Long-term follow-up of patients with spinal muscular atrophy Treated with OAV101 IT or OAV101 IV in Clinical Trials

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This study has been transitioned to CTIS with ID 2024-511707-42-00 check the CTIS register for the current data. The purpose of this study is to collect long-term follow-up safety and efficacy data on patients with SMA who were treated with OAV101...

Ethical review	Approved WMO
Status	Pending
Health condition type	Muscle disorders
Study type	Observational invasive

Summary

ID

NL-OMON56701

Source
ToetsingOnline

Brief title
OAV101

Condition

- Muscle disorders
- Neuromuscular disorders

Synonym
spinal muscular atrophy

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Research and Development

Intervention

Keyword: Interventional, Long-term follow-up, OAV101, Spinal Muscular Atrophy

Outcome measures

Primary outcome

Primary objective(s)

* To assess long-term safety in terms of treatment-emergent serious adverse events (SAEs) and treatment-emergent adverse events of special interest (AESIs)

Endpoint(s) for primary objective(s)

* Number and proportion of patients reporting treatment-emergent serious adverse events (SAEs) by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) for the entire duration of the study (i.e., up to 15 years)
* Number and proportion of patients reporting treatment-emergent adverse events of special interest (AESIs) by AESI category and MedDRA SOC and PT within each AESI category for the entire duration of the study (i.e., up to 15 years)

Secondary outcome

* To assess long-term efficacy of OAV101 treatment
* To assess long-term safety for measures other than adverse events

Endpoint(s) for secondary objective(s)

* The number and proportion of participants demonstrating each developmental milestone according to the Developmental Milestone Checklist
* The number and proportion of participants demonstrating maintenance of each

developmental milestone

* Change from Baseline in the Hammersmith Functional Motor Scale - Expanded

(HFMSE) total score

* Change from Baseline in the Revised Upper Limb Module (RULM) total score

* Number and proportion of patients with potentially clinically significant

vital sign findings, summarized individually for each vital sign parameter

* Number and proportion of patients with potentially clinically significant

laboratory values, summarized individually for each laboratory parameter

Study description

Background summary

Spinal Muscular Atrophy (SMA) is a neurogenetic disorder caused by a loss or mutation in the survival motor neuron 1 gene (SMN1) on chromosome 5q13, which leads to reduced SMN protein levels and a selective dysfunction of motor neurons. SMA is an autosomal recessive, early childhood disease with an incidence of approximately 1:10,000 live births (Ogino et al 2004, Sugarman et al 2012). SMA is the leading cause of infant mortality due to genetic diseases. Disease severity and clinical prognosis depends on the number of copies of SMN2. In its most common and severe form (Type 1), hypotonia and progressive weakness are recognized in the first few months of life, leading to diagnosis by 6 months of age and then death due to respiratory failure by age 2 years. Motor neuron loss in SMA Type 1 is profound in the early postnatal period (or may even start in the pre-natal period), whereas motor neurons in Type 2 and 3 SMA patients adapt and compensate during development and persist into adult life. The findings from various neurophysiological and animal studies have shown an early loss of motor neurons in the embryonic and early postnatal periods (Swoboda et al 2005, Le et al 2011, Farrar et al 2013).

SMN protein depletion is the root cause across all SMA patient phenotypes and the disease pathogenesis, regardless of age. SMA is caused by abnormally low levels of the ubiquitously expressed SMN protein, resulting from a combination of homozygous deletions or mutations of the telomeric copy of the SMN gene (SMN1) on chromosome 5q and the presence of 1 or more copies of SMN2 (Lefebvre et al 1995), an almost identical but only partially functional centromeric copy which is unique to humans (Rochette et al 2001). The relevant difference

between these two genes, a single nucleotide transition at exon 7, affects a splice site enhancer such that the majority of transcripts of SMN2 lack exon 7 (SMNΔ7), resulting in greatly reduced levels of functional, full-length SMN protein (Monani et al 1999). When the SMN1 gene is unable to supply SMN protein to the motor neurons, the only source of SMN protein is the SMN2 gene. The amount of neuronal SMN protein determines patient phenotype primarily by the number of SMN2 genes.

In support of the hypothesis that gene copy numbers of SMN2 primarily drive phenotypic presentation of SMA, a large review examined the association between SMN2 copy number and SMA phenotype (Calucho et al 2018). The authors showed that 79% of patients with two copies of SMN2 developed SMA Type I, 16% developed SMA Type 2 and 5% developed SMA Type 3; 54% of patients with three copies of SMN2 developed SMA Type 2, 31% developed SMA Type 3 and 16% developed SMA Type 1; and among patients with four copies of SMN2, most had mild SMA variants with only 1% developed SMA Type 1 and 11% developed SMA Type 2. In keeping with the importance of SMN production by SMN2, few individuals with SMN1 mutations and >=6 copies of SMN2 develop symptoms and those who are affected develop only mild forms of SMA (Bernal et al 2010, Riessland et al 2017). SMN is part of the machinery which assembles spliceosomal components (Pellizzoni et al 1998). Ventral spinal cord motor neurons are specifically sensitive to SMN deficiency and are affected in all types of SMA (Burghes and Beattie 2009).

Irrespective of phenotypic classification, expert consensus is that all patients with biallelic pathogenic SMN1 variants and up to 4 SMN2 copies should receive SMN dependent therapy (Glascock et al 2018, Glascock et al 2020). Therapeutically increasing SMN levels leads to the most striking results in patients with SMA Type 1 (Mercuri et al 2018, Pechmann et al 2019, Pane et al 2019, Aragon Gawinska et al 2020). These results are thought to be most beneficial with early intervention, preventing neurodegeneration and the associated progressive deterioration that is seen in all Type 1 SMA infants. These patients now experience improvement in their functional abilities and attain developmental milestones that had never previously been achieved in this population (Mercuri et al 2018, Pechmann et al 2018, Pane et al 2019, Aragon Gawinska et al 2020). A proportion of these infants acquire the ability to sit independently, and treatment can enable them to stand (usually with support), depending on how soon treatment is initiated after onset of symptoms. In children with SMA Type 2, treatment also clearly reduces progression of the disease compared with the natural history. For these patients, to stand alone and develop the ability to walk with or without support is a possibility.

SMA is conventionally classified into 4 phenotypes on the basis of age of onset and highest motor function achieved, with an additional phenotype (Type 0) to describe the severe forms of antenatal-onset spinal muscular atrophy (Kolb and Kissel 2011, Mercuri et al 2012). SMA Type 1 patients present with symptoms within the first 6 months of life, the most prominent being lack of head

control, and by definition never attain independent sitting. SMA Type 1 is the leading genetic cause of infant death. In contrast, SMA Type 2 manifests within the first 18 months of life and follows a slower disease progression as compared to SMA Type 1. Children with SMA Type 2 are able to maintain sitting unassisted but never walk independently and have a life expectancy of 20-40 years of age. SMA Type 3 patients attain the ability to walk unaided (Type 3a have onset <3 years of age; Type 3b have onset > 3 years of age). SMA Type 4 is an adult-onset form of the disease. Figure 1 1 summarizes SMA subtypes and associated clinical features as well as the relationship of the SMA subtypes to SMN2 gene copy numbers.

OAV101 gene therapy mechanism of action: OAV101 is a single treatment for patients with 5q SMA. OAV101 is a non-replicating recombinant adeno*associated virus serotype 9 (AAV9) containing the human SMN complementary deoxyribonucleic acid (cDNA) under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid (CB) promoter (Figure 1 2). One of the two adeno-associated virus (AAV) inverted terminal repeats has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription.

The mechanism of action of OAV101 is the delivery of a functional copy of the gene encoding for the SMN protein into target cells, the loss of which is the root cause of all forms of (5q) SMA. The goal is to increase SMN protein levels in motor neurons prior to the development of irreversible injury and motor neuron loss, thereby modifying the patient*s SMA phenotype to a milder course with improved quality of life and prolonged survival.

Recombinant AAVs are not known to actively integrate into the host genome, but rather persist episomally within the target cells. Thus, its expression is eventually lost in a dividing cell population (Hudry and Vandenberghe 2019). OAV101 is specifically designed to form a circular concatemeric transgene that harbors even lower potential for deoxyribonucleic acid (DNA) integration or alteration. Moreover, AAVs cannot replicate within the host cell in absence of a helper virus, such as adenovirus, herpes simplex virus, human papillomavirus or vaccinia virus for productive infection.

Study objective

This study has been transitioned to CTIS with ID 2024-511707-42-00 check the CTIS register for the current data.

The purpose of this study is to collect long-term follow-up safety and efficacy data on patients with SMA who were treated with OAV101 by IV or IT administration. Safety and efficacy will be assessed for 15 years following OAV101 administration.

Study design

This is a global, prospective, multi-center study that is designed to assess the long-term safety and efficacy of OAV101 in participants who participated in OAV101 clinical trials. The assessments of safety and efficacy in Study COAV101A12308 will continue for 15 years from the date of OAV101 administration in the parent study. The number of study visits required in this long-term follow-up will depend on the length of time since the OAV101 administration. For example, patients followed for 1 year in the parent study will participate for up to 14 years following an immediate and seamless transition from the parent study (End of Study (EOS) Visit) to the Enrollment Visit in Study COAV101A12308.
The study is comprised of a Baseline Period and 3 Follow-up Periods (Table 8-1). Follow-up Periods 1 and 2 consist of in-person visits and Period 3 consists of tele-visits.
For Follow-up Periods 1 and 2, which includes Baseline through Year 5 visits, assessments will be performed at the Investigational site. For the first 2 years (Follow-up Period 1), visits will occur every 6 months. For Years 3 to 5 (Follow-up Period 2) follow-up visits will be conducted annually.
During Follow-up Period 3 (Year 6 to up to Year 15 after OAV101 administration), participants/caregivers will be contacted using tele-visits annually for remote assessments. All patients will enter the study at the baseline visit and continue until 15 years since OAV101 administration is reached. Total duration of participation in the study will be dependent upon time of enrollment relative to OAV101 administration and will vary by participant.

Study burden and risks

N/A

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

Participants eligible for inclusion in this study must meet all of the following criteria:
1. Participated in an OAV101 clinical trial.
2. Written informed consent must be obtained before any assessment is performed.
3. Patient/Parent/legal guardian willing and able to comply with study procedures.

Exclusion criteria

There are no specific exclusion criteria for this study.

Study design

Design

Study phase:	3
Study type:	Observational invasive
Masking:	Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2023
Enrollment:	2
Type:	Anticipated

Ethics review

Approved WMO Date:	26-01-2023
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-04-2024
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-04-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-05-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-511707-42-00
EudraCT	EUCTR2021-006781-21-NL
CCMO	NL83125.000.23
Other	US NCT number: NCT05335876 EudraCT Number: 2021-006781-21