# Novartis - SMART

A Phase IIIb, Open-label, Single-arm, Single-dose, Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of Gene Replacement Therapy With Intravenous OAV101 (AVXS-101) in Pediatric Patients With Spinal Muscular Atrophy (SMA)

## Summary

This is a gene replacement therapy trial where participants with SMA will receive a single intravenous dose of OAV101 (AVXS-101). This study will investigate the safety, tolerability, and effectiveness of OAV101 (AVXS-101). The participants will be monitored for 48 hours after the dose to ensure that no serious side effects have taken place. They will then will be asked to return for follow-up appointments over the next 12 months. After the study is complete, participants will be invited to enroll into a long-term follow-up study to collect additional safety and efficacy data.

## Study Number: NCT04851873

## Description by Novartis Gene Therapies

This is an open-label, single arm, multi-center study to evaluate the safety, tolerability and efficacy of IV OAV101 in SMA participants. The study will enroll participants that weigh  8.5 kg and  21 kg. An even weight distribution across the desired range will be achieved by aiming to enroll approximately 6-10 participants across 3 weight brackets ( 8.5-13 kg, > 13-17 kg, > 17-21 kg). Participants will receive a single administration of IV OAV101.

Participants who meet eligibility criteria at screening and baseline visits will receive a single-dose of IV OAV101 on Day 1 (Treatment period) and will be followed for a period of 12 months. The study will include a standard screening period that can last up to 45 days, during which eligibility will be assessed and baseline assessments will be performed prior to treatment.

For the study duration, participants will complete visits as defined in the Schedule of Assessments. Prednisolone

AUSNMD

**Trial Status**
Fully recruited

**Locations**
Melbourne - Melbourne Children's Campus, Fully recruited, Sydney - Children's Hospital, Fully recruited

**Trial Sponsor**
Novartis Gene Therapies

**Age**
3 months to 17 years

**SMASubtype**
Type 1

**SMN2 Copy Numbers Required**
No restriction

**Mode of delivery**
IV

**MRI**
No

**Phase**
3

**Length Of Participation**
12 months

**Recruitment Target**
24

**Therapeutic Category**
Gene therapy

treatment will be given per study protocol. On Day -1, participants will be admitted to the hospital for pre-treatment baseline procedures. On Day 1, participants will receive a 1-time IV infusion of OAV101 and will undergo in-patient safety monitoring over the next 48 hours, after which the participant may be discharged, based on Investigator judgment.

Safety monitoring will be performed as per study schedule and protocol requirement. Safety for the participants enrolled in the study will be evaluated by the study team together with Data Monitoring Committee (DMC) as described in the charter. An interim analysis for safety and efficacy maybe performed once the last participant completes 6-months of follow-up, and will include all available data up until that data cut-off. Final analysis will be planned after the 12 months visits (End of Study (EOS)).

After study completion eligible participants will be invited to enroll into Long Term follow-up study to collect additional safety and efficacy data.

### Primary Outcome Measures

- Number of participants with treatment emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) [ Time Frame: 12 months ]

  An AE is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study.

- Number of participants with important identified and important potential risks (Adverse Events of Special Interest (AESI)) [ Time Frame: 12 months ]

  The following are important identified and important potential risks (AESI) associated with OAV101: Hepatotoxicity, Thrombocytopenia, Cardiac adverse events, Sensory abnormalities suggestive of ganglionopathy, and Thrombotic microangiopathy. These will be assessed by the investigator.

- Change from baseline in vital signs measurements - systolic and diastolic blood pressure
  [ Time Frame: 12 months ]

  Change from baseline in vital signs measurements - systolic and diastolic blood pressure (mmHg)
- Change from baseline in vital signs measurements - respiratory rate [ Time Frame: 12 months ]

  Change from baseline in vital signs measurements - respiratory rate (breaths per minute)
- Change from baseline in vital signs measurements - pulse [ Time Frame: 12 months ]

  Change from baseline in vital signs measurements - pulse (beats per minute)
- Change from baseline in vital signs measurements - temperature [ Time Frame: 12 months ]

  Change from baseline in vital signs measurements - temperature (degrees Celsius)
- Change from baseline in vital signs measurements - oxygen saturation level [ Time Frame: 12 months ]

  Change from baseline in vital signs measurements - oxygen saturation level (%)

### Secondary Outcome Measures

- Achievement of development motor milestones according to the modified and combined WHO-MGRS and Bayley scale of Infant and Toddler Development. [ Time Frame: 12 months ]

  The World Health Organization-Multicentre Growth Reference Study (WHO-MGRS) and Bayley scale of Infant and Toddler Development will be modified and combined into a single scale expressly for this study, to measure developmental motor milestones. These will be assessed via the milestone checklist, formed of 10 yes/no questions with optional video documentation. The developmental milestones are: head control, sitting with support, sitting without support, sitting without support for 30 seconds, hands-and-knees crawling, pulls to stand, standing with assistance, walking

with assistance, standing alone and walking alone. A yes response indicates that the patient reached a particular development milestone.

- Change from baseline in Hammersmith Functional Motor Scale - Expanded (HFMSE), as appropriate according to participant age [ Time Frame: 12 months ]

  The HFMSE was devised for use in children with SMA to give objective information on motor ability and clinical progression. The HFMSE is formed of 33 assessments rated from 0 (unable to perform functional task) to 2 (able to perform functional task unassisted). Higher scores indicated higher levels of motor ability.

- Change from baseline in Revised Upper Limb Module (RULM), as appropriate according to participant age. [ Time Frame: 12 months ]

  The RULM assesses motor performance in the upper limbs from childhood through adulthood in ambulatory and non-ambulatory individuals with SMA. 'The scale consists of an entry item to establish functional levels and 19 items covering distal to proximal movements. The entry item is a modified version of the Brooke scale, including activities ranging from no functional use of hands (score 0) to full bilateral shoulder abduction (score 6). The entry item does not contribute to the total score but serves as a functional classification of overall upper limb functional ability. Of the remaining 19 items, 18 are scored on a 3 point scoring system and 1 item is scored on a 2 point scoring system. The test is performed unilaterally using the limb preferred by the participant. The total score ranges from 0, if all the items cannot be performed, to 37, if all the activities are achieved fully without any compensation. ' Higher scores indicate higher levels of motor ability.

**Can I take part?**

**Inclusion Criteria**

- Symptomatic SMA diagnosis based on gene mutation analysis with bi-allelic survival motor neuron 1 (SMN1) mutations (deletion or point mutations) and any copy of the survival motor neuron 2 (SMN2) gene.

- Weight  8.5 kg and  21 kg at the time of Screening Visit 2

- Naive to treatment or have discontinued an approved drug/therapy

### Exclusion Criteria

- Previous OAV101 use or previous use of any AAV9 gene therapy

- Body Mass Index (BMI) < 3rd percentile based on World Health Organization (WHO) Child Growth Standard

- Participant with history of aspiration pneumonia or signs of aspiration (eg, coughing or sputtering of food) within 4 weeks prior to screening

- Anti-Adeno-associated virus serotype 9 (AAV9) antibody titer > 1:50 as determined by ligand binding immunoassay at the time of screening

- History of gene therapy, hematopoietic transplantation, or solid organ transplantation

Other inclusion/exclusion criteria may apply.

For contact details and to find out more, please refer to ausnmd.org.