

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

Laurent Servais,<sup>1-3</sup> Thomas O. Crawford,<sup>4</sup> Kelley Capocelli,<sup>5</sup> Bert Yao,<sup>5</sup> Giridhar S. Tirucherai,<sup>5</sup> Yang Xu,<sup>5</sup> Guolin Zhao,<sup>5</sup> Jing L. Marantz,<sup>5</sup> Basil T. Darras<sup>6</sup>

<sup>1</sup>MDUK Oxford Neuromuscular Centre, University of Oxford, Oxford, UK; <sup>2</sup>NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK; <sup>3</sup>Neuromuscular Reference Centre, University Hospital of Liège, Liège, Belgium; <sup>4</sup>Johns Hopkins Medicine, Baltimore, MD, USA; <sup>5</sup>Scholar Rock, Inc., Cambridge, MA, USA; <sup>6</sup>Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

## INTRODUCTION

- Spinal muscular atrophy (SMA) is a neuromuscular disorder characterized by neuronal degeneration and muscle atrophy, leading to weakness and progressive motor function loss<sup>1</sup>
- 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<sup>2</sup>
- 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**)<sup>3,4</sup>
- In the randomized, double-blind, placebo-controlled, global Phase 3 SAPHIRE 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<sup>5</sup>
- 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**

SMN-targeted therapies target motor neuron degeneration<sup>6</sup>

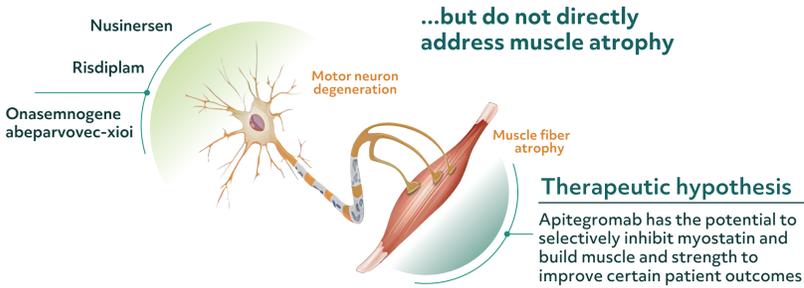


Figure adapted from: SMA Foundation Overview. Accessed Feb 11, 2025. <http://www.smafoundation.org/wp-content/uploads/2012/03/SMA-Overview.pdf>. SMA, spinal muscular atrophy; SMN, survival motor neuron.

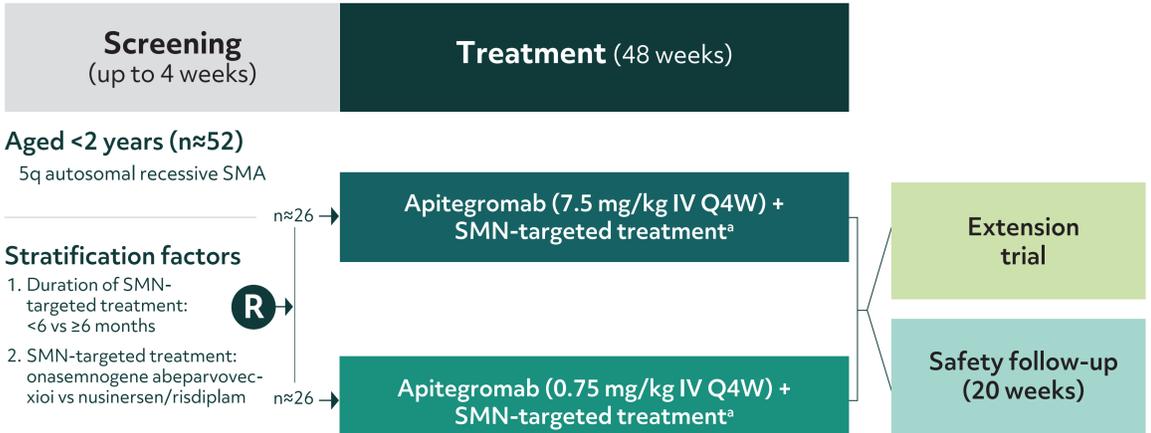
## OBJECTIVE

- 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**



<sup>a</sup>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	Key exclusion criteria
<ul style="list-style-type: none"> <li>✓ Aged &lt;2 years</li> <li>✓ Confirmed diagnosis of 5q autosomal recessive SMA</li> <li>✓ Confirmed presence of SMN2 gene copy or copies</li> <li>✓ Has been treated with onasemnogene abeparvovec-xioi or is continuing treatment with nusinersen or risdiplam<sup>a</sup></li> <li>✓ Has delayed motor milestones for their age attributed to SMA or a CHOP-INTEND score &lt;55</li> </ul>	<ul style="list-style-type: none"> <li>✗ Nutritional status that is not anticipated to be stable throughout the trial or medical necessity of a gastric feeding tube</li> <li>✗ 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</li> </ul>

<sup>a</sup>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
<ul style="list-style-type: none"> <li>• Population model-based parameters, such as clearance, <math>V_c</math>, <math>V_d</math>, and <math>V_p</math></li> <li>• Serum concentrations of apitegromab and total latent myostatin</li> <li>• Change from baseline in BSID-4 Gross Motor Subscale raw score at 48 weeks</li> <li>• Relationship between serum concentrations of apitegromab and total latent myostatin</li> <li>• Population PK/PD model-based parameters (eg, <math>I_{max}</math>, <math>IC_{50}</math>, and <math>K_{out}</math>)</li> <li>• Incidence of TEAEs and SAEs by severity</li> </ul>

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

## References

- Mercuri E, et al. *Nat Rev Dis Primers*. 2022;8(1):52.
- Crawford TO, et al. *Neurology*. 2024;102(5):e209151.
- Crawford TO, et al. *Front Neurol*. 2024;15:1419791.
- Pirruccello-Straub M, et al. *Sci Rep*. 2018;8(1):2292.
- Crawford TO, et al. *Lancet Neurol*. 2025;24(9):727-739.
- Hua Y, et al. *Nature*. 2011;478(7367):123-126.

## Acknowledgments

- We are grateful to all the patients who are willing to participate in this study and to their families, caregivers, healthcare professionals, and patient advocacy groups for their dedication and support.
- Medical writing and editorial support were provided by Aidan Moriarty, PhD, and Shannon Davis of Apollo Medical Communications, part of Helios Global Group, and funded by Scholar Rock, Inc.
- Project management support was provided by Taryn Bosquez-Berger, PhD, CMPP, of Scholar Rock, Inc.

## Disclosures

LS has received grants and personal fees from AveXis/Novartis Gene Therapies, Biogen, and Roche and personal fees from Biohaven, Cytokinetics, and Scholar Rock, Inc., outside the submitted work. TOC is the lead principal investigator of the Scholar Rock-sponsored, Phase 2 TOPAZ trial and a consultant and/or advisory board member for AveXis/Novartis Gene Therapies, Biogen, Pfizer, and Roche/Genentech. KC, BY, GST, YX, GZ, and JLM are employees of and stockholders in Scholar Rock, Inc. BTD has served as an ad hoc scientific advisory board member for AveXis/Novartis Gene Therapies, Biogen, Roche/Genentech, Merck, Sarepta Therapeutics, and Scholar Rock, Inc.; steering committee member for the Roche FIREFISH and MANATEE studies; and Data and Safety Monitoring Board member for Amicus and Lexeo Therapeutics; he has no financial interests in these companies. He has also received royalties for books and online publications from Elsevier and Wolters Kluwer.



To download a copy of this poster, scan QR code.