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

Protocol Number: COAV101A12001

REDACTED PROTOCOL

Version: 4.0
Original Protocol Date: 20-Mar-2018
Amendment 1 Date: 11-Sep-2019
Amendment 2 Date: 19-Apr-2021
Amendment 3 Date: 28-Sep-2023

Compound: OAV-101

Sponsor

Novartis Gene Therapies Inc.

(previously known as AveXis Inc)

2275 Half Day Road

Suite 200

Bannockburn, Illinois 60015

United States

Title	A Prospective, Long-Term Registry of Patients with a Diagnosis of Spinal Muscular Atrophy (SMA) - RESTORE
Protocol version identifier	Version 4.0
Date of last version of protocol	Original Protocol (Version 1.0) 20-Mar-2018 Amendment 1 (Version 2.0) 11-Sep-2019 Amendment 2 (Version 3.0) 19-Apr-2021 Amendment 3 (Version 4.0) 28-Sep-2023
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 OAV-101.
Countries of registry	Patients will be recruited from the following regions: o Australia/Asia Pacific o Europe o Middle East and Africa o Latin America o North America
Author	Novartis Gene Therapies Inc.

1. Table of Contents

Cover Page 1

1. Table of Contents 3

2. List of Abbreviations and Definitions of Terms 5

3. Responsible Parties 9

4. Abstract 10

5. Amendments and Updates 13

6. Milestones 32

7. Rationale and Background 33

8. Research Question and Objectives 35

9. Research Methods 36

9.1. Registry Design 36

9.2. Setting 36

9.2.1. Selection of Registry Population 36

9.2.2. Registry Procedures 37

9.2.3. Schedule of Assessments 37

9.2.4. Participation and Retention Strategies 39

9.2.5 Patients Lost to Follow-up 40

9.3 Variables 40

9.4. Data Sources 44

9.5. Registry Size 44

9.6. Data Management 45

9.7. Data Analysis 45

9.8. Quality Control 46

9.8.1. Monitoring 46

9.8.2. Inspection and Auditing Procedures 46

9.8.3. Source Document Maintenance 47
9.8.4. Record Maintenance 47
9.9. Limitations of the Research Methods 47
9.10. Other Aspects 48
10. Protection of Human Patients 49
11. Management and Reporting of Adverse Events 51
11.1. Definitions 52
12. Plans for Disseminating and Communicating Registry Results 54
12.1. Publications 54
13. References 55
14. Investigator Protocol Signature Page 57
Annex 1. List of Stand-alone Documents 58
Annex 2. ENCePP Checklist for Study Protocols 59

List of Tables

Table 1: Schedule of Assessments 38
Table 2: Registry Variables 41
Table 3: Upper and Lower Limits of a 95% CI for Two Year Overall SMA Survival or Depending on the Copy Number 45
Table 4: Adverse Event Collection Requirements 51

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AAV9	Adeno-Associated Virus serotype 9
ACEND	Assessment of Caregiver experience in neuromuscular disease
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
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BiPAP	Bilevel Positive Airway Pressure
CB	Chicken β-actin-hybrid promoter
cDNA	Complementary Deoxyribonucleic Acid
CFR	Code of Federal Regulations
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence Interval
CMV	Cytomegalovirus
CuidAME	Registry for longitudinal data collection of Spanish SMA patients
CUP	Compassionate Use Program
eCRF	Electronic Case Report Form
CRF	Case Report Form
CRO	Contract Research Organization

DALY	Disability-adjusted Life Years
de novo	Of new
DNA	Deoxyribonucleic acid
EAP	Expanded Access Program
eCOA	Electronic Clinical Outcome Assessment
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ePRO	Electronic Patient Reported Outcome
EU	European Union
FEV1	Forced Expiratory Ventilation in 1 second
FVC	Forced Vital Capacity
G-BA	Gemeinsamer Bundesausschuss
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practices
HCT	Hematocrit
HFMSE	Hammersmith Functional Motor Scale - Expanded
HINE-2	Hammersmith Infant Neurological Examination – Section 2
HRQoL	Health-related Quality of Life
ICD	International Classification of Diseases
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	Information Technology
MAH	Marketing Authorization Holder
MAP	Managed Access Program
6MWT	Six Minute Walk Test
MedDRA	Medical Dictionary for Regulatory Activities
n	Number
[redacted]	[redacted]
NESS	New England Survey Systems
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
QALY	Quality-adjusted Life-year
QPPV	Qualified Person Responsible For Pharmacovigilance
RBC	Red Blood Cell Count
RESTORE	The RESTORE Registry is a prospective, multicenter, multinational, observational study
RULM	Revised Upper Limb Module

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
TMA	Thrombotic microangiopathy
Treat-NMD	Treat Neuro Muscular Disease
UK	United Kingdom
US	United States
WBC	White Blood Cell Count
WHO	World Health Organization
WHO MGRS	World Health Organization Multicenter Growth Reference Study

3. Responsible Parties

Sponsor	Novartis Gene Therapies, Inc. 2275 Half Day Road, Suite 200 Bannockburn, IL 60015 Office Phone: 847.572.8280 Toll-free Phone: 844.428.3947 medinfo.gtx@novartis.com medinfo.emea.gtx@novartis.com
Contract research organization (CRO)	[redacted] Tel: [redacted]

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 survival motor neuron (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 [15].

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 OAV-101. As of the date of this amendment, 590 patients have been enrolled from 13 countries.

Research Question and Objectives

This registry will assess long-term outcomes of patients with a genetically confirmed diagnosis of SMA. It will also characterize and assess long-term safety and effectiveness of OAV-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 OAV-101 including the analysis of reported events that might be suggestive of hepatotoxicity, thrombocytopenia, thrombotic microangiopathy (TMA), cardiac adverse events (AEs) and sensory abnormalities suggestive of ganglionopathy in SMA patients treated with OAV-101, which are known as AESIs
- To assess permanent ventilation-free survival of all patients with SMA[1]
- To assess overall survival of all patients with SMA

Secondary objectives

- To assess healthcare utilization
- To assess caregiver burden
- To assess patient functional independence
- To characterize the natural history/epidemiology of patients with less than 4 copies of the Survival Motor Neuron 2 Gene *SMN2*
- To characterize the use of systemic glucocorticosteroids and other systemic immunosuppressive medication

[1] Permanent ventilation is defined as requiring invasive ventilation (tracheostomy), or respiratory assistance for 16 or more hours per day (including non-invasive ventilatory support) continuously for 14 or more days in the absence of an acute reversible illness, excluding perioperative ventilation [6].

Registry Design

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

Population

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

Inclusion Criteria:

- Patients **not treated with OAV-101** with a diagnosis of SMA genetically confirmed on or after 24-May-2018
  OR
  Patients **treated with OAV-101** with a genetically confirmed diagnosis of SMA regardless of the date of diagnosis.
  AND
- 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 who are participating in a Compassionate Use Program (CUP) for OAV-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 a genetic or clinical diagnosis of SMA. Patients who are participating in long-term follow-up studies of Zolgensma (such as LT-001 or LT-002) are not eligible to enroll in the registry. However, patients who have completed OAV-101 clinical trials and are not participating in the long-term follow up studies may enroll in this registry. Patients who are enrolled in the registry and are subsequently enrolled in an investigational clinical trial involving an investigational medicinal product to treat SMA will be discontinued from the registry.

Variables

The following categories of registry variables will be collected for each patient including the date each assessment was performed:

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

Data Sources

Data will be received from existing registries that have agreed to share their data. This data will be received either at the patient-level or in aggregate, depending on the agreement. Additional data will be collected prospectively from *de novo* sites using electronic data capture (EDC) forms, which sites will complete using patient medical charts. Additionally, for *de novo* patients, data may be collected by patients or caregivers, as appropriate, using Patient Reported Outcome (PRO) Questionnaires and caregiver surveys. Data may also be received from the OAV-101 CUPs whether or not patients are in an existing registry or are from *de novo* sites. Where applicable, retrospective data will also be collected from at least the time of initiating the first dose of first SMA therapy up to the date of registry enrollment. This is to address a request from the G-BA to include safety relevant data for all patients who are eligible for the G-BA study (Protocol COAV101A1DE01) regardless of treatment through 31-Dec-2026.

Registry Size

The registry will enroll at least 500 patients with a diagnosis of genetically confirmed 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 relevant subgroups, 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.

5. Amendments and Updates

Version 2.0 was the first protocol amendment. Significant changes are set out in the table below.

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 Block B, The Crescent Building Northwood, Santry Dublin 9 D09 C6X8 Ireland
MAH contact person	To be determined	[redacted] MD, PhD [redacted]
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 incidence of thrombocytopenia, hepatotoxicity and cardiac AEs in SMA patients treated with AVXS-101 • To assess overall survival of all patients with SMA

<table>
<tr><th>Section</th><th>Version 1.0</th><th>Version 2.0</th></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>
<tr><td>Milestones</td><td><table>
<tr><td>Start of recruitment and baseline data collection</td><td>Jun-2018</td></tr>
<tr><td>End of recruitment and baseline data collection</td><td>Jun-2023</td></tr>
<tr><td>End of data collection</td><td>Jun-2038</td></tr>
<tr><td>Final report of study results</td><td>Oct-2038</td></tr>
</table></td><td><table>
<tr><td>Registration in PAS Register</td><td>Upon EU Marketing Authorization</td></tr>
<tr><td>Start of recruitment and baseline data collection</td><td>Sep-2018</td></tr>
<tr><td>End of recruitment and baseline data collection</td><td>Jun-2023</td></tr>
<tr><td>Progress reports</td><td>Annually with periodic benefit-risk evaluation report (PBRER) following EU Marketing Authorization</td></tr>
<tr><td>Interim analyses</td><td>Annually</td></tr>
</table></td></tr>
</table>

Section	Version 1.0	Version 2.0
		End of data collection: Jun-2038 Final report of registry results: Oct-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 [redacted]
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

Section	Version 1.0	Version 2.0
		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 (HFMSE)
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	Version 1.0	Version 2.0
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.

Section	Version 1.0	Version 2.0
		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 14-May-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

Section	Version 1.0	Version 2.0
		• 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, [redacted] 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 Centers for Pharmacoepidemiology and Pharmacovigilance (EnCEPP) checklist

Version 3.0 is the second protocol amendment. Significant changes are set out in the table below.

Section	**Version 2.0**	**Version 3.0**
Multiple	AveXis Inc	Administrative change: Novartis Gene Therapies Inc.
Sponsor approval	[redacted] Title: [redacted] [redacted] Title: [redacted]	Administrative change: [redacted] Title: [redacted] [redacted], MD, MHSA Title: [redacted] [redacted] MPH Title: [redacted]
MAH Contact Person	[redacted]	Administrative change: [redacted]
Milestones	Annually with PBRER following EU Marketing Authorization	Safety interim report with Periodic Safety Update Reports (PSURs) Efficacy and Safety interim report within the European Medicines Agency (EMA) annual Regulatory renewal procedure
7. Rationale and Background	Not applicable	Section edited to correct references and to condense background content to elements relevant for the registry background. Update to countries where Zolgensma is approved. Addition of "In developing this protocol, the recommendations of SMA patient representatives have been taken into account."

Section	Version 2.0	Version 3.0
8. Research Question and Objectives	Primary objectives To assess the effectiveness of treatments for SMA To assess long-term safety of AVXS-101 To characterize the risks of thrombocytopenia, hepatotoxicity and cardiac AEs in SMA patients treated with AVXS-101 To assess overall survival of all patients with SMA	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 characterize the risk of hepatotoxicity, thrombocytopenia, TMA, cardiac adverse events and sensory abnormalities suggestive of ganglionopathy in SMA patients treated with AVXS-101, To assess permanent ventilation-free survival of all patients with SMA* To assess overall survival of all patients with SMA
8. Research Question and Objectives	Secondary objectives To assess healthcare utilization To assess caregiver burden To assess patient functional independence	Secondary objectives Edited to provide clarification and specificity of secondary objective To assess healthcare utilization To assess caregiver burden To assess patient functional independence To characterize the natural history/epidemiology of patients with less than 4 copies of the *SMN2* gene. To characterize the use of systemic glucocorticosteroids and other systemic immunosuppressive medication used to help manage the humoral immune response to the AAV9 vector. *Permanent ventilation is defined as requiring invasive ventilation (tracheostomy), or respiratory assistance for 16 or more hours per day (including

Section	Version 2.0	Version 3.0
		noninvasive ventilatory support) continuously for 14 or more days in the absence of an acute reversible illness, excluding perioperative ventilation.
9.1 Registry Design		Edited for clarification, to avoid repetition and to remove obsolete language in relation to the Compassionate Use Programs
9.2. Setting		Updated to reflect current list of proposed countries Edited to reflect that the consecutive enrollment refers to *de novo* patients as the sponsor is unable to mandate the enrollment into existing registries
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.	Edited to clarify the following: The RESTORE registry will enroll at least 500 patients as per the inclusion criteria. There will be no cap on enrollment
9.2.1.1. Eligibility Criteria	<u>Inclusion Criteria</u> Patients with 5qSMA, genetically confirmed on or after 24-May-2018, regardless *SMN2* copy number. Appropriate consent/assent has been obtained for participation in the registry.	<u>Inclusion Criteria</u> Patients not treated with AVXS-101 with SMA genetically confirmed on or after 24-May-2018 OR Patients treated with AVXS-101 with SMA genetically confirmed regardless of the date of diagnosis AND Appropriate consent/assent has been obtained for participation in the registry. Clarification that patients that are participating in long-term follow-up studies of Zolgensma (such as LT-001 or LT-002) are not eligible to enroll in the registry. However, patients who have completed

Section	Version 2.0	Version 3.0
		clinical trials and are not participating in the long-term follow up studies may enroll in this registry.
9.2.2. Registry Procedures		Edited to eliminate repetition Addition of "Data will be entered at baseline upon patient enrollment and entered periodically thereafter for all routine clinical practice patient visits. For example, all laboratory values collected at routine clinical visits occurring between month 6 and month 12 of a patient's participation in the registry should be entered at the 12-month time point. All data will include the date each assessment was performed".
9.2.3. Variables Confirmation of eligibility		Addition of "if legally allowed" for Race and Ethnicity Addition of Discontinuation from registry and date of and reason for discontinuation
9.2.3. Variables Clinical characteristics	Recumbent Length/height	~~Recumbant~~ Length/height
9.2.3. Variables Treatment		Addition of: Anti AAV9 antibody prior to treatment with AVXS-101 Glucocorticosteroid treatment (removed AVXS 101 treatment only) Indication for use Risdiplam treatment
9.2.3. Variables Patient Assessments	Pulmonary Medications	Removed pulmonary medications as not collected in registry. Addition of: Ventilatory Support

Section	Version 2.0	Version 3.0
		Tracheostomy Non-Invasive Ventilatory Support (Bilevel positive airway pressure [BiPAP]) Defined survival endpoint met (yes/no) Dysphagia function assessment Speech function assessment Echocardiography Normal/Abnormal Ejection Fraction Structural or Functional Abnormalities Motor Function Regain of lost function Revised Upper Limb Module (RULM) 6-minute walk test (6MWT) Neurological assessment Troponin 1
9.2.3. Variables Musculoskeletal management		Addition of: Musculoskeletal Findings (contractures, dysplasia, fractures, spinal curvature, pelvic obliquity, other) Orthoses (Ankle-foot orthesis, supramalleolar orthesis, knee, ankle, foot orthesis, bracing, other) Devices and mobility equipment (device, wheelchair)
9.2.3. Variables Patient/Caregiver Reported Outcomes		Assessment of Caregiver Experience in Neuromuscular Disease (ACEND)

Section	Version 2.0	Version 3.0
9.2.3. Variables AEs		Definition of AESIs added for completeness: Hepatotoxicity Sensory Abnormalities Suggestive of Ganglionopathy Cardiac AEs Transient Thrombocytopenia TMA Gene Therapy Related Delayed AEs New malignancies New incidence of autoimmune disorder New incidence neurologic disorder
Developmental Milestone Checklist	Yes/No	Not Achieved/Age Achieved/Age Lost To allow for a more informative response
9.4. Data Sources		Text edited for clarity and also to reflect process
9.5. Registry Size		Text updated to align with the SAP Version 1.0:
9.7. Data Analysis		Text updated to align with the SAP Version 1.0:
9.9. Limitations of the Research Methods		However, in the EU the approved indication for AVXS-101 is for patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene. In order to ensure enrolment of those older patients with SMA Type II or Type III who have been treated with AVXS-101, the protocol allows for

Section	Version 2.0	Version 3.0
		patients treated with AVXS-101, whatever the date of SMA diagnosis.
9.9. Limitations of the Research Methods	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 14-May-2018 will be included in the final analysis, but with restrictions to data analyzed.	Removed as no longer relevant.
11. Management and Reporting of Adverse Events/Adverse Reactions		Safety reporting has not been changed, but that language has been improved and expanded to increase clarity and avoid misinterpretation by participating healthcare providers.
11. Management and Reporting of Adverse Events/Adverse Reactions		Text added to ensure reports of pregnancies are collected: Any pregnancy in a patient treated with AVXS-101: Pregnancy Report Form to be completed and sent to Novartis Gene Therapy pharmacovigilance or designee within 24 hours from investigator/site awareness of the event

Version 4.0 is the third protocol amendment. Significant changes are set out in the table below.

Section	Version 3.0	Version 4.0
Multiple	AVXS	OAV-101
Countries of Registry Introductory Pages 9.2 Setting	Individual country list provided worldwide	Patients will be recruited from the following regions: o Australia/Asia Pacific o Europe o Middle East and Africa o Latin America o North America
Introductory Pages	EU Marketing Authorisation details	EU Marketing Authorisation details removed
Introductory Pages	Sponsor approval	Removed to be a stand-alone page independent of protocol
CRO	[redacted]	[redacted]
4. Abstract 8. Research Questions and Objectives	• To assess the long-term safety of AVXS-101 • To characterize the risk of hepatotoxicity, thrombocytopenia, thrombotic microangiopathy (TMA), cardiac adverse events (AEs) and sensory abnormalities suggestive of ganglionopathy in SMA patients treated with AVXS-101	• To assess the long-term safety of OAV-101 including the analysis of reported events that might be suggestive of hepatotoxicity, thrombocytopenia, thrombotic microangiopathy (TMA), cardiac adverse events (AEs) and sensory abnormalities suggestive of ganglionopathy in SMA patients treated with OAV-101, which are known as AESIs
Abstract	Not applicable	Patients who are enrolled in the registry and are subsequently enrolled in an investigational clinical trial involving an

Section	Version 3.0	Version 4.0
9.2.1.1 Eligibility Criteria		investigational medicinal product to treat SMA will be discontinued from the registry.
Abstract	Not applicable	Where applicable, retrospective data will also be collected from at least the time of initiating the first dose of first SMA therapy up to the date of registry enrollment. This is to address a request from the G-BA to include safety relevant data for all patients who are eligible for the G-BA study (Protocol COAV101A1DE01) regardless of treatment through 31-Dec-2026.
Abstract 9.7 Data Analysis	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.	The analysis population will consist of all patients enrolled. By default, the data will be presented by relevant subgroups, and separately by Therapy Assignment(s), including combination therapies, if applicable.
6. Milestones	End of recruitment and baseline data collection: Jun-2023	End of recruitment and baseline data collection 31-Dec-2026.
9.1 Registry Design 9.2.3. Schedule of Assessments		Additionally, retrospective data will be collected from at least the time of initiating the first dose of first SMA therapy up to the date of registry enrollment. This is to address a request from the G-BA to include safety relevant data for all patients who are eligible for the G-BA study (Protocol COAV101A1DE01) regardless of treatment through 31-Dec-2026.
9.2 Setting	Centers may be identified from those participating in existing SMA registries including but not limited to the international SMA consortium (iSMAC), Treat Neuro Muscular Disease (Treat-NMD), SMArtCARE, Cure SMA, French SMA AP-	Centers may be identified from those participating in existing SMA registries including but not limited to the international SMA consortium (iSMAC), SMArtCARE, Cure SMA, French SMA Registry, CuidAME (Spain) or may be recruited *de novo* by the RESTORE registry.

Section	Version 3.0	Version 4.0
	HP Registry or may be recruited *de novo* by the RESTORE registry	
9.2.3	N/A	Additionally, retrospective data will be collected at a minimum from the time of initiating the first dose of first SMA therapy up to the date of registry enrollment. This is to address a request from the G-BA to include safety relevant data for all patients who are eligible for the G-BA study (Protocol COAV101A1DE01) regardless of treatment through 31-Dec-2026.
Table 1 Schedule of Assessments	Other SMA treatment/start date/stop date (s), if applicable Ventilatory Assessment (Invasive and Non-Invasive) Date and cause of death	Other SMA treatment /start date/stop date (s), if applicable Ventilatory Assessment (Invasive and Non-Invasive), duration of ventilatory support Chewing function assessment Date and cause of death (including autopsy date and findings where applicable)
Table 2 Variables	• Other SMA Treatments	• Date of enrolment in clinical trial • Other SMA Treatments: albuterol/salbutamol, riluzole, L-carnitine, sodium phenylbutyrate, valproate, hydroxyurea • Duration of ventilator support • Chewing function assessment
9.4 Data Sources	Not applicable	The ICF will include consent for data to be collected retrospectively from as far back as date of birth up to the date of registry enrollment.
9.4 Data Sources	Once written informed consent has been obtained, the registry Investigator will complete the baseline data collection for each patient.	Once written informed consent has been obtained, the registry Investigator will complete the baseline data collection for each patient, including, where applicable, retrospective data from at least the time of initiating the first dose of first SMA therapy up to the date of registry enrollment. This is to address a request from the G-BA to include safety relevant data for all patients who are eligible for the G-BA study (Protocol COAV101A1DE01) regardless of treatment through 31-Dec-2026.
9.5 Registry Size	Enrollment will be open for 5 years and the registry will follow	Enrollment will be open until 31-Dec-2026 and the registry will follow patients for up to 15 years, or until 30-Jun-2038, or

Section	Version 3.0	Version 4.0
	patients for 15 years or until they are discontinued for any reason, including death- whichever comes first	they are discontinued for any reason, including death- whichever comes first.
9.7 Data Analysis	Annually, interim Efficacy and Safety reports will be provided with the annual European regulatory renewal procedure.	Annually, interim Efficacy and Safety reports will be provided to fulfill HA commitment worldwide (as applicable).
9.9 Limitations		Another limitation, which is inherent to a registry design is that there is variation in the duration of observation and the start of the observation period relative to SMA treatment. Further, collection of retrospective data on patients who initiated SMA treatment prior to registry enrollment could result in under-reporting of AEs in this time period, although the specific data will be abstracted from existing medical records and not subject to recall bias. There are some AESI specific to nusinersen (i.e., hydrocephalus, renal toxicity, respiratory tract infection, epileptic seizure, post lumbar puncture syndrome) that will be collected for all patients who are eligible for the G-BA study regardless of treatment through 31-Dec-2026. This is to address a request from the G-BA to include these events in a G-BA-mandated study protocol (Protocol COAV101A1DE01). This could result in a different AE profile between the two products given the longer commercial availability of nusinersen prior to study enrollment.
11. Management and Reporting of Adverse Events	Not applicable	Added Table 4 Adverse Event collection requirements.
11. Management and Reporting of	For the remainder of the registry (i.e., after 12 months of RESTORE enrollment), the following will be collected for	For the remainder of the registry (i.e., after 12 months of RESTORE enrollment or 12 months after starting SMA treatment after enrollment), the following will be collected

Section	Version 3.0	Version 4.0
Adverse Events	patients regardless of which SMA treatment they have received: o All AESIs regardless of causality • Hepatotoxicity • Sensory abnormalities suggestive of ganglionopathy • Cardiac AEs • Transient thrombocytopenia • TMA • Gene Therapy related delayed AEs • New malignancies • New autoimmune disorder	for patients regardless of which SMA treatment they have received and regardless of causality and seriousness : o Hepatotoxicity o Sensory abnormalities suggestive of ganglionopathy o Cardiac AEs o Transient thrombocytopenia o Thrombotic microangiopathy o Gene Therapy related delayed AEs ▪ New malignancies ▪ New incidence of an autoimmune disorder ▪ New incidence of a neurological disorder ▪ New incidence of a haematological disorder o Hydrocephalus* o Renal toxicity* o Respiratory tract infection* o Epileptic seizure* o Post lumbar puncture syndrome* *This is to address a request from the Gemeinsamer Bundesausschuss (G-BA) to include these events in a G-BA-mandated study (Protocol COAV101A1DE01). This is to address a request from the G-BA to include these events in a G-BA-mandated study (Protocol COAV101A1DE01). These AESI for nusinersen will be collected for all patients eligible for the G-BA study regardless of treatment through 31-Dec-2026.

6. Milestones

Milestone	Planned date
Registration in PAS Register	Upon EU Marketing Authorization
Start of recruitment and baseline data collection	Sep-2018
End of recruitment and baseline data collection	31-Dec-2026
Progress reports/Interim analyses	Safety interim report with PSURs Annual Efficacy/Safety interim report to fulfill HA commitment worldwide (as applicable).
End of data collection	30-Jun-2038
Final report of registry results	Oct-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 [15].

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 [14]. 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 survival. The findings from various neurophysiological and animal studies have shown an early loss of motor neurons in the embryonic and early postnatal periods [16;11;5].

Until recently, the mainstay of treatment for these patients was supportive medical care. However, advances in medical treatment focusing on gene replacement, modulation of splicing, motor neuron protection and muscle enhancement are continually changing the management and prognosis of these patients.

OAV-101 is a non-replicating recombinant adeno-associated virus serotype 9 (AAV9)-based vector containing the complementary deoxyribonucleic acid (cDNA) of the human SMN gene under the control of the cytomegalovirus (CMV) enhancer/chicken β-actin-hybrid promoter (CB). OAV-101 is produced in human embryonic kidney cells by recombinant deoxyribonucleic acid (DNA) technology. The goal of OAV-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 OAV-101 infusion (<1:50). OAV-101 was approved by Food and Drug Administration in the United States (US) on 24-May-2019, by the Pharmaceuticals and Medical Devices Agency, Japan on 19-Mar-2020, and by the European Commission on 18-May-2020. Additional approvals for OAV-101 haven been obtained in other countries including Brazil, Israel, Canada, Argentina, Taiwan, and Australia.

There is, so far, 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 [12] and up to 10 years in a dog model of hemophilia [2]. In clinical trials, persistence of therapeutic effect has been demonstrated for up to 10 years in hemophilia [13] and up to 3 years in hemophilia [3]. In SMA, transgene persistence has been shown for 250 days in mouse models [6]. Long-term follow up of patients treated with OAV-101 in Study COAV101A12101 to date has documented durability of therapeutic effect after a mean duration of follow up of 62 months and for as long as 74 months as of 11-Jun-2020, as demonstrated by persistence of previously gained and achievement of new 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 OAV-101

administration. These data, along with long term safety are being collected in the RESTORE registry and the ongoing long-term follow up studies (LT-001 and LT-002).

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 clinical or genetically confirmed diagnosis of SMA.

In developing this protocol, the recommendations of SMA patient representatives have been taken into account.

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

8. Research Question and Objectives

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

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 OAV-101 including the analysis of reported events that might be suggestive of hepatotoxicity, thrombocytopenia, thrombotic microangiopathy (TMA), cardiac adverse events (AEs) and sensory abnormalities suggestive of ganglionopathy in SMA patients treated with OAV-101, which are known as AESIs
- To assess permanent ventilation-free survival of all patients with SMA[2]
- To assess overall survival of all patients with SMA

Secondary objectives

- To assess healthcare utilization
- To assess caregiver burden
- To assess patient functional independence
- To characterize the natural history/epidemiology of patients with less than 4 copies of the *SMN2* gene.
- To characterize the use of systemic glucocorticosteroids and other systemic immunosuppressive medication .

[2] Permanent ventilation is defined as requiring invasive ventilation (tracheostomy), or respiratory assistance for 16 or more hours per day (including non-invasive 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 standard of care, i.e., the diagnostic and clinical treatment/practice process that a clinician chooses according to their clinical judgement for that SMA patient. No additional visits or investigations will be performed beyond standard of care. Patients will be followed for up to 15 years from enrollment, or until 30-Jun-2038 or death or withdrawal from the registry, whichever is sooner. Additionally, retrospective data will be collected from at least the time of initiating the first dose of first SMA therapy up to the date of registry enrollment for patients who are eligible for Novartis G-BA NIS study (CAOV101A1DE01). This is to address a request from the G-BA to include safety relevant data for all patients who are eligible for the G-BA study (Protocol COAV101A1DE01) regardless of treatment through 31-Dec-2026.

9.2. Setting

Patients will be recruited from the following regions:

- Australia/Asia Pacific
- Europe
- Middle East and Africa
- Latin America
- North America

Centers may be identified from those participating in existing SMA registries including but not limited to the international SMA consortium (iSMAC), SMArtCARE, Cure SMA, French SMA Registry, CUIDAME (Spain) 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 OAV-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.

RESTORE *de novo* patients will be enrolled consecutively 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 as per the inclusion criteria. The registry will attempt to enroll all patients treated with OAV-101 including any patients treated in a CUP such as a MAP, EAP, SPI or NPP regardless of the date of clinical diagnosis or genetic confirmation of SMA. There will be no cap on enrollment.

9.2.1.1. Eligibility Criteria

Inclusion Criteria

- Patients **not treated with OAV-101** with a genetically confirmed diagnosis of SMA on or after 24-May-2018
  OR
  Patients **treated with OAV-101** with genetically confirmed diagnosis of SMA regardless of the date of diagnosis
  AND
- 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 OAV-101 (Zolgensma) such as a MAP, an EAP, SPI or NPP are eligible to enroll in the registry regardless of the date of clinical diagnosis or genetic confirmation of SMA. Patients that are participating in long-term follow-up studies of Zolgensma (such as LT-001 or LT-002) are not eligible to enroll in the registry. However, patients who have completed clinical trials and are not participating in the long-term follow up studies may enroll in this registry. Patients who are enrolled in the registry and are subsequently enrolled in an investigational clinical trial involving an investigational medicinal product to treat SMA will be discontinued from the registry.

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 up to 15 years, or until 30-Jun-2038, death or if a patient is withdrawn from the registry at the discretion of the patient / patient's parent/legal representative or the Investigator.

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

For any patients participating in RESTORE registry and not participating in a CUP for OAV-101, no treatments will 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 standard of care.

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 standard of care at the site.

Data will be entered at baseline upon patient enrollment and entered periodically thereafter for all routine clinical practice patient visits. For example, all laboratory values collected at routine clinical visits occurring between month 6 and month 12 of a patient's participation in the registry should be entered at the 12-month time point. All data will include the date each assessment was performed.

Additionally, retrospective data will be collected at a minimum from the time of initiating the first dose of first SMA therapy up to the date of registry enrollment. This is to address a request from the G-BA to include safety relevant data for all patients who are eligible for the G-BA study (Protocol COAV101A1DE01) regardless of treatment through 31-Dec-2026.

Table 1: Schedule of Assessments

	Enrollment (including retrospective data collection where applicable[9])	**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 OAV-101 CUP[4]	X	X
Demographics	X	
Gestational age	X	
Weight at diagnosis	X	
Weight	X	X
Length/height at diagnosis	X	
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
OAV-101 treatment/date, if applicable	X	X
Anti AAV9 antibody (OAV-101 patients only)[5]	X[5]	X[5]
Glucocorticosteroid Treatment	X	X
Nusinersen treatment/start date/stop date(s), if applicable	X	X
Risdiplam treatment/start date/stop date (s), if applicable	X	X
Other SMA treatment (albuterol/salbutamol, riluzole, L-carnitine, sodium phenylbutyrate, valproate, hydroxyurea) start date/stop date (s), if applicable	X	X
Pulmonary Exam	X	X
Ventilatory Assessment (Invasive and Non-Invasive), duration of ventilatory support	X	X
Nutritional Assessment	X	X

	Enrollment (including retrospective data collection where applicable[9])	**Follow-up[2]**
Dysphagia function assessment	X	X
Speech function assessment	X	X
Chewing function assessment	X	X
Echocardiography	X	X
Motor milestone assessment	X	X
Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)	X	X
Hammersmith Infant Neurological Examination – Section-2 (HINE-2) (Motor Milestones)	X	X
HFMSE	X	X
RULM	X	X
6MWT[6]	X	X
Neurological assessment	X	X
Laboratory Assessments	X	X
Hospitalizations, Emergency Room visits, visits to other Healthcare Professionals, date, reason		X
Musculo-skeletal deformities (including contractures, scoliosis, hip subluxation)	X	X
Musculoskeletal Management (orthoses, devices, and mobility equipment)	X	X
Patient/Caregiver burden (ePRO[7]/eCOA[8])	X	X
AEs, AESIs, SAEs, ADRs[3]	X	X
Date and cause of death (including autopsy date and findings) where applicable		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 standard of care
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 OAV-101
[6] For patients who are able to ambulate independently without orthotics or assistive devices
[7] Electronic Patient Reported Outcome
[8] Electronic Clinical Outcome Assessment
[9] This is to address a request from the G-BA to include safety relevant data for all patients who are eligible for the G-BA study (Protocol COAV101A1DE01) regardless of treatment through 31-Dec-2026.

9.2.4. Participation and Retention Strategies

Individual patient follow-up is up to 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, or a whole site ceases to be part of the registry, every effort should be made to ensure a transition or contingency plan in an event of investigator retiring or changing sites is in place to ensure continued follow up of 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 Patients 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 within 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. It is especially important to collect the data variables to address the primary objectives of the protocol, including the survival and motor milestone achievement data, in line with the standard of care in local clinical practice.

Table 2: Registry Variables

Category	Variables
Confirmation of Eligibility, Socio-demographics, Registry status, OAV-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 (if legally allowed) o Ethnicity (if legally allowed) • 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 c.859G>C o Weight, length, height, head/chest circumference o Other Medical History o Relevant Surgical Procedures o Family History of SMA
Treatments	• OAV-101 Treatment (if applicable) o Anti AAV9 antibody prior to treatment with OAV-101 o Date of treatment, dose • Glucocorticosteroid treatment o Indication for use o Date of treatment start o Doses and dose changes o Date treatment ended • Nusinersen treatment (12 mg) o Dosing Stage o Dates of Doses o Stop date, if applicable • Risdiplam treatment o Date of treatment start o Dose and dose changes o Stop date • Other SMA or SMA symptoms related treatments (including albuterol/salbutamol, riluzole, L-carnitine, sodium phenylbutyrate, valproate, hydroxyurea o Dose and frequency o Start and stop dates
Patient Assessments	• Pulmonary Exam o Interpretation (Normal/Abnormal) o Pulmonary Function Test ▪ Forced Vital Capacity, FVC (Liter) ▪ Forced Expiratory Ventilation in 1 second, FEV1 (Liter)

	▪ FEV1/FVC Ratio (%) • Ventilatory Support o Tracheostomy o Non-Invasive Ventilatory Support (BiPAP) ▪ Defined survival endpoint met (yes/no) o Duration of ventilator support • 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 • Dysphagia function assessment • Speech function assessment • Chewing function assessment • Echocardiography o Normal/Abnormal o Ejection Fraction o Structural or Functional Abnormalities • Motor Function Assessments o *Developmental Milestones [18, 1] Regain of lost function o CHOP INTEND motor function o HINE-2 (Motor Milestones) o HFMSE o RULM • 6MWT** • Neurological assessment • Laboratories o Laboratory Assessments, date of assessment, result, units and reference range: ▪ Albumin ▪ Aspartate aminotransferase (AST) ▪ Alanine aminotransferase (ALT) ▪ Alkaline phosphatase ▪ Total Bilirubin ▪ Direct Bilirubin ▪ Total Protein ▪ Platelets ▪ White Blood Cell Count (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 • Insurance type (in US)
Musculoskeletal Management	• Musculoskeletal Findings (contractures, dysplasia, fractures, spinal curvature, pelvic obliquity, other) • Orthoses (Ankle-foot orthesis, supramalleolar orthesis, knee, ankle, foot orthesis, bracing, other) • Devices and mobility equipment (device, wheelchair)
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 • ACEND

AEs (see section 11)	○ Hepatotoxicity ○ Sensory Abnormalities Suggestive of Ganglionopathy ○ Cardiac AEs ○ Transient Thrombocytopenia ○ Thrombotic microangiopathy ○ Gene Therapy Related Delayed AEs ▪ New malignancies ▪ New incidence of an autoimmune disorder ▪ New incidence of a neurologic disorder ▪ New incidence of a haematological disorder ○ Hydrocephalus* ○ Renal toxicity* ○ Respiratory tract infection* ○ Epileptic seizure* ○ Post lumbar puncture syndrome* • ADRs • SAEs • Death ○ Date of Death ○ Primary Cause of Death * This is to address a request from the G-BA to include these events in a G-BA-mandated study (Protocol COAV101A1DE01). These AESI for nusinersen will be collected for all patients who are eligible for the G-BA study regardless of treatment through 31-Dec-2026.

*The Developmental Milestones form will be completed as decided by the Investigator. Milestone achievement (See Annex 1) is defined per the World Health Organization Multicenter Growth Reference Study (WHO MGRS) definitions (18) or Bayley Scales of Infant and Toddler Development, 3rd Ed. (1).
** For patients who are able to ambulate independently without orthotics or assistive devices

Developmental Milestone checklist:

Current Status Achieved	Development milestone [17] Bayley Scales of Infant and Toddler Development® [1]/WHO-MGRS [17]
Not Achieved/Age Achieved/Age Lost	Child holds head erect without support [1]
Not Achieved/Age Achieved/Age Lost	Sitting with support [1]
Not Achieved/Age Achieved/Age Lost	Sitting without support [17]
Not Achieved/Age Achieved/Age Lost	Ability to crawl [17]
Not Achieved/Age Achieved/Age Lost	Pulls to stand [1]
Not Achieved/Age Achieved/Age Lost	Stands with assistance [17]
Not Achieved/Age Achieved/Age Lost	Stand-alone [17])
Not Achieved/Age Achieved/Age Lost	Walk with assistance [17])
Not Achieved/Age Achieved/Age Lost	Walk alone [17]

9.4. Data Sources

Data will be received from existing registries that have agreed to share their data. These data will be received either at the patient-level or in aggregate, depending upon the agreement. Additional data will be collected prospectively from *de novo* sites using EDC forms, which sites will complete using the SMA patient medical charts. Additionally, for *de novo* patients, data may be collected by patients or caregivers, as appropriate using PRO questionnaires and caregiver surveys. The registry will also collect data from patients in the OAV-101 CUPs whether or not they are in an existing registry or are from *de novo* sites.

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. The ICF will include consent for data to be collected retrospectively from as far back as date of birth up to the date of registry enrollment.

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, including, where applicable, retrospective data from at least the time of initiating the first dose of first SMA therapy up to the date of registry enrollment. This is to address a request from the G-BA to include safety relevant data for all patients who are eligible for the G-BA study (Protocol COAV101A1DE01) regardless of treatment through 31-Dec-2026. 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 become 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 clinical or genetic diagnosis of SMA and as per the inclusion criteria, with the intent of including all patients treated with OAV-101 in a real-world setting. Enrollment will be open until 31-Dec-2026 and the registry will follow patients for up to 15 years, until 30-Jun-2038, or until they are discontinued for any reason, including death-whichever comes first. There is no cap on enrollment.

The sample size is driven by expected incidence of SMA diagnosis, assuming treatment with OAV-101 over a 5-year period, and not by any specific hypothesis to be tested or desired precision of estimates. A formal comparative analysis would utilize full hypothesis testing. The current study objectives are based upon a real-world evidence project, and data collected are reflective of currently developing

treatments and practices. Therefore, qualitative comparisons (descriptive statistics) will be utilized to identify differences in the treatments.

A sample size of 500 is considered to be sufficient to show that the expected OAV-101 survival rate for patients with 1 or 2 SMN2 gene copy numbers is greater than the historic 2-year survival rate. Assuming the survival rate in patients with SMN2 copy numbers 3 and 4 is less than expected (80% for example), then this sample size is also sufficient to show a survival rate with a 95% upper confidence limit under 90%. See Table 3. This table assumes the distribution of copy number is 25, 300, 125 and 50 for numbers 1,2,3 and 4 respectively.

Table 3: Upper and Lower Limits of a 95% CI for Two Year Overall SMA Survival or Depending on the Copy Number

	Copy 1 N = 25		Copy 2 N = 300		Copy 3 N = 125		Copy 4 N = 50	
Rate	95% LL	95% UL	95% LL	95% UL	95% LL	95% UL	95% LL	95% UL
95.0%	82.8%	99.9%	92.3%	97.2%	90.5%	98.1%	86.7%	99.4%
90.0%	73.7%	98.7%	85.9%	92.9%	83.5%	94.5%	79.9%	96.5%
80.0%	63.3%	93.0%	75.3%	84.3%	72.7%	86.6%	68.3%	89.9%
60.0%	41.8%	78.3%	54.5%	65.5%	51.6%	68.4%	46.8%	73.2%

95% CI based on exponential model assuming a 10% dropout rate. nQuery 8.51

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/CRO 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 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 relevant subgroups and separately by Therapy Assignment(s), including combination therapies, if applicable.

The 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 and other time-to-event analyses will be presented using Kaplan-Meier methods.

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.

Interim Safety Reports will be provided with PSURs. Annually, interim Efficacy and Safety reports will be provided to fulfill HA commitment worldwide (as applicable).

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, remote 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. Similarly, if the government regulatory authorities notify the Sponsor or the SCC of an inspection, the site PI will be notified immediately.

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. 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 genetically 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 OAV-101, this registry may include patients who were treated in a CUP for OAV-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 OAV-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 OAV-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. However, in the EU the approved indication for OAV-101 is for patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene with less than 4 copies of the SMN2 gene. In order to allow for enrolment of those older patients with SMA Type II or Type III who have been treated with OAV-101, the protocol allows for patients treated with OAV-101, whatever the date of SMA diagnosis.

Another limitation, which is inherent to a registry design is that there is variation in the duration of observation and the start of the observation period relative to SMA treatment. Further, collection of retrospective data on patients who initiated SMA treatment prior to registry enrollment could result in under-reporting of AEs in this time period, although the specific data will be abstracted from existing medical records and not subject to recall bias: the rates from prospective reporting of these AEs may be different (due to active elicitation) compared to the rates of retrospective reporting.

There are some AESI specific to nusinersen (i.e., hydrocephalus, renal toxicity, respiratory tract infection, epileptic seizure, post lumbar puncture syndrome) that will be collected for all patients who are eligible for the G-BA study regardless of treatment through 31-Dec-2026. This is to address a request from the G-BA to include these events in a G-BA-mandated study (Protocol COAV101A1DE01). This could result in a different AE profile between the two products given the longer commercial availability of nusinersen prior to study enrollment.

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 and assent, if applicable 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:

1. Electronically, in which the patient's name may be entered into the NESS database via the secure RESTORE Registry Portal; or
2. 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, [redacted] 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 Novartis Gene Therapies 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 Novartis Gene Therapies for the purposes of a regulatory audit.

Documents that are not for submission to Novartis Gene Therapies, Inc 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 Novartis Gene Therapies, and auditing by Novartis Gene Therapies 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, the Guide on Methodological Standards in Pharmacoepidemiology issued by The ENCePP, and ICH Harmonised Guideline, Good Clinical Practice (GCP).

11. Management and Reporting of Adverse Events

For the patients who are participating in the RESTORE registry and not participating in any other existing SMA disease registry, the Investigator is responsible for recording in the eCRF the AEs as outlined below:

- Collect all AEs (regardless of causality, including SAEs and AESIs as defined below) as per Table 4.

Table 4: Adverse Event Collection Requirements

#	Scenario	Safety collection requirement
1	Patient starts SMA treatment and is subsequently enrolled in RESTORE	Retrospectively report all AEs that started on or after first SMA treatment up to enrolment AND prospectively report all AEs for 12 months following enrollment in RESTORE
2	Patient is enrolled in RESTORE without having received SMA treatment and starts SMA treatment at a later date	Prospectively report all clinical events for 12 months from the time the patient starts first SMA treatment

- Investigators are required to assign a causality assessment to any one of the approved SMA treatments, OAV-101, nusinersen, or risdiplam, or any other SMA treatment which subsequently becomes available. Refer to the text box below for additional SAE reporting requirements for patients treated with OAV-101.

- For the remainder of the registry (i.e., after 12 months of RESTORE enrollment or 12 months after starting SMA treatment after enrollment), the following will be collected for patients regardless of which SMA treatment they have received and regardless of causality and seriousness:

    - Hepatotoxicity
    - Sensory abnormalities suggestive of ganglionopathy
    - Cardiac AEs
    - Transient thrombocytopenia
    - Thrombotic microangiopathy
    - Gene Therapy related delayed AEs
        - New malignancies
        - New incidence of an autoimmune disorder
        - New incidence of a neurological disorder
        - New incidence of a haematological disorder
    - Hydrocephalus*
    - Renal toxicity*
    - Respiratory tract infection*

  - Epileptic seizure*
  - Post lumbar puncture syndrome*

  *This is to address a request from the G-BA to include these events in a G-BA-mandated study (Protocol COAV101A1DE01). These AESI for nusinersen will be collected for all patients eligible for the G-BA study regardless of treatment through 31-Dec-2026.

- For the remainder of the registry (i.e., after 12 months of RESTORE enrollment or 12 months after starting SMA treatment after enrollment). all non-serious ADRs (i.e., non-serious AEs that have been assessed as related to OAV-101, nusinersen, or risdiplam, or any other SMA treatment which subsequently becomes available, by the Investigator)
  - All SAEs regardless of causality. Refer to the text box below for additional SAE reporting requirement for patients treated with OAV-101.

For **SAEs**: **If a SAE occurs to a treated patient with OAV-101 after informed consent** (irrespective of whether the patient also received nusinersen, risdiplam, or any other SMA treatment which subsequently becomes available): the SAE must be reported to Novartis Gene Therapies pharmacovigilance or designee **within 24 hours** from investigator/site awareness of the event(s)

Any pregnancy in a patient treated with OAV-101: Pregnancy Report Form to be completed and sent to Novartis Gene Therapies pharmacovigilance or designee **within 24 hours** from investigator/site awareness of the event.

Investigators are also responsible for reporting any AEs or pregnancy to nusinersen, risdiplam or/and any other subsequently available SMA treatments to the respective manufacturers and respective Health Authorities as per local regulations for commercialized treatments.

It is proposed not to collect all AEs for the full 15 year follow up period beyond the first 12 months following enrollment in the registry or 12 months following SMA treatment. 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 remaining comorbidities in some patients.

Data transferred from existing SMA Registries

If available, patient-level data on AEs and comorbidities or conditions collected from 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 a SAE or/and AESI for OAV-101 treated patients (irrespective of whether the patient also received nusinersen or/and risdiplam) i.e., hepatotoxicity, cardiac events, thrombocytopenia, thrombotic microangiopathy, dorsal root ganglia inflammation, new malignancies, new incidence of autoimmune disorder, new incidence of neurological disorder, new incidence of haematological disorder will be forwarded to Novartis Gene Therapies, Inc Global Patient Safety/Pharmacovigilance or designee. These events will be entered into the Novartis Gene Therapies, Inc safety database.

11.1. Definitions

Clinical Event: Any untoward medical occurrence in a patient not receiving SMA treatment.

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.

ADR: 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.

SAE: 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.

13. References

1. Albers CA, Grieve AJ. Test Review: Bayley, N. (2006). Bayley Scales of Infant and Toddler Development- Third Edition. San Antonio, TX: Harcourt Assessment. J Psychoeduc Assess. 2007; 25(2):180-198.

2. Buchlis G, Podsakoff GM, Radu A, et al. Factor IX expression in skeletal muscle of a severe hemophilia B patient 10 years after AAV-mediated gene transfer Blood. 2012 Mar 29;119(13):3038-41. doi: 10.1182/blood-2011-09-382317. Epub 23-Jan-2012.

3. Cideciyan AV, et al. Proc Natl AcAD Sci USA 2013; 110(6)E517-E525.PMID: 23341635.

4. Code of Conduct. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance website. http://www.encepp.eu/code_of_conduct/index.shtml. Updated 19-Mar-2018. Accessed 19-Mar-2018.

5. Farrar MA, Vucic S, Johnston HM, Kiernan MC. Corticomotoneuronal integrity and adaptation in spinal muscular atrophy. *Arch Neurol*. 2012b; 69(4):467-473.

6. Finkel, R. S., McDermott, M. P., Kaufmann, P., Darras, B. T., Chung, W. K., Sproule, D. M., Kang, P. B., Foley, A. R., Yang, M. L., Martens, W. B., Oskoui, M., Glanzman, A. M., Flickinger, J., Montes, J., Dunaway, S., O'Hagen, J., Quigley, J., Riley, S., Benton, M., Ryan, P. A., De Vivo, D. C. (2014). Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology, 83(9), 810–817. https://doi.org/10.1212/WNL.0000000000000741.

7. Foust KD, Wang X, McGovern VL, et al. Rescue of the spinal muscular atrophy phenotype in a mouse model by early postnatal delivery of SMN. Nat Biotechnol. 2010 Mar;28(3):271-4. doi: 10.1038/nbt.1610. Epub 28-Feb-2010.

8. Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3. http://annals.org. Accessed 19-Jun-2018.

9. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH harmonised guideline. Good clinical practice (GCP). E6(R3). Draft version, 19-May-2023. Accessed 08-Aug-2023. https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

10. International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals. http://www.icmje.org/recommendations/. Updated Dec-2017. Accessed 19-Mar-2018.

11. International Society for Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices (GPP). *Pharmacoepidemiol Drug Saf*. 2008; 17(2):200-8.

12. Le TT, McGovern VL, Alwine IE, et al. Temporal requirement for high SMN expression in SMA mice. *Hum Mol Genet*. 2011;20(18):3578-3591.

13. Nathwani AC, Tuddenham EG, Rangarajan S, et al. Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. N Engl J Med. 2011 Dec 22;365(25):2357-65. doi: 10.1056/NEJMoa1108046. Epub 10-Dec-2011.

14. Nathwani AC, Reiss UM, Tuddenham EG, et al. Long-term safety and efficacy of factor IX gene therapy in hemophilia B. N Engl J Med. 2014 Nov 20;371(21):1994-2004. doi: 10.1056/NEJMoa1407309.

15. Oskoui M, Levy G, Garland CJ et al. The changing natural history of spinal muscular atrophy type 1. *Neurology 2007; 69; 1931-1936, DOI: 10.1212/01.wnl.0000290830.40544.b9*.

16. Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. *Eur J Hum Genet*. 2012; 20(1):27-32.

17. Swoboda KJ, Prior TW, Scott CB, et al. Natural history of denervation in SMA: relation to age, SMN2 copy number, and function. *Ann Neurol*. 2005; 57(5):704-712.

18. WHO Multicentre Growth Reference Study Group, de Onis M. WHO Child Growth Standards based on length/height, weight and age. Acta Paediatrica. 2006; 95:76-85.

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: COAV101A12001

Original Protocol: Version 1.0., 20-Mar-2018

Protocol Amendment 3: Version 4.0, 28-Sep-2023

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

Performance Criteria For World Health Organization (WHO) Developmental Milestones

Gross Motor Milestone	Performance Criteria
Sitting without support	Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position.
Hands-and-knees crawling	Child alternately moves forward or backward on hands and knees. The stomach does not touch the supporting surface. There are continuous and consecutive movements, at least 3 in a row.
Standing with assistance	Child stands in upright position on both feet, holding onto a stable object (e.g., furniture) with both hands without leaning on it. The body does not touch the stable object, and the legs support most of the body weight. Child thus stands with assistance for at least 10 seconds.
Walking with assistance	Child is in upright position with the back straight. Child makes sideways or forward steps by holding onto a stable object (e.g., furniture) with 1 or both hands. One leg moves forward while the other supports part of the body weight. Child takes at least 5 steps in this manner.
Standing alone	Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds.
Walking alone	Child takes at least 5 steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object.

WHO = World Health Organization
Source: WHO Multicentre Growth Reference Study Group [2006]

Performance Criteria for Bayley Scales Infant and Toddler Development (Version 3) Developmental Milestones

Developmental Milestone	Performance Criteria
Head Control – Gross Motor Subtest Item #4	Child holds head erect for at least 3 seconds without support
Rolls from Back to Sides – Gross Motor Subtest Item #20	Child turns from back to both right and left sides
Sits Without Support – Gross Motor Subtest Item #26	Child sits alone without support for at least 30 seconds
Stands With Assistance – Gross Motor Subtest Item #33	Child supports own weight for at least 2 seconds
Crawls – Gross Motor Subtest Item #34	Child makes forward progress of at least 5 feet by crawling on hands and knees
Pulls to Stand – Gross Motor Subtest Item #35	Child raises self to standing position using chair or other convenient object for support
Walks With Assistance – Gross Motor Subtest Item #37	Child walks by making coordinated, alternated stepping movements
Stands Alone – Gross Motor Subtest Item #40	Child stands alone for at least 3 seconds after you release his or her hands
Walks Alone – Gross Motor Subtest Item #42	Child takes at least 3 steps without support, even if gait is stiff-legged and wobbly

Source: Albers CA, Grieve AJ. Test Review: Bayley, N. [2007].

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[3]	☒	☐	☐	6
1.1.2 End of data collection[4]	☒	☐	☐	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?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.7

Comments:

[3] 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.
[4] Date from which the analytical dataset is completely available.

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)	☐	☒	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
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. Health-related quality of life (HRQoL,), quality-adjusted life year (QALYs,), (Disability-adjusted life year) 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 the 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 the 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?	☐	☒	☐	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Details will be provided in the 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 information technology (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 Board been 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: [redacted] MBBS, LLM

Date (dd/Month/year): **Signature:** [redacted] *Electronically signed by:* [redacted] *Reason: Author* *Date: Nov 6, 2023 15:13 GMT+1*

Signature: **Email:** [redacted]