A PROSPECTIVE, LONG-TERM REGISTRY OF PATIENTS WITH A DIAGNOSIS OF SPINAL MUSCULAR ATROPHY (SMA) - (RESTORE)

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Compound: AVXS-101

Sponsor

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Title	A Prospective, Long-Term Registry of Patients with a Diagnosis of Spinal Muscular Atrophy (SMA) - RESTORE
Protocol version identifier	Version 2.1 (draft)
Date of last version of protocol	11 Sept 2019
European Union (EU) Post-authorization Study (PAS) register number	Not yet available
Active substance	Not applicable
Medicinal product	Not applicable
Product reference	Not applicable
Procedure number	Not applicable
Marketing authorization holder (MAH)	Not applicable
Joint post-authorization safety study (PASS)	No
Research question and objectives	This prospective observational registry will assess long-term outcomes of patients with a diagnosis of SMA, including long-term safety and effectiveness of AVXS-101.
Countries of registry	

Region	**Country**
AUS/APAC	Australia, Hong KongJapan, S. Korea, Singapore, Taiwan
CEE	Austria, Belgium, Czech Republic, Denmark, France, Germany, Hungary, Italy, Ireland, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden,

		Switzerland, United Kingdom	
	MEA	Israel, Kingdom of Saudi Arabia, Kuwait, Qatar, Russia, Turkey	
	Latin America	Argentina, Brazil, Mexico	
	North America	Canada, United States of America	
Author	AveXis Inc.		

Marketing Authorization Holder

MAH	AveXis EU Limited Companies Registration Office Number: 556815 Regus, Block B, The Crescent Building Northwood, Santry Dublin 9 D09 C6X8
MAH contact person	[Name] [Contact] [Contact] Novartis Pharma AG [Contact] [Contact] [Contact] Email: [Contact] Phone: [Contact]

Sponsor Approval

This registry will be conducted with the highest respect for the individual participants in accordance with the requirements of this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki and all applicable local laws and regulations, including, without limitation, data privacy laws and regulations.

Name: Olga Santiago Title: [Contact]	Date
Name: [Name] Title: [Contact], [Contact]	Date
Name: [Name] Title: [Contact] on behalf of [Contact]	Date

1. Table of Contents

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2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AAV9	Adeno-Associated Virus serotype 9
a priori	From the earlier
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AP-HP	Assistance Publique- Hôpitaux de Paris
ASO	Antisense Oligonucleotide
AST	Aspartate Aminotransferase
CB	Chicken β-actin-hybrid promoter
CFR	Code of Federal Regulations
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence Interval
CMV	Cytomegalovirus
CUP	Compassionate Use Program
eCRF	Electronic Case Report Form
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DRG	Dorsal Root Ganglia

de novo	Of new
EAP	Expanded Access Program
eCoA	Electronic Clinical Outcome Assessment
EDC	Electronic Data Capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPAR	European Public Assessment Report
ePRO	Electronic Patient Reported Outcome
EU	European Union
FDA	Food and Drug Administration
FEV1	Forced Expiratory Ventilation in 1 second
FVC	Forced Vital Capacity
GLP	Good Laboratory Practice
GPP	Good Pharmacoepidemiology Practices
HCT	Hematocrit
HINE	Hammersmith Infant Neurological Examination
ICF	Informed Consent Form
ICH	International Council on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
iSMAC	International Spinal Muscular Atrophy Consortium

IT	Intrathecal
MAH	Marketing Authorization Holder
MAP	Managed Access Program
mRNA	Messenger Ribonucleic Acid
n	Number
NESS	New England Survey Systems
NeuroNEXT	The Network for Excellence in Neuroscience Clinical Trials
NOAEL	No Observable Adverse Effect Level
NPP	Named Patient Program
PAS	Post-Authorization Study (ies)
PASS	Post-authorization Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PedsQL	The Pediatric Quality of Life Inventory
PHI	Personal Health Information
PRO	Patient Reported Outcome
PSUR	Periodic Safety Update Report
RBC	Red Blood Cell Count
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SMA	Spinal Muscular Atrophy

SMArtCARE	A platform to collect real-life outcome data of patients with SMA
SMN	Survival Motor Neuron
SMN1	Survival Motor Neuron 1 Gene
SMN2	Survival Motor Neuron 2 Gene
SOP	Standard Operating Procedure
SPI	Single Patient Investigational New Drug
Treat-NMD	Treat Neuro Muscular Disease is a global academic network that focuses on advancing research in neuromuscular disorders
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cells Count

3. Responsible Parties

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4. Abstract

Title

A Prospective, Long-Term Registry of Patients with a Diagnosis of Spinal Muscular Atrophy (SMA) (RESTORE).

Rationale and Background

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 1:10,000 live births [Sugarman 2012]. SMA is the leading cause of infant mortality due to genetic diseases [Kaufmann 2011].

Until recently, the mainstay of treatment for these patients was supportive medical care. However, advances in medical treatment focusing on gene replacement, gene enhancement, motor neuron protection and muscle enhancement is likely to change the management and prognosis of these patients in the future.

The purpose of this registry is to assess the long-term outcomes of patients with SMA in the context of advances in treatment options and also to characterize and assess long-term safety and effectiveness of AVXS-101.

Research Question and Objectives

This registry will assess long-term outcomes of patients with a diagnosis of SMA. It will also characterize and assess long-term safety and effectiveness of AVXS-101 in the real-world setting.

Primary objectives

- To assess the effectiveness of treatments for SMA
  - To characterize the motor performance (motor milestones and motor function)
- To assess the long-term safety of AVXS-101
-
- To assess survival of all patients with SMA*

Secondary objectives

- To assess healthcare utilization
- To assess caregiver burden
- To assess patient functional independence

*Survival is defined as time from birth to either death or permanent ventilation. Permanent ventilation is defined as requiring invasive ventilation (tracheostomy), or respiratory assistance for 16 or more hours per day (including noninvasive ventilatory support) continuously for 14 or more days in the absence of an acute reversible illness, excluding perioperative ventilation.

Registry Design

This is a prospective, multi-center, multinational, non-interventional observational registry of patients with a diagnosis of SMA.

Population

Patients from centers worldwide will be recruited according to the eligibility criteria. Consecutive patients will be enrolled at each site in order to minimize selection bias.

Inclusion Criteria:

- Patients with SMA, genetically confirmed on or after 24 May 2018.
- Appropriate consent/assent has been obtained for participation in the registry.

Exclusion Criteria:

- Currently enrolled in an interventional clinical trial involving an investigational medicinal product to treat SMA.

Note: Patients that are participating in a Compassionate Use Program (CUP) for AVXS-101 (Zolgensma) such as a Managed Access Program (MAP), an Expanded Access Program (EAP), Single Patient Investigational New Drug (IND) (SPI) or Named Patient Program (NPP) are eligible to enroll in the registry regardless of the date of genetic confirmation of SMA.

Variables

The following categories of registry variables will be collected for each patient:

- Confirmation of eligibility, socio-demographics, enrollment in other existing registries, any concomitant enrollment in an AVXS-101 CUP where data is being entered into this registry
- Clinical characteristics
- Treatments
- Patient assessments
- Hospitalization and Healthcare Resource Utilization
- Patient/Caregiver reported outcomes
- AEs

Data Sources

Prospective data for SMA patients, with genetically confirmed diagnosis on or after 24 May 2018, will be extracted from existing registries that have agreed to share their data. Additional data will be collected from *de novo* sites using electronic data capture (EDC) forms, which sites will complete from patient medical charts. Additionally, for *de novo* patients, data may be collected by Patient Reported Outcome (PRO) Questionnaires and caregiver surveys. The registry may also collect data from patients in the AVXS-101 CUP's whether or not they are in an existing registry or are from *de novo* sites.

Registry Size

The registry will enroll at least 500 patients with a diagnosis of SMA.

Data Analysis

Data will be analyzed per the statistical analysis plan (SAP). The analysis population will consist of all patients enrolled. By default, the data will be presented by SMN2 copy number, and separately by Therapy Assignment(s), including combination therapies, if applicable. Descriptive statistics will be presented for the primary analysis. No formal *a priori* hypothesis testing will be performed. Continuous variables will be summarized using the number of observations, mean, 95% confidence interval (CI) for the mean, standard deviation (SD), standard error (SE), median, minimum, and maximum. Categorical data will be summarized using counts and percentages. Incidence rates (per person-years) and 95% CIs of AEs will be calculated. Survival will be presented using Kaplan-Meier methods. CUP patients will be excluded from analysis around the natural history. Further data analysis may be undertaken to meet specific regulatory requests.

5. Amendments and Updates

Version 2.0 was the first protocol amendment. Significant changes are set out in the table below. This table will be updated further upon approval of the updated protocol currently as version 2.1 (draft):

Section	Version 1.0	Version 2.0
All	Not applicable	Addition of RESTORE as name of registry
All	Study/registry	Consistent use of term "registry" throughout the protocol
All	Not applicable	Reference to CUP patients participating in RESTORE
MAH	AveXis EU Ltd	AveXis EU Limited Companies Registration Office Number: 556815 Regus, Block B, The Crescent Building Northwood, Santry Dublin 9 D09 C6X8 Ireland
MAH contact person	To be determined	[Name] MD, PhD [Contact]
Research Question	This prospective observational registry will assess long-term outcomes of patients with a diagnosis of SMA.	This prospective observational registry will assess long-term outcomes of patients with a diagnosis of SMA and also characterize and assess long-term safety and effectiveness of AVXS-101.
Primary Objectives	• To assess the effectiveness of treatments for SMA • To assess long-term safety • To assess overall survival of all patients with SMA	• To assess the effectiveness of treatments for SMA • To assess the long-term safety of AVXS-101 • To characterize the risks of thrombocytopenia, hepatotoxicity

<table>
<tr><td></td><td></td><td>and cardiac AEs in SMA patients treated with AVXS-101
• To assess overall survival of all patients with SMA</td></tr>
<tr><td>Registry Design</td><td>Not applicable</td><td>Any patients participating in a CUP for AVXS-101 such as a MAP, an EAP, SPI or NPP will be managed according to the relevant protocol which will also reflect recommended clinical practice.</td></tr>
<tr><td>Inclusion criteria</td><td>• Patients with a genetic confirmation of SMA
• Appropriate consent/assent has been obtained for participation in the registry</td><td>• Patients with SMA, genetically confirmed on or after 24 May 2018
• Appropriate consent/assent has been obtained for participation in the registry</td></tr>
<tr><td>Exclusion criteria</td><td>• None</td><td>• Currently enrolled in an interventional clinical trial involving an investigational product to treat SMA.

Note: patients that are participating in a CUP for AVXS-101 (Zolgensma) such as a MAP, an EAP, SPI or NPP are eligible to enroll in the registry regardless of the date of genetic confirmation of SMA</td></tr>
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		risk evaluation report (PBRER) following EU Marketing Authorization
		Interim analyses: Annually
		End of data collection: June 2038
		Final report of registry results: October 2038
Section 7	Not applicable	Addition of safety specification for AVXS-101
Section 7	Not applicable	This RESTORE registry protocol will serve as a basis for any required country-specific protocol adaptations including but not limited to Japan and Korea.
Section 9	Not applicable	Addition of SMArtCARE and French SMA Assistance Publique- Hôpitaux de Paris (AP-HP) to existing registries and deletion of the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT)
Section 9.2.1	The registry will attempt to enroll all patients treated with AVXS-101	The registry will attempt to enroll all patients treated with AVXS-101 including any patients treated in a CUP such as a MAP, EAP, SPI or NPP regardless of the date of genetic confirmation of SMA.
Section 9.2.2	AVXS-101 will not be provided or paid for by the Sponsor. Assessments are as per usual care and will not be provided or paid for by the Sponsor.	Any patients participating in a CUP for AVXS-101 such as a MAP, EAP, SPI or

		NPP will be managed according to the relevant protocol which will also reflect recommended clinical practice. For any patients participating in RESTORE registry and not participating in a CUP for AVXS-101, no treatments will be provided or paid for by the Sponsor. Assessments are as per usual care and will not be provided or paid for by the Sponsor.
Schedule of Assessments	Not applicable	Addition of: Concomitant enrollment in CUP Relevant surgical procedures Head/chest circumference Pulmonary medications Orthoses, Devices and Mobility Equipment
Schedule of Assessments	Length/height	Recumbent length/height
Schedule of Assessments	Ventilatory support	Tracheostomy and other ventilatory support with hours per day and frequency
Schedule of Assessments	Hospitalizations, date, reason	Hospitalizations, Emergency Room Visits, Visits to other Healthcare Professionals, date, reason
Schedule of Assessments	Patient contact information	Patient/caregiver contact information
Schedule of Assessments	Family History	Family History of SMA

Schedule of Assessments	Weight at enrollment	Weight
Schedule of Assessments	Medical History	SMA Medical History, SMA Symptoms and SMA Functional Status
Schedule of Assessments	CHOP-INTEND Score	CHOP-INTEND
Schedule of Assessments	Hammersmith Functional Motor Scale	Hammersmith Functional Motor Scale Expanded
Schedule of Assessments	Liver function tests	Laboratory Assessments
Schedule of Assessments	Adverse Event of Special Interest (AESI)	AEs, AESI, serious adverse event (SAE), adverse drug reaction (ADR)
Schedule of Assessments	Concomitant medications/start date/stop date	Other SMA treatment/start date/stop date(s), if applicable
Variables	Not applicable	Updated to reflect final case report form (CRF) and changes listed above under schedule of assessments
Section 9.2.4	Not applicable	Deletion of patient retention tools
Section 9.4	All data will be collected from medical records via the EDC at annual intervals	All data will be collected from medical records via the EDC at the following intervals: Enrollment, Month 6, Month 12, Month 18, Month 24 and annually thereafter (Years 3-15)
Section 9.6	Not applicable	In the case of required registry data standards not being met, existing registries may be required to modify their data standards to participate in the RESTORE registry
Section 9.7	Not applicable	If sufficient numbers of AVXS-101 CUP patients are enrolled, the assumption will be examined by comparing descriptive statistics of demographic, medical history and baseline data. CUP patients

		will be excluded from analysis around the natural history. Further data analysis may be undertaken to meet specific regulatory requests.
Section 9.7	Not applicable	Interim analyses will be performed on an annual, biannual or ad hoc basis as needed by the sponsor.
Section 9.7	Not applicable	Where feasible, data from country specific protocols based upon RESTORE will be included in analyses.
Section 9.9	Not applicable	In order to minimize the potential for survivor bias, patients are eligible to enroll in the registry if a genetic confirmation of SMA was made on or after 24 May 2018. Whilst this will not eliminate survivor bias completely as there may be some patients where a diagnosis was made on or after 24 May 2018 but who are deceased at the time the site begins to enroll patients, it will significantly minimize the risk compared to there being no set cut-off date of diagnosis date. For patients who participate in an AVXS-101 CUP, the date of diagnosis of 24 May 2018 does not apply. The rationale for this reflects the spirit of a CUP, which is designed to be inclusive of any patient not eligible or unable to partake in an AVXS-101 clinical trial. All patients in a CUP should have the opportunity to participate in the registry in order that long-term follow up data can be obtained. Any CUP patient enrolled into the registry with a date of diagnosis prior to May 24, 2018 will be included in the final analysis, but with restrictions to data analyzed.

Section 10	The physician must ensure that each patient's anonymity is maintained. On electronic case report form (eCRFs) and other documents submitted to the registry, patients must not be identified by name.	The Investigator must ensure that each patient's anonymity is maintained. On eCRFs and other documents submitted to the registry, patients must not be identified by name. The only exception is the Consent process in which the caregiver provides consent: 1. Electronically, in which the patient's name may be entered into the New England Survey Systems (NESS) database via the secure RESTORE Registry Portal; or 2. By paper, in which the scanned executed informed consent form (ICF) (which may contain the patient's name) is uploaded to the NESS database via the secure RESTORE Registry Portal. Personal Health Information (PHI) collected by the RESTORE Registry Portal is protected by NESS Standard Operating Procedures (SOPs) using encryption. PHI has been defined as: • Executed Informed Consent • Executed Assent • Caregiver's Name, Email Address, and Phone Number • Patient's Name, Email Address, Phone Number, and Date of Birth • Primary Physician's Name, Clinic Name, Mailing Address, Email Address, and Phone Number • Primary Physician Office Contact's Name and Phone Number

		Only authorized personnel at NESS, UBC Study Monitors, and the site will have access to PHI. At the end of the study, all PHI data collected via the RESTORE Registry Portal will be destroyed per NESS SOPs at the direction of the sponsor. Measures will be implemented to ensure the security and compliance of all data hosted within the database environment. These measures cover all aspects of network, individual systems/devices, user account, web and email protection.
Section 11	Reporting limited to AESI and SAEs	Reporting for de novo patients described to include all AEs for first 12 months following AVXS 101 and for first 12 months for other treatment. Subsequently all ADRs and SAE will be reported Provision for data transfer from existing SMA registries
Section 12	Not applicable	Reference made to publication committee
Annex 2	-	Addition of European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EnCEPP) checklist

6. Milestones

Milestone	Planned date
Registration in PAS Register	Upon EU Marketing Authorization
Start of recruitment and baseline data collection	September 2018
End of recruitment and baseline data collection	June 2023
Progress reports/Interim analyses	Safety: With Periodic Safety Update R eports (PSURs) Efficacy: Annually with conditional approval renewal
End of data collection	June 2038
Final report of registry results	October 2038

7. Rationale and Background

Spinal muscular atrophy (SMA) is a neurogenetic disorder caused by a loss or mutation in the *SMN1* gene 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 a global average incidence of 1:10,000 live births [Sugarman 2012]. SMA is the leading cause of infant mortality due to genetic diseases [Kaufmann 2011]. Disease severity and clinical prognosis depend 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 two [Oskoui 2007]. 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 neuron loss in SMA Type 2 and 3 SMA is less aggressive leading to later symptom onset and longer life survival. The findings from various neurophysiological and animal studies have shown an early loss of motor neurons in the embryonic and early postnatal periods [Swoboda 2005; Le 2011; Farrar 2012].

Until recently, the mainstay of treatment for these patients was supportive medical care. However, advances in medical treatment focusing on gene replacement, gene enhancement, motor neuron protection and muscle enhancement is likely to change the management and prognosis of these patients in the future.

Nusinersen is an antisense oligonucleotide (ASO) whose therapeutic approach to treat SMA is based upon increasing the amount of full-length protein produced from the *SMN 2* gene by modulating its messenger ribonucleic Acid (mRNA) splicing pattern [Spinraza EPAR 2017]. It is designed for intrathecal (IT) chronic administration and was approved by the Food and Drug Administration (FDA) in December 2016 and in the EU in June 2017.

AVXS-101 is a non-replicating recombinant adeno-associated virus serotype 9 (AAV9) containing the human *SMN* gene under the control of the cytomegalovirus (CMV) enhancer/chicken β-actin-hybrid promoter (CB). The goal of AVXS-101 treatment is transduction of motor neurons by a viral vector containing the gene for SMN, which results in increased SMN protein expression in motor neurons, thereby preventing cell death, improving neuronal and muscular function, and increasing overall patient survival. It is delivered by a one-time intravenous infusion. An anti-AAV9 antibody testing should be performed prior to AVXS-101 infusion (<1:50). AVXS-101 was approved by FDA in the US on 24 May 2019.

In clinical trials of AVXS-101, events of elevated transaminases were observed, some of which were serious. In a US Managed Access Program, with AVXS-101, there was a report of acute liver injury in a patient with pre-existing increases in liver transaminases after receiving AVXS-101. The patient recovered within 4 months after receiving steroid therapy. Transient thrombocytopenia has been observed and is generally, mild, and resolved during the observation period.

Cardiac degeneration, fibrosis and atrial thrombosis were reported in non-clinical toxicity studies in mice and the clinical significance of this finding is uncertain. The available clinical cardiovascular safety data have not provided evidence for a cardiovascular safety problem in humans.

A non-GLP biodistribution and safety study was performed in cynomolgus monkeys (*Macaca fascicularis*) to evaluate the transduction efficiency and safety of intrathecally administered AVXS-101 at a dose of 3 x 10^{13} vg/animal alone and in combination with 2 iohexol-based contrast agents. All 12 animals on study survived and were euthanized 2 weeks post-injection with no clinical evidence of toxicity. However, inflammation of the dorsal root ganglia (DRG) was noted during histopathology evaluation of select tissues. The inflammation was characterized by minimal to marked infiltration of mononuclear inflammatory cells, primarily lymphocytes, into the cervical, thoracic, lumbar, and sacral DRG and associated nerves. Minimal inflammation was associated with scattered infiltrates or small aggregates of mononuclear cells in the DRG, without evidence of neuronal necrosis. With mild to marked inflammation, aggregates to sheets of mononuclear cells were present, along with neuronal satellitosis, neuronal necrosis, or neuronal loss with rare mineralization. Inflammation was observed in ganglia from all examined levels, but incidence and severity were generally greater in the sacral DRG. Moderate to marked inflammation was only observed in the sacral DRG of 2 of the 12 animals on study. The animals were not administered corticosteroids.

The DRG was not identified as a target organ of toxicity in previous AVXS-101 studies conducted in mice (ICV route of administration) or cynomolgus monkeys (IV or IT routes of administration). However, similar findings have been reported after administration of an AAV9 vectors in monkeys and minipigs (20, 21).

In pivotal GLP-compliant 3-month mouse toxicology studies, the main target organs of toxicity were the heart and liver. Following IV infusion in the mouse, vector and transgene were widely distributed with the highest expression generally observed in heart and liver, and substantial expression in the brain and spinal cord. AVXS-101-related findings in the ventricles of the heart were comprised of dose-related inflammation, edema, and fibrosis, and in the atrium, inflammation and thrombosis. Liver findings were comprised on hepatocellular hypertrophy, Kupffer cell activation, and scattered hepatocellular necrosis. A no observable adverse effect level (NOAEL) was not identified for AVXS-101-related heart and liver findings in the mouse, and the maximum tolerated dose was defined as 1.5×10^{14} vg/kg, providing a safety margin of approximately 1.4-fold relative to the recommended therapeutic dose of 1.1×10^{14} vg/kg. The translatability of the observed findings in mice to primates is not known at this time.

There is limited but accumulating data regarding transgene persistence and durability of therapeutic effects observed after AAV gene therapy. Transgene persistence has been demonstrated in animal models of hemophilia B for up to 5.5 years in non-human primates [Nathwani 2011] and up to 10 years in a dog model of haemophilia [Buchlis 2012]. In clinical trials, persistence of therapeutic effect has been demonstrated for up to 10 years in hemophilia [Nathwani 2014] and up to 3 years in haemophilia [Cideciyan 2013]. In SMA, transgene persistence has been shown for 250 days in mouse models [Foust 2010]. Long-term follow up of patients treated with AVXS-101 in Study CL-101 to date has documented durability of therapeutic effect after a mean duration of follow up of 57 months and for as

long as 68.6 months as of 31st December 2019, as demonstrated by persistence of previously gained motor/developmental milestones over the long-term follow up period. Additional data is needed to confirm long-term durability of efficacy including the data in older patients greater than or equal to 6 months of age at the time of AVXS-101 administration. This data will be collected in the RESTORE registry and ongoing long-term follow up studies (LT-001 and LT-002). Additionally, data on long-term safety will be collected.

This prospective registry will seek to enroll a broad sample of patients diagnosed with SMA. Long-term outcomes of patients will be characterized through this registry. This registry will seek to enroll at least 500 patients with a genetically confirmed diagnosis of SMA.

This RESTORE registry protocol will serve as a basis for any required country-specific protocol adaptations including but not limited to Japan and Korea.

8. Research Question and Objectives

This prospective observational registry will assess long-term outcomes of patients with a diagnosis of SMA and also to characterize and assess long-term safety and effectiveness of AVXS-101.

Primary objectives

- To assess the effectiveness of treatments for SMA
  - To characterize the motor performance (motor milestones and motor function)
- To assess long-term safety of AVXS-101
- To assess survival of all patients with SMA*

Secondary objectives

- To assess healthcare utilization
- To assess caregiver burden
- To assess patient functional independence

*Survival is defined as time from birth to either death or permanent ventilation. Permanent ventilation is defined as requiring invasive ventilation (tracheostomy), or respiratory assistance for 16 or more hours per day (including noninvasive ventilatory support) continuously for 14 or more days in the absence of an acute reversible illness, excluding perioperative ventilation.

9**. Research Methods**

9.1. Registry Design

This is a prospective, multi-center, multinational, non-interventional, observational registry of patients diagnosed with SMA. All patients will be managed according to the clinical site's normal clinical practice, i.e., the diagnostic and clinical treatment/practice process that a clinician chooses according to their clinical judgement for an SMA patient. Clinical care will not be driven by this protocol. No additional visits or investigations will be performed beyond normal clinical practice. Patients will be followed for 15 years from enrollment or until death, whichever is sooner. Any patients participating in a CUP for AVXS-101 such as a MAP, an EAP, Single Patient IND (SPI) or NPP will be managed according to the relevant protocol which will also reflect recommended clinical practice.

9.2. Setting

Patients from centers worldwide, including but not limited to the following, will be recruited.

Region	**Country**
AUS/APAC	Australia, Hong Kong, Japan, S. Korea, Singapore, Taiwan
CEE	Austria, Belgium, Czech Republic, Denmark, France, Germany, Hungary, Italy, Ireland, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden, Switzerland, United Kingdom
MEA	Israel, Kingdom of Saudi Arabia, Kuwait, Qatar, Russia, Turkey
Latin America	Argentina, Brazil, Mexico
North America	Canada, United States of America

Centers may be identified from those participating in existing SMA registries including but not limited to international SMA consortium (iSMAC), Treat-NMD, SMArtCARE, Cure SMA, French SMA AP-HP Registry or may be recruited *de novo* by the RESTORE registry. Patients may be enrolled in either one of the existing SMA registries with their data transferred to this registry database or they may participate in this registry without being enrolled in an existing registry. Data from patients who will receive AVXS-101 via a CUP may also be collected in the registry regardless of whether or not they are in an existing registry or are from *de novo* sites.

Consecutive patients will be enrolled into the registry in order to minimize selection bias.

For centers recruited *de novo* by the RESTORE registry, Investigators will be asked to provide the required documentation and approvals per local regulations. Once a site is activated, Investigators will

be able to consent patients using their Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved ICF and enroll patients into the registry.

9.2.1. Selection of Registry Population

The RESTORE registry will enroll at least 500 patients with a diagnosis of SMA where the genetic confirmation of SMA was made on or after 24 May 2018. The registry will attempt to enroll all patients treated with AVXS-101 including any patients treated in a CUP such as a MAP, EAP, SPI or NPP regardless of the date of genetic confirmation of SMA. There will be no cap on enrollment.

9.2.1.1. Eligibility Criteria

Inclusion Criteria

- Patients with SMA, genetically confirmed on or after 24 May 2018.
- Appropriate consent/assent has been obtained for participation in the registry.

Exclusion Criteria

- Currently enrolled in an interventional clinical trial involving an investigational product to treat SMA.

Note: patients that are participating in a CUP for AVXS-101 (Zolgensma) such as a MAP, an EAP, SPI or NPP are eligible to enroll in the registry regardless of the date of genetic confirmation of SMA.

9.2.2. Registry Procedures

Patient care will follow the normal treatment practices for SMA in the respective country and clinical site. No additional diagnostic or monitoring procedures will be applied. The treatment decision will be made prior to the decision to enroll the patient into the registry. The choice of ongoing medical treatment for the duration of the registry will be made independently by the Investigator in the regular course of practice and will not be influenced by participation in this registry.

Investigators are free to add or withdraw any medication but will continue to monitor the patient for the full 15 years, until death or if a patient is withdrawn from the registry at the discretion of the patient / patient's parent/legal representative or Investigator.

Any patients participating in a CUP for AVXS-101 such as a MAP, EAP, SPI or NPP will be managed according to the relevant protocol which will also reflect recommended clinical practice.

For any patients participating in RESTORE registry and not participating in a CUP for AVXS-101, no treatments will be provided or paid for by the Sponsor. Assessments are as per usual care and will not be provided or paid for by the Sponsor.

9.2.3. Schedule of Assessments

No mandatory visits, tests, or assessments are required for this registry. All visits will be scheduled and conducted according to the clinical site's normal clinical practice.

A Schedule of Assessments (Table 1) has been provided to indicate the assessments that the Sponsor will capture through the course of the registry, noting that there may be some missing data if any assessments are not performed as part of normal clinical practice.

Entry of data should include all available data following the previous data entry. For example, all laboratory values should be entered between last and current data entry.

Table 1: Schedule of Assessments

	Enrollment	Follow-up[2]
Parental/legal guardian consent/patient assent	X	
Patient/Caregiver contact information[1]	X	X
Secondary contact information[1]	X	X
Concomitant enrollment in AVXS-101 CUP[4]	X	X
Demographics	X	
Gestational age	X	
Weight at diagnosis	X	
Weight	X	X
Recumbent length/height at diagnosis	X	
Recumbent length/height	X	X
Head/chest circumference	X	X
Date and age at SMA diagnosis	X	
Genetic status, SMN2 copy number, point mutation, genetic modifier mutation information	X	
Family history of SMA	X	
SMA Medical history, SMA Symptoms and SMA functional status	X	X
Relevant Surgical Procedures	X	X
AVXS-101 treatment/date, if applicable	X	X
Anti AAV9 antibody (AVXS-101 patients only)	X[5]	X[5]
Prophylactic Glucocorticosteroid Treatment (AVXS-101 group only)	X	X
Nusinersen treatment/start date/stop date(s), if applicable	X	X
Other SMA treatment/start date/stop date(s), if applicable	X	X
Pulmonary assessment	X	X
Pulmonary medications	X	X
Ventilatory Support (Tracheostomy and other non-invasive ventilatory support) o	X	X
Nutritional assessment	X	X
Echocardiography	X	X
Orthoses, Devices and Mobility Equipment	X	X

	Enrollment	Follow-up[2]
Motor milestone assessment	X	X
Hammersmith Infant Neurological Examination (HINE)	X	X
Hammersmith Functional Motor Scale Expanded	X	X
CHOP-INTEND	X	X
Hospitalizations, Emergency Room visits, visits to other Healthcare Professionals, date, reason		X
Laboratory Assessments	X	X
AEs including malignancies, AESIs, SAEs, ADRs[3]		X
Functional independence (	X	X
Patient/Caregiver burden (ePRO/eCOA))	X	X
Date and cause of death		X
Changes in Contact Information for Patient or Secondary Contacts[1]		X
Discontinuation from registry: date, reason for discontinuation		X

[1] Contact information to be maintained in accordance with all applicable local laws
[2] Data collection will be done at intervals according to normal clinical practice.
3 See section 11 for full details on AE reporting for the duration of the registry.
4 A patient may already be enrolled in the registry and subsequently participate in an EAP/MAP/SPI/NPP or may enroll in the EAP/MAP/SPI/NPP and registry simultaneously.
[5]. Prior to treatment with AVXS-101

9.2.4. Participation and Retention Strategies

Individual patient follow-up is 15 years after enrollment. The consenting patient/parent/guardian (or assenting patient) will complete a patient and parent/legal guardian contact form (including physical name, address, mailing address, phone number, and e-mail address) and will also be asked to identify one or more secondary contacts such as the patient's primary care physician and a contact outside of the patient's household who may know the patient's whereabouts if contact cannot be made by the site directly with the parent/legal guardian. This information will not be entered into the registry database. This information will be used to minimize loss to follow-up.

In the event an Investigator retires, or discontinues participation from the registry, a transition plan will be put in place to enable continuing participation by the patient.

In the event a patient moves to a new location or chooses to leave their current Investigator, parents/guardians/patients are provided with information as to how to locate a participating Investigator in their area or how to provide the registry information to a new Investigator that may not yet be participating.

The goal of these strategies is to enhance patient retention, potentially resulting in a lower drop-out rate and improved quality of data. Over the course of a long-term registry, patient death may occur. Additionally, patients may develop serious co-morbidities that cause them to become lost to follow-up

from this registry. Every effort will be made to ensure adequate follow-up and ongoing contact with patients.

9.2.5 Lost to Follow-up

If there has been no activity by the patient in 12 months, the Investigator (or designee) will attempt to contact the parent/guardian and document the reason. For patients who have not made a visit/contact to the Investigator over a 12-month period, secondary contacts will be contacted to obtain the patient's vital status and possible new contact information. Patients for whom no information is available after at least weekly documented attempts over a 6-week period will be considered lost to follow-up.

In countries where vital statistics records and other sources of information are available, the registry will seek to obtain the patient's vital status through these sources for patients who are lost to follow-up. Use of vital records matching will be indicated in the ICF. Only under these circumstances, the registry Coordinating Center will request patient identifying information from the Investigator if allowed by local regulation.

9.3 Variables

Case report forms (CRFs) will be specifically designed for the collection of data from this registry or existing registries. An overview of the categories of registry variables to be collected for each patient is summarized in

Table 2: Registry Variables

Category	Variables
Confirmation of Eligibility, Socio-demographics, Registry status, AVXS-101 CUP status	• Date of informed consent/assent for registry enrollment • Eligibility Assessment based on criteria outlined in protocol section 9.2.1.1 • Socio-demographic characteristics o Year of Birth o Gestational age o Gender o Race o Ethnicity • Consent Withdrawal • Date of withdrawal Reason for withdrawal • Discontinuation from registry o Date of discontinuation o Reason for discontinuation
Clinical Characteristics of Patient	• Relevant Medical History o SMA History of Patient ▪ Date and age of diagnosis ▪ SMA Type ▪ Genetic Status ▪ SMN2 copy number ▪ Point mutation ▪ Presence of genetic modifier 859G>C Weight, recumbent length, height, head/chest circumference

	o Other Medical History o Relevant Surgical Procedures o Family History of SMA
Treatments	• AVXS-101 Treatment (if applicable) o Anti AAV9 antibody prior to treatment with AVXS-101 o Date of treatment, dose • Prophylactic Glucocorticosteroid Treatment (AVXS-101 group only) o Date of treatment start o Doses and dose changes o Date treatment ended • Nusinersen treatment (12mg) o Dosing Stage o Date of Dose o Start and stop dates • Other SMA Treatments o Dose and frequency o Start and stop dates
Patient Assessments	• Pulmonary Medications o Taken since SMA Diagnosis o Medication o Start and Stop Date o Ongoing status • Pulmonary Exam o Interpretation (Normal/Abnormal) o Pulmonary Function Test ▪ Forced Vital Capacity, FVC(L) ▪ Forced Expiratory Ventilation in 1 second, FEV1 (L) ▪ FEV1/FVC Ratio (%) • Ventilatory Support o Tracheostomy o Non-Invasive Ventilatory Support (BiPAP) ▪ Defined survival endpoint met (yes/no) • Nutritional Assessment o Use of non-oral procedures used to administer food o Date of placement, Date of removal, o Sufficient caloric intake and percentage • Echocardiography o Normal/Abnormal o Ejection Fraction o Abnormalities • Motor Milestone Assessments o Developmental Milestones o Children's Hospital of Philadelphia infant test of neuromuscular disorders (CHOP INTEND) o HINE-2 (Motor Function) o Hammersmith Functional Motor Scale - Expanded • Laboratories o Laboratory Assessments, date of assessment, result and units: ▪ Albumin ▪ Aspartate aminotransferase (AST) ▪ Alanine aminotransferase (ALT) ▪ Alkaline phosphatase

	▪ Total Bilirubin ▪ Direct Bilirubin ▪ Total Protein ▪ Platelets ▪ White Blood Cell (WBC) ▪ Red Blood Cell Count (RBC) ▪ Hemoglobin ▪ Hematocrit (HCT) ▪ Troponin-I
Hospitalization and Healthcare Resource Utilization	• Emergency Room Visits and Hospitalizations o Date and Duration of Hospitalizations o Reason of Hospitalizations • Other therapies and visits • Orthoses, Devices and Mobility Equipment • Insurance type (in United States [US])
Patient/Caregiver Reported Outcomes	• Work Productivity and Activity Impairment Questionnaire SMAv2 • Zarit Burden Interview • The Pediatric Quality of Life Inventory (PedsQL) Child report • PedsQL Parent report concerning child
AEs	• AEs (Per criteria in Section 11 and including malignancies • AESI • ADRs • SAEs • Death o Date of Death o Primary Cause of Death

9.4. Data Sources

Prospective data for SMA patients may be extracted from existing registries that have agreed to share their data. Additional data will be collected from *de novo* sites using EDC forms, which sites will complete from the SMA patient medical charts. Additional data may also be collected from parents/legal guardians/patients regarding PRO questionnaires and caregiver surveys. The registry will also collect data from patients in the AVXS-101 CUPs whether or not they are in an existing registry or are from *de novo* sites.

Patients enrolled in other SMA registries may not require additional consent/assent. At the initial visit for a patient enrolled *de novo*, the investigator (or designee) will provide an overview of the registry to the patient and/or parent/guardian and invite him/her to participate. Once written informed consent has been obtained, the registry Investigator will complete the baseline data collection for each patient. Follow-up data for patient visits will be recorded in the patient chart in accordance with the clinical site's standard of care or clinical judgment. Data will be collected from medical records via the EDC at the following intervals: Enrollment, Month 6, Month 12, Month 18, Month 24 and annually thereafter (Years 3-15).

The technologies used for this registry such as EDC or electronic patient reported outcome (ePRO) will be compliant with 21 Code of Federal Regulations (CFR) Part 11, EudraLex Annex 11, General Data Protection Regulation, and local data privacy requirements and will be evaluated on an ongoing basis throughout the duration of the registry to ensure upgrades are made when necessary.

During the course of the study, it may be necessary to revise the data collection elements as data on novel treatments becomes more mature. Should this be necessary, the protocol and data collection elements will be revised. Participating registries and clinicians will be informed of the possibility of data collection changes and this will be specified in the relevant contractual agreements.

9.5. Registry Size

The registry will enroll at least 500 patients with a diagnosis of SMA. The registry will attempt to enroll all patients treated with AVXS-101. Enrollment will be open for 5 years. Sample size is driven by expected incidence of SMA diagnosis assuming treatment with AVXS-101 over a 5-year period and not by any specific hypothesis to be tested or desired precision of estimates. There is no cap on enrollment.

SMA incidence is not widely documented, but it has been published that the distribution is 60% as SMA Type 1, 20% SMA Type 2, and 20% SMA Type 3 as reported by Verhaart 2017. Assuming the minimum number of patients of 500, this will result in 300 Type 1 patients, 100 Type 2, and 100 Type 3 patients. The population of 300 SMA Type 1 patients will be sufficiently sized to adequately characterize continuous outcomes and event rates down to 1% with precision represented by a 95% confidence interval (CI) of (0.1, 3.0).

9.6. Data Management

In order to minimize the burden to investigators, this registry will use data transferred from existing SMA registries (where available) and/or an EDC system. Some or all patient data (e.g., PROs) may be directly entered into an electronic device (ePRO). For electronic clinical outcome assessment (eCoA) data, where there is no prior written or electronic record of the data, the EDC form will serve as the source and the investigator will receive an archival copy at the end of the registry for retention. Site personnel will be trained on the EDC, ePRO and eCoA technologies.

Data verification will take place and any data verification activities will be executed in compliance with a Data Management Plan (including electronic edit checks). As medical coding is required, this will be reviewed by qualified personnel. Data verification requirements might need to be amended based on any observed data trends. This will only be done for any data entered directly into the registry eCRF and not from data transferred from current registries. The Sponsor/contract research organization will ensure that existing registries meet required registry data standards including data verification. In the case of required registry data standards not being met, existing registries may be required to modify their data standards to participate in the RESTORE registry.

Patients who are lost to follow-up or who withdraw from the registry will be discontinued from the registry following confirmation from site and a reason for withdrawal will be collected when available.

9.7. Data Analysis

Data will be analyzed per the SAP. The detailed SAP will be developed upon the approval of the final registry protocol.

The analysis population will consist of all enrolled patients. All data for each patient will be used up to the point of end of follow-up or early withdrawal (including withdrawal of consent). By default, data will be presented by SMN2 copy number, and separately by Therapy Assignment(s), including combination therapies, if applicable.

The primary analysis will present data using descriptive statistics. No formal *a priori* hypothesis testing will be performed. Continuous variables will be summarized using the number of observations (n), mean, 95% CI for the mean, SD, SE, median, minimum, and maximum. Categorical data will be summarized using counts and percentages. Incidence rates (using per person-years) and 95% CIs will be calculated for AEs, hospitalizations, and Emergency Room Visits. Survival will be presented using Kaplan-Meier methods.

. CUP patients will be excluded from analysis around the natural history. Further data analysis may be undertaken to meet specific regulatory requests.

There is the potential for missing data since standard of care may differ between sites. All rates and CIs for individual responses will be performed on actual data.

Progress Reports/Interim analyses of safety will be provided with the PSURs and of efficacy will be provided annually with the conditional approval renewal.

Where feasible, data from country specific protocols based upon RESTORE will be included in analyses.

9.8. Quality Control

The Sponsor has ethical, legal, and scientific obligations to conduct this registry in accordance with established research principles, local treatment practices and regulations, and International Council on Harmonization (ICH) guidelines. As such, in order to fulfill these obligations and to maintain current knowledge of the registry progress, the Sponsor's monitors or representatives will regularly contact the clinical sites during registry conduct either by telephone or in-person visits. Regular inspection of the registry data may be conducted in order to assess patient enrollment, compliance with protocol procedures, completeness and accuracy of data entered on the registry. Verification of eCRF data against original source documents, and occurrence of SAEs may be done at selected sites and/or for selected patients.

9.8.1. Monitoring

Due to the nature of this registry, in-house site management and centralized monitoring will be the main strategies employed. This risk-based monitoring approach will be detailed in the Registry Monitoring Plan. The Sponsor-assigned monitors may conduct site visits as needed to the clinical facilities for

monitoring various aspects of the registry. The Investigator must agree to Sponsor authorized personnel having direct access to the clinical (or associated) files for all patients- considered for registry entry for verifying entries made in the registry and assist with their activities, if requested. The Investigator should make adequate time and space for monitoring.

The site must complete the eCRFs or transfer data to the registry in a timely manner and on an ongoing basis to allow review per the Registry Monitoring Plan. This monitoring strategy will only apply to those sites entering data directly into the registry EDC and no monitoring will be done onsite at existing registries.

9.8.2. Inspection and Auditing Procedures

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are fulfilled.

The Sponsor or its representative may conduct audits at the clinical sites including, but not limited to, presence of required documents, the informed consent process, and comparison of CRFs with source documents. All medical records (progress notes) must be available for audit. The Investigator agrees to participate with audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the Investigator during or after the registry. The Investigator or designee should contact the registry immediately if this occurs. He/she must cooperate fully with regulatory authorities or other audits conducted in a reasonable manner.

9.8.3. Source Document Maintenance

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs, and recorded data from automated instruments.

All source documents from this registry will be maintained by the Investigator and made available for inspection by authorized persons. The original signed ICF for each patient shall be filed with records kept by the Investigator and a copy shall be given to the patient.

9.8.4. Record Maintenance

Records must be retained in accordance with the current ICH Guidelines. All essential registry documents, including records of patients, source documents, and eCRFs, must be kept on file.

The investigator will not dispose of any records relevant to this registry without written permission from the Sponsor and will provide the Sponsor the opportunity to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this registry. Such documentation is subject to inspection by the Sponsor, its representatives, and regulatory authorities.

If an investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records must be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

9.9. Limitations of the Research Methods

This registry recruits patients from a variety of settings and backgrounds with a confirmed diagnosis of SMA allowing assessment of the long-term outcomes of patients with a diagnosis of SMA. To evaluate patients who are treated with AVXS-101, this registry may include patients who were treated in a CUP for AVXS-101 such as a MAP, EAP, SPI or NPP. It will also allow for evaluation of usual care treatments, including concomitant use of other therapies to treat SMA. It will also include patients enrolled in existing SMA registries. However, given that the registry will provide data for clinical management of patients with SMA across many countries, there is a potential limitation due to the likely variation in the standard of care across countries or regions and variation in treatments based on cultural norms with further potential of missing data for some measures.

Patients who do not receive AVXS-101 will likely be different as a group than those who are candidates to receive this gene therapy, calling into question their validity as an appropriate comparator group. However, the data on the natural history of disease collected as part of this registry will provide a background context against which to compare the data from patients treated with AVXS-101.

In order to minimize the potential for survivor bias, patients are eligible to enroll in the registry if a genetic confirmation of SMA was made on or after 24 May 2018. Whilst this will not eliminate survivor bias completely as there may be some patients where a diagnosis was made on or after 24 May 2018 but who are deceased at the time the site begins to enroll patients, it will significantly minimize the risk compared to there being no set cut-off date of diagnosis date.

For patients who participate in an AVXS-101 CUP, the date of diagnosis of 24 May 2018 does not apply. The rationale for this reflects the spirit of a CUP, which is designed to be inclusive of any patient not eligible or unable to partake in an AVXS-101 clinical trial. All patients in a CUP should have the opportunity to participate in the registry in order that long-term follow up data can be obtained. Any CUP patient enrolled into the registry with a date of diagnosis prior to May 24, 2018 will be included in the final analysis, but with restrictions to data analyzed.

9.10. Other Aspects

Not applicable.

10. Protection of Human Patients

Prior to any data collection under this protocol, a written ICF and a privacy statement, if required, must be signed by the parent/guardian and, where appropriate if assent is required, by the patient, in accordance with local practice and regulations. Information about the registry will be explained to the parent/guardian and patient where appropriate. A copy of the ICF, signed and dated by the parent/guardian and patient where appropriate, must be given to the parent/guardian/patient. Confirmation of a parent/guardian's informed consent and where appropriate the patients' assent must be documented in the patient's medical records prior to any data collection under this protocol. The ICF must not be altered without the prior agreement of the relevant IRB/IEC and the Sponsor. For sites participating in the registry but only sharing data from their existing registry, the Sponsor will ensure

that the ICF is fit for purpose and covers not only consent into that registry but data sharing outside of that registry and the country in which the registry is being conducted.

If a pediatric patient reaches the age of majority during the course of the registry, the patient, if competent to do so, will be required to provide his/her consent to remain in the registry and allow for data collection from the date of majority onwards.

All information obtained during the conduct of the registry with respect to the patient's state of health will be regarded as confidential. For disclosure of any such information, an agreement will be obtained in writing.

The Investigator must ensure that each patient's anonymity is maintained. On eCRFs and other documents submitted to the registry, patients must not be identified by name. The only exception is the Consent process in which the caregiver provides consent:

3. Electronically, in which the patient's name may be entered into the NESS database via the secure RESTORE Registry Portal; or
4. By paper, in which the scanned executed ICF (which may contain the patient's name) is uploaded to the NESS database via the secure RESTORE Registry Portal.

Personal Health Information (PHI) collected by the RESTORE Registry Portal is protected by NESS SOPs using encryption. PHI has been defined as:

- Executed Informed Consent
- Executed Assent
- Caregiver's Email Address, and Phone Number
- Patient's Name, Email Address, Phone Number, and Date of Birth
- Primary Physician's Name, Clinic Name, Mailing Address, Email Address, and Phone Number
- Primary Physician Office Contact's Name and Phone Number

Only authorized personnel at NESS, UBC Study Monitors, and the site will have access to PHI. At the end of the study, all PHI data collected via the RESTORE Registry Portal will be destroyed per NESS SOPs at the direction of the sponsor.

Measures will be implemented to ensure the security and compliance of all data hosted within the database environment. These measures cover all aspects of network, individual systems/devices, user account, web and email protection.

In order to comply with government regulatory guidelines and to ensure patient safety, it may be necessary for AveXis and the registry, the local research review board, or regulatory authorities to review patients' medical records as they relate to this registry. Only the patient's unique number on the eCRFs will identify him/her, but full names may be made known to a drug regulatory authority or other authorized government or health care officials, if necessary, and to personnel designated by AveXis for the purposes of a regulatory audit.

Documents that are not for submission to AveXis or the registry (e.g., consent forms) will be maintained by the Investigator in strict confidence, except to the extent necessary to allow monitoring by AveXis, and auditing by AveXis and regulatory authorities. No documents identifying patients by name will leave the clinical site or NESS database, and patient identity will remain confidential in all publications related to the registry.

Prior to the collection of any registry related data, IRB/IEC approval of the protocol, informed consent and all patient enrollment materials will be obtained in each country and for each site, as applicable. The registry will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, applicable privacy laws, and local regulations for each participating site.

This registry will be conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology and the Guide on Methodological Standards in Pharmacoepidemiology issued by The ENCePP.

11. Management and Reporting of Adverse Events/Adverse Reactions

De novo patients

De novo patients are defined as patients who are participating in the RESTORE registry but not participating in any other SMA disease registry. The Investigator is responsible for recording in the EDC all AEs following the process noted below for *de novo* patients entering the RESTORE registry.

- For the first 12 months following AVXS-101 treatment (or any other one-time treatment for SMA which subsequently becomes available) collect all AEs and SAEs regardless of causality. Investigators are required to assign a causality assessment.
- For the **duration** of treatment with nusinersen (or any other specific treatment for SMA, which subsequently becomes available) collect all AEs and SAEs regardless of causality. Investigators are required to assign a causality assessment. Investigators are also responsible for reporting these events to the manufacturers/Health Authorities as per local regulations for commercialized treatments.
- For the remainder of the registry, the following will be collected for patients regardless of which SMA treatment they have received:
    - All AESIs
    - All Non-serious ADRs (i.e., non-serious AEs that have been assessed as related by the investigator)
    - All SAEs, including malignancies and deaths

The following operational definitions apply to the AESIs:

- Hepatotoxicity (above the upper limit of normal (ULN); elevated bilirubin). The accompanying clinical correlate consists of anorexia, nausea, vomiting, abdominal pain, jaundice, altered mental status (hepatic encephalopathy) and vitamin-K related coagulopathy.
- Thrombocytopenia defined as below the upper limits of normal. Clinical bleeding event associated with thrombocytopenia are relevant to this investigation (e.g., bruising, petechiae, melena, hematemesis, purpura, mucosal hemorrhage) including any bleeding event for which platelet transfusion was indicated.

- Cardiac AEs (through signs and symptoms suggestive of cardiac dysfunction or abnormal echocardiogram or abnormal laboratory findings). Clinical manifestations are expected to include cardiac arrhythmias, fatigue, peripheral edema and dyspnea (clinical features of heart failure).
- Inflammation of the Dorsal Root Ganglia cells. e.g., as evidence by abnormalities in proprioceptive, vibratory, tactile and pain sensation.

The Investigator is responsible for ensuring the AE form is completed in the EDC including; serious/non-serious assessment, causality assessment, description of event, start/stop dates, common terminology criteria for adverse events (CTCAE) grade, and outcome. The investigator is also responsible for completing a paper form for safety reporting to AveXis pharmacovigilance or designee as follows:

For **SAEs and non-serious AESIs**: SAE/AESI Form to be completed and sent to AveXis pharmacovigilance or designee **within 24 hours** from investigator/site awareness of the event(s) on **only patients treated with AVXS-101**.

It is proposed not to collect all AEs for the full 15 year follow up period beyond the first 12 months following AVXS-101 treatment or following cessation of other SMA treatments. Instead, collection will be limited to ADRs, AESIs and SAEs. Collection of all AEs would not provide any additional data of relevance taking into account the nature of SMA i.e., being a chronic disease with multiple comorbidities. Additionally, as patients will have less frequent follow up in the latter years following treatment, collection of all AEs is likely to be inaccurate and limited.

Data transferred from existing SMA Registries

If available, patient-level data on AEs and comorbidities collected from consenting patients in existing SMA registries will be imported into a common data model and analyzed separately from the data from *de novo* patients. Any data pertaining to AESI for AVXS-101 i.e., hepatotoxicity, cardiac events, thrombocytopenia, dorsal root ganglia inflammation, will be forwarded to AveXis Global Patient Safety/Pharmacovigilance or designee. These events will be entered into the AveXis safety database.

11.1. Definitions

Adverse Event: Any untoward medical occurrence in a patient or clinical-trial subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Drug Reaction:

A response to a medicinal product, which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse, lack of efficacy and medication errors.

Adverse Event of Special Interest: An AESI (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring may be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

Serious Adverse Event: Any AE is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Any suspected transmission via a medicinal product of an infectious agent should be processed as serious.

12. Plans for Disseminating and Communicating Registry Results

12.1. Publications

With the exception of the publication of a single investigator's data, publication of Registry results will be guided by the Registry Steering Committee-Publication sub Committee and in accordance with the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Auditing, and Publication of Scholarly Work in Medical Journals (Dec 2017) and Good Publication Practice for Communicating Company-Sponsored Medical Research. The Publication Committee will provide input into the publication plan including the planning of any sub-analyses that would be of interest to the scientific/medical community.

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14. Investigator Protocol Signature Page

Protocol Title: A Prospective, Long-Term Registry of Patients with a Diagnosis of Spinal Muscular Atrophy (SMA) - RESTORE

Protocol Number: AVXS-101-RG-001

Original Protocol Version or Date: V 1.0: 20 March 2018

Protocol Amendment Version or Date:

I have reviewed the content of this protocol and agree to participate in the registry and adhere to all regulations that govern the conduct of this registry.

Site Principal Investigator Name (printed):

Site Address:

Site Principal Investigator's Signature	Signature Date

Annex 1. List of Stand-alone Documents

None

Annex 2. ENCePP Checklist for Study Protocols

Study title:
A Prospective, Long-Term Registry of Patients with a Diagnosis of Spinal Muscular Atrophy (SMA) - RESTORE

EU PAS Register® number: Not available **Study reference number (if applicable):** AVXS-101-RG-001

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7,8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis (-es) is (are) to be tested?	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.7

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Further details will be provided in the Statistical Analysis Plan

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.1
4.2.2 Age and sex	☐	☐	☒	
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☒	☐	☐	9.2
4.2.5 Duration of follow-up	☒	☐	☐	9.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☒	☐	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☐	☒	☐	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	

Comments:

Details will be provided in Statistical Analysis Plan

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	

Comments:

Details will be provided in Statistical Analysis Plan

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☒	☐	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☒	☐	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☒	☐	

Comments:

Details will be provided in Statistical Analysis Plan

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Details will be provided in Statistical Analysis Plan

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Details will be provided in Statistical Analysis Plan

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☐	☒	☐	
10.2 Is study size and/or statistical precision estimated?	☐	☒	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Details will be provided in Statistical Analysis Plan

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	10
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Boardbeen described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: [Name], MBBS, LLM

Date: dd/Month/year

Signature: _____