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Statistical Analysis Plan (SAP)

COAV101A1IC01 / NCT05073133

A PHASE IV OPEN-LABEL, SINGLE-ARM, SINGLE-DOSE, MULTICENTER STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFICACY OF GENE REPLACEMENT THERAPY WITH INTRAVENOUS OAV101 (AVXS-101) IN PEDIATRIC PATIENTS FROM LATIN AMERICA AND CANADA WITH SPINAL MUSCULAR ATROPHY (SMA) - OFELIA

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V3.0, 20 July 2023 for Protocol COAV101A1IC01.

The SAP signature page applies to both SAP text and SAP Templates (outputs shells or Table/ Listing/ Figure (TLF) shells). Templates must be sent to the client with the first draft SAP text.

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Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
[redacted]	[redacted]	[redacted]	[redacted]
2.0	13 Jan 2023	[redacted]	Removed the [redacted] as per Protocol Amendment 1, dated 24 Mar 2022.
2.1	19 Apr 2023	[redacted]	Modified the classification criteria for adverse events of special interest and included assessment of elevation criteria for liver function based on laboratory data by weight bracket
3.0	20 July 2023	[redacted]	Added the classification criteria for shift tables in which laboratory tests are not defined by CTCAE version 4.03 Specified the evaluation criteria for the Developmental Motor Milestone Checklist assessment [redacted]

[redacted]

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TABLE OF CONTENTS

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1. ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutical Chemical
BLQ	Below limit of quantification
BMI	Body Max Index
CRF	Case report form
CTCAE	Common Toxicity grading Adverse event
DMC	Data monitoring committee
eCRF	Electronic Case Report Form
ENR	Patient Enrolled Set
EOS	End of study
FAS	Full Analysis Set
[redacted]	[redacted]
PRO	Patient reported outcome
PT	Preferred term
ROM	Range of motion
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SMA	Spinal muscular atrophy
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings, and Figures

[redacted]

TOD	Target organ damage
TTNT	Time to next treatment
ULQ	upper limit of quantification
WHO-MGRS	World Health Organization Multicenter Growth Reference Study

[redacted]

2. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of effectiveness and safety of OAV101 (AVXS-101) in pediatric patients with spinal muscular atrophy (SMA). It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 0.0 dated 20 July 2021and amendment 1.0 dated 24 March 2022 and Case Report Forms (CRFs) version 1.1 dated 20 January 2022.

3. STUDY OBJECTIVES

3.1 Primary Objectives

To assess the safety and tolerability of IV OAV101 over an 18-months post-infusion period in participants with SMA weighing to ≤ 17 kg.

3.2 Secondary Objectives

The secondary objective is:

To evaluate the efficacy of IV OAV101 at 6-, 12-, and 18-months post-infusion in participants with SMA weighing ≤ 17 kg, as measured by the following:

- World Health Organization-Multicenter Growth Reference Study (WHO-MGRS)

[redacted]

[redacted]

4. STUDY DESIGN

4.1 General Description

This is an open-label, single arm, multi-center study to evaluate the safety, tolerability, and efficacy of IV OAV101 in symptomatic SMA pediatric participants. The study will enroll participants that weigh ≤ 17 kg.

Participants who meet eligibility criteria at Screening and Baseline visits will receive a single dose of IV OAV101 on Day 1 (Treatment period) at the approved dose of 1.1e14 vg/kg and will be followed for a period of 18 months. The study will include a 20-day screening period in which there will be 2 Screening visits, during which, eligibility will be assessed (Screening 1), weight will be collected for dose calculation (Screening 2), and baseline assessments will be performed prior to treatment. For the study duration, participants will be completing visits as defined in the Schedule of Assessments. On Day -1, participants will be admitted to the hospital for pre-treatment baseline procedures including prednisolone treatment per study protocol. On Day 1, participants will receive a single IV infusion of OAV101. Participants may be discharged 12-48 hours after the infusion, based on Investigator judgment.

Safety monitoring will be performed on an ongoing basis per protocol requirement and will be evaluated by the clinical safety team as well as DMC. An interim analysis for safety and efficacy will be performed once the last participant completes 6-months of follow-up and will include all available data up until that data cut-off. Final analysis will be planned once all participants have completed Month 18 End of Study (EOS) assessments.

After study completion eligible participants will be invited to enroll into RESTORE registry study to collect additional safety and efficacy data.

4.2 Schedule of Events

The schedule of events can be found in *Section 8. Visit schedule and assessments* of the protocol.

[redacted]

4.3 Changes to Analysis from Protocol

Not applicable.

5. PLANNED ANALYSES

1. Two interim analyses
2. Final analysis

5.1 Interim Analyses

The interim analyses are intended to provide an early safety readout from the study. No study design change or adaptation will be implemented based on the outcome of the interim analyses. The interim analyses will be performed once the last participant reaches the 6-months (week 26) and 12-month (week 52) time point and will include all available data up until that data cut-off. See section *12.6 Interim analyses* of the protocol for more details.

Derivations and definitions for the interim analyses will be based on those required for the final analysis contained in this analysis plan unless deviations are stated within the text. The list of outputs provided with the full set of output templates (planned for the final analysis) will highlight which of these outputs will also be provided for the interim analyses.

5.2 Final Analysis

All final, planned analyses identified in this SAP will be performed by [redacted] Biostatistics following Client Authorization of this Statistical Analysis Plan.

6. ANALYSIS SETS

6.1 All Patients Enrolled Set [ENR]

The all Patients enrolled (ENR) set will contain all Patients who provide informed consent for this study.

[redacted]

6.2 Full Analysis Set [FAS]

The full analysis set (FAS) will contain all enrolled patients who received the study medication. The same set will be considered for the safety analysis set (SAF).

7. GENERAL CONSIDERATIONS

The overall observation period will be divided into two mutually exclusive segments:

1. Pre-treatment period: from day of participant's informed consent to the day before infusion of OAV101
2. On-treatment period: from day of infusion of OAV101 through to the last study visit.

7.1 Reference Start Date

Reference start date is defined as the day of the study medication dosing (Day 1) and will appear in every listing where an assessment date or event date appears.

7.2 Baseline

Baseline is defined as the last non-missing measurements taken prior to reference start date (including unscheduled assessments) and after the study enrollment.

7.3 Unscheduled visits

Data from unscheduled visits will not be summarized in combination with the data from the scheduled visits. However, the data will be used to for shift tables and determine the safety assessments. Any measurement that indicates clinically significant abnormal values either from clinical or laboratory evaluations, will be considered for safety assessment.

7.4 Windowing Conventions

The following table describes assignment of visit windows to the following data for purposes of analysis:

[redacted]

Table 1. windowing conventions

Visit assigned	Day	Window
Screening visit 1	-20	+5
Screening visit 2	-14	±2
Baseline	-1	None
Day 1	1	None
Day 2	2	None
Day 3	3	None
Week 1	8	±2
Week 2	15	±2
Week 3	22	±2
Week 4	29	±2
Week 6	43	±5
Week 8	57	±5
Week 10	71	±14
Week 12	85	±14
Week 26	183	±14
Week 52	365	±21
Week 78 (EOS)	547	±21

For any laboratory procedures it is expected a window of ± 24 hours. However, any laboratory exam/testing performed outside the specified window will be considered for data analysis purpose (shift tables and liver function).

7.5 Common Calculations

No statistical hypothesis testing is intended; therefore, only descriptive analysis will be summarized for the collected data. The results will be expressed as absolute frequencies and

[redacted]

percentages (%) for categorical variables. Percentages will be calculated over the number of patients with available (non-missing) data. Mean and standard deviation or medians and quartiles (25th–75th percentile) ranges will be described for continuous variables, along with the minimum and maximum values. The 95% CI will be calculated as appropriate. The count of missing observations will be provided in all tables.

For quantitative measurements, change from baseline will be calculated as:
Test Value at Visit X – Baseline Value

7.6 Software Version

All analyses will be conducted using Python version 3.6.9 or later, SAS version 9.4 or later, or a comparable statistical software package. The statistical software used will be reported at the final clinical study report.

8. STATISTICAL CONSIDERATIONS

8.1 Statistical Bias Reduction

As a prospective observational study, the main source of bias would be missing data. Handling missing data is described in the following sections.

8.2 Covariates and Factors captured in the study

The following covariates and factors are captured in the study and presented in the analyses:

- Demographic data:
  - Gender
  - Age at study enrollment, in months
  - Age at OAV101 dosing, in months
- Medical history
  - Age at SMA diagnosis, in months

- SMA type (Type I, Type 2, Type 3A)
- Number of SMN2 copies
- Family history (carrier parents, siblings with SMA)
- Previous SMA treatment (nursinersen, risdiplam), with start and end date
- Previous medical condition not related to SMA
- Hospitalization history (from birth until study enrollment)

- Examination
  - Height
  - Weight
  - BMI
  - Physical examination
  - Neurological examination
  - Vital signs (systolic and diastolic blood pressure, pulse rate, respiration rate, body temperatures, SpO2)

- Developmental Motor Milestone Checklist assessment

8.3 Missing data

The number of missing data will be reported for each variable of interest in the analysis. Missing data will be described separately, and no data imputation will be used.

[redacted]

8.4 Sensitivity analysis

Given the descriptive nature of the summary of primary safety endpoints, no sensitivity analysis is planned.

[redacted]

9. OUTPUT PRESENTATIONS

The conventions for presentation of data in outputs is appended to this SAP (20.1. Appendix 1).

10. DISPOSITION AND WITHDRAWALS

All patients who provide informed consent and that received the OAV101 infusion will be accounted for in this study.

Patient disposition, withdrawals, and protocol violations (as defined in section 6.3), including inclusion and exclusion criteria will be presented for all enrolled patients.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the FAS.

No statistical testing will be carried out for demographic or clinical characteristics. Only descriptive data will be reported (frequency, mean ± standard deviation, median, interquartile range, minimum and maximum).

[redacted]

Demographic characteristics:

- Date of birth
- Age at enrollment: calculated as time (in months) from date of birth to study enrollment (date of informed consent signature).
- Gender (female, male)
- Country (Argentina, Brazil)

Clinical characteristics at baseline

- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/ m^2)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiration rate (breath per minute)
- Body temperature (°C)

- Laboratory tests
  - Hemogram
  - Chemistry/Liver function
  - Coagulation panel
  - Troponin
  - Virus serology
  - Urinalysis
  - Electrocardiogram
  - Echocardiogram

SMA medical history:

- Date of SMA diagnose
- Age at SMA diagnosis: calculated as the time (in months) from date of birth until SMA diagnosis
- SMA type: type 1, type 2, or type 3A
- Number of SMN2 copies: 0 until 5
- Carrier screening (yes/no)
  - Carrier parents (mother, father, both)
- Siblings with SMA (yes/no)
- Previous treatment for SMA (yes/no)
  - Nursinersen: start and end date of dosing, if applicable

- Risdiplam: start and end date of dosing, if applicable

11.1 Derivations

- BMI (kg/ m^2) = weight (kg)/ height (m^2)

12. CONCOMITANT MEDICAL CONDITIONS

Concomitant medical condition will be presented for the FAS.

Concomitant illnesses will be coded using MedDRA version 25 or later.

Concomitant medical conditions are those other than the indication being studied which started prior to or at Screening and are ongoing at the date of Screening.

Medical condition will be presented by SOC and PT.

13. MEDICATIONS

Medications will be presented for the FAS and coded using WHO drug dated March-2022 or later.

The Anatomical Therapeutic Chemical (ATC) class coding will follow level 3 structure.

See Appendix 2 for handling of partial dates for medications.

'Concomitant' medications are medications which:

- Started prior to, on or after the study medication dosing and started no later than 30 days following end of study,
- AND ended on or after the date study medication dosing or were ongoing at the end of the study.

14. STUDY MEDICATION EXPOSURE

Exposure to study medication will be presented for the FAS.

For the data analysis OAV101 will be considered as primary study medication and the corticosteroid as secondary study medication.
The date of OAV101 dosing will be taken from eCRF OAV101 infusion form.
The date of first corticosteroid administration will be taken from the eCRF Pre-infusion corticosteroid form. The date of last corticosteroid administration will be taken from the eCRF Prophylactic corticosteroid - Post-infusion details form.
Interruptions, compliance, and dose changes are not considered for duration of exposure and will be summarized separately.

15. PRIMARY OUTCOMES

15.1 Safety Outcome

All outputs for primary outcomes will be based on the FAS.
The primary outcomes are related to the safety assessments:

- Evaluation of treatment emergent AEs and SAEs
- Evaluation of important identified and potential risks
- Evaluate changes from baseline in vital signs, cardiac safety assessments, and clinical laboratory results

15.1.1 Adverse Events

Adverse Events (AEs) will be coded using MedDRA, Version 25 or later.
Treatment Emergent Adverse Events (TEAEs) are defined as AEs that started or worsened in severity on or after the OAV101 dosing through the last study visit.
Adverse events of special interest (AESI) are defined by the important identified risk an important potential risk as presented in the effective Risk Management Plan (RMP). The AESI will be summarized following the classification presented in Table 2.

[redacted]

Table 2: Adverse events of special interest classification

AESI	Search methodology (MedDRA version 25.0 or later) [MedDRA Code]
Hepatotoxicity	Hepatic disorders SMQ (Broad) [20000005]
Transient thrombocytopenia	Haemorrhages SMQ (Broad) [20000038] Haematopoietic thrombocytopenia SMQ (Broad) [20000031] HLT: Platelet disorders NEC [10035533]
Thrombotic microangiopathy	PTs: Thrombotic microangiopathy [10043645] Haemolytic uraemic syndrome [10018932] Atypical haemolytic uraemic syndrome [10079840]
Cardiac events	Cardiomyopathy SMQ (Broad) [20000150] Ischaemic heart disease SMQ (Broad) [20000043] Cardiac arrhythmias SMQ (Broad) [20000049] Embolic and thrombotic events SMQ (Broad) [20000081] Myocardial infarction SMQ (Broad) [20000047] Cardiac failure SMQ (Broad) [20000004] Hypertension SMQ (Broad) [20000147]
Sensory Abnormalities Suggestive of Ganglionopathy	PTs: Akinaesthesia [10051224] Allodynia [10053552] Anaesthesia [10002091] Anaesthesia dolorosa [10054878] Areflexia [10003084] Burning feet syndrome [10070237] Burning sensation [10006784] Central pain syndrome [10064012]

[redacted]

AESI	Search methodology (MedDRA version 25.0 or later) [MedDRA Code]
	Complex regional pain syndrome [10064332] Decreased vibratory sense [10067502] Discomfort [10013082] Dysaesthesia [10013886] Formication [10017062] Hyperaesthesia [10020568] Hyperpathia [10065952] Hypoaesthesia [10020937] Hyporeflexia [10021089] Hyporesponsive to stimuli [10071552] Intercostal neuralgia [10049949] Joint position sense decreased [10081223] Loss of proprioception [10057332] Nerve conduction studies abnormal [10029175] Nerve stimulation test abnormal [10029192] Neuralgia [10029223] Neuritis [10029240] Neurological symptom [10060860] Neuromuscular pain [10074313] Notalgia paraesthetica [10072643] Pain [10033371] Pain threshold decreased [10066956] Paradoxical pain [10067055] Paraesthesia [10033775] Peripheral nervous system function test abnormal [10034591] Peripheral sensorimotor neuropathy [10056673] Peripheral sensory neuropathy [10034620] Radicular pain [10059604]

AESI	Search methodology (MedDRA version 25.0 or later) [MedDRA Code]
	Reflex test abnormal [10068273] Reflexes abnormal [10038254] Reversed hot-cold sensation [10073738] Sensorimotor disorder [10062162] Sensory disturbance [10040026] Sensory ganglionitis [10066196] Sensory integrative dysfunction [10048871] Sensory level abnormal [10061567] Sensory loss [10040030] Skin burning sensation [10054786] Slow response to stimuli [10041045] Synaesthesia [10078814] Temperature perception test decreased [10068015] Tenderness [10043224] Thermoanaesthesia [10068010] Thermohypoaesthesia [10068009] Tinel's sign [10052492] Trichodynia [10079852] Unresponsive to stimuli [10045555] Vibratory sense increased [10068327]

AESI: Adverse event of special interest; HLT: High Level Terms; PT: Preferred Terms; SMQ: Standardized MedDRA Queries

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

The incidence of TEAEs and AESIs will be summarized. Descriptive summary statistics for the change from baseline in cardiac safety assessments (ECG, Echocardiogram, troponin), clinical laboratory measurements (including hematology and liver function assessments), and vital signs will be summarized descriptively by visit/timepoint. A summary of all laboratorial assessments (including scheduled and unscheduled visits) will be summarized separately. Mean, standard deviation, median, minimum, and maximum will be presented for continuous variables. Categorical data will be presented as frequencies and percentages. For each applicable visit/timepoint, only participants with a baseline and a measurement for that timepoint will be included in the summary.

15.1.2 All TEAEs and AESI

Incidence of all TEAEs/AESIs and Serious TEAEs/AESIs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity and relationship to study medication.

15.1.2.1 Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as possible related or not possible related TEAEs with a missing relationship to study medication are regarded as possible related to study medication (OAV101). If Patient reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication is used in the corresponding relationship summaries.

15.1.3 TEAEs Leading to Discontinuation of Study Medication

Not applicable.

15.1.4 Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as “Serious” on the Adverse Events page of the (e)CRF. A summary of serious TEAEs/AESIs by SOC and PT will be prepared.

.

15.1.5 Adverse Events Leading to Death

TEAEs leading to Death are those events which are recorded as “Fatal” on the Adverse Events page of the (e)CRF. A summary of TEAEs/AESIs leading to death by SOC and PT will be prepared.

15.1.6 CTC Grading for Adverse Events

AEs will be graded using the Common Toxicity grading (CTC) system version 4.03 as defined in the following link:
https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf
CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests where grades are not defined by CTCAE version 4.03, results will be categorized as low/normal/high based on laboratory normal ranges, according to each center.
The following listings/summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE version 4.03 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE version 4.03:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE version 4.03 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE version 4.03:

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value. Definition of low and high worst post-treatment values were considered as follows:

- For all post-baseline visits (including unscheduled visits), in cases where the laboratory result is outside the normality range (i.e. <LLN or >ULN), the greatest deviation from the normality range will be considered as the worst post-treatment value. That is, if the largest deviation from normality is <LLN, the patient will be considered as "Low". If the greatest deviation is >ULN, the patient will be classified as "High". Cases where all post-baseline visits results are within the normal range will be classified as "Normal".

15.2 Deaths

If any patients die during the study the information will be presented in a summary table and a data listing.

15.3 Laboratory Evaluations

Results from the local laboratory will be included in the reporting of this study for Hematology, Blood Chemistry, Virus Serology, Troponin, Coagulation Panel, Urinalysis, Electrocardiogram, and Echocardiogram. A list of laboratory assessments to be included in the outputs is included in the protocol section *8.4.1 Laboratory evaluations*.

Central laboratory evaluation will be included in the reporting of this study for anti-AAV9 Ab

Presentations will use SI Units. If necessary, laboratory conversion will be applied. Quantitative laboratory measurements reported as below the lower limit of quantification (BLQ), will be represented as the lower limit value; measurements reported as above the upper limit of quantification (ULQ), will be converted to the higher limit value for the purpose of quantitative summaries, but will be presented as recorded, i.e. as “< X” or “> X”> in the listings.

Note: handling of retests and unscheduled measurements are included in Section 7 to save repetition in different sections of the SAP.

The following summaries will be provided for laboratory data:

- Change from baseline by visit (for quantitative measurements) (only scheduled visits)

- Incidence of abnormal values according to normal range criteria that resulted in an adverse event (according to CTCAE grading), considering scheduled and unscheduled visit assessments.
- Shift from baseline by visit according to Common Toxicity (CTC) grading system, if applicable, considering scheduled and unscheduled visit assessments.
- Patients meeting elevation criteria for liver function test based on laboratory data by weight bracket and overall (considering scheduled and unscheduled visit assessments) (ALT > 2 x ULN; ALT >3 x ULN; ALT > 5 x ULN; ALT >10 x ULN; ALT >20 x ULN; AST > 2 x ULN; AST > 3 x ULN; AST > 5 x ULN; AST > 10 x ULN; AST > 20 x ULN; ALT or AST > 2 x ULN;; ALT or AST > 5 x ULN; ALT or AST > 8 x ULN; ALT or AST > 10 x ULN; ALT or AST > 20 x ULN; Total bilirubin > 2 x ULN; Total bilirubin > 3 x ULN; ALT or AST > 3 x ULN and Total bilirubin > 2 x ULN; ALT or AST > 3 x ULN and Total bilirubin > 2 x ULN and ALP ≥ 2 x ULN; ALT or AST > 3 x ULN and Total bilirubin > 2 x ULN and ALP < 2 x ULN)
- Time until hepatotoxicity since baseline (considering scheduled and unscheduled visit assessments)
- Time until cardiac event since baseline (considering scheduled and unscheduled visit assessments)
- Frequency of hepatotoxicity (considering scheduled and unscheduled visit assessments)
- Frequency of cardiac event (considering scheduled and unscheduled visit assessments)
- Listing of laboratory data outside the normal range (considering scheduled and unscheduled visit assessments)

15.3.1 Laboratory Specific Derivations

Liver event:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x ULN

- Total bilirubin (TBL) >1.5 x ULN

Cardiac event:

- Presence of clinically relevant finding on ECG and/or Echocardiogram

15.4 Vital Signs

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse rate (bpm)
- Respiratory Rate (breaths/ min)
- Temperature (ºC)
- SpO_2 (%)
- Weight (kg)
- Height (cm)
- BMI (kg/ m^2)

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit
- Incidence of abnormal values
- Listing of Patients meeting abnormal criteria

15.4.1 Vital Signs Abnormal Criteria

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined abnormal criteria:

Table 3. Abnormal criteria for vital signs assessments

Vital sign	Value		Patient age at visit	
			< 18 years	≥ 18 years

Systolic blood pressure (mmHg)	High		≥ 95th percentile of the age and height group[1]	≥ 180 with increase from updated baseline[5] or ≥ 20 mmHg
	Low		≤ 5th percentile of the age and height group[1]	≤ 90 with decrease from updated baseline[5] or ≥ 20 mmHg
Diastolic blood pressure (mmHg)	High		≥ 95th percentile of the age and height group[1]	≥ 105 with increase from updated baseline[5] or ≥ 15 mmHg
	Low		≤ 5th percentile of the age and height group[1]	≤ 50 with decrease from updated baseline[5] or ≥ 15 mmHg
Oral body temperature (°C)	High		≥ 38.4	≥ 39.1
	Low		≤ 35.0	≤ 35.0
Pulse rate (bpm)[2]	High	12-18 months	> 140	≥ 120 with increase from updated baseline[5] or ≥ 15 mmHg
		18-24 hours	> 135	
		2-3 years	> 128	
		3-4 years	> 123	
		4-6 years	> 117	
		6-8 years	> 111	
		8-12 years	> 103	
		12-15 years	> 96	
		≥ 15 years	> 92	
	Low	12-18 months	< 103	≤ 50 with decrease from updated baseline[5] or ≥ 15 mmHg
		18-24 hours	< 98	
		2-3 years	< 92	
		3-4 years	< 86	
		4-6 years	< 81	
		6-8 years	< 74	
		8-12 years	< 67	
		12-15 years	< 62	
		≥ 15 years	< 58	

[redacted]

Weight	High		Increase from baseline[3] of ≥ 2 BMI-for-age percentile cetagories[4]	Weight increase from updated baseline[5] of ≥ 10%
	Low		Decrease from baseline[3] of ≥ 2 BMI-for-age percentile cetagories[4]	Weight decrease from updated baseline[5] of ≥ 10%
Respiratory rate (breath per minutes)[2]	High	12-18 months	> 46	≥ 30
		18-24 hours	> 40	
		2-3 years	> 34	
		3-4 years	> 29	
		4-6 years	> 27	
		6-8 years	> 24	
		8-12 years	> 22	
		12-15 years	> 21	
		≥ 15 years	> 20	
	Low	12-18 months	< 28	≤ 10
		18-24 hours	< 25	
		2-3 years	< 22	
		3-4 years	< 21	
		4-6 years	< 20	
		6-8 years	< 18	
		8-12 years	< 16	
		12-15 years	< 15	
		≥ 15 years	< 13	

[1] Blood pressure percentiles were calculated for each blood BP record using the method described in Appendix B of National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004

[2] Fleming et al 2011

[3] Baseline BMI-for-age weight status categories are underweight (less than the 5th percentile), healthy weight (5th percentile to less than the 85th percentile), overweight (85th to less than the 95th percentile) and obese (equal to our greater than 95th percentile).

[4] BMI-for-age percentiles categories (P3, P5, P10, P25, P50, P75, P85, P90, P95, P99 are obtained from the WHO Growth Charts (http://www.who.int/childgrowth/en/); For patients less than 2 years old, growth charts are based on recumbent length instead of height, which is not collected in the study. As an approximation, height collected in the study is considered as equal to the

[redacted]

[redacted]

recumbent length

[5] Updated baseline was the last value collected before the 18th birthday.

15.5 Other Safety Assessments

Not applicable

16. SECONDARY OUTCOMES

All secondary outcomes will be analyzed for FAS.

16.1 Effectiveness outcome

The number and proportion of participants achieving each WHO developmental milestone will be presented at 6-, 12-, and 18- months post-infusion.

The analysis will take into account the following intercurrent events using a composite strategy:

- Intake of prohibited concomitant medications (as described in protocol section *6.6.2 Prohibit medications*)
- Discontinuation from study due to reasons other than death

This means that if the any of the intercurrent events of interest occur the participant will be regarded as a non-responder from when the first intercurrent event of interest occurs.

16.1.1 Effectiveness Variable(s) & data analysis

The Developmental Motor Milestone Checklist variables are described below:
Sitting without support: will be considered as “Sitting without support” the participants who achieves, at each visit, all the two categories below:

- Child sits up straight with the head erect for at least 10 seconds, AND
- Child does not use arms or hands to balance body or support position.

[redacted]

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Hands-and-knees crawling: will be considered as “Hands-and-knees crawling” the participants who achieves, at each visit, all the three categories below:

- Child alternately moves forward or backward on hands and knees, AND
- The stomach does not touch the supporting surface, AND
- There are continuous and consecutive movements, at least 3 in a row.

Standing with assistance: will be considered as “Standing with assistance” the participants who achieves, at each visit, all the three categories below:

- Child stands in upright position on both feet, holding onto a stable object (eg, furniture) with both hands without leaning on it, AND
- The body does not touch the stable object, and the legs support most of the body weight, AND
- Child thus stands with assistance for at least 10 seconds.

Walking with assistance: will be considered as “Walking with assistance” the participants who achieves, at each visit, all the four categories below:

- Child is in upright position with the back straight, AND
- Child makes sideways or forward steps by holding onto a stable object (eg, furniture) with 1 or both hands, AND
- One leg moves forward while the other supports part of the body weight, AND
- Child takes at least 5 steps in this manner.

Standing alone: will be considered as “Standing alone” the participants who achieves, at each visit, all the three categories below:

- Child stands in upright position on both feet (not on the toes) with the back straight, AND
- The legs support 100% of the child’s weight. There is no contact with a person or object, AND
- Child stands alone for at least 10 seconds.

Walking alone: will be considered as “Walking alone” the participants who achieves, at each visit, all the three categories below:

- Child takes at least 5 steps independently in upright position with the back straight, AND
- One leg moves forward while the other supports most of the body weight, AND
- There is no contact with a person or object.

Every milestone will be summarized as the proportion of patients with each criterion met at baseline, week 26, week 52, and week 78. Only descriptive analysis will be performed, and data will be summarized as frequency and percentage.

[redacted]

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[redacted]

[redacted]

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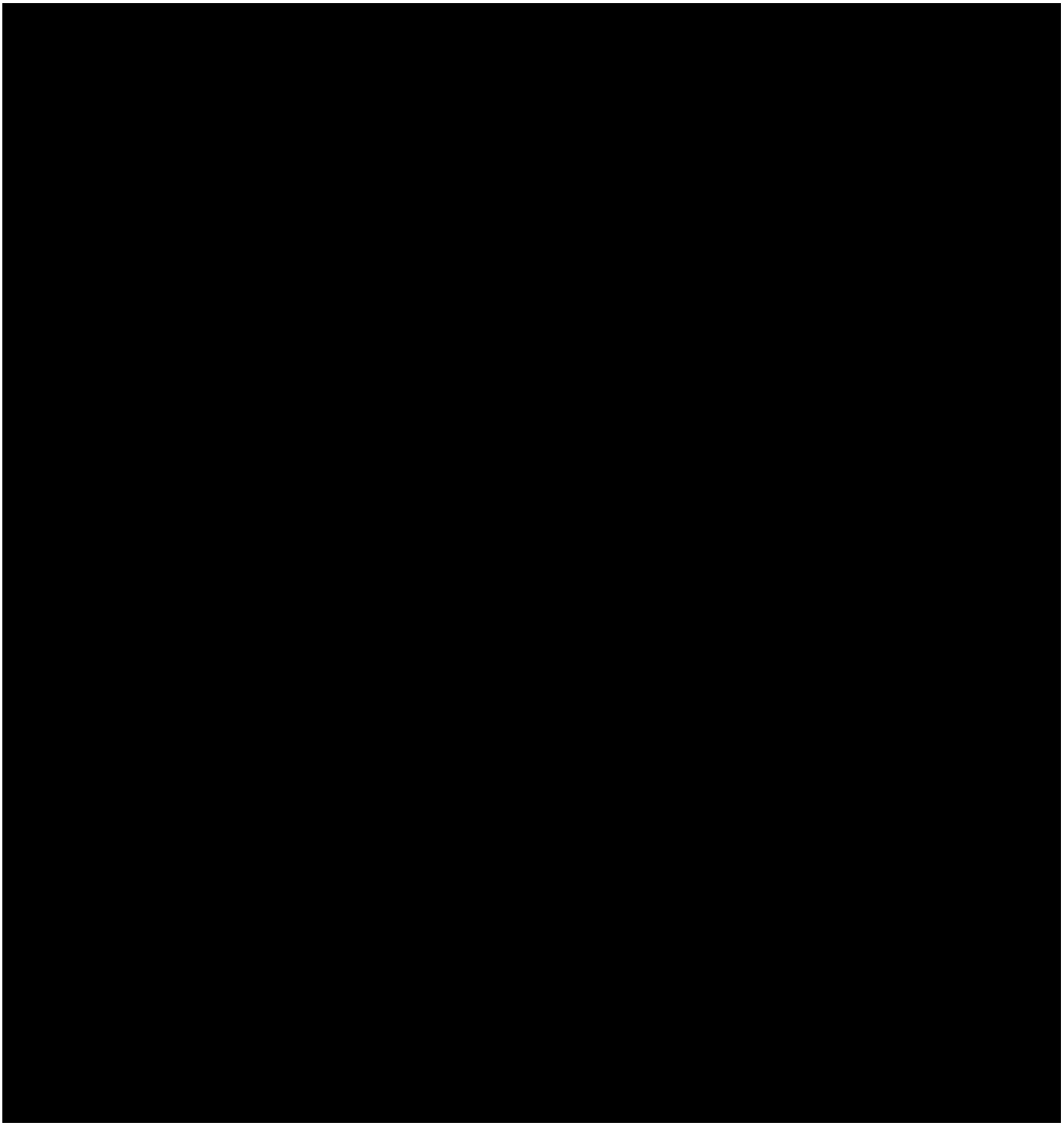

[redacted]

[redacted]

[redacted]

19. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Comments

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database.

[redacted]

20. REFERENCES

Not applicable.

20.1 APPENDIX 1. Programming Conventions for Outputs

Dates & Times

Depending on data available, dates will take the form dd-mmm-aaaa. Partial data is allowed (see Appendix 2). Time will be represented as hh:mm (24hs format).

To convert a duration or an age from days to months or years, the following conversion factors will be used:

- 1 month = 30.4375 days
- 1 year = 365.25 days

Spelling Format

English US

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

Center ID

Patient ID

date (where applicable)

20.2 APPENDIX 2. Partial Date Conventions

Appendix table 1. Algorithm for TEAEs and AESIs

START DATE	STOP DATE	ACTION
Known	Known	If start date < study medication (med) start date, then not TEAE If start date >= study medication start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

Appendix table 2. Algorithm for Prior and Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

20.3 APPENDIX 3. Tables, Listings and Figures

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