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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Zolgensma

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Procedure no: EMEA/H/C/004750/P46/018

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 03 December 2021, the MAH submitted a completed paediatric study for Spinal Muscular Atrophy Type 1 with One or Two SMN2 Copies, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure(s).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study AVXS-101-CL-306, Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1 With One or Two SMN2 Copies Delivering AVXS-101 by Intravenous Infusion, is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

AVXS-101 is a gene therapy biological product that encodes for the human SMN (hSMN) protein. AVXS-101 is comprised of a non-replicating, non-integrating recombinant self-complementary adeno-associated virus serotype 9 (AAV9) capsid shell containing the cDNA of the human SMN gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB) as well as 2 AAV inverted terminal repeats (ITR) from the AAV serotype 2 (AAV2) DNA. The SMN gene present in AVXS-101 is designed not to integrate into the patient chromosome, but rather to reside as a DNA episome in the nucleus of transduced cells. AVXS-101 contains no DNA from the wild-type AAV9, rendering AVXS-101 incapable of replicating itself. AVXS-101 is designed to increase the expression levels of the SMN protein in the motor neurons before the onset of irreversible motor neuron loss.

AVXS-101 infusion was administered under sterile conditions in a paediatric intensive care unit or other appropriate setting (e.g., interventional suite, operating room, dedicated procedure room) with immediate access to acute critical care management.

Investigational product provided is listed in Table 1.

Table 1 Investigational product

	Investigational product
Product Name	AVXS-101 (OAV101)
Unit Dose	1.1E14 vg/kg
Route of Administration	IV infusion
Physical Description	Clear, colorless to faint white solution
Batch (lot) number	

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- AVXS-101-CL-306; Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two SMN2 Copies Delivering AVXS-101 by Intravenous Infusion

2.3.2. Clinical study

Description

This was a Phase 3, open-label, single-arm, single-dose, gene replacement therapy study to investigate the efficacy and safety of a single IV infusion of AVXS-101 (also known as OAV101) in patients with SMA Type 1 with 1 or 2 copies of the SMN2 gene. Eligible patients were < 6 months (< 180 days) of age at the time of administration of AVXS 101 (Day 1). The study was conducted in Asia.

Methods

Study participants

Main Inclusion criteria:

1. Patients with SMA Type 1 as determined by diagnosis of SMA based on gene mutation analysis with bi-allelic *SMN1* mutations (deletion or point mutations) and 1 or 2 copies of *SMN2* (inclusive of the known *SMN2* gene modifier mutation (c.859G>C)).
2. Patients must be < 6 months (< 180 days) of age at the time of AVXS-101 infusion.
3. Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy.

Main Exclusion criteria:

1. Previous, planned or expected scoliosis repair surgery/procedure prior to 18 months of age
2. Use of invasive ventilatory support (tracheotomy with positive pressure) or pulse oximetry < 95% saturation at screening
    a. Pulse oximetry saturation must not decrease ≥ 4 percentage points between screening and dosing with confirmatory oximetry reading
    b. Patients may have been put on non-invasive ventilatory support for less than 12 hours per day at the discretion of their physician or trial staff
3. Use or requirement of non-invasive ventilatory support for 12 or more hours daily in the two weeks prior to dosing
4. Patient with signs of aspiration based on a swallowing test or whose weight-for-age fell below the 3rd percentile based on WHO Child Growth Standards (WHO-MGRS 2006a) and unwilling to use an alternative method to oral feeding
5. Anti-AAV9 antibody titre > 1:50 as determined by enzyme-linked immunosorbent assay (ELISA) binding immunoassay. If a potential patient demonstrated anti-AAV9 antibody titre > 1:50, he or she may have retested within 30 days of the screening period and been eligible to participate if the anti-AAV9 antibody titre upon retesting was ≤ 1:50
6. Clinically significant abnormal laboratory values (GGT, ALT, AST, total bilirubin > 2× the ULN, creatinine ≥ 1.0 mg/dL, haemoglobin < 8 or > 18 g/dL; WBC > 20,000 per cmm) prior to gene

replacement therapy. Patients with an elevated bilirubin level that was unequivocally the result of neonatal jaundice should have not been excluded.

7. Patients < 35 weeks gestational age at time of birth

CHMP comments

The main inclusion criteria for study CL-306 were identical to the inclusion criteria for the pivotal study of the initial MAA (CL-303), which is appreciated.

The main exclusion criteria are largely comparable to the exclusion criteria used in the pivotal study. However, slight differences were observed in exclusion criteria with respect to oxygen saturation and use of non-invasive ventilatory support: pulse oximetry could be <95% in the current CL-306 study compared to <96% in the pivotal study and use of non-invasive ventilatory support for 12 or more hours daily in the 2 weeks prior to screening in the current study compared to <6 hours/day in the pivotal trial. This could potentially allow slightly worse patients to be included in the current study, which could impact the treatment outcome.

Of note, the exclusion criteria used in the current study are identical to the exclusion criteria used in study AVXS-101-CL-302, which was designed as the European counterpart of the pivotal study CL-303.

Treatments

AVXS-101 was delivered one time through a venous catheter inserted into a peripheral limb vein (arm or leg) at a dose of 1.1E14 vg/kg. AVXS-101 was slowly infused over approximately 60 minutes.

In the original protocol, patients were to be given prophylactic prednisolone 1 mg/kg/day starting on Day -1 until at least 30 days post-AVXS-101 infusion. Patients enrolled per Global Protocol v4.0 Amendment 3 and afterward were to be given prophylactic prednisolone at approximately 2 mg/kg/day or an equivalent dose of another glucocorticoid if prednisolone was unavailable or in the opinion of the Investigator prednisolone was not tolerated, on Day -1, Day 1, and Day 2, and then 1 mg/kg/day starting on Day 3 and until at least 30 days post-AVXS-101 infusion. After 30 days post-AVXS-101 infusion, the dose of prednisolone was tapered for patients whose GGT, ALT, and AST values were below the threshold of 2 × ULN.

CHMP comments

Patients received a single dose of AVXS-101 at a dose of 1.1×10^{14} vg/kg, which is identical to the posology recommended in the SmPC.

Prophylactic prednisolone treatment in the study was altered during the study to align with the urgent safety measure implemented March 2019. Prophylactic prednisolone is used to dampen the immune response to the adeno-associated virus (AAV) derived therapy. The SmPC recommends the use of 1 mg/kg/day prednisolone from 24 hours prior to AVXS-101 treatment to 30 days post infusion. At the MAA, it was not considered sufficiently substantiated that a higher dose was more effective in suppressing anti-AAV immunity and therefore, the 1 mg/kg/day dose was included in the SmPC, however, investigation of a higher dose of prednisolone pretreatment (2 mg/kg/day for the first 3 days) was agreed. It is expected that if and when evidence to substantiate the 2 mg/kg/day dose is available, the applicant will assess whether an amendment of the SmPC is necessary.

Objectives/Endpoints

Primary

• Determine efficacy by demonstrating achievement of developmental milestone of sitting without support for at least 10 seconds at 18 months of age as defined by WHO Motor Developmental Milestones.

Secondary

• Determine efficacy based on survival at 14 months of age. Survival is defined by the avoidance of combined endpoint of either (a) death or (b) permanent ventilation which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

Exploratory

• Achievement of motor milestones, CHOP-INTEND scores and Bayley's scale scores are amongst the exploratory endpoints of this study.

CHMP comments

The endpoints included in the study are agreed. Scientific advice on the design of Study CL-303 received on 26 JAN 2017, considered that a primary endpoint of "Independent sitting for at least 10 seconds at the 18-month study visit" was clinically relevant. In addition, the secondary endpoint of event-free survival, with events defined as either death or permanent (≥16 hours per day) ventilatory support, at 14 months of age, is a widely recognized and clinically meaningful endpoint.

The endpoints defined in the current study are identical to the endpoints used for study CL-302.

Sample size

The study was originally designed to have sufficient power, when combined with an identically designed study AVXS-101-CL-302 (COAV101A12301), to establish efficacy with regard to the primary and secondary endpoints. Due to the narrowed scope in sample size and change in data analysis of AVXS-101-CL-306 (COAV101A12304), no combined analysis or stand-alone analysis were conducted.

CHMP comments

As scope of the study changed and no statistical analysis was planned anymore, sample size calculation became superfluous.

The study changed to an exploratory study. Sample size is limited, but can be accepted based on rarity of the disease.

Randomisation and blinding (masking)

Not applicable as this was an open-label, single arm study.

CHMP comments

The open-label design without a comparator arm was considered acceptable given the expected effect size and well characterized natural history.

Statistical Methods

The final analysis was primarily composed by individual data listings and patient profiles after the final database lock. No inferential statistical approaches were performed.

CHMP comments

Only descriptive analyses were performed. Based on sample size (n=2) this is acceptable.

Results

Participant flow

A total of 2 patients were enrolled and received AVXS-101 treatment; both enrolled patients completed the study. Three patients failed to be enrolled due to screen failure. No enrolled patients had the SMN2 gene modifier mutation (c.859G>C) based on genetic reconfirmation.

CHMP comments

It is reassuring that both participants enrolled in the study completed the study.

Recruitment

The study was conducted in 1 study centre.

First participant first visit was on 31 May 2019 and last subject last visit took place on 29 Jun 2021.

Baseline data

The demographic and baseline characteristic for the Safety population are summarized in Table 2.

Both patients had biallelic deletion mutations of SMN1 (exon 7/8 common homozygous deletions) and 2 copies of SMN2. Subject displayed hypotonia at baseline, while subject displayed both absence of deep tendon reflex and hypotonia.

CHMP comments

Both participants were symptomatic at baseline, had bi-allelic deletion of the SMN1 gene and 2 copies of the SMN2 gene. Both displayed symptoms from birth and were diagnosed within 2 weeks of birth.

Based on the more extensive surgical history for subject, subject appeared to have a more severe SMA phenotype. This could impact outcome measures.

Number analysed

The ITT population consisted of symptomatic patients with biallelic deletion mutations of SMN1 (exon 7/8 common homozygous deletions) and 2 copies of SMN2 without the known gene modifier mutation (c.859G>C) who receive an IV infusion of AVXS-101 at less than 180 days of age.

The All Enrolled population and safety population consisted of all patients who received an IV infusion of AVXS-101.

The All Enrolled, ITT, and Safety populations are equivalent and included 2 enrolled patients.

CHMP comments

All participants were analysed.

Efficacy results

Primary efficacy results

Patient achieved the primary endpoint of 'sitting without support' at the age of 12.7 months (380 days), which was outside of the normal developmental window (age ≤ 279 days); Patient did not achieve the primary endpoint during the study.

CHMP comments

One patient reached the primary endpoint and 1 did not. These numbers are too small to draw any meaningful conclusions. This result is in line with the results of study CL-302 in which 43.8% of the ITT population achieved the primary endpoint of sitting without support for at least 10 seconds at any visit up to and including the 18 month visit.

During the pivotal study, 63.6% of participants achieved sitting without support for at least 10 seconds.

Secondary efficacy results

Both patients survived event-free, defined as avoidance of either death or permanent ventilation, ≥ 14 months of age; both patients survived event-free at 18 months of age.

CHMP comments

The result of event-free survival to ≥ 14 months of age is in line with the results of study CL-302 in which 96.9% of the ITT population achieved this endpoint. In addition, it is also in line with study CL-303, in which 20 out of 22 enrolled patients (90.9%) survived event-free to both 14 and 18 months of age.

Exploratory efficacy results

Developmental milestones:

- Patient achieved the developmental milestone of 'rolls from back to sides' as defined by Bayley criteria.
- Patient achieved developmental milestones of 'head control', 'rolls from back to sides', 'sits without support' as defined by Bayley criteria; and 'sitting without support' (primary endpoint) as defined by WHO-MGRS criteria.

Bayley scales of infant and toddler development fine and gross motor subtests:

- Patient showed a 23-point improvement in Fine Motor subtest raw score from 3 points at baseline to 26 points at Age 18 Month Visit. The patient's Gross Motor subtest raw score increased from 0 at baseline to 8 points at Age 18 Months Visit.

- Patient showed a 32-point improvement in Fine Motor subtest raw score from 3 points at baseline to 35 points at Age 18 Month Visit. The patient's Gross Motor subtest raw score increased from 4 points at baseline to 29 points at Age 18 Months Visit.

CHOP INTEND:

- Patient showed a 31-point improvement in CHOP INTEND score from 20 total score at baseline to 51 total score at Age 18 Months Visit.
- Patient showed a 14-point improvement in CHOP INTEND score from 46 total score at baseline to 60 total score at Age 18 Months Visit

Independence of ventilation support:

- Patient received non-invasive ventilatory support (BiPAP) starting on Day 61 and ongoing at the last study visit. The reason for ventilatory support was due to progression of disease without acute cause. Patient also received cough assist during Day 362 to Day 461
- Patient achieved independence of ventilatory support at all timepoints through the study.

Independence of nutritional support:

- Patient received feeding support of nasogastric tube from Day -6 to Day 465 and gastrostomy tube from Day 466 and ongoing at the last study visit.
- Patient did not require any feeding support during the study.

Ability to thrive

The ability to thrive was defined as the ability to tolerate thin liquids, not requiring nutrition through mechanical support, and maintaining weight consistent with age. Using this definition, no patients achieved the ability to thrive at any post-dose time points including the Age 18 Months Visit.

CHMP comments

First and foremost, the number of participants, 2, is too small to draw any firm conclusions.

Both patients achieved motor milestone(s), confirmed by independent central video review. Both patients achieved "rolls from back to sides", while only the participant who achieved the primary efficacy endpoint also achieved developmental milestones of 'head control', 'sits without support' as defined by Bayley criteria. In both studies CL-303 and CL-302 patients achieved motor milestones.

Both participants showed an improvement in performance on both the Bayley Scales gross motor and fine motor subtests. This is in line with the previous studies CL-303 and CL-302. Absent gene replacement therapy, few untreated children with SMA type 1 would ever achieve a raw score greater than zero on the gross motor subtest. Both participants achieved higher raw scores on the gross motor subset: achieved a raw score of 8 at End of study Visit and subject achieved a score of 29. However, the scaled score, reflecting performance according to age as compared with other, normally-developing children of the same age, was 1 for both patients. As the mean score is 10, with SD of ± 3 points; this indicates that they fell outside the 2SD of normal development.

Both patients achieved a CHOP-INTEND score ≥50 at age 18 months. Patients with untreated SMA Type 1 almost never achieve a CHOP-INTEND score ≥ 40. Again, the results are in line with the both study CL-303 and CL-302, in which improvement of CHOP-INTEND scores were seen: with 63.6% of

patients achieving a CHOP-INTEND score of ≥50 during study CL-303 and 42.4% of patients during study CL-302.

Of note, the CHOP-INTEND baseline score of 46 at baseline for patient is considered high, however, based on natural history the CHOP-INTEND score should decline over time as irreversible damage increases. Therefore, the increase in CHOP-INTEND score is still considered a clinical benefit of the treatment.

Of the 2 patients in the current study, 1 did not require any form of ventilation support while the other receive BiPAP during the study. These results are in line with study CL-302, as 42.4% did not require ventilatory support and 57.6% used BiPAP, and study CL-303, as 15 of 22 patients (68.1%) did not require any non-invasive ventilatory support at any point during the study.

Of the 2 patients in the current study, 1 did not require any feeding support while the other received feeding support by nasogastric tube and gastrostomy (with Nissen fundoplication). During study CL-302 12 patients (36.4%) received feeding support.

Both patients did not thrive. Subject received feeding support and did not maintain weight ≥3rd percentile. Subject was not able to maintain weight ≥3rd percentile. During study CL-303, 40.9% of patients were able to thrive, defined as the ability to tolerate thin liquids, to not receive nutrition through mechanical support, and to maintain weight consistent with age.

Safety results

The safety of IV administration of AVXS-101 in patients with SMA Type 1 has been assessed in the completed Study AVXS-101-CL-306.

CHMP comments

The study was open-label and patients received a single infusion intravenous. The patients were followed up to an age of 18 months, indicating a relatively limited follow-up time.

The assessment of safety in this study is limited, as only 2 patients were included in the study. In addition, the assessment of safety is hampered by the fact that the AE's reported could also be related to SMA type 1 and it's complications and, due to common childhood diseases or both.

Patient exposure

AVXS-101 was administered as an IV infusion under the supervision of the investigational site personnel. The treatment compliance - as determined by total volume administered/planned weight-adjusted dose administered - was 100% for each patient, see Table 3.

Table 3 Study treatment exposure and compliance

Patient ID	Gender/ age at time of dosing	Start time/stop time/duration (min)	Planned dose in volume (mL)	Total dose volume administered (mL)	Compliance (%)[1]	Infusion interrupted? If yes, reason
		10:20/11:36/76	22.0	22.0	100	Yes Mechanical/ technical
		10:25/11:30/65	19.3	19.3	100	No

[1] Percentage compliance (%) = 100% × total volume administered/total planned volume administered.
Source: Listing 16.2.5.1

CHMP comments

Patients were treated with AVXS-101 according to posology recommended in the SmPC.

Adverse Events

All patients experienced at least 1 TEAE during the study, with an overall total of 30 TEAEs. An overview of TEAEs is provided in Table 4. None of the TEAEs, SAE, or AESI was considered related to AVXS-101 by the Investigator.

Table 4 Overview of TEAEs (Safety population)

Adverse event category	AVXS-101 (N = 2) n (%) [number of events]
Any TEAE	2 (100) [30]
TEAEs related to study treatment	0
TEAEs of Grade 3 severity or higher	1 (50) [1]
Serious TEAEs	1 (50) [1]
Serious TEAEs related to study treatments	0
TEAEs leading to study discontinuation	0
TEAEs leading to death	0
Adverse events of Special Interest	1 (50) [1]
Hepatotoxicity	0
Thrombocytopenia	1 (50) [1]
Cardiac adverse events	0
Sensory abnormalities suggestive of ganglionopathy	0
Thrombotic microangiopathy	0

Note: Percentages are based on the number of patients in the population. For each catagory, patients are included only once, even if they experienced multiple events in that category.
Source: Table 14.3.1.1

CHMP comments

Both patients experienced at least 1 TEAE. In total 30 TEAEs were observed. Most being mild to moderate in intensity, as only 1 ≥ grade 3 TEAE occurred during the study.

Treatment Emergent Adverse Events

A summary of TEAEs by SOC and PT is provided in Table 4. The most frequently reported TEAEs by PT were dysphagia, pyrexia, and upper respiratory tract infection.

None of the TEAEs were considered related to the treatment

Table 5 TEAEs overall by system organ class and preferred term (Safety population)

System Organ Class Preferred Term	AVXS-101 (N = 2) n (%) [number of events]
Any TEAE	2 (100) [30]
Congenital, familial and genetic disorders	1 (50) [1]
Cleft palate	1 (50) [1]
Gastrointestinal disorders	2 (100) [8]
Dysphagia	2 (100) [4]
Gastrointestinal hypomotility	1 (50) [1]
Gastrooesophageal reflux disease	1 (50) [1]
Hiatus hernia	1 (50) [1]
Upper gastrointestinal haemorrhage	1 (50) [1]
General disorders and administration site conditions	1 (50) [4]
Pyrexia	1 (50) [4]
Infections and infestations	2 (100) [7]
Gingivitis	1 (50) [1]
Pharyngitis	1 (50) [1]
Upper respiratory tract infection	1 (50) [4]
Urinary tract infection	1 (50) [1]
Investigations	1 (50) [1]
Glucose urine present	1 (50) [1]
Metabolism and nutrition disorders	2 (100) [2]
Failure to thrive	2 (100) [2]
Renal and urinary disorders	1 (50) [1]
Glycosuria	1 (50) [1]
Respiratory, thoracic and mediastinal disorder	1 (50) [3]
Respiratory distress	1 (50) [1]
Rhonchi	1 (50) [1]
Tachypnea	1 (50) [1]
Skin and subcutaneous tissue disorder	1 (50) [3]
Dermatitis diaper	1 (50) [1]
Eczema	1 (50) [1]
Rash	1 (50) [1]

Source: Table 14.3.1.2

CHMP comments

Both patients were reported to experience any adverse event (AE). When compared at the MedDRA system organ class level, most AE's were reported for the domain Gastrointestinal disorders, Infections and Infestations, Respiratory, Thoracic and Mediastinal Disorders and Skin and Subcutaneous Tissue Disorders (see Table 5). This is comparable to the AEs observed in the studies submitted during MAA.

Some of the observed AE's may fit with the normal development of infants; like common childhood infections (e.g. pharyngitis, upper respiratory tract infection), dermatitis diaper and rash. Others may also be disease related such as failure to thrive, respiratory events or dysphagia.

In subject, the first reported TEAE (respiratory distress) occurred 14 days after treatment. All TEAEs were considered unrelated. Pyrexia occurred at the earliest 90 days after treatment for this patient. It

is agreed that this is considered unrelated. All TEAEs, except for 1 occurrence of dysphagia (grade 3), were mild (grade 1) in intensity. All TEAEs resolved, except for failure to thrive and dysphagia.

In subject, the first reported TEAE (acute upper respiratory infection) occurred 9 days after treatment. All TEAEs were considered unrelated by the investigator. This can be agreed. However, the first TEAE of acute upper respiratory infection could potentially be related to prednisolone treatment. All TEAEs were mild in intensity. Three TEAEs were considered unresolved at study termination: failure to thrive, submucosal cleft palate and dysphagia.

Adverse Events of special interest

Five categories of AESIs were assess in this study: hepatotoxicity, thrombocytopenia, cardiac adverse events, thrombotic microangiopathy, and sensory abnormalities suggestive of ganglionopathy.

No treatment-emergent AESIs were identified in hepatotoxicity, cardiac adverse events, thrombotic microangiopathy, and sensory abnormalities suggestive of ganglionopathy related SMQs.

Patient experienced a thrombocytopenia-related AESI of upper gastrointestinal haemorrhage (Day 326 to Day 448) by PT (Listing 16.2.7.8.2). The event was Grade 1 (mild) in severity; it was resolved and considered not related to the study treatment by the Investigator. The event of upper gastrointestinal haemorrhage was not associated with a low platelet value as the platelet counts for this patient were within the normal range of 189-459 × 10^9/L during this period.

CHMP comments

The AE of upper gastrointestinal haemorrhage mapped to the thrombocytopenia category and was therefore considered an AESI. The narrative detailed the following:

On 06-Jun-2019 (Day -1), the local laboratory value included platelet counts of 425 × 10^9/L (RR: 229-597 ×10^9/L). On 27-Apr-2020 (Day 326), the subject developed upper gastrointestinal haemorrhage (grade 1, no laboratory values reported). No treatment was reported. On 27-Aug-2020 (Day 448), the subject recovered from upper gastrointestinal haemorrhage. On the same day, the local laboratory value included platelet counts of 319 × 10^9/L (RR: 189-459 × 10^9/L).

Based on the listings of clinical haematology values, platelet counts were within normal range during the period that the upper gastrointestinal haemorrhage occurred. It is therefore agreed that this AESI does not indicate sign of thrombocytopenia and is not considered related to the treatment.

Serious adverse events and deaths

Patient experienced an SAE of dysphagia that led to a hospitalization. The event occurred on Day 462 and was resolved on Day 470 without treatment. The SAE was considered not related to the study treatment by the Investigator.

No patient died during the study.

CHMP comments

On 02-Dec-2019 (Day 179), subject developed dysphagia (grade 1, non-serious), which worsened to grade 3 on 10-Sep-2019 (Day 462). The patient underwent gastrostomy and laparoscopic nissen fundoplication surgery. On 19-Sep-2019, dysphagia improved to grade 1. It is agreed that the dysphagia is most likely caused by the underlying disease.

Laboratory Findings

Haematology

High levels of haemoglobin that were outside of normal range were observed in both patients. At Visit 13 (Month 8), Patient (age 9.3 months) had a haemoglobin value of 157 g/L (normal range: 101-127 g/L) that was flagged as PCS (> 155 g/L).

CHMP comments

Both patients showed transient increased haemoglobin and haematocrit values at numerous times during the study, however they were more consistently seen in patient. Patient had high levels of haemoglobin (above normal range of 101-127 g/L) starting Month 6, which returned to within normal range after Month 17 and was ≥155 g/L only at Month 8. Due to the delayed onset (Month 6), the abnormal post-baseline haemoglobin levels are most probably related to the underlying disease (oxygenation and ventilation requirements).

Patient had high levels of leukocytes (18.9 $*10^9$/L; normal range 6-14.99$*10^9$/L) at Month 4 (PCS; >17.5), which returned to normal level the following visit.

Considering the fact that increases were transient in nature and seen in previous studies, these findings were not considered a new safety signal.

Clinical chemistry

Transient elevations in transaminase values were observed. No patients with a Grade 3 ALT, AST, alkaline phosphatase or total bilirubin were reported. No patients meeting the ALT $\geq 3\times$ ULN and total bilirubin value $\geq 2\times$ ULN criterion were reported.

High levels of troponin were flagged for both patients:

- Patient had troponin values of 0.098 ug/L at screening, 0.114 µg/L at Day 7, and 0.121 µg/L at Day 30 that were outside of the normal range (0-0.039 µg/L) and flagged as potentially clinically significant (PCS; > 0.05 µg/L).
- Patient had a troponin value of 0.067 µg/L (normal range: 0-0.039 µg/L) at screening that was flagged as PCS (> 0.05 µg/L).

High level of bilirubin was also flagged for patient at screening; this patient had a bilirubin value of 166.72 µmol/L (normal range: 5.13-17.1 µmol/L) that was marked as PCS (>33.4 µmol/L). This event was considered to be neonatal jaundice by the Investigator and documented in the medical history.

CHMP comments

Both patients had increased levels of alkaline phosphatase from screening (grade 1) that remained high throughout the study period. This increase is therefore not considered transient. As it was present at screening, it is not considered related to the treatment.

Transient increases in ALT and AST were observed (all not over grade 1) for patient. Patient did not show any increases in ALT, while AST was increased from Month 7 until end of the study, all measurements not over CTCAE grade 1. As the AST was ongoing at end of study it is not considered transient. However, similar increases in AST that were ongoing at study end were observed in the pivotal study CL-303. This is not considered a new safety signal.

Levels of troponin-I outside protocol criterion (> 0.05 µg/L) were observed for both patients from screening up till Month 2. Of note, a study of 869 healthy infants defined the upper reference limit for cardiac troponin I in healthy term new-borns as 0.183 µg/L. None of the patients in Study CL-306 had cardiac troponin I levels exceeding this value.

Transient increases and decreases in bilirubin and direct bilirubin were observed for patient. In patient, a potentially clinically relevant increase in bilirubin was observed at screening, considered related to neonatal jaundice, which is agreed. The levels of bilirubin and direct bilirubin, decreased to normal values at Day 7 after treatment with AVXS-101. Transient decreases in bilirubin were seen throughout the study.

The only potentially clinically relevant findings, outside screening, were on troponin I, which considering these findings were within the reference value of 0.183 µg/L, obtained from a study using 869 infants, is not considered clinically relevant.

None of the laboratory values were considered an AE of grade 3 of higher. None of the patients had ALT ≥ 3x ULN or total bilirubin ≥ 2x ULN. The clinical chemistry did not reveal any new safety signals.

Urinalysis

No clinical meaningful findings in urinalysis were noted.

CHMP comments

For patient, an AE of glucose in urine was reported at Day 476. In the urinalysis listing at Day 476 a glucose result of 2000 (4+) was reported (no normal range presented), where it was negative previously. The AE is considered resolved at Day 478, however at end of study glucose measures 250 (2+). The MAH is asked to present the corresponding unit for glucose for the test to determine whether the measurement of 250 is considered within normal range (**OC**).

Discontinuations due to AEs

No study discontinuation is reported.

CHMP comments

None of the participants discontinued.

Immunological events

Both treated patients had anti-AAV9 antibody titres of ≤ 1:50 at screening as required by the study protocol, and patients' biological mothers also had anti-AAV9 antibody titres of ≤ 1:50 at screening.

Both treated patients had a treatment-induced anti-AAV9 antibody response:

- Patient had anti-AAV9 antibody titres of <1:50 on Day 7, 1:800 on Day 14, 1:3200 on Day 21, and 1:6400 on Day 30.
- Patient had anti-AAV9 antibody titres of 1:1600 on Day 7 and 1:800 on Day 14, Day 21, and Day 30.

All patients had an anti-hSMN titre of < 1:12.5 at baseline. No post-treatment increases in anti-SMN antibody titres were observed.

CHMP comments

Anti-AAV9 titres > 1:50 at baseline was one of the exclusion criteria. Both patients had anti-AAV9 antibody titres of ≤ 1:50; patient 037-001 1:12.5 and patient 037-002 ≤ 1:12.5. At follow-up, increase in Anti-AAV9 titres was observed as expected after a pseudo-viral infection.

No immunological response was observed for hSMN. This is expected since SMN1 is an endogenous protein also present in SMA although in insufficient amounts.

2.3.3. Discussion on clinical aspects

For this Article 46 procedure, the MAH submitted the final report for study AVXS-101-CL-306, which was a phase 3, open-label, single-arm, single-dose gene replacement therapy study to investigate the efficacy and safety of a single IV infusion of AVXS-101 (also known as OAV101) in patients with SMA Type 1 with 1 or 2 copies of the SMN2 gene.

Design of the study

The design of the study was identical to study AVXS-101-CL-302, which was designed as the European counterpart for study AVXS-101-CL-303 (the pivotal study included in the MAA submission). Patients received a single dose of AVXS-101 at a dose of 1.1 x 1014 vg/kg, which is identical to the posology recommended in the SmPC. The SmPC recommends the use of 1 mg/kg/day prednisolone from 24 hours prior to AVXS-101 treatment to 30 days post infusion, however, during the current study a dose of 2 mg/kg/day was used. The investigation of a higher dose of prednisolone pre-treatment (2 mg/kg/day for the first 3 days) has been agreed during the MAA procedure.

The scope of the study changed, as the results of the current study were supposed to be combined with the results of study AVXS-101-CL-302 which, over the course of the study, was not considered relevant anymore due to sufficient evidence of efficacy in study AVXS-1014-CL-302 alone. The study changed to an exploratory study.

Sample size is extremely limited with 2 participants. The sample size precludes any conclusions being drawn from this study. Only descriptive analyses were performed.

Both participants were symptomatic at baseline, had bi-allelic deletion of the SMN1 gene and 2 copies of the SMN2 gene. Both displayed symptoms from birth and were diagnosed within 2 weeks of birth (at day 8 and at day 11). Based on the more extensive surgical history for subject, subject appeared to have a more severe SMA phenotype, which could potentially impact outcome measures.

Efficacy results

As stated previously, due to the limited sample size (n=2) no firm conclusions can be drawn based on this study.

Patient achieved the both primary and secondary endpoints, while patient only achieved the secondary endpoint of event-free survival. Compared to patient, patient overall developed better achieving more motor milestones, higher improvement on Bayley Scales gross motor and fine motor subtests and higher CHOP-INTEND scores. Patient did not require any type of ventilation or feeding support, while patient required BiPAP and feeding support. This might be due to the fact that patient appeared to have a less severe phenotype at baseline.

Overall, treatment benefit was shown by the fact that both patients achieved event-free survival at both 14 months and 18 months of age. In addition, both patients achieved a CHOP-INTEND score ≥50

at age 18 months. Patients with untreated SMA Type 1 almost never achieve a CHOP-INTEND score ≥ 40.

However, both patients showed a failure to thrive. Subject received feeding support and did not maintain weight ≥3rd percentile. Subject was not able to maintain weight ≥3rd percentile. In addition, the scaled Bayley score, reflecting performance according to age as compared with other, normally developing children of the same age, was 1 for both patients. As the mean score is 10, with SD of ± 3 points; this indicates that both patients fell outside the 2SD of normal development.

Overall, the efficacy results of study AVXS-101-CL-306 were in line with the results of study AVXS-101-CL-302.

Safety

The assessment of safety in this study is limited, as only 2 patients were included in the study and patients were followed up to an age of 18 months reflecting a limited follow-up time. In addition, the assessment of safety is hampered by the single-arm design which makes it difficult to disentangle whether an AE is due to treatment with AVXS-101 and accompanied corticosteroid use, due to SMA1 or its complications or due to natural occurring background childhood diseases.

The safety profile observed in study AVXS-101-CL-306 is comparable to the safety profile presented in the submitted data for the original MAA.

Both patients experienced at least 1 TEAE. Of the 30 TEAEs observed, most were considered mild to moderate in intensity and were reported for the domain Gastrointestinal disorders, Infections and Infestations, Respiratory, Thoracic and Mediastinal Disorders and Skin and Subcutaneous Tissue Disorders. All AE's were considered unrelated to the treatment by the investigator, which can be agreed. However, the first TEAE reported in patient, of acute upper respiratory infection could potentially be related to prednisolone treatment.

One patient experienced upper gastrointestinal haemorrhage, recorded as an AESI, as it mapped to the thrombocytopenia category. The AE was mild in severity and resolved. This AESI was not considered related to the treatment, as according to the haematology listings platelet values at the time of the bleeding event were normal. No treatment-emergent AESIs were identified in other AESI categories.

One SAE of grade 3 dysphagia occurred during the study. This SAE was considered unrelated to treatment, and more likely caused by the underlying disease. None of the patients died or discontinued study treatment.

The clinical chemistry did not reveal any new safety signals. One transient event of glucosuria occurred in one patient which is likely unrelated to the study drug given the late onset on day 476.

Overall, AVXS-101 was shown to be relatively safe. No new safety signals were identified.

3. Rapporteur's overall conclusion and recommendation

The efficacy and safety results of study AVXS-101-CL-306 were in line with the results obtained during the identically designed study AVXS-101-CL-302. As only 2 patients were included in the currently submitted study and no new safety signals were observed, it is agreed that the SmPC does not need to be updated with this information.

☒ Fulfilled

No regulatory action required.

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1) The MAH is asked to present the corresponding unit for glucose for the test to determine whether the measurement of 250 (+2) at end of study for patient is considered within normal range.

The timetable is a 30 day response timetable with clock stop.

5. Assessment of the MAH responses to Request for supplementary information

Question 1

The MAH is asked to present the corresponding unit for glucose for the test to determine whether the measurement of 250 (+2) at end of study for patient is considered within normal range.

Novartis response

The MAH would like to confirm that the corresponding unit for the urine test strip (dipstick) results refer to glucose concentration in mg/dL. Furthermore, the MAH would like to highlight that the test methodology (dipstick) used is based on a threshold analysis with detection threshold concentration corresponding to > 100 mg/dL (1+). In line with this, any report of glucosuria (i.e. a detectable concentration of glucose in urine by a clinical test including urine dipstick) is considered abnormal. As summarized in CL-306 Clinical Study Report [Listing 16.2.7.1], patient had a nonserious adverse event (AE) of urine glucose increase reported on study Day 476 which had resolved on Day 478. In addition, another non-serious AE of glucosuria was reported on study day 511 with the event ongoing at the end of the study. Both the events were mild, considered unrelated to the study treatment by investigator with no treatment administered for any of the events.

Assessment of the response

The applicant has clarified that a positive dipstick measurement per definition is abnormal. Given the transient nature of the glucosuria, which could be caused by several different factors including a high carbohydrate meal, the event does not raise a safety concern. In addition, the occurrence of the event 476 days after dosing indicates that it is not likely to be related to the study drug.

Conclusion

Issue resolved