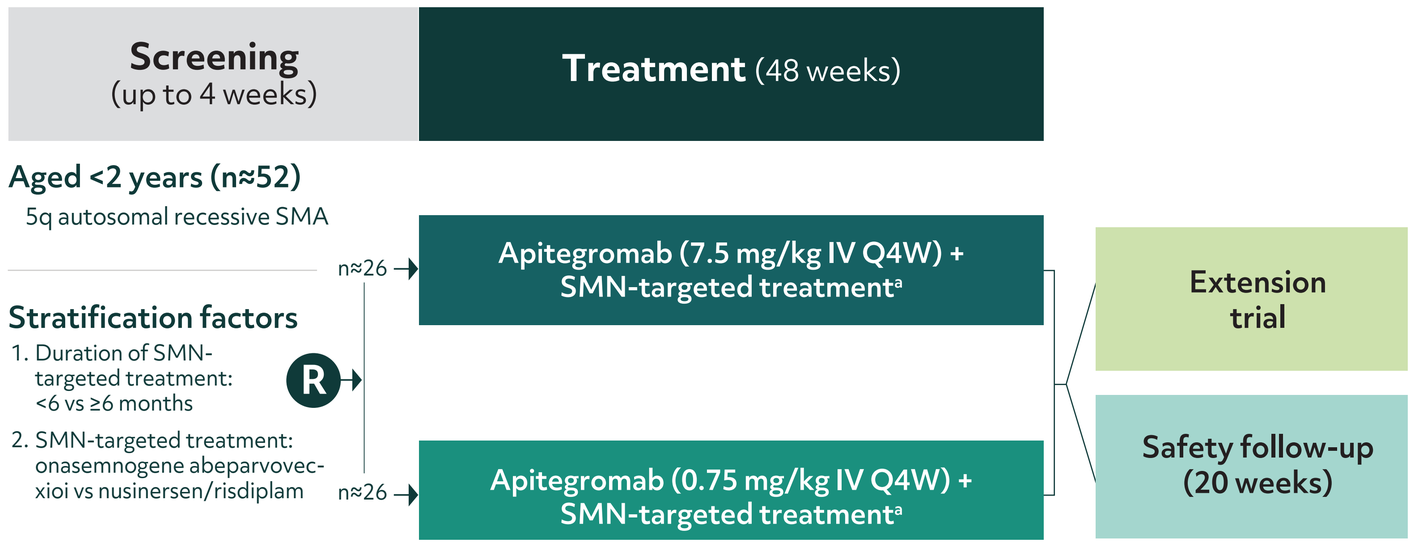
OBJECTIVE

- The Phase 2 OPAL trial (NCT07047144) aims to assess the pharmacokinetics (PK), pharmacodynamics (PD), efficacy, safety, and tolerability of apitegromab in children aged <2 years with SMA

METHODS

- OPAL is a Phase 2, randomized, double-blind, multiple-dose trial of apitegromab for the treatment of children aged <2 years with SMA
- This trial is expected to be conducted across 30 sites in the United States and Europe
- Recruitment will aim for approximately 52 participants with SMA, who will be randomized 1:1 (n≈26/dose group) to receive apitegromab 0.75 or 7.5 mg/kg by intravenous infusion every 4 weeks (**Figure 2**)
  - This trial will include a screening period of up to 4 weeks and a 48-week treatment period (12 doses), followed by either participation in an extension trial or a 20-week safety follow-up period
- Dose selection of apitegromab 0.75 and 7.5 mg/kg was informed by simulations using population PK and PK/PD modeling in people aged ≥2 years with SMA, incorporating body weight scaling and maturational changes in clearance
  - Simulations indicate that participants aged <2 years require an approximately 25% lower dose (7.5 mg/kg) to achieve exposure similar to that in children aged 2-5 years (10 mg/kg) due to differences in maturational clearance
  - Complete target saturation is predicted at the 7.5 mg/kg dose, whereas a 10-fold lower dose of 0.75 mg/kg would achieve approximately 50% of this PD effect and remain pharmacologically active
  - An interim PK/PD analysis is planned when the 15th participant completes 12 weeks of treatment
  - The 2 doses for this trial are expected to enable clear characterization of PK/PD and exposure-response relationships and identify the dose of apitegromab for people living with SMA aged <2 years

Figure 2. Trial design



[a]SMN-targeted treatment includes previous treatment with onasemnogene abeparvovec-xioi or current treatment with nusinersen or risdiplam but does not include treatment with nusinersen or risdiplam after onasemnogene abeparvovec-xioi treatment.
IV, intravenous; Q4W, every 4 weeks; R, randomization; SMA, spinal muscular atrophy; SMN, survival motor neuron.

- Key inclusion criteria include age <2 years, confirmed diagnosis of 5q autosomal recessive SMA, and having received an SMN-targeted treatment (**Table 1**)
- Key trial endpoints are listed in **Table 2**
- Safety and tolerability will be assessed throughout the trial

Table 1. Key eligibility criteria

Key inclusion criteria	Aged <2 years Confirmed diagnosis of 5q autosomal recessive SMA Confirmed presence of *SMN2* gene copy or copies Has been treated with onasemnogene abeparvovec-xioi or is continuing treatment with nusinersen or risdiplam[a] Has delayed motor milestones for their age attributed to SMA or a CHOP-INTEND score <55
Key exclusion criteria	Nutritional status that is not anticipated to be stable throughout the trial or medical necessity of a gastric feeding tube Major orthopedic issues, such as severe scoliosis or contractures, or other physical limitations that may substantially limit the evaluation of motor function outcome measures throughout the trial

[a]Individuals who received or are scheduled to receive nusinersen or risdiplam after receiving onasemnogene abeparvovec-xioi are not eligible.
CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SMA, spinal muscular atrophy.

Table 2. Key endpoints

Key endpoints	Population model-based parameters, such as clearance, V_c, V_d, and V_p Serum concentrations of apitegromab and total latent myostatin Change from baseline in BSID-4 Gross Motor Subscale raw score at 48 weeks Relationship between serum concentrations of apitegromab and total latent myostatin Population PK/PD model-based parameters (eg, I_{max}, IC_{50}, and K_{out}) Incidence of TEAEs and SAEs by severity

BSID-4, Bayley Scales of Infant and Toddler Development, Fourth Edition; IC_{50}, concentration of apitegromab to achieve half the inhibiting effect; I_{max}, maximum inhibiting effect; K_{out}, first-order degradation rate of total latent myostatin; PD, pharmacodynamics; PK, pharmacokinetics; SAE, severe adverse event; TEAE, treatment-emergent adverse event; V_c, central volume of distribution; V_d, volume of distribution; V_p, peripheral volume of distribution.

CONCLUSION

- The Phase 2 OPAL trial will be the first to evaluate apitegromab, a muscle-targeted treatment, in children aged <2 years with SMA

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