Protocol Number: AVXS-101-CL-306

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

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User	Role	Job Title	Version	Decision	Date Signed
[redacted]	Final Approvers	Executive Medical Director	6.0	Approve	12 Nov 2020 06:00 PM CST
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AVXS-101
AVXS-101-CL-306

Protocol Title:	Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two *SMN2* Copies Delivering AVXS-101 by Intravenous Infusion
Indication Studied:	Spinal Muscular Atrophy Type 1
Sponsor Address:	Novartis Gene Therapies, Inc. 2275 Half Day Road, Suite 200 Bannockburn, IL 60015
Protocol Version/Date:	6.0 Incorporating Amendment 5 / 11 Nov 2020

The trial will be completed according to the guidelines of Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

Confidentiality Statement

1. ADMINISTRATIVE INFORMATION

1.1. Approval

REPRESENTATIVES FROM Novartis Gene Therapies:

This trial will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical trial protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council for Harmonisation (ICH), Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2)
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations

SIGNATURES (may be applied electronically and will therefore be maintained in the electronic system):

[redacted]
Senior Director, Clinical Development
Novartis Gene Therapies, Inc.

Date (ddMmmyyyy)

[redacted]
Vice President, Regulatory Affairs
Novartis Gene Therapies, Inc.

Date (ddMmmyyyy)

[redacted]
Vice President, Clinical Development & Analytics
Novartis Gene Therapies, Inc.

Date (ddMmmyyyy)

[redacted]
Associate Director, Clinical Operations
Novartis Gene Therapies, Inc.

Date (ddMmmyyyy)

[redacted]
Senior Director, Biostatistics
Novartis Gene Therapies, Inc.

Date (ddMmmyyyy)

[redacted]
Vice President & Head, Global Patient Safety
Novartis Gene Therapies, Inc.

Date (ddMmmyyyy)

1.2. Investigator's Agreement

I have received and read the Investigator's Brochure for AVXS-101. I have read the AVXS-101-CL-306 protocol and agree to conduct the trial in accordance with the relevant current protocol.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I agree to personally conduct or supervise the investigation(s). I also agree to promptly report to the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects. I agree to protect the safety, rights, privacy, and well-being of trial participants. I agree to comply with:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council for Harmonisation, Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2)
- All applicable local and regional laws and regulations, including, without limitation, data privacy laws and regulations including but not limited to Medical Care Act, Pharmaceutical Affairs Act, regulations on human trials 2009, Human Subject Research Act 2011, regulations for Good Clinical Practice 2005, Human Biobank Management Act 2012, regulations for registration of medicinal products, regulation for drug samples or complementary drugs.
- Terms outlined in the trial site agreement
- Responsibilities of the Investigator (per regulatory guidelines and applicable regulations)
- I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in this protocol.

Confidentiality Statement

The confidential information in this document is provided to you as a Principal Investigator or Consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

_____
Printed Name of Principal Investigator

_____
Signature of Principal Investigator

_____
Date (ddMmmyyyy)

1.3. Contact Information

Role in Study	Contact information
Novartis Gene Therapies Medical Director	[redacted] Senior Director, Clinical Development [redacted]
24-Hour Emergency Contact	Please see Study Contact List in Investigator Site File

Additional study contact information is provided in the Study Contact List.

2. SYNOPSIS

Name of Sponsor/Company: Novartis Gene Therapies, Inc.	
Name of Investigational Product: AVXS-101	
Name of Active Ingredient: Survival Motor Neuron Gene by Self-Complementary Adeno-Associated Virus Serotype 9 (AAV9)	
Title of Trial: Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two SMN2 Copies Delivering AVXS-101 by Intravenous Infusion	
Estimated number of Trial Center(s) and Countries or Regions: Approximately 3 Asian Investigative Sites located in the following countries: Japan, South Korea, Taiwan. Japan is participating in this global study under a Japan-specific version of the AVXS-CL-101-306 protocol.	
Investigators: Multicenter Trial - Investigator Information on File at Novartis Gene Therapies, Inc.	
Studied Period (years): Estimated date first patient enrolled: Q3 2018 Estimated date last patient completed: Q3 2021	**Phase of Development:** 3

Objectives: Primary

- Determine efficacy by demonstrating achievement of developmental milestone of sitting without support for at least 10 seconds up to 18 months of age as defined by World Health Organization (WHO) Motor Developmental Milestones.

Secondary

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

Exploratory

- [redacted]
- [redacted]
- [redacted]

[redacted]

Safety

- Evaluate the safety of AVXS-101 in patients with SMA Type 1.

Methodology:

Phase 3, open-label, single-arm, single-dose, trial of AVXS-101 (gene replacement therapy) in patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria and are genetically defined by a biallelic pathogenic mutation of the survival motor neuron 1 gene (SMN1) with one or 2 copies of survival motor neuron 2 gene (SMN2). At least 6 patients < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1) will be enrolled.

The trial includes a screening period, a gene replacement therapy period, and a follow-up period. During the screening period (Days –30 to –2), patients whose parent(s)/legal guardian(s) provide informed consent will complete screening procedures to determine eligibility for trial enrollment. Patients who meet the entry criteria will enter the in-patient gene replacement therapy period (Day –1 to Day 3). On Day –1, patients will be admitted to the hospital for pre-treatment baseline procedures. On Day 1, patients will receive a one-time intravenous (IV) infusion of AVXS-101 and will undergo in-patient safety monitoring over the next 48 hours. Patients may be discharged 48 hours after the infusion, based on Investigator judgment. During the outpatient follow-up period (Days 4 to End of Trial at 18 months of age), patients will return at regularly scheduled intervals for efficacy and safety assessments until the End of Trial when the patient reaches 18 months of age. After the End of Trial visit, patients will be invited to participate in a long-term follow up trial conducted under a separate protocol. Patients who discontinue the trial prematurely will also be invited to participate in the long-term follow-up study.

All post-treatment visits will be relative to the date on which gene replacement therapy is administered until the patient is 14 months of age, after which all visits will be relative to the patient's date of birth. All visits will be scheduled based on a 30-day month calendar.

In an attempt to dampen the host immune response to the adeno-associated virus (AAV) derived therapy, all patients will receive prophylactic prednisolone at approximately 2 mg/kg/day (or an equivalent dose of another glucocorticoid if prednisolone is unavailable or in the opinion of the investigator prednisolone is not tolerated) on Day -1, Day 1, and Day 2, and then 1 mg/kg/day starting on Day 3 and until at least 30 days post-AVXS-101 infusion. After 30 days post-AVXS-101 infusion, the dose of prednisolone (or, if needed, equivalent glucocorticoid) can be tapered for patients whose gamma glutamyl transferase (GGT), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values are below the threshold of 2 × Upper Limit of Normal (ULN) in accordance with the following treatment guideline: taper from 1 mg/kg/day to 0.5 mg/kg/day during Weeks 5 and 6 post-AVXS-101 infusion, then taper to 0.25 mg/kg/day during Weeks 7 and 8, and then discontinue prednisolone at Week 9. If the GGT, AST or ALT values are > 2× ULN, the dose of prednisolone should be maintained until the GGT, AST, and ALT values decrease below threshold at which point the taper may continue. Variance from these recommendations will be at the discretion of the Investigator based on potential safety issues for each patient. If another glucocorticoid is used in place of prednisolone by the investigator, similar considerations should be taken into account after 30 days and tapered as appropriate and at the discretion of the investigator.

Efficacy will be assessed by achievement of the key developmental milestone of sitting without support for at least 10 seconds based on WHO motor development milestones at any point up to and including the 18 months of age trial visit, and survival at 14 months of age.

Safety will be assessed through monitoring adverse events (AEs), concomitant medication usage, physical examinations, vital sign assessments, cardiac assessments, and laboratory evaluations. A Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC) will review safety data on a quarterly basis. A detailed description of the DSMB/DMC, its role in this trial, and the timing and process of the scheduled reviews will be described in a DSMB/DMC Charter.

Number of Patients (planned): At least 6 patients were planned to be enrolled as part of the combined analysis with Study AVXS-101-CL-302. At the time of this protocol was amended (Protocol version 6.0 amendment 5 dated 11 Nov 2020), the enrollment was closed with 2 active enrolled patients as the combined analysis is no longer to be performed.

Diagnosis and Main Criteria for Inclusion: Inclusion Criteria:

1. Patients with SMA Type 1 as determined by the diagnosis of SMA based on gene mutation analysis with biallelic *SMN1* mutations (deletion or point mutations) and one or 2 copies of *SMN2* [inclusive of the known *SMN2* gene modifier mutation (c.859G>C)]
2. Patients must be < 6 months (< 180 days) of age **at the time** of AVXS-101 infusion.
3. Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy.
4. Up-to-date on childhood vaccinations as per local health authorities.
5. Parent(s)/legal guardian(s) willing and able to complete the informed consent process and comply with trial procedures and visit schedule.

Exclusion Criteria:

1. Previous, planned or expected scoliosis repair surgery/procedure prior to 18 months of age.
2. Use of invasive ventilatory support (tracheotomy with positive pressure) or pulse oximetry < 95% saturation at screening
   a. Pulse oximetry saturation must not decrease ≥ 4 percentage points between screening and dosing with confirmatory oximetry reading
   b. Patients may be put on non-invasive ventilatory support for less than 12 hours per day at the discretion of their physician or trial staff.
3. Use or requirement of non-invasive ventilatory support for ≥12 hours daily in the 2 weeks prior to dosing.
4. Patient with signs of aspiration based on a swallowing test or whose weight-for-age falls below the 3rd percentile based on WHO Child Growth Standards and is unwilling to use an alternative method to oral feeding.
5. Active viral infection (includes human immunodeficiency virus [HIV] or positive serology for hepatitis B, C, or E or known Zika virus infection).
6. Serious non-respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening.
7. Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening.
8. Severe non-pulmonary/respiratory tract infection (e.g., pyelonephritis, or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in

the opinion of the Principal Investigator, creates unnecessary risks for gene replacement such as:

a. Major renal or hepatic impairment
b. Known seizure disorder
c. Diabetes mellitus
d. Idiopathic hypocalciuria
e. Symptomatic cardiomyopathy.

9. Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients.
10. Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, or immunosuppressive therapy within 3 months prior to gene replacement therapy (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab).
11. Anti-AAV9 antibody titer > 1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay. Should a potential patient demonstrate Anti-AAV9 antibody titer > 1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the Anti-AAV9 antibody titer upon retesting is ≤ 1:50.
12. Clinically significant abnormal laboratory values (GGT, ALT, AST, total bilirubin > 2× the ULN, creatinine ≥ 1.0 mg/dL, hemoglobin [Hgb] < 8 or > 18 g/dL; white blood cell [WBC] > 20,000 per cmm) prior to gene replacement therapy. Patients with an elevated bilirubin level that is unequivocally the result of neonatal jaundice shall not be excluded.
13. Participation in recent SMA treatment clinical trial (with the exception of observational cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product or therapy administered with the intent to treat SMA (e.g., nusinersen, valproic acid,) at any time prior to screening for this trial. Oral β-agonists must be discontinued at least 30 days before gene therapy dosing. Inhaled albuterol specifically prescribed for the purposes of respiratory (bronchodilator) management is acceptable and not a contraindication at any time prior to screening for this trial.
14. Expectation of major surgical procedures during the trial assessment period (e.g., spinal surgery or tracheostomy).
15. Parent(s)/legal guardian(s) unable or unwilling to comply with trial procedures or inability to travel for repeat visits.
16. Parent(s)/legal guardian(s) unwilling to keep trial results/observations confidential or to refrain from posting confidential trial results/observations on social media sites.
17. Parent(s)/legal guardian(s) refuses to sign consent form.
18. Patient < 35 weeks gestational age at time of birth.

Investigational Product, Dosage and Mode of Administration:

Patients will receive a one-time dose of AVXS-101 at 1.1 × 1014 vg/kg, a dose determined to be equivalent to the dose received by the Cohort 2 patients in the Phase 1 study (AVXS-101-CL-101) by direct testing using improved analytical methods.

Duration of Treatment:

AVXS-101 will be administered as a one-time IV infusion over approximately 60 minutes.

Reference Therapy, Dosage and Mode of Administration: Not Applicable

Criteria for Evaluation: Efficacy:

Primary

- Proportion of symptomatic SMA Type 1 patients who are homozygous negative for *SMN1* exon 7 and have 2 copies of *SMN2* without the *SMN2* genetic modifier that achieve the ability to sit without support for at least 10 seconds up to and including the 18 months of age trial visit. Sitting without support is defined by the WHO Multicentre Growth Reference Study (WHO MGRS) confirmed by video recording, as a patient who sits up straight with head erect for at least 10 seconds; [redacted]

Secondary

- Survival at 14 months of age amongst symptomatic SMA Type 1 patients who are homozygous negative for *SMN1* exon 7 and have 2 copies of *SMN2* without the *SMN2* genetic modifier. Survival is defined by the avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

Exploratory

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Safety:

Assessment of the safety and tolerability of AVXS-101 treatment includes evaluation of AEs, laboratory data, vital signs, and concomitant medications.

Statistical Methods:

This is a Phase 3 trial assessing the efficacy and safety of AVXS-101. Details of all analyses will be contained within the Statistical Analysis Plan.

The Intent-to-Treat (ITT) population will consist of symptomatic patients with biallelic SMN1 deletions and 2 copies of SMN2 without the genetic modifier (c.859G>C).

Due to the small number of patients enrolled in this study, the primary, secondary, and exploratory efficacy endpoints as well as safety assessments will be provided in data listings only.

3. TABLE OF CONTENTS, LISTS OF TABLES AND FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this trial protocol.

Abbreviation or Specialist Term	Explanation
AAV	Adeno-associated virus
AAV9	Adeno-associated virus serotype 9
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
ASO	Antisense oligonucleotide
AST	Aspartate aminotransferase
AT	Aminotransferase
BSIDv03	Bayley Scales of Infant and Toddler Development, version 3
BUN	Blood urea nitrogen
CB	Chicken-β-actin-hybrid
cDNA	complimentary Deoxyribonucleic Acid
cGMP	Current Good Manufacturing Practice
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CK	Creatine kinase
CMV	Cytomegalovirus
CNS	Central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
Day 1	First 24-hour interval after the start of gene replacement therapy infusion
Day –1	24-hour interval prior to the start of gene replacement therapy infusion
DMC	Data Monitoring Committee
DRG	Dorsal root ganglia
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunospot
ET	Early termination
FVB	Friend Virus B-Type
GCP	Good Clinical Practice
GFP	Green fluorescent protein
GGT	Gamma glutamyl transferase
GLP	Good Laboratory Practice
HEENT	Head, eyes, ears, nose, and throat

Abbreviation or Specialist Term	Explanation
HgB	Hemoglobin
HIV	Human immunodeficiency virus
ICD-10 code	International Statistical Classification of Diseases and Related Health Problems
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN-γ	Interferon gamma
INR	International normalized ratio
IRB	Institutional Review Board
ISF	Investigator site file
IT	Intrathecal
ITR	Inverted terminal repeat
ITT	Intent-to-treat
IV	Intravenous
LFE	Liver function enzymes
LFT	Liver function test
LV EF	Left ventricular ejection fraction
LV FS	Left ventricular fractional shortening
MAP	Managed Access Program
MedDRA	Medical Dictionary for Regulatory Activities
MGRS	Multicenter Growth Reference Study
NCI	National Cancer Institute
NHP	Non-human primates
NOAEL	No observable adverse effect level
PBMC	Peripheral blood mononuclear cells
PICU	Pediatric intensive care unit
PNCR	Pediatric Neuromuscular Clinical Research Network
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sc	Self-complementary
scAAV	Self-complimentary adeno-associated virus
scAAV9.CB.SMN	Self-complimentary adeno-associated virus serotype 9 chicken-β-actin- hybrid survival motor neuron
SDA	Source data verification
SoA	Schedule of Assessments
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
SMN1	Survival motor neuron 1 gene

Abbreviation or Specialist Term	Explanation
SMN2	Survival motor neuron 2 gene
SUSAR	Suspected unexpected serious adverse reaction
TBL	Total bilirubin
TMA	Thrombotic microangiopathy
TMF	Trial Master File
ULN	Upper limit of normal
US	United States
vg/kg	Vector genome per kilogram
WBC	White blood cell
WHO	World Health Organization
WT	Wild type

5. INTRODUCTION

Trial AVXS-101-CL-306 is a Phase 3 clinical gene therapy trial investigating the efficacy and safety of a single intravenous (IV) infusion of AVXS-101 in at least 6 patients with Type 1 spinal muscular atrophy (SMA) with one or 2 copies of *SMN2*. This trial is conducted by Novartis Gene Therapies, Inc. (formerly AveXis, Inc. with company's name change).

The survival motor neuron (SMN) gene will be transferred using self-complementary adeno-associated virus (scAAV) Type 9 under control of the chicken-β-actin hybrid promoter. Pre-clinical studies have demonstrated survival of the SMNΔ7 mouse model for SMA from a median of 15.5 days to over one year, following IV delivery to the peripheral vein. Additionally, preliminary results from a completed Phase 1 clinical trial (AVXS-101-CL-101) of AVXS-101 in SMA Type 1 patients demonstrates broad improvements in survival, motor function, pulmonary function, and nutritional function (Section 5.4).

5.1. Background

Spinal muscular atrophy is a neurogenetic disorder caused by a loss or mutation in the survival motor neuron 1 gene (*SMN1*) on chromosome 5q13, which leads to reduced SMN protein levels and a selective dysfunction of motor neurons. Spinal muscular atrophy is an autosomal recessive, early childhood disease with an incidence of approximately 1:10,000 live births [Sugarman et al, 2012] Spinal muscular atrophy is the leading cause of infant mortality due to genetic diseases. Disease severity and clinical prognosis depends on the number of copies of survival motor neuron 2 gene (*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 before 6 months of age and early death due to respiratory failure before 2 years of age. Motor neuron loss in SMA Type 1 is profound in the early post-natal period (or may even start in the prenatal period), whereas motor neurons in SMA Type 2 and Type 3 patients adapt and compensate during development and many will persist into adult life. The findings from various neurophysiological and animal studies have shown an early loss of motor neurons in the embryonic and early post-natal periods [Swoboda et al, 2005; Le et al, 2011; Farrar et al, 2012]. From a clinical perspective, these findings emphasize the importance of first targeting the SMA Type 1 group for gene transfer of *SMN2* in hopes of rescuing neurons at this critical stage. The goal in continuing the development plan for AVXS-101 is to modify the SMA Type 1 phenotype, which will hopefully lead to a milder disease course and prolonged survival as seen in SMA Type 2 and Type 3 patients.

Therapeutic efforts in SMA have focused on the potential for small molecules to increase SMN protein levels. These include deacetylase inhibitors, such as valproic acid, sodium butyrate, phenylbutyrate, and trichostatin A. These agents activate the *SMN2* promoter, resulting in increased full-length SMN protein in SMA animal models [Riessland et al, 2010; Dayangac-Erden et al, 2011]. However, clinical studies employing several of these agents, most notably phenylbutyrate, valproic acid, and hydroxyurea, have not resulted in clinical benefit [Kissel et al, 2011; Swoboda et al, 2010; Mercuri et al, 2004; Chen et al, 2010; Darbar et al, 2011]. In the United States, the Food and Drug Administration (FDA) recently approved nusinersen, an antisense oligonucleotide (ASO) drug designed to increase the production of the SMN protein by modulating the splicing of the *SMN2* gene, thereby compensating for the underlying genetic defect. Nusinersen has also received regulatory approvals in the European

Union and in other countries including Japan, South Korea, and Taiwan. Clinical studies have shown some modest promise in improving motor function; however, the treatment must be administered indefinitely on a quarterly basis via intrathecal injection, requires a lengthy induction period prior to effectiveness, and has safety considerations that require clinical monitoring. A single-dose IV administration trial of AVXS-101 will provide information on the potential that gene transfer has in treating SMA Type 1 patients and will hopefully show promise for success in modifying the disease prognosis.

This is a single-dose trial that will include at least 6 Type 1 patients with one or 2 copies of *SMN2*. The rationale for IV dosing is based upon the need for rapid, systemic impact given the severity of the disease in SMA Type 1 and its potential impact on systems outside of the central nervous system (CNS) such as the peripheral and autonomic nervous systems, heart, pancreas and gastrointestinal tract.

5.2. Rationale for Gene Transfer to SMA Type 1 Patients

Patients with SMA Type 1 have been chosen as the target population for this gene therapy trial based on studies of the natural history of this disease. The classification of SMA is shown below (Table 1) in which SMA Types 0 to 4 are described. Spinal muscular atrophy is conventionally classified into 4 phenotypes on the basis of age at onset and highest motor function achieved, with an additional phenotype (Type 0) to describe the severe forms of antenatal-onset SMA [Mercuri et al, 2012].

Table 1 - Spinal Muscular Atrophy Classification

Type	Age at Symptom Onset		Maximum Motor Function	Life Expectancy	*SMN2* Copy No.
0	Fetal		Nil	Days – Weeks	1
1	< 6 Months	1A: B-2 Weeks 1B: < 3 Months 1C: > 3 Months	Never sits	< 2 years	1, **2**, 3
2	6 – 18 Months		Never walks	20 – 40 years	2, **3**, 4
3	1.5 – 10 Years	3A: < 3 Years 3B: > 3 Years	Walks, regression	Normal	3, **4**, 5
4	> 35 Years		Slow decline	Normal	4, 5

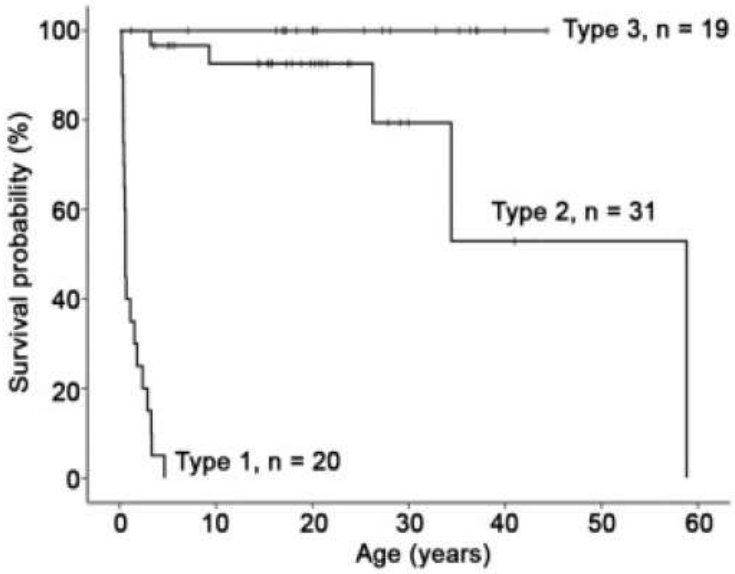
Source: Adapted from [Kolb and Kissel, 2011]
SMN2 = survival motor neuron 2 gene
Bold underline = predominant *SMN2* copy number that defines the SMA Type; the other copy numbers represent a small percentage of the designated SMA Type.

Spinal muscular atrophy Type 1 patients, by definition, never attain independent sitting and have hypotonia within the first 6 months of life. Spinal muscular atrophy Type 1 is the leading genetic cause of infant death with an onset at ≤ 6 months of age (Table 1). In contrast, SMA Type 2 manifests within the first 18 months, and children afflicted with this condition are able to maintain sitting unassisted but never walk independently. Spinal muscular atrophy Type 3 patients attain the ability to walk unaided (Type 3a have onset 18 months to 3 years of age; Type 3b have onset > 3 years of age). Spinal muscular atrophy Type 4 is an adult onset disease. The genetic cause for SMA is well established and is intimately involved with one's prognosis. All forms of SMA are autosomal recessive in inheritance and are caused by deletions or mutations of the *SMN1* gene.

Humans also carry a second nearly identical copy of the *SMN1* gene called *SMN2* [Lefebvre et al, 1995]. Both the *SMN1* and *SMN2* genes express SMN protein; however, the amount of functional full-length protein produced by *SMN2* is only 10% to 15% of that produced by *SMN1* [Lefebvre et al, 1995; Lorson et al, 1999; Monani et al, 1999]. Although *SMN2* cannot completely compensate for the loss of the *SMN1* gene, patients with milder forms of SMA generally have higher *SMN2* copy numbers [Lefebvre et al, 1997; Park et al, 2010]. Quantitative analysis of *SMN2* copies in 375 patients with Type 1, 2, or 3 SMA showed a significant correlation between *SMN2* copy number and SMA Type, as well as, duration of survival. In a large early trial by Feldkotter et al 2002, 2 copies of *SMN2* was 97% predictive for developing SMA Type 1, 3 copies of *SMN2* was 83% predictive for developing SMA Type 2, and 4 copies of *SMN2* was 84% predictive of SMA Type 3 [Feldkotter et al, 2002]. As these percentages do not reflect the possible impact of modifier mutations such as that described by Prior et al 2009 [Prior et al, 2009], they may understate the relationship between copy number (in the absence of a genetic modifier) and clinical phenotype. Among 113 patients with Type 1 SMA, 9 with one *SMN2* copy lived < 11 months, 88/94 with two *SMN2* copies lived < 21 months, and 8/10 with three *SMN2* copies lived 33 to 66 months. Even more refined data describing this relationship has been generated and has also influenced our choice of the trial target group.

The severity of SMA Type 1 is demonstrated by prognosis as illustrated in Kaplan-Meier survival curves shown in Figure 1.

Figure 1 - Kaplan-Meier Survival Curves and Survival Probabilities for SMA Types 1, 2, and 3



Source: [Farrar et al, 2013]
n = number of patients

In Figure 1, the relative stability of the clinical course of SMA Type 2 and Type 3 is dramatically illustrated. Perhaps most importantly, these findings show that outcome differences are related to the number of *SMN2* copies that enable motor neurons to adapt and compensate during the growth of the child and persist into adult life. This contrasts with SMA Type 1 where motor neuron loss is profound in the early post-natal period (or may even start in the prenatal period, especially for SMA Type 1 patients presenting in first 3 months of life). The findings in Figure 1 confirm other pieces of evidence from neurophysiological studies and animal studies that also show early loss of motor neurons in the embryonic and early post-natal periods [Swoboda et al, 2005; Le et al, 2011; Farrar et al, 2012].

There is reason to believe that there are few safety issues to be concerned about when targeting the SMA Type 1 group in this gene therapy clinical trial. In humans, a high copy number of *SMN2* poses no risk (as seen in Type 2, 3, and 4 patients who have high *SMN2* copy number), allowing for use of robust, ubiquitous expression systems (like the CB-promoter) to ensure sustained, high-level SMN gene expression. Additionally, it is important to point out that recombinant scAAV can be employed for this trial because of the small size of the SMN gene. This enables efficient packaging and allows for efficient gene transfer with lower viral titers (a safety consideration), compared with prototypical single-stranded adeno-associated virus vectors.

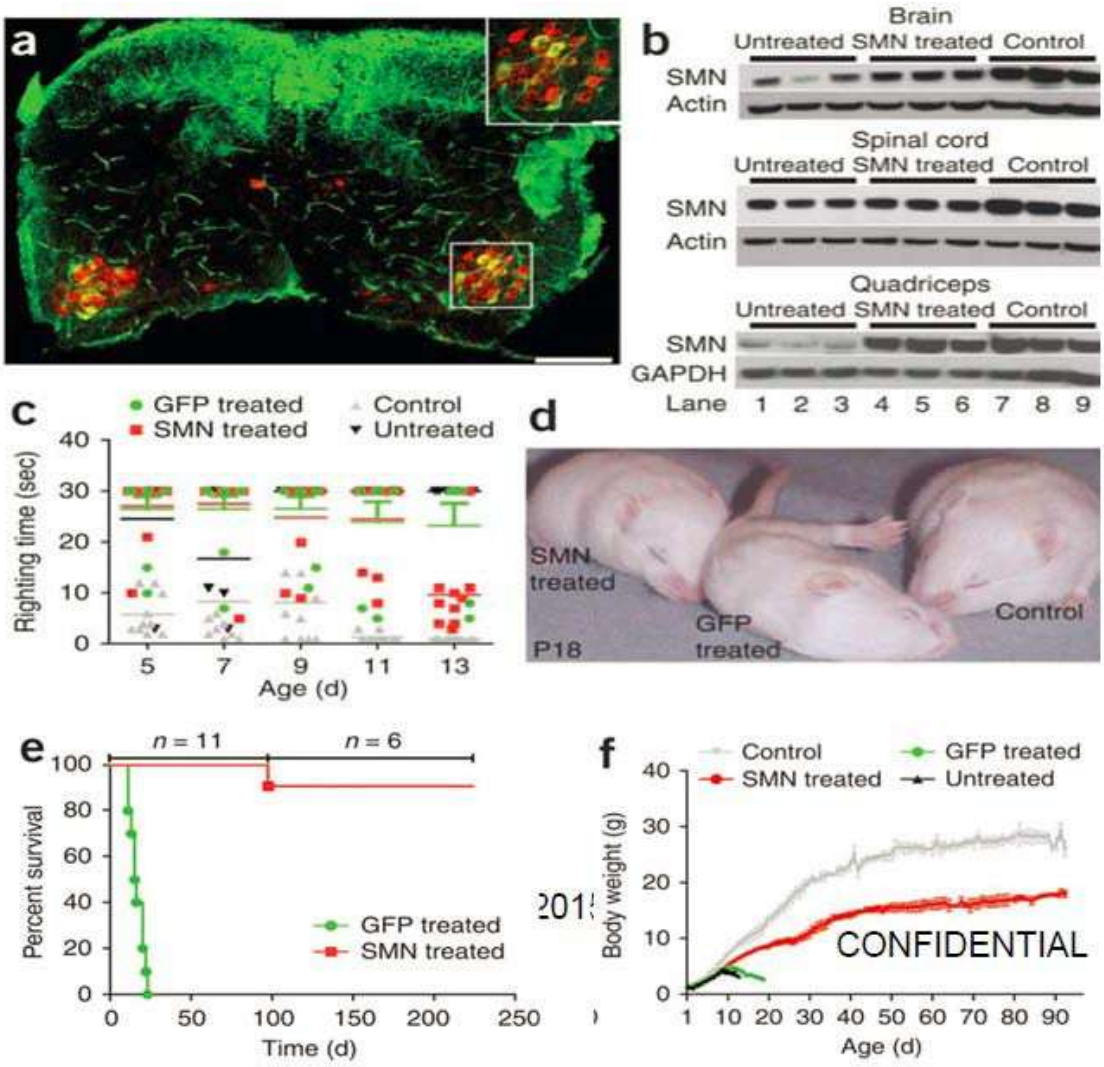
Recent studies using self-complimentary adeno-associated virus serotype 9 chicken-β-actin-hybrid survival motor neuron (scAAV9.CB.SMN) show a robust post-natal rescue of SMNΔ7 mice with correction of motor function, neuromuscular electrophysiology and survival after a one-time delivery of vector [Foust et al, 2010]. Intravenous scAAV9 is able to transduce neurons, muscle and vascular endothelium, all of which have been proposed as target cells for SMA treatment.

5.3. Nonclinical Studies

A mouse model was developed by the [redacted] after a generation of evaluating various transgenic permutations. It was found that the double transgenic, referred to as the SMNΔ7 mouse, provided the most suitable model to trial gene transfer [Butchbach et al, 2007]. Studies performed in the [redacted] have shown that injecting 5×10^{11} viral genomes of scAAV9.CB.SMN into the facial vein on post-natal Day 1 rescues mice in the SMNΔ7 mouse model [Foust et al, 2010]. Figure 2 shows the results of these studies, including staining of transduced spinal motor neurons, SMN protein expression levels, righting ability, and weight and survival curves. Approximately 42 ± 2% of lumbar spinal motor neurons were transduced in scAAV9.CB.GFP treated mice. SMN transduction was shown by real time polymerase chain reaction (RT-PCR) in the mice. Green fluorescent protein (GFP) transduction was observed by microscopy. Both constructs were in adeno-associated virus serotype 9 (AAV9) and had transduction of motor neurons. Survival motor neuron protein levels were increased as well, in brain, spinal cord, and muscle of scAAV9.CB.SMN-treated animals, compared to untreated SMNΔ7 mice (although lower than wild type [WT] controls). SMNΔ7 animals treated with either scAAV9.CB.SMN or scAAV9.CB.GFP on post-natal Day 1 (P1) were assessed for their righting ability and were compared to WT control mice and untreated mice. Wild type controls could right themselves quickly, whereas the SMN- and GFP-treated SMA animals showed difficulty at P5. However, by P13, 90% of SMN-treated animals could right themselves compared with 20% of GFP-treated controls and 0% of untreated SMA animals. At P18, SMN-treated animals were larger than GFP-treated animals, but smaller than WT controls. Locomotive ability of the SMN-treated mice was nearly identical to WT controls, as assayed by open field testing and wheel running.

Survival of SMN-treated SMNΔ7 animals compared with GFP-treated SMNΔ7 animals was significantly improved. No GFP-treated control animals survived past P22 and had a median life span of 15.5 days. The weights of GFP mice peaked at P10 and then precipitously declined until death, while SMN mice showed a steady weight gain until around P40 with it stabilizing at 17 g (about half the weight of WT controls). The smaller size of corrected animals is likely related to the tropism and incomplete transduction of scAAV9, resulting in a ‘chimeric’ animal in which some cells were not transduced. Additionally, the smaller size suggests an embryonic role for SMN protein. Most remarkably, SMN-treated mice survived well past 250 days of age.

Figure 2 - Trial Results, Including Staining of Transduced Spinal Motor Neurons, SMN Expression Levels, Righting Ability, and Weight and Survival Curves

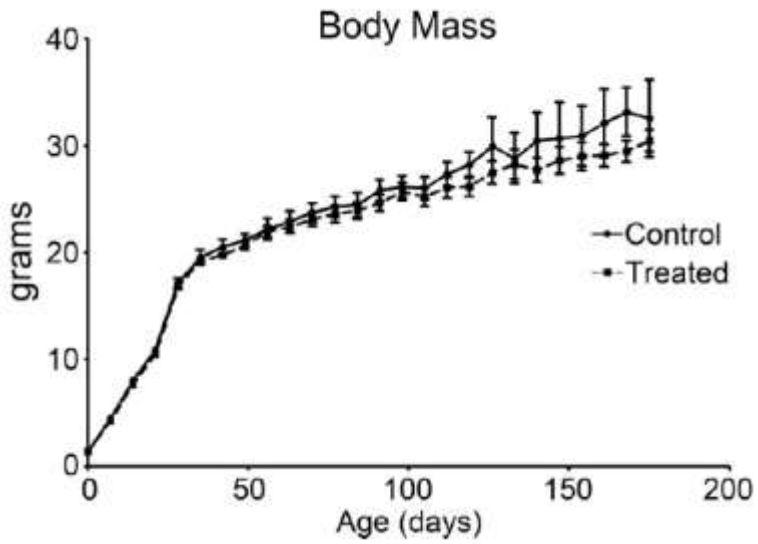


Source: [Foust et al, 2010]
CNS = central nervous system; GFP = green fluorescent protein; SMN = survival motor neuron; WT = wild type

a. Shows transduced motor neurons in lumbar spinal cord
b. Western Blots of SMN expression in CNS and muscle
c. Improved righting ability of SMN-treated- similar to WT controls by post-natal Day 13 (P13)
d. SMN-treated are larger than GFP-treated at P18
e. Survival of SMN-treated markedly improved compared to GFP-treated
f. Body weight increased in SMN-treated vs GFP

In non-Good Laboratory Practice (non-GLP) studies, 24 mice and 4 non-human primates (NHPs) were injected, by way of vascular delivery, with AVXS-101. To assess toxicity and safety, AVXS-101 was injected into post-natal Day 1 (P1) wild type Friend Virus B-Type (FVB) mice with either vehicle (3 males/6 females) or 3.3×10^{14} vg/kg of AVXS-101 (previously known as scAAV9.CB.SMN (6 males/9 females) via the facial temporal vein. This dose was previously shown to be most efficacious in the SMNΔ7 mouse model [Foust et al, 2010]. P1 mice were used in anticipation of simulating potential clinical studies in infants. All mice survived the injection procedure and the initial 24-hour observation period without any signs of distress or weight loss. Body mass was measured and hands-on observations were performed weekly for the remainder of the trial; neither revealed any difference between control and treated cohorts (Figure 3).

Figure 3 - Body Mass of Treated and Control Mice Showed No Difference



At 60, 90 and 180 days post-injection, blood from the mice was collected for hematology studies including complete blood counts with differentials. At 90, 120 and 180 days post-injection, blood was collected for clinical chemistries assessment (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, creatinine, blood urea nitrogen [BUN], electrolytes, and creatine kinase [CK]). For histopathology, 13 mice were necropsied at 120 days post-injection and 8 mice at 180 days. There were no clinically significant results observed during from the hematology, clinical chemistry, and histopathology portions of the trial and trends of both groups were comparable. Of note, no significant lesions were present in any brain or spinal cord sections, although, the sections were frozen and thicker than 5 microns which may obscure subtle changes in cellular morphology.

In the safety trial for the 4 male cynomolgus macaques, animals were injected at 90 days of age to closely mimic the likely age of administration of treatment in SMA Type 1 infants. The AVXS-101 vector was administered one time by catheterization of the saphenous vein with a dose of 6.7×10^{13} vg/kg, which corresponds to the lowest dose tested for which SMNΔ7 mice showed a significant increase of survival. Animals were followed for six months until they were sacrificed at approximately 9 months of age. No adverse effects were seen, and all clinical

chemistries were normal. T-cell immune response was tested using Enzyme-linked immunospot (ELISpot) in peripheral blood mononuclear cells (PBMCs), and all were negative at 6 months post-injection.

In these non-GLP studies, serum chemistry and hematology data were unremarkable as was the histopathology assessment. The NHPs mounted appropriate immune responses to capsid (but not to transgene), with very high transgene expression persisting at 6 months post-injection. In conclusion, these studies provide strong evidence that systemically-delivered scAAV9.CB.SMN is safe and well tolerated, even at the high doses required for penetration of the blood-brain barrier [Foust et al, 2010].

When newborn FVB mice were given a single IV injection of AVXS-101 at levels up to 3.3×10^{14} vg/kg on Day 1, there was neither test article-related mortality nor evidence of toxicity seen at time points up to 24 weeks after administration. Treatment-related decreases in mean body weight and mean body weight gain, as well as lower activated partial thromboplastin time (APTT) values, were mild effects of treatment, but did not result in toxicity. Activity of AVXS-101 was demonstrated by the biodistribution and the presence of a specific transgene ribonucleic acid (RNA) expression in brain and spinal cord, the main targeted therapeutic tissues. Low levels of antibodies to the AAV9 capsid were found after 12 and 24 weeks in males and females given 3.3×10^{14} vg/kg (Group 3). No alteration was observed in clinical pathology and histopathology analyses.

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

The DRG was not identified as a target organ of toxicity in previous AVXS-101 studies conducted in mice (ICV route of administration) or cynomolgus monkeys (IV or IT routes of administration). However, similar findings have been reported after administration of AAV9-vectors in monkeys and minipigs [Hinderer et al, 2018; Hordeaux et al, 2018].

In pivotal GLP compliant 3-month mouse toxicology studies, the main target organs of toxicity were the heart and liver. Following IV infusion in the mouse, vector and transgene were widely distributed with the highest expression generally observed in heart and liver, and substantial expression in the brain and spinal cord. AVXS-101-related findings in the ventricles of the heart were comprised of dose-related inflammation, edema and fibrosis, and in the atrium,

inflammation and thrombosis. Liver findings were comprised on hepatocellular hypertrophy, Kupffer cell activation, and scattered hepatocellular necrosis. A no observable adverse event level (NOAEL) was not identified for AVXS-101-related heart and liver findings in the mouse, and the Maximum Tolerated Dose was defined as 1.5×10^{14} vg/kg, providing a safety margin of approximately 1.4-fold relative to the recommended therapeutic dose of 1.1×10^{14} vg/kg. The translatability of the observed findings in mice to primates is not known at this time.

5.4. Clinical Studies

First-in-human trial AVXS-101-CL-101 is a completed 2-year trial which evaluated the efficacy and safety of AVXS-101 in 15 SMA Type 1 patients with 2 copies of *SMN2*. All patients have received a single IV dose of AVXS-101 in 2 cohorts: Cohort 1 (n = 3) received 6.7×10^{13} vg/kg and Cohort 2 (n = 12) received 2.0×10^{14} vg/kg (proposed therapeutic dose). After the End of Trial visit, patients were invited to participate in a long-term follow up study conducted under a separate protocol.

Based on data obtained in Study AVXS 101-CL-101, the following conclusions can be made regarding the efficacy of AVXS-101:

- AVXS-101 administration had a positive effect on survival. Twenty-four months after dosing, all 15 patients were alive and free of permanent ventilation 24 months after dosing and all Cohort 2 patients had survived free of permanent ventilation, a statistically significant difference compared with the natural history rate of 8% [Finkel et al, 2014].
- Developmental milestones, confirmed by independent video review, were achieved and maintained over time.
    - In Cohort 2, 11 patients (91.7%) could hold their head erect without support for ≥ 3 seconds and sit with support, 9 patients (75.0%) were able to sit without support for ≥ 30 seconds, and 2 patients each (16.7% each) were able to stand with assistance, stand alone, walk with assistance, and walk alone.
- The improvements in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scores from baseline in both cohorts were sustained over time.
- Nearly all Cohort 2 patients (11/12, 91.7%) achieved a score ≥ 50 on the CHOP INTEND, approximating the range of scores for SMA Type 2 children reported in the Pediatric Neuromuscular Clinical Research Network (PNCR) study [Finkel et al, 2014].
- Other clinically meaningful developmental milestones were maintained 24 months after AVXS-101 infusion:
    - Of the 7 patients in Cohort 2 who did not require non-oral nutrition prior to AVXS-101 dosing, 5 (71.4%) maintained the ability to thrive.
    - Eleven Cohort 2 patients (91.7%) were still able to swallow effectively enough to feed orally.
    - Seven of 15 patients (46.7%) remained independent of ventilatory support.

Additional ongoing and planned clinical studies of AVXS-101 are further described in the Investigator Brochure.

5.5. Risks

A full understanding of all the risks associated with AVXS-101 is not known at this time. Potential risks of AVXS-101 are discussed below and further details are provided in the AVXS-101 Investigator's Brochure.

Important identified risks associated with AVXS-101 include hepatotoxicity, mainly elevations in serum transaminases. Liver findings in mice were comprised of hepatocellular hypertrophy, Kupffer cell activation, and scattered hepatocellular necrosis, while in NHP the findings were limited to single cell necrosis of hepatocytes associated with slight mononuclear cell infiltrates. In both species, these microscopic findings may have correlated with increased liver enzyme activity. In mice, the liver findings were minimal to slight in severity, and partially to fully reversible over 12 weeks. Administration of AAV vector may result in hepatotoxicity as seen in pivotal GLP compliant 3-month mouse toxicology studies, in which the main target organs of toxicity were the heart and liver, consistent with an immune mediated mechanism for transaminase elevations. Elevations in liver transaminases have been observed with AAV gene therapy in humans [Manno et al, 2006]. Adverse events within the hepatotoxicity category and clinical laboratory values showed elevations in liver transaminases and, in some cases, acute liver injury. In clinical trials, these adverse events were clinically asymptomatic, resolved with prednisolone treatment, and no patient met clinical criteria for Hy's Law (Section 14.5.1). Of note, all patients received prophylactic prednisolone therapy. Although 2 patients in the United States Managed Access Program (US MAP) experienced liver function test (LFT) elevations that met the biochemical definition of Hy's Law, these cases were confounded by one or more alternate etiologies, which include elevated LFTs at baseline, family history of elevated LFTs, and/or use of potentially hepatotoxic concomitant medications. In both cases, liver injury resolved with prednisolone administration. The post-marketing safety experience is consistent with that of the clinical trials and MAP/RESTORE.

A transient decrease in platelet counts has been observed with both IV and less frequently with IT administration, typically at Day 7. The majority of values remained above the lower limit of normal. Decreases were clinically asymptomatic and transient. This risk can be effectively managed through monitoring platelet counts for 1 month following dosing, and appropriate prednisolone treatment (or an equivalent corticosteroid in countries where prednisolone is not available) use.

Nonclinical cardiovascular toxicity findings that could potentially be relevant to the clinical use of AVXS-101 have been reported in 2 mouse toxicology studies of AVXS-101. Similar findings were reported in both studies. Findings in the ventricles of the heart were comprised of inflammation, edema and fibrosis. Primary findings in the atrium of the heart were thrombosis and inflammation. The underlying mechanism of these findings and the translatability of the observed findings in mice to primates are not known at this time. No intracardiac thrombi were observed. Echocardiogram findings did not show evidence of clinical pathology, as LV EF and LV FS indicated normal cardiac systolic function. Troponin I data is limited, therefore no meaningful conclusion can be made. However, no patterns suggestive of clinical toxicity associated with Troponin-I have been identified. The available clinical cardiovascular safety data have not provided evidence for a cardiovascular safety problem in humans.

In an exploratory non-GLP study, inflammation of the DRG (characterized by infiltration of mononuclear inflammatory cells, along with neuronal satellitosis and neuronal necrosis or loss) was observed 14 days after cynomolgus monkeys were administered AVXS-101 intrathecally. Although the inflammation was observed in ganglia from all examined levels (cervical, thoracic, lumbar, and sacral), the incidence and severity were generally greater in the sacral DRG. Neuronal toxicity is therefore a potential risk following IT administration of AVXS-101; the risk after IV administration is not clear.

A thorough review of the safety data from patients treated with AVXS-101 did not identify any adverse events related to sensory changes. Therefore, given the acute nature (14 days) for the development of the DRG findings in cynomolgus monkeys relative to the duration (months to years) of the completed and ongoing clinical studies, there are no immediate clinical implications for patients who have been treated with AVXS-101 in ongoing trials. Study participants will be closely monitored for any clinical manifestations of a potential DRG involvement.

In the clinical trials with AVXS-101, patients were required to have an anti-AAV9 antibody titer of ≤ 1:50 prior to treatment with AVXS-101. Thus, the safety of AVXS-101 in patients with anti AAV9 antibody titers >1:50 has not been studied. All patients who had post-treatment AAV9 assessments showed increases in anti-AAV9 titer, an expected response to the administration of AVXS-101 administration. No patient developed antibodies to SMN protein. Sporadic increases in T-cell responses to AAV9 peptide were observed; however, these were not persistent, and no trends were observed. No T-cell response to SMN were observed.

No cases of thrombotic microangiopathy (TMA) have been reported in the AVXS-101 clinical trials. However, a search in the Novartis Argus Safety database that includes sources outside of clinical trials found 2 cases of TMA as of 11-Jun-2020, with a third case reported as of 01-Jul-2020. The 3 case reports were received within less than 1 year, with similar times to onset and consistent clinical presentations. A causal association with AVXS-101 cannot be ruled out. As such, this finding represents a new safety signal and Novartis Gene Therapies, Inc. (Novartis Gene Therapies, hereafter) has updated the Core Data Sheet and subsequent labeling accordingly. TMA is added to the Investigator's brochure and informed consent to increase the level of awareness and timely management of this clinically treatable condition. For detailed information on risks and benefits, see the current AVXS-101 Investigator’s Brochure.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective is to:

- Determine efficacy by demonstrating achievement of developmental milestone of sitting without support up for at least 10 seconds up to 18 months of age as assessed by WHO Motor Developmental Milestones (Appendix 5).

6.2. Secondary Objective

The secondary objective is to:

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

6.3. Exploratory Objectives

[redacted]

6.4. Safety Objectives

The safety objective is to:

- Evaluate the safety of AVXS-101 in patients with SMA Type 1.

7. INVESTIGATIONAL PLAN

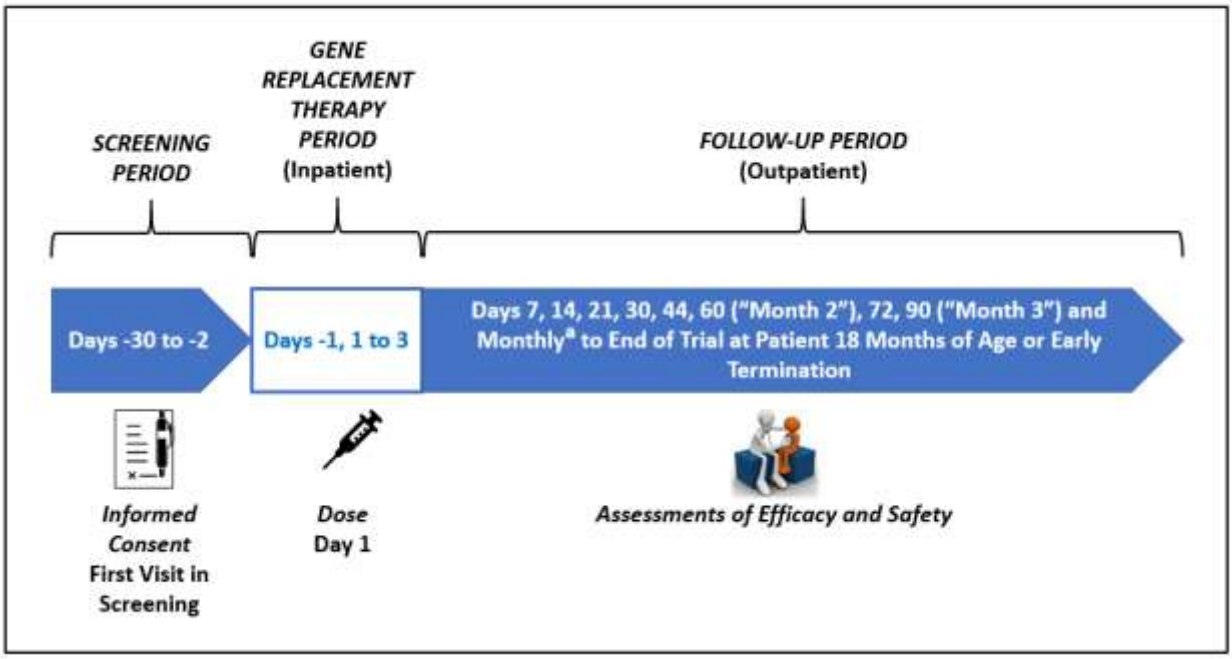
7.1. Overall Trial Design

This is a Phase 3, open-label, single-arm, single-dose trial of AVXS-101 (gene replacement therapy) in patients with SMA Type 1 with one or 2 copies of *SMN2*. At least 6 patients < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1) will be enrolled.

The trial includes 3 trial periods: screening, gene replacement therapy, and follow-up (Figure 4). During the screening period (Days –30 to –2), patients whose parent(s)/legal guardian(s) provide informed consent will undergo screening procedures to determine eligibility for trial enrollment. Patients who meet the entry criteria will enter the in-patient gene replacement therapy period (Day –1 to Day 3). On Day –1, patients will be admitted to the hospital for pre-treatment baseline procedures. On Day 1, patients will receive a one-time intravenous (IV) infusion of the equivalent of AVXS-101 cohort 2 dose received in the AVXS-101-CL-101 trial over approximately 60 minutes and will undergo in-patient safety monitoring over the next 48 hours. Patients may be discharged 48 hours after gene replacement therapy, based on Investigator judgment. During the outpatient follow-up period (Days 4 to End of Trial at 18 months of age), patients will return at regularly scheduled intervals for efficacy and safety assessments until the patient reaches 18 months of age. Any missed visit should be rescheduled as soon as possible, but within the visit windows shown in the Schedule of Assessments (SoA). All visits will be scheduled based on a 30-day month calendar.

After dosing follow-up visits will be conducted according to the SoA (Appendix 1). All post-treatment visits will be relative to the date on which gene replacement therapy is administered until the patient is 14 months of age, after which all visits will be relative to the patient's date of birth. For the 14 and 18 months of age visits, the patient will return within 0 to 14 days **after** the date on which the patient reaches 14 and 18 months of age, respectively. The 18 months of age visit will also serve as the End of Trial visit. After the End of Trial visit, patients will be invited to participate in a long-term follow-up study under a separate protocol. Patients who discontinue prematurely will also be invited to participate in the long-term follow-up study.

Figure 4 - Trial Design



Note: After the End of Trial visit at 18 months of age or at the time of early discontinuation patients will be invited to participate in a long- term follow-up study conducted under a separate protocol.

a All post-treatment visits will be relative to the date on which gene replacement therapy is administered until the patient is 14 months of age, after which all visits will be relative to the patient's date of birth. *Note: Depending on the patient's age at dosing, the duration of participation at the end-of-trial visit can vary from approximately 12 months (baby dosed at approximately 6 months of age) to approximately 18 months (baby dosed near birth "0 months of age").* All visits will be scheduled based on a 30-day month calendar.

In an attempt to dampen the host immune response to the AAV-derived therapy, all patients will receive prophylactic prednisolone according to the regimen described in Section 9.2.1.

Efficacy will be assessed by achievement of the key developmental milestone of sitting without support for at least 10 seconds at any time up to and including the 18 months of age trial visit, and survival at 14 months of age (as defined in Section 14.1.1). Safety will be assessed through monitoring AEs, concomitant medication usage, physical examinations, vital sign assessments, cardiac assessments, and laboratory evaluations (Section 12).

In the event that unforeseen catastrophic or other serious situations (such as the COVID-19 pandemic) impact the ability to conduct the study on-site, alternative methods of continuing study assessments may be implemented. Alternative visits include phone calls, virtual contacts through teleconsult or videoconference, or visits by site staff/home nursing providers to the patient's home depending on local regulations, institutional policies, and capabilities of the investigative site. Alternative visits may take place instead of on-site visits until such time that the patient can safely return to the site. The process for obtaining remote informed consent must be followed if alternative study visits will be conducted (Section 18.3).

Throughout the study, the scheduling of study visits should adhere to the overall study schedule and visit windows defined in the protocol. For each study visit, all study procedures and assessments should be performed or completed in accordance with the schedule of events. Local institutions or other alternatives may be utilized.

Importantly, in instances in which the final scheduled study visit is not possible to be conducted at the study site, the final scheduled study visit should be performed all or by an alternative visit within the protocol-defined visit window. Critical data that pertain to the primary and secondary endpoints and other information such as adverse events, concomitant medications, use of feeding or ventilatory support, or other safety data that may be obtained remotely should be collected as part of the final study visit and within the protocol-defined visit window.

Procedures such as laboratory and other safety assessments that cannot be performed or obtained as part of a remote visit may be performed separately and preferably within the protocol-defined visit window.

Additionally, a Data Safety Monitoring Board/Data Monitoring Committee (DSMB/DMC) will review safety data on a quarterly basis. A detailed description of the DSMB/DMC, its role in this trial, and the timing and process of the scheduled reviews will be described in a DSMB/DMC Charter.

7.2. Number of Patients

At least 6 patients was planned to be enrolled as part of the combined analysis with Study AVXS-101-CL-302. At the time of this protocol was amended (Protocol version 6.0 amendment 5 dated 11 Nov 2020), the enrollment was closed with 2 active enrolled patients as the combined analysis is no longer to be performed.

7.3. Criteria for Trial Termination

An independent DSMB/DMC will conduct quarterly and ad hoc reviews of the emerging safety data throughout the trial as described in Section 15.

The trial may be terminated for the following reasons:

- Development of unacceptable toxicity, defined as the occurrence of any unanticipated CTCAE Grade 3 or higher AE/toxicity that is possibly, probably, or definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires medical treatment.
- DSMB/DMC can recommend early termination of the trial for safety reasons.
- Trial is terminated by Sponsor.
- Regulatory Authority recommendation.

8. ELECTION AND WITHDRAWAL OF PATIENTS

Patients with SMA Type 1 who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1) with proven biallelic mutations of the *SMN1* gene and one or 2 copies of the *SMN2* will be enrolled in this trial.

8.1. Patient Inclusion Criteria

Patients must meet all of the following inclusion criteria:

1. Patients with SMA Type 1 as determined by diagnosis of SMA based on gene mutation analysis with biallelic *SMN1* mutations (deletion or point mutations) and one or 2 copies of *SMN2* [inclusive of the known *SMN2* gene modifier mutation (c.859G>C)]
2. Patients must be < 6 months (< 180 days) of age **at the time** of AVXS-101 infusion
    a. Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy
    b. Up-to-date on childhood vaccinations as per local health authorities.
    c. Parent(s)/legal guardian(s) willing and able to complete the informed consent process and comply with trial procedures and visit schedule

8.2. Patient Exclusion Criteria

Patients must not meet any of the following exclusion criteria:

1. Previous, planned or expected scoliosis repair surgery/procedure prior to 18 months of age
2. Use of invasive ventilatory support (tracheotomy with positive pressure) or pulse oximetry < 95% saturation at screening
    a. Pulse oximetry saturation must not decrease ≥ 4 percentage points between screening and dosing with confirmatory oximetry reading
    b. Patients may be put on non-invasive ventilatory support for less than 12 hours per day at the discretion of their physician or trial staff
3. Use or requirement of non-invasive ventilatory support for 12 or more hours daily in the two weeks prior to dosing
4. Patient with signs of aspiration based on a swallowing test or whose weight-for-age falls below the 3rd percentile based on World Health Organization (WHO) Child Growth Standards [WHO 2006] and unwilling to use an alternative method to oral feeding
5. Active viral infection (includes human immunodeficiency virus [HIV] or positive serology for hepatitis B, C, or E, or known Zika virus infection)
6. Serious non-respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening
7. Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening

8. Severe non-pulmonary/respiratory tract infection (e.g., pyelonephritis, or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Principal Investigator, creates unnecessary risks for gene replacement such as:
    a. Major renal or hepatic impairment
    b. Known seizure disorder
    c. Diabetes mellitus
    d. Idiopathic hypocalciuria
    e. Symptomatic cardiomyopathy
9. Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients
10. Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, or immunosuppressive therapy within 3 months prior to gene replacement therapy (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab)
11. Anti-AAV9 antibody titer > 1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay. Should a potential patient demonstrate Anti-AAV9 antibody titer > 1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the Anti-AAV9 antibody titer upon retesting is ≤ 1:50
12. Clinically significant abnormal laboratory values GGT, ALT, AST, total bilirubin >2x the ULN, creatinine ≥ 1.0 mg/dL, hemoglobin [Hgb] < 8 or > 18 g/dL; white blood cell [WBC] > 20,000 per cmm) prior to gene replacement therapy. Patients with an elevated bilirubin level that is unequivocally the result of neonatal jaundice shall not be excluded.
13. Participation in recent SMA treatment clinical trial (with the exception of observational cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product or therapy administered with the intent to treat SMA (e.g., nusinersen, valproic acid) at any time prior to screening for this trial. Oral beta-agonists must be discontinued at least 30 days prior to dosing. Inhaled albuterol specifically prescribed for the purposes of respiratory (bronchodilator) management is acceptable and not a contraindication at any time prior to screening for this trial
14. Expectation of major surgical procedures during the trial assessment period (e.g., spinal surgery or tracheostomy)
15. Parent(s)/legal guardian(s) unable or unwilling to comply with trial procedures or inability to travel for repeat visits
16. Parent(s)/legal guardian(s) unwilling to keep trial results/observations confidential or to refrain from posting confidential trial results/observations on social media sites
17. Parent(s)/legal guardian(s) refuses to sign consent form
18. Patients < 35 weeks gestational age at time of birth

8.3. Patient Withdrawal Criteria

Patients may be discontinued from the trial for the following reasons:

- Death
    - An autopsy and/or post-mortem tissue/organ collection will be requested for any patient who expires following participation (see Post-Mortem Tissue and Organ Collection Plan in Appendix 2) as allowed per country/regional laws/regulations
- Failure to comply with protocol-required visits or trial procedures for 3 or more consecutive visits that are not rescheduled, unless due to hospitalization
- Parent(s)/legal guardian(s) withdraws consent
- Investigator discretion

End-of-trial procedures should be completed within 14 days for any patient who prematurely discontinues the trial for any reason, as indicated in Appendix 1. Patients who terminate the study early for reasons other than death will be offered enrollment in a long-term follow-up study.

In instances in which a patient withdraws from the study prior to the last scheduled visit, the investigator should differentiate between factors that are related to a catastrophe (such as the inability to travel, local ordinances or other restrictions, etc.) versus withdrawal of consent.

9. TREATMENT OF PATIENTS

It is the responsibility of the Investigator to ensure the safe storage and administration of gene replacement therapy.

9.1. Description of Trial Product

AVXS-101 is a non-replicating recombinant adeno-associated virus serotype 9 (AAV9) containing the human survival motor neuron *(SMN)* gene under the control of the cytomegalovirus (CMV) enhancer/chicken β-actin-hybrid promoter (CB). One of the two adeno-associated vector (AAV) inverted terminal repeats (ITRs) has been modified to promote intramolecular annealing of the transgene, thus forming a double stranded transgene ready for transcription.

Table 2 - Investigational Product

	Investigational Product
Product Name	AVXS-101
Unit Dose	1.1×10^{14} vg/kg; equivalent to the dose received by the Cohort 2 in the Phase 1 study (AVXS-101-CL-101) as determined by direct product testing with improved analytical methods.
Route of Administration	Intravenous infusion
Physical Description	AVXS-101 is a clear to slightly opaque, colorless to faint white solution, free of visible particulates

9.2. Prior and Concomitant Medications

Prior and concomitant medications will be captured in the electronic Case Report Form (eCRF) from 2 weeks prior to administration of gene replacement therapy through the last trial visit.

9.2.1. Prophylactic Administration of Prednisolone

An antigen specific T-cell response to the AAV vector was observed in the Phase 1 clinical trial (AVXS-101-CL-101) investigating AVXS-101 treatment via IV infusion [data on file]. This is an expected response between 2 to 4 weeks following gene replacement therapy. One possible consequence to such antigen specific T-cell response is clearance of the transduced cells and loss of transgene expression.

In an attempt to dampen the host immune response to the AAV-based therapy, all patients will receive prophylactic prednisolone at approximately 2 mg/kg/day (or an equivalent dose of another glucocorticoid if prednisolone is unavailable or in the opinion of the investigator prednisolone is not tolerated [Zoorob and Cender, 1998]) on Day -1, Day 1, and Day 2, and then 1 mg/kg/day starting on Day 3 and until at least 30 days post-AVXS-101 infusion. After 30 days post-AVXS-101 infusion, the dose of prednisolone can be tapered for patients whose GGT, ALT, and AST values are below the threshold of 2 × ULN. To summarize, the overall course of prednisolone should proceed in accordance with the following treatment guideline:

- Day -1, Day 1, and Day 2: 2 mg/kg/day
- Day 3 until at least 30 days post AVXS-101 infusion: 1 mg/kg/day

- Weeks 5 and 6 post AVXS-101 infusion: 0.5 mg/kg/day
- Weeks 7 and 8 post AVXS-101 infusion: 0.25 mg/kg/day
- Week 9 post AVXS-101 infusion: prednisolone discontinued

Liver function testing should guide each step of the taper, and liver function enzymes (LFEs) should be checked prior to prednisolone discontinuation. If the GGT, AST or ALT values are > 2× ULN then the present dose of prednisolone should be adjusted as needed until the GGT, AST, and ALT values decrease below threshold, at which point the taper may continue. LFTs should also be checked approximately 2 weeks after the taper has concluded and prednisolone has been discontinued to evaluate for rebound elevation of GGT, AST, or ALT levels. Variance from these recommendations will be at the discretion of the Investigator based on potential safety issues for each patient. If another glucocorticoid is used in place of prednisolone by the investigator, similar considerations should be taken into account after 30 days and tapered as appropriate and at the discretion of the investigator.

9.2.2. Prohibited Medications

Concomitant use of any of the following medications is prohibited:

- Drugs for treatment of myopathy or neuropathy, or agents used to treat diabetes mellitus
- Therapy received with the intent to treat SMA (e.g., nusinersen, valproic acid); oral β-agonists must be discontinued at least 30 days prior to gene therapy dosing. Inhaled β-agonists may be used to treat respiratory complications of SMA provided such medications are dosed at clinically appropriate levels
- Any investigational medication other than AVXS-101 is prohibited during the trial
- Ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, or immunosuppressive therapy within 3 months prior to AVXS-101 dosing (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab)

Corticosteroid usage following completion of the prednisolone taper is permissible as part of routine clinical management. The use of corticosteroids in such circumstances should be documented appropriately as a concomitant medication, and the event precipitating its usage should be appropriately documented as an adverse event.

Should the use of corticosteroids (aside from inhaled corticosteroids for bronchospasm) be considered as part of care during the course of the prednisolone taper, this medical management should be discussed with the medical monitor.

9.2.3. Vaccinations

Where feasible, the vaccination schedule should be adjusted appropriately to accommodate the prednisolone use. When avoiding vaccination while on steroids represents an undue delay or interruption of a vaccination schedule, vaccination should continue at the discretion and judgement of the treating physician given 1) the importance of maintaining childhood vaccination in this population and 2) the published literature that indicates that vaccination while on steroid doses 1 mg/kg/day or below is safe and effective [Pickering et al, 2012].

Vaccinations that include palivizumab (also known as Synagis®) prophylaxis to prevent respiratory syncytial virus (RSV) infections are also recommended [Palivizumab *Summary of Product Characteristics*, 2018; American Academy of Pediatrics: Policy Statement, 2009].

9.3. Treatment Compliance

AVXS-101 will be administered as a one-time IV injection.

9.4. Randomization and Blinding

This is an open-label trial.

10. TRIAL PRODUCT MATERIALS AND MANAGEMENT

AVXS-101 is manufactured in accordance with current Good Manufacturing Practices (cGMP).

10.1. Trial Product

AVXS-101

10.2. Trial Product Dose and Dose Justification

Patients will receive a one-time dose of AVXS-101 at 1.1×10^{14} vg/kg via IV infusion, equivalent to the dose received by Cohort 2 in the Phase 1 trial (AVXS-101-CL-101).

Two doses were studied in the Phase 1 clinical study (AVXS-101-CL-101); the higher dose (dose received by the Cohort 2 patients) was chosen for the present study as data have demonstrated both a dose response and significant clinical benefit, thus identifying it as the proposed therapeutic dose. In the Phase 1 study, AVXS-101 demonstrated a dose response, with efficacy greater, as observed by motor milestone achievement and CHOP INTEND scores, at the higher dose (received by Cohort 2) than at the lower dose (received by Cohort 1). Direct testing of the actual lot of Investigational Medicinal Product (IMP) used in the AVXS-101-CL-101 study by an improved and more fully qualified analytical method has assigned a value of 1.1×10^{14} vg/kg to the actual dose received by Cohort 2 in this Phase 1 study. The same method has been used to establish an equivalent dose for the Phase 3 IMP. This vg/kg value has been further verified in an improved and more fully qualified SMNΔ7 Mouse Biopotency assay to support a similar extension of mouse lifetime in direct comparative assessment between the Phase 1 and Phase 3 IMP.

10.3. Trial Product Packaging and Labeling

AVXS-101 kits will be labeled with a specific kit number and lot number assigned at the cGMP facility. The content of the labeling is in accordance with the local regulatory specifications and requirements.

10.4. Trial Product Storage and Destruction

AVXS-101 kits will be stored in a locked, limited access room under the responsibility of the Investigator or other authorized persons (e.g., pharmacists) in accordance with local regulations, policies, and procedures. Control of storage conditions, especially control of temperature (e.g., refrigerated/freezer storage) and information on in-use stability and instructions for handling prepared AVXS-101 should be managed in accordance with the Pharmacy Manual.

The vessel used for delivery of the vector should be resealed in the procedure room and processed for destruction in accordance with the Pharmacy Manual and applicable biohazardous waste guidelines for disposal.

10.5. Trial Product Preparation

Preparation of AVXS-101 will be done aseptically under sterile conditions and will be received ready for infusion.

AVXS-101 will arrive as outlined in the Pharmacy Manual. The total vector genome dose will be calculated based on the patient's body weight; sites will receive a patient-specific dose for each patient enrolled.

The dose-delivery vessel will be delivered to the designated pediatric intensive care unit (PICU), patient room or other appropriate setting (e.g., interventional suite, operating room, dedicated procedure room) with immediate access to acute critical care management. The vessel will be delivered in accordance with the Pharmacy Manual.

10.6. Trial Product Administration

AVXS-101 infusion will be administered under sterile conditions in a PICU or other appropriate setting (e.g., interventional suite, operating room, dedicated procedure room) with immediate access to acute critical care management. AVXS-101 will be delivered one-time through a venous catheter inserted into a peripheral limb vein (arm or leg) at a dose equivalent to the cohort 2 dose administered in the AVXS-101-CL-101 trial. AVXS-101 should be slowly infused over approximately 60 minutes, utilizing an infusion set and syringe pump in accordance with the Pharmacy Manual.

Following administration of gene replacement therapy, patients should return to an appropriate designated setting to ensure close monitoring of vital signs and adverse events. Vital signs will be continuously monitored throughout the gene replacement therapy infusion as described in Section 12.1.3. Patients should be maintained in the PICU or other appropriate setting for 48 hours after the start of gene replacement therapy.

10.7. Dose Adjustment Criteria

The trial investigates a one-time IV infusion of AVXS-101; no dose adjustments are possible.

10.8. Trial Product Accountability

The pharmacist or designee will maintain accurate records of the quantities of AVXS-101 received, dispensed, destroyed, and/or returned to Novartis Gene Therapies. The pharmacist or designee will document the date and time of delivery of the dose vessel to the dose procedure room as well as the time the used vessel was processed for destruction as per the Pharmacy Manual.

10.9. Trial Product Handling and Disposal

All materials used for injection, including sterile drapes, needles, and syringes in contact with the vector must be sealed in leak-proof containers. All waste must be sealed in bags bearing the biohazard symbol and disposed of in a biohazard waste container.

All transfers must be done in spill-proof containers. Individuals manipulating the vector will be required to wear personal protective equipment, such as gloves.

Any quality issue noticed with the receipt or use of AVXS-101 (e.g., deficiency in condition, appearance, pertaining to documentation, labeling, expiration date, etc.) should be promptly reported to the Sponsor in accordance with procedures outlined in the Pharmacy Manual.

Under no circumstances will the Investigator supply AVXS-101 to a third party, allow AVXS-101 to be used other than as directed by this clinical trial protocol, or dispose of AVXS-101 in any other manner.

11. ASSESSMENT OF EFFICACY

Efficacy will be assessed by achievement of the key developmental milestone of sitting without support for at least 10 seconds at any time up to and including the 18 months of age trial visit and survival at 14 months of age (as defined in Section 14.1.1). Efficacy assessments will be performed at the times specified in the Schedule of Assessments (Appendix 1) and should be the first assessments performed at any scheduled visit. All post-treatment visits will be relative to the date on which gene replacement therapy is administered until the patient is 14 months of age, after which all visits will be relative to the patient's date of birth.

In the event of unforeseen catastrophe or other serious situation (such as the COVID-19 pandemic) that occurs during the study, which limits or prevents on-site study visits, alternative methods of data collection pertaining to efficacy assessments may be considered. Critical data that pertain to the primary and secondary endpoints should be collected according to the overall study schedule and within the protocol-defined visit window. The maintenance of the overall visit schedule and visit windows is especially important for the final scheduled study visit, as this may impact the overall interpretation of the evaluation of efficacy. As described in Section 7.1, allowances are made for the collection of data remotely, when necessary.

Video recordings demonstrating the attainment of any new developmental milestones should be obtained within the protocol-defined visit window, including those that are required to be assessed as part of the final study visit or are related to primary or secondary endpoints (e.g, sitting without support). This may include submission of recordings made by the family or others as described in Section 11.3.

Alternative methods of data collection for efficacy assessments depending on local regulations, institutional polices, and capabilities may include:

- developmental/motor efficacy assessments by a qualified clinical evaluator during a visit to the participant´s home
- home videos or other recordings which demonstrate the achievement of developmental milestones that are specified in the protocol, including those to be assessed at the final scheduled study visit
- use of ventilatory, cough or feeding support by the participant, evaluated during phone calls, virtual contacts (e.g., teleconsult) or visits by site staff/home nursing service to the participant´s home, or during visits by the participant to a local hospital.

11.1. Developmental Milestones

Developmental milestones will be assessed according to the 6 gross motor milestones definitions from the WHO MGRS (Appendix 5) and the BSIDv03 (Appendix 3 and Appendix 4), and will be analyzed to assess efficacy. Achievement of each developmental milestone will be determined by the qualified site clinical evaluator (physical or occupational therapist or national equivalent) and confirmed by the central reviewer based on an assessment of the submitted video (Section 11.3). Developmental milestones will be determined at each monthly visit as shown in the SoA (Appendix 1).

At the 18 months of age visit all milestones (Appendix 4 and Appendix 5) should be assessed, documented, and video recorded regardless of previous attainment. End of study developmental milestone may be submitted for review by an independent central reviewer.

11.2. Motor Function Tests

11.2.1. World Health Organization Multicentre Growth Reference Milestones

The WHO Multicentre Growth Reference Study Group milestones defined for this study include six gross motor milestones (Appendix 5) [WHO 2006; Wijnhoven et al, 2004]:

- Sitting without support
- Crawling
- Standing with assistance
- Standing alone
- Walking with assistance
- Walking alone

These six gross motor milestones will be assessed by a qualified clinical evaluator according to the SoA (Appendix 1). If the Bayley Gross Motor Subtest Item 22 (Appendix 3), sits without support for five seconds, is achieved at a visit, then the WHO milestone for sitting without support for at least 10 seconds (Appendix 5) should be assessed at that visit and all subsequent visits. Each developmental milestone assessment will be evaluated according to the WHO defined performance criteria and will be video recorded in accordance with the AVXS-101-CL-306 Physical Assessments Manual and may be submitted for review by a central reviewer (Section 11.3).

11.2.2. Bayley Scales for Infant and Toddler Development/Developmental Milestones

The BSIDv03 (Appendix 3) is a standardized, norm-referenced infant assessment of developmental functioning across 5 domains of cognitive, language, motor, social-emotional, and adaptive behavior [Albers and Grieve, 2007]. The Bayley Scales will be administered by a qualified clinical evaluator in accordance with the Physical Assessments Manual. The items from the BSIDv03 Gross Motor Subtest defined as developmental milestones for this protocol are specified in Appendix 4.

During the Screening visit, the clinical evaluator will complete an assessment of baseline milestone achievement in accordance with Appendix 3; this assessment must address all milestones/items noted in Appendix 3, Gross Motor Subtest that are at or below the child's baseline function, and be recorded on video. The findings must be documented in the source. Items that are below the baseline level of assessment that are not successfully achieved during the baseline evaluation should be repeated at subsequent visits until successfully performed.

The milestone of sitting independently (BSIDv03 Gross Motor Item #26) should be assessed, documented, and video recorded at every subsequent visit, until attainment of milestone, regardless of starting point on the scale. This milestone must also be assessed at the 18 months of age visit, regardless of previous attainment.

As the Bayley Scales do not necessarily require the child to repeat previously attained milestones, it is essential that each attained milestone be captured on video.

The gross and fine motor subtests of the motor domain will be administered according to the SoA (Appendix 1).

Each Bayley Scales assessment will be video recorded in accordance with the AVXS-101-CL-306 Physical Assessments Manual and may be submitted for review by a central reviewer (Section 11.3).

11.2.3. CHOP INTEND

The CHOP INTEND (Appendix 6) is a motor function scale developed and validated for use specifically to monitor motor function status and decline amongst children with SMA Type 1 [Glanzman et al, 2011; Glanzman et al, 2010] and will be administered by a qualified clinical evaluator. The CHOP INTEND scale examines several aspects of motor function, including head control, righting reactions, and trunk movements in supported sitting, supine, and prone positions (Appendix 6). Anti-gravity movements in assisted rolling, ventral suspension, and supported standing will also be measured. Additional information on contractures will also be collected as described in the Physical Assessments Manual.

The CHOP INTEND will be performed according to the SoA (Appendix 1). For purposes of efficacy assessments, the CHOP INTEND assessment performed at Day -1 will be treated as the baseline assessment.

Patients who achieve three consecutive CHOP INTEND scores ≥ 58 will not undergo any additional CHOP INTEND examinations.

Each CHOP INTEND exam will be video recorded in accordance with the AVXS-101-CL-306 Physical Assessments Manual and may be submitted for review by a central reviewer (Section 11.3).

11.3. Video Evidence

Clinic assessments (WHO Motor Developmental Milestones, Bayley Developmental Milestones, Bayley Scales and CHOP INTEND) required at each trial visit will be video recorded in an effort to produce compelling, demonstrable, documented evidence of efficacy, as determined by changes in functional abilities. Novartis Gene Therapies will provide a secure and confidential upload process for transfer and storage of the videos from investigational sites to a contracted third-party vendor that will compile and arrange videos as per Novartis Gene Therapies requirements. Any/all videos received at Novartis Gene Therapies or the contracted vendor will be treated as confidential trial data and will be either the sole property of Novartis Gene Therapies or permanently licensed to Novartis Gene Therapies to use and disclose as described in this protocol. Novartis Gene Therapies and the contracted vendor will provide this secure, encrypted transfer and storage solution to properly protect the identities of patients/families on the videos, which may be shared with regulatory agencies, the medical community, and/or in appropriate venues to discuss the results of this clinical trial.

Videos demonstrating Developmental Milestones which meet WHO and BSIDv03 criteria will be submitted to an independent, central reviewer for unbiased assessment of developmental milestone achievement. The independent central reviewer will document whether the video

displays evidence of having achieved each developmental milestone. The date of developmental milestone achievement will be computed as the earliest date on which video evidence demonstrates the achievement of the specified developmental milestone.

Additionally, the parent(s)/legal guardian(s) may submit additional videos demonstrating achievement of developmental milestones at any time during the trial. These videos will be handled in the same manner in which the trial-derived videos are handled.

12. ASSESSMENT OF SAFETY

In the event of unforeseen catastrophe or other, serious situation (such as the COVID-19 pandemic) that occurs during the study, which limits or prevents on-site study visits, regular phone or virtual video calls may occur (as per the Schedule of Assessments) for safety monitoring and discussion of the participant´s health status. Visits by site staff/home nursing service to the participant´s home, or visits by the participant to a local hospital, laboratory, or imaging center, for performing certain safety assessments, depending on local regulations and capabilities, can replace on-site study visits, if necessary. Analysis of laboratory samples (e.g., chemistry, hematology, urinalysis) may be performed at a local laboratory, if it is not possible to follow the central laboratory process. Other safety assessments that cannot be conducted by telephone (such as vital signs, weight, length, cardiac testing etc.) may similarly be collected by the methods described above.

12.1. Safety Parameters

Safety parameters include physical examinations, pulmonary examinations, vital signs, capillary blood gas assessments, weight and length measurements, 12-lead ECGs, echocardiograms, 24-hour Holter monitoring, swallowing tests, laboratory assessments, adverse event monitoring, and photographs of the infusion site. In general, safety assessments will be performed at the times specified in the SoA (Appendix 1). All post-treatment visits are relative to the date on which gene replacement therapy is administered until the patient reaches 14 months of age, after which all visits are relative to the patient's date of birth.

12.1.1. Demographic/Medical History

Demographic/medical history information will be collected at screening and captured in the eCRF. Information that will be collected includes:

- Familial history of SMA including affected siblings or parent carriers
- Gestational age at birth
- Length/height/head circumference at birth
- Hospitalization information from time of birth including number, duration, and reason for hospitalizations including International Statistical Classification of Diseases and Related Health Problems (ICD-10 codes), if available
- Historical ventilatory support, if any
- Historical feeding support, if any

Patients are encouraged to follow all routinely scheduled immunizations, as recommended by the local health authority (e.g., the Japan Pediatric Society, Taiwan Immunization Schedule, or Korean Pediatric Society) throughout the trial. Vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended.

12.1.2. Physical Examinations

Physical examinations will be conducted by the Investigator or designee as specified in the SoA (Appendix 1). The Day 1 physical examination will be performed prior to the start of gene replacement therapy infusion. Physical examinations include a review of the following systems: head, eyes, ears, nose and throat (HEENT), lungs/thorax, cardiovascular, abdomen, musculoskeletal, dermatologic, lymphatic, neurologic, and genitourinary. Specifically, the neurological exam should include detailed, age-appropriate sensory testing (such as examination of proprioceptive, vibratory, tactile and pain sensation) at each visit. Any clinically significant abnormal finding should be recorded as an adverse event. Further clinical evaluation should be considered as per judgment of the investigator.

The head circumference shall be measured with each physical examination. To measure head circumference, the examiner should securely wrap a flexible measuring tape around the circumference of the head, above the eyebrows over the broadest part of the forehead, above the ears, and over the most prominent part of the occiput. The measurement should be taken 3 times, and the largest measurement should be recorded to an accuracy of 0.1 centimeters.

12.1.3. Vital Signs/Weight and Length

Vital sign parameters include blood pressure, respiratory rate, pulse, temperature, and pulse oximetry. Vital signs will be obtained as specified in the SoA (Appendix 1). On Day 1, vital signs will be continuously monitored throughout the gene replacement therapy infusion and recorded pre-dose and every 15 (± 5) minutes from the start of the infusion for the first 4 hours after the start of infusion, and then every hour (± 15 minutes) until 24 hours after the start of infusion. Temperature will be recorded pre- and post-infusion.

Weight and length will be measured at each trial visit as specified in the SoA (Appendix 1). On Day 1, weight and length will be measured pre-dose.

12.1.4. Electrocardiogram

A 12-lead ECG will be performed as specified in the SoA (Appendix 1).

Additional electrophysiological monitoring will be at the discretion of the Investigator as per local institutional guidelines.

The ECG will be interpreted locally by a cardiologist or designee for immediate safety evaluation. The ECG tracings or ECG machine data will be collected for centralized review and interpretation by a cardiologist.

12.1.5. Echocardiogram

A standard transthoracic echocardiogram will be performed as specified in the SoA (Appendix 1). The echocardiogram will be interpreted locally by a cardiologist or designee for immediate safety evaluation. The echocardiograms will also be collected for centralized review and interpretation by a cardiologist.

12.1.6. Continuous ECG Recording (24-Hour Holter Monitoring)

Twenty-four-hour Holter monitoring will take place as specified in the SoA (Appendix 1).

Holter monitors will be provided to study sites along with a dedicated laptop for uploading the data from the memory cards for centralized review and analysis by a cardiologist or designee within 24 hours of data upload. Novartis Gene Therapies will be notified of any safety concerns from the centralized review (Appendix 1).

12.1.7. Pulmonary Examinations

Pulmonary examinations will be performed by a pulmonologist (or appropriate individual as per standard institutional practice) as specified in the SoA (Appendix 1). Prior to trial entry, a pulmonologist (or appropriate individual as per standard institutional practice) will review and document ventilator usage in the 2 weeks prior to screening.

Patients may be fitted with non-invasive ventilatory support at the discretion of the pulmonologist (or appropriate individual as per standard institutional practice) and/or Investigator. Non-invasive ventilatory support equipment will be provided by Novartis Gene Therapies through a third party vendor if not covered by the patient's insurance. Should the patient require non-invasive ventilatory support at any time during the trial, the usage should be recorded in eCRF.

Patients requiring non-invasive ventilatory support will be asked to bring the machine to each trial visit.

12.1.8. Swallowing Test

A standard bedside, non-barium (unless required by institutional policy) swallowing test will be performed as specified in the SoA (Appendix 1) to determine if the patient has signs of aspiration for consistencies tested during the assessment. The swallowing test at Screening can be performed at the investigator site. If the test is positive for aspiration, there may be a recommendation for the patient to use an alternate method to oral feeding for the duration of the trial at the determination of the Investigator and treating clinician.

12.1.9. Photographs of Infusion Site

Photographs will be taken of the infusion site as specified in the SoA (Appendix 1) to monitor healing of the infusion site. The Day 1 infusion site photograph will be performed prior to the start of gene replacement therapy infusion. Novartis Gene Therapies will provide a secure and confidential upload process for transfer and storage of the photographs from the investigative sites to a contracted third-party vendor that will compile and arrange photographs as per Novartis Gene Therapies requirements. Any/all photographs received at Novartis Gene Therapies or the contracted vendor will be treated as confidential trial data and will be the sole property of Novartis Gene Therapies. Novartis Gene Therapies and the contracted vendor will provide this secure, encrypted transfer and storage solution to properly protect the identities of patients/families in the photographs, which may be shared with regulatory agencies, the medical community, and/or in appropriate venues to discuss the results of this clinical trial.

12.1.10. Laboratory Assessments

Blood samples will be collected at each scheduled visit as specified in the SoA (Appendix 1) and in accordance with the laboratory manual(s) provided for this study. On Day -1, required blood samples will be collected locally prior to the start of gene replacement therapy infusion. Any clinically significant laboratory value will be repeated at the discretion of the Investigator.

Table 3 - Total Blood Volume

Visit	Tests	Total Volume (mL)[b]
Screening	Hematology, chemistry, Troponin I, virus serology, ELISA immunology sample (AAV9/SMN Ab), diagnostic genetic re-confirmation sample	15.4 [b]
Day –1	Hematology, chemistry, capillary blood gas	3.3 [b]
Day 2	Hematology, chemistry, capillary blood gas	3.3 [b]
Day 7	Hematology, chemistry, Troponin I, immunology sample	9.6 [b]
Day 14	Hematology, chemistry, immunology sample	3.3 [b]
Day 21	Hematology, chemistry, immunology sample	3.3 [b]
Day 30	Hematology, chemistry, Troponin I, immunology sample	9.6 [b]
Day 44	Chemistry	1.3[b]
Day 60	Hematology, chemistry, Troponin I	4.9 [b]
Day 72	Chemistry	1.3[b]
Month 3/4/5/7/8/ 10/11/13/14/16/17	Hematology, chemistry	26.6 [b]
Month 6/9/12/15	Hematology, chemistry, Troponin I	14.4 [b]
End of Study/ET	Hematology, chemistry, Troponin I	3.6 [b]
Maximum Total Volume for Trial[a]		**99.9 [b]**

ET = early termination

[a] Patients will have different numbers of monthly visits, depending on their age at dosing. Maximum total volume based on a maximum of 16 monthly visits. Additionally, lower blood volumes may be sufficient at some visits where testing can be combined.

[b] Safety laboratory samples to be drawn by local laboratory; smaller volumes may be utilized.

In a case where sufficient blood cannot be collected from a patient, blood will be used in the following priority order with the first having greatest priority and last having the least priority:

1. Safety labs: chemistry → hematology → Troponin I
2. Serum antibody to AAV9 and SMN
3. Genetic reconfirmation testing

If there is insufficient blood volume to include the genetic reconfirmation testing sample at the screening visit, patient must return before Visit 2. All patients must have genetic reconfirmation testing completed.

12.1.10.1. Hematology

Hematology analysis will include a complete blood count with differential and platelet count with smear. Samples will be collected and processed by the sites' local laboratories. Blood samples for hematology analysis will be collected in accord with the SoA (Appendix 1).

12.1.10.2. Blood Chemistry

Samples will be collected and processed by the sites' local laboratories. Blood samples for chemistry analysis will be collected in accord with the SoA (Appendix 1).

Chemistry analysis will include the following at all trial visits:

- Serum GGT
- AST/ALT
- Serum total bilirubin
- Direct bilirubin
- Albumin
- Glucose
- Creatinine kinase
- Creatinine
- BUN
- Electrolytes (potassium, chloride, CO_2, calcium, inorganic phosphorus, sodium, magnesium)
- Alkaline phosphatase

Patients will have Troponin I collected on the visits specified in the SoA (Appendix 1).

12.1.10.3. Urinalysis

Urine samples will be collected and process by the sites' local laboratories in accord with the SoA (Appendix 1). Urinalysis will include the following parameters:

- Color
- Clarity/turbidity
- pH
- Specific gravity
- Glucose
- Ketones
- Nitrites
- Leukocyte esterase
- Bilirubin

- Blood
- Protein
- Red Blood Cell
- White Blood Cell
- Squamous epithelial cells
- Casts
- Crystals
- Bacteria
- Yeast

12.1.10.4. Virus Serology

The administration of an AAV vector has the risk of causing immune-mediated hepatitis. For patients who have HIV or positive serology for hepatitis B, C, or E, administration of AAV vector may represent an unreasonable risk; therefore, negative serology testing must be confirmed at screening, prior to treatment. These samples will be collected at screening (SoA, Appendix 1) and processed by the sites' local laboratories.

12.1.10.5. Capillary Blood Gas

Capillary blood gas (pCO_2, pO_2, total CO_2) and pH will be measured locally at Day -1 and Day 2 (SoA, Appendix 1). A puncture or small incision will be made with a lancet or similar device into the cutaneous layer of the patient's skin at a highly vascularized area (heel, finger, toe). To accelerate blood flow and reduce the difference between the arterial and venous gas pressures, the area will be warmed prior to the puncture. As the blood flows freely from the puncture site, the sample will be collected in a capillary tube.

12.1.10.6. Immunology Testing (ELISA)

Blood samples for immunology testing will be collected and shipped to the central laboratory in accordance with the laboratory manual to test for serum antibodies to AAV9 and SMN (ELISA). Blood samples will be collected as specified in the SoA (Appendix 1).

12.1.10.7. AAV9 Antibody Screen in Mother

There is potential that the biological mother of the patient may have pre-existing antibodies to AAV9 that may be transferred to the patient through breast milk or, theoretically, via placental transfer in utero. Informed consent will be requested from the mother of the patient to screen the mother for circulating antibodies to AAV9. Once informed consent has been obtained, the mother will have her blood drawn from a peripheral vein and shipped to the central laboratory for screening of anti-AAV9 antibodies. If AAV9 antibodies are identified, the investigator should discuss with the biological mother whether to continue or stop breastfeeding.

Patients whose biological mothers are involved with their care but do not consent to AAV9 antibody screening are not eligible to participate.

Patients consuming banked breast milk from donor sources that cannot be tested for anti-AAV9 antibodies must be transitioned to formula prior to participation.

12.1.10.8. Blood for Diagnostic Confirmation Testing

A blood sample will be collected during the screening visit and shipped to the central laboratory in accordance with the laboratory manual for reconfirmation of *SMN1* deletions/mutations, *SMN2* copy number, and absence or presence of exon 7 gene modifier mutation (c.859G>C).

This will be done to ensure consistency in diagnostic testing practices.

12.1.10.9. Saliva, Urine, and Stool Collection

Studies have shown that some vector can be excreted from the body for a few weeks after injection; this is called "viral shedding." Vector shedding can be found in the blood, urine, saliva, and stool for up to a few weeks following infusion. The risks associated with the shed vector are not known at this time; however, the risk is thought to be low as the vector cannot replicate. Regardless, IRB/IEC- approved instructions should be provided to the patient's family and care giver(s) regarding use of protective gloves if/when they come into direct contact with the patient's bodily fluids and/or waste, as well as good hand-hygiene for a minimum of four weeks after gene replacement therapy. Additionally, patients are prohibited from donating blood for two years following the vector infusion.

Saliva, urine, and stool samples will be collected and shipped to the central laboratory for viral shedding studies as specified in the SoA (Appendix 1). Samples will be collected, prepared, and shipped as per the laboratory manual.

13. ADVERSE AND SERIOUS ADVERSE EVENTS

13.1. Definition of Adverse Events

13.1.1. Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no trial treatment has been administered.

All AEs (related or not related) that occur after signing of the informed consent through the last trial visit will be collected and recorded in the eCRF.

All AEs will be classified in accordance with the CTCAE version 4.03 (or later version, upon agreement of Novartis Gene Therapies) outlined in Table 4.

Table 4 - Common Terminology Criteria for Adverse Events

Grade	Definition
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.[a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.[b]
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE.

Source: Common Terminology Criteria for Adverse Events (version 4.03) [NCI, 2010]

[a] ADL, Activities of daily living; Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Additionally, a DSMB/DMC will review safety data on a quarterly basis. A detailed description of the DSMB/DMC, its role in this trial, and the timing and process of the scheduled reviews will be described in a DSMB/DMC Charter.

13.1.2. Serious Adverse Event

An SAE is an AE occurring during any trial phase (e.g., screening, baseline, treatment, washout, or follow-up), and at any dose of the investigational product, or comparator that fulfils one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity

- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

All SAEs (related and unrelated) that occur after signing of the informed consent through the last trial visit must be collected and recorded on forms provided by the Contract Research Organization within 24 hours of the site becoming aware.

13.1.3. Adverse Events of Special Interest

The following are considered AEs of special interest (AESIs):

- Hepatotoxicity
- Thrombocytopenia
- Cardiac adverse events
- Sensory abnormalities suggestive of ganglionopathy

Grade 3 or higher elevated liver enzyme events related to AVXS-101 must be collected and recorded on the forms provided. These events should be reported within 24 hours of occurrence whether or not they are deemed to be an SAE.

13.2. Relationship to Trial Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related, Probably Related, or Definitely Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”

If the relationship between the AE/SAE and the investigational product is determined to be “possible” or “probable” then the event will be considered related to the investigational product for the purposes of expedited regulatory reporting.

13.3. Recording Adverse Events

Adverse events spontaneously reported by the patient and/or in response to an open question from the trial personnel or revealed by observation will be recorded during the trial at the investigational site. Information about AEs (related and unrelated) after signing of the informed consent form until the last study visit are to be collected. Serious adverse event information will be collected from signing of the informed consent form through 30 days after the last trial visit. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time [if start date during inpatient period]), resolution (date and time [if start date during inpatient period]), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the trial.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 13.1.2. An AE of severe intensity may not be considered serious.

13.4. Reporting Serious Adverse Events

All SAEs (related and unrelated) will be recorded after signing the informed consent through the last trial visit. Any SAEs considered possibly, probably, or definitely related to the investigational product and discovered by the Investigator at any time after the trial should be reported. All SAEs must be reported to Novartis Gene Therapies or designee within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by fax or e-mail to Novartis Gene Therapies or designee. Note: elective procedures or minor surgeries where hospitalization is required should not be reported as SAEs.

Additional follow-up information, if required or available, should all be faxed or e-mailed to Novartis Gene Therapies or designee within 24 hours of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or trial file.

Novartis Gene Therapies is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

13.5. Expedited Safety Reporting to Regulatory Authorities

All serious, unexpected, suspected adverse reactions (SUSARs) will be reported to regulatory authorities within the 15-day expedited timeline. Unexpected *fatal or life-threatening* suspected adverse reactions will be reported according to the 7-day timeline.

14. STATISTICS

This section summarizes key aspects of the analysis plan including definitions of primary, secondary, and exploratory efficacy endpoints and safety endpoints. Additional details regarding methods for the final data presentation will be provided in a separate Statistical Analysis Plan (SAP). The SAP will detail all data displays and will be executed according to Standard Operating Procedures in a controlled environment.

14.1. Study Endpoints

The following endpoints will not be analyzed formally but will be presented in data listings.

14.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is:

Proportion of symptomatic SMA Type 1 patients who are homozygous negative for *SMN1* exon 7 and have 2 copies of *SMN2* without the *SMN2* genetic modifier that achieve the ability to sit without support for at least 10 seconds at any visit up to and including the 18 months of age visit. It is defined by the WHO MGRS, confirmed by video recording, as a patient who sits up straight with head erect for at least 10 seconds; [redacted]

14.1.2. Secondary Efficacy Endpoint

The secondary efficacy endpoint is:

Survival at 14 months of age amongst symptomatic SMA Type 1 patients who are homozygous negative for *SMN1* exon 7 and have 2 copies of *SMN2* without the *SMN2* genetic modifier.

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

- An “acute reversible illness” is defined as any condition other than SMA that results in increased medical intervention (i.e., increased requirement for respiratory support; use of other concomitant medications as rescue) requirements and is expected to be reversible or improved following definitive intervention (i.e., surgery, antibiotics) or introduction of escalated supportive care, such as hospitalization (i.e., for upper respiratory infection, spontaneous fracture). The specific duration of the condition antecedent intervention shall not be considered in the definition of “acute.” The date of “definitive intervention” shall be defined as the date of provision of a procedure (i.e., surgery, etc.) or medication (i.e., antibiotics) intended to cure or substantially improve the condition. For conditions such as viral respiratory infections for which supportive care is provided, the date of “definitive intervention” shall be considered the date of hospitalization or substantial escalation of care.
- “Perioperative” use reflects any alteration of ventilatory use related to a surgical or other medical procedure of any nature for which the patient received medications that could impair or interfere with respiratory function.

- For a patient who develops an acute reversible illness and/or requires perioperative ventilatory support, a recovery period not to exceed 21 days following the date of definitive intervention will be instituted. Following this recovery period, the condition will be considered subacute and the patient will become evaluable with regards to the surrogate survival endpoint (requirement of ventilatory support of ≥ 16 hours/day for 14 or more days).

14.1.3. Exploratory Endpoints

[redacted]

[redacted]

14.1.4. Safety Endpoints

Assessment of the safety and tolerability of AVXS-101 treatment includes evaluation of AEs, laboratory data, vital signs, and concomitant medication.

14.2. Statistical Analysis Populations

14.2.1. Intent-to-Treat Population

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

14.2.2. Ability to Thrive ITT Population

The ability to thrive combined study ITT population will consist of symptomatic patients with biallelic deletion mutations of *SMN1,* 2 copies of *SMN2* without the genetic modifier (c.859G>C)*,* intact swallowing and receiving no enteral (mechanical) nutrition at baseline, who receive an IV infusion of AVXS-101 and have at least one post-baseline efficacy evaluation.

14.2.3. All Enrolled Population

The all enrolled population will consist of all patients who receive an IV infusion of AVXS-101.

14.2.4. Safety Population

The safety analysis population will consist of all patients who receive an IV infusion of AVXS-101.

14.3. Sample Size Calculation

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

14.4. Efficacy Analysis

14.4.1. General Considerations

This trial will assess the efficacy of AVXS-101 administered IV in terms of functional independent sitting and survival rate.

Unless otherwise specified, the baseline measurement is defined as the last non-missing measurement collected prior to or on the day of gene replacement therapy infusion (i.e., on or before Day 1 visit).

14.4.2. Primary and Secondary Efficacy Analysis

Primary and secondary efficacy endpoints will be presented in data listings where patients will be identified as to the analysis set(s) to which they belong. Endpoints defined as proportions will be presented as a dichotomous outcome for each patient.

14.5. Safety Analysis

Safety will be assessed through the incidence and severity of AEs, vital sign assessments, cardiac assessments, laboratory evaluations (chemistry, hematology, immunology, urinalysis), physical examinations, and use of concomitant medications. Adverse events will be coded in accordance with the most current version of the MedDRA coding dictionary. Safety assessment will be presented in data listings.

14.5.1. Hy's Law Criteria

In order to assess hepatotoxicity, all elevations in liver transaminases are evaluated using Hy's Law criteria as these help to determine the risk of drug-induced liver injury. All elevations in liver transaminases will be assessed against these criteria. Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo;
2. Among trial patients showing such aminotransferase (AT) elevations, often with ATs much greater than 3×ULN, one or more patients also shows elevation of serum total bilirubin (TBL) to ≥2×ULN, without initial findings of cholestasis (elevated serum ALP);
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, pre-existing or acute liver disease, or another drug capable of causing the observed injury [FDA (2009)].

15. DATA SAFETY MONITORING BOARD

The DSMB/DMC is an independent multidisciplinary group consisting of clinicians and a biostatistician that, collectively, have experience in the management of patients with SMA Type 1 and other diseases, and in the conduct and monitoring of randomized clinical studies with interim analyses. The DSMB/DMC will be chartered to oversee the safety of patients during the conduct of the trial and will act in an advisory capacity to Novartis Gene Therapies. A detailed description of the DSMB/DMC, its role in this trial, and the timing of the scheduled reviews will be described in a DSMB/DMC Charter.

The DSMB/DMC will routinely convene on a quarterly basis to review emerging safety data from the trial. Following each meeting, the DSMB/DMC will make a recommendation as to whether or not the accumulated safety data warrants a suspension or discontinuation of the trial, a modification to the trial, or any additional comments or recommendations related to safety. The DSMB/DMC will prepare and provide minutes of their meetings to Novartis Gene Therapies who will provide copies to the regulatory authorities as appropriate.

16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

16.1. Trial Monitoring

Before an investigational site can enter a patient into the trial, a representative of Novartis Gene Therapies will visit the investigational trial site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Novartis Gene Therapies or its representatives. This will be documented in a Clinical Trial Agreement between Novartis Gene Therapies and the Investigator.

During the trial, a monitor from Novartis Gene Therapies or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the trial. This will require direct access to all original records for each patient (e.g., clinic charts, electronic medical records)
- Record and report any protocol deviations not previously sent to Novartis Gene Therapies
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Novartis Gene Therapies and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

In the event of unforeseen catastrophe or other serious situation (such as the COVID-19 pandemic) that occurs during the study, which limits or prevents on-site visits, remote site monitoring visits may be conducted. This should not include remote source data verification (SDV), unless in exceptional circumstances, depending upon local regulations and prior informed consent having been obtained from participating patients.

16.2. Audits and Inspections

Authorized representatives of Novartis Gene Therapies, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Novartis Gene Therapies audit or inspection is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Council for Harmonization (ICH), and any applicable regulatory requirements. The Investigator should contact Novartis Gene Therapies immediately if contacted by a regulatory agency about an inspection.

16.3. Institutional Biosafety Committee

As this trial involves gene therapy, the Principal Investigator must obtain approval/favorable opinion for the investigation from a designated institutional or independent biosafety committee (IBC) in accordance with institutional requirements and/or guidelines.

16.4. Institutional Review Board/Independent Ethics Committee

The Principal Investigator must obtain IRB/IEC approval for the investigation (see Section 18.1). Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this trial including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

17. QUALITY CONTROL AND QUALITY ASSURANCE

Qualified individuals designated by the Sponsor will monitor all aspects of the study according to GCP, standard operating procedures (SOPs), and for compliance with applicable government regulations. Please see Section 16.1 for more details regarding the quality control and monitoring process. Novartis Gene Therapies may also conduct a quality assurance audit any time during or after the completion of the study. Please see Section 16.2 for more details regarding the audit process.

The Investigator agrees to allow these Sponsor representatives direct access to the clinical data and supplies, dispensing and storage areas and if requested, agrees to cooperate fully or assist the Sponsor representative. The Investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by the Sponsor or its designees.

Noncompliance with the protocol, ICH, GCP, or local regulatory requirements by an Investigator, site staff, or representatives of the Sponsor will lead to prompt action by the Sponsor to secure compliance. Continued noncompliance may result in termination of the corresponding party's involvement in the study. The IRB/IEC and relevant regulatory authority will also be informed.

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Novartis Gene Therapies may conduct a quality assurance audit. Please see Section 16.2 for more details regarding the audit process.

18. ETHICS

18.1. Ethics Review

The final trial protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval to Novartis Gene Therapies before he or she can enroll any patient into the trial.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the trial. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other trial conducted with the investigational product. Novartis Gene Therapies or designee will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this trial including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

18.2. Ethical Conduct of the Trial

The trial will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Appendix 7) and are consistent with ICH/GCP, applicable regulatory requirements.

18.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the parent(s)/legal guardian(s) are given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the trial. The parent(s)/legal guardian(s) must also be notified that they are free to discontinue the patient from the trial at any time. The parent(s)/legal guardian(s) should be given the opportunity to ask questions and allowed time to consider the information provided.

The signed and dated informed consent must be obtained before conducting any trial procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the parent(s)/legal guardian(s).

There will be 3 informed consent forms:

- Parent(s)/legal guardian(s) informed consent form
- Biological mother baseline AAV9 antibody screening informed consent form
- Autopsy informed consent form (see Appendix 2; if the parent(s)/legal guardian(s) decline an autopsy, it will not prevent the patient from participating in the trial)

In the event of unforeseen catastrophe or other serious situation (such as the COVID-19 pandemic) that occurs during the study, the ability to obtain a standard written informed consent may be challenged due to limits that prevent an on-site visit. In this situation, the Investigator may conduct the informed consent discussion remotely (e.g., telephone, videoconference). Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate informed consent forms (ICFs) by trial participant and person obtaining informed consent; a video or other recording of the consent process and affirmation of consent may be considered to supplement the documentation of obtaining consent, if allowable by local regulations etc.).

19. DATA HANDLING AND RECORDKEEPING

19.1. Electronic Case Report Forms

Adequate and accurate case records will be maintained, and all relevant observations and data related to the trial will be recorded. This will include medical history/ physical examination, hematology, clinical chemistry and serology results, a check list of inclusion and exclusion criteria, product administration, and a record of sample collection, hemodynamic measurements, clinical assessments, AEs, and final evaluation.

Electronic CRFs will be used in this trial. The eCRF will be electronically signed and dated by the Principal Investigator or his designee after his/her review. After the completion of the trial, completed eCRFs will be retained in the archives.

Completed eCRFs will be reviewed by the trial monitor against the source documentation for accuracy and completeness. Once signed by the Investigator, the monitor will transmit the completed eCRFs to data management for data validation and database analysis.

19.2. Inspection of Records

Novartis Gene Therapies or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the trial. The Investigator agrees to allow the monitor to inspect the product storage area, trial product stocks, product accountability records, patient charts and trial source documents, and other records relative to trial conduct.

19.3. Retention of Records

All primary data that are a result of the original observations and activities of the trial and that are necessary for the reconstruction and evaluation of any trial report will be retained in a secure archive at the trial site for a period not less than 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have lapsed since the formal discontinuation of the clinical development of the investigational product. All country/region specific requirements that may be more stringent than the 2 years included in ICH shall be followed.

The site will maintain essential documents as required by ICH-GCP. The site must keep these documents available for review by the Sponsor, IRB/IEC, and/or regulatory bodies.

20. PUBLICATION POLICY

The Investigator is obliged to provide the Sponsor with complete test results and all data derived by the Investigator from the trial. During the trial, only the Sponsor may make trial information available to other trial Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical trial site agreement, any public disclosure (including publicly accessible websites) related to the protocol or trial results, other than trial recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the trial (including data and information generated by the Investigator) without the consent of the Investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Trial Site Agreement. In the event of any discrepancy between the protocol and the Clinical Trial Site Agreement, the Clinical Trial Site Agreement will prevail.

If the trial is being conducted as part of a multicenter clinical trial, data from all sites participating in the trial will be pooled and analyzed by the Sponsor or the Sponsor's designee. The first publication of the trial results shall be made in conjunction with the results from other trial sites as a multicenter publication. If a multicenter publication is not forthcoming within 24 months of completion of the trial at all sites, the Investigator may publish or present the results generated at his or her site.

The Investigator will provide the Sponsor with a copy of any proposed publication or presentation for review and comment at least 60 days prior to such presentation or submission for publication. The Sponsor shall inform the Investigator in writing of any changes or deletions in such presentation or publication required to protect the Sponsor's confidential and proprietary technical information and to address inaccurate data or inappropriate interpretations in the context of any pooled multicenter results. At the expiration of such 60-day period, the Investigator may proceed with the presentation or submission for publication unless the Sponsor has notified the institution or the Investigator in writing that such proposed publication or presentation discloses the Sponsor's confidential and proprietary technical information. Further, upon the request of the Sponsor, the Investigator will delay the publication or presentation for an additional 90 days to permit the Sponsor to take necessary actions to protect its intellectual property interests.

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22. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Trial Period	Screening	Gene Replacement Therapy (In-patient)				Follow-up (Outpatient)										Notes
Nominal Study Day (Visit Relative To Dose)	**–30 to –2**	**-1**	**1**	**2**	**3**	**7**	**14**	**21**	**30**	**44**	**60 (or Month 2)**	**72**	**90 (or Month 3**	**Month 4,5,7,8,10,11,13**	**Month 6,9,12**	**End of Trial (18 months of age or ET)**	Depending on the patient's age at dosing, the duration of participation can vary from approximately 12 months (baby dosed at approximately 6 months of age) to approximately 18 months (baby dosed near birth, "0 months of age").
Visit According To Months of Age														**14,16,17**	**15**		
Window	(No Window)					**± 2 days**					**± 7 days (Except +0–14 days at 14 Months of Age)**					**+0–14 days**	
Informed Consent	X																See Section 18.3
AVXS-101 Infusion			X														See Section 10.6. Day 1 assessments will be performed prior to the start of gene replacement therapy infusion.
BSIDv03/WHO Developmental Milestones (with video)	X								X		X		X	X	X	X	See Sections 11.1, 11.2.1, 11.2.2, and 11.3.
BSIDv03 Gross and Fine Motor Subtests (with video)	X								X		X		X	X	X	X	See Sections 11.1, 11.2.1, 11.2.2 and 11.3.
CHOP INTEND (with video)	X	X				X	X	X	X		X		X	X	X	X	See Sections 11.2.3 and 11.3. Patients who achieve 3 consecutive CHOP-INTEND scores ≥ 58 will not continue CHOP-INTEND assessments.
Demographic/Medical History	X																See Section 12.1.1.
Physical Exam	X		X	X	X	X	X	X	X		X		X	X	X	X	See Section 12.1.2
Vital Signs/Weight & Length	X	X	(X)	X	X	X	X	X	X		X		X	X	X	X	See Section 12.1.3. (X): Vital signs will be continuously monitored throughout the infusion of gene replacement therapy and recorded every 15 minutes (+/- 5 minutes) post dose for the first 4 hours after the start of infusion, then every hour (+/- 15 minutes) until 24 hours after the start of infusion. Axillary

Trial Period	Screen-ing	Gene Replacement Therapy (In-patient)				Follow-up (Outpatient)											Notes
Nominal Study Day (Visit Relative To Dose)	**–30 to –2**	**-1**	**1**	**2**	**3**	**7**	**14**	**21**	**30**	**44**	**60 (or Month 2)**	**72**	**90 (or Month 3**	**Month 4,5,7,8,10,11,13**	**Month 6,9,12**	**End of Trial (18 months of age or ET)**	Depending on the patient's age at dosing, the duration of participation can vary from approximately 12 months (baby dosed at approximately 6 months of age) to approximately 18 months (baby dosed near birth, "0 months of age").
Visit According To Months of Age														**14,16,17**	**15**		
Window	(No Window)					**± 2 days**					**± 7 days (Except +0–14 days at 14 Months of Age)**					**+0–14 days**	
																	temperature will be recorded pre- and post-infusion.
12-Lead ECG	X			X					X				(X)	(X)	(X)	X	See Sections 12.1.4, 12.1.5, and 12.1.6.
Echocardiogram	X								X				(X)	(X)	(X)	X	(X): Completed every 3 months, starting at Month 3 until 12 months post-dose.
24-hour Holter Monitor	X	X	X	X	X				X		X		(X)	(X)	(X)	X	
Pulmonary Examination	X	X		X	X	X	X	X	X		X		X	X	X	X	See Section 12.1.7.
Swallowing Test	X														(X)	(X)	See Section 12.1.8. (X): Completed every 6 months, starting at Month 6 through the End of Trial at 18 months of age.
Photograph of Infusion Site			(X)	X	X	X	X	X	X								See Section 12.1.9. (X): Day 1 infusion site photograph will be performed prior to the start of gene replacement therapy infusion.
Hematology/Chemistry /Urinalysis	X	X		X		X	X	X	X	(X)*	X	(X)*	X	X	X	X	See Sections 12.1.10.1, 12.1.10.2 and 12.1.10.3. (X)*: Liver function test (AST, ALT, total bilirubin, direct bilirubin, alkaline phosphatase, GGT) only.
Troponin I	X					X			X		X				X	X	See Section 12.1.10.2.
Virus Serology	X																See Section 12.1.10.4.
Capillary Blood Gas		X		X													See Section 12.1.10.5.
Immunological Testing: ELISA (anti-AAV9/SMN Ab)	X					X	X	X	X								See Section 12.1.10.6.
AAV9 Ab Screen in Biological Mother	X																See Section 12.1.10.7.

Trial Period	Screen-ing	Gene Replacement Therapy (In-patient)				Follow-up (Outpatient)											Notes
Nominal Study Day (Visit Relative To Dose)	**–30 to –2**	**-1**	**1**	**2**	**3**	**7**	**14**	**21**	**30**	**44**	**60 (or Month 2)**	**72**	**90 (or Month 3**	**Month 4,5,7,8,10,11,13**	**Month 6,9,12**	**End of Trial (18 months of age or ET)**	Depending on the patient's age at dosing, the duration of participation can vary from approximately 12 months (baby dosed at approximately 6 months of age) to approximately 18 months (baby dosed near birth, "0 months of age").
Visit According To Months of Age														**14,16,17**	**15**		
Window	(No Window)					**± 2 days**					**± 7 days (Except +0–14 days at 14 Months of Age)**					**+0–14 days**	
Blood for Diagnostic Confirmation Testing	X																See Section 12.1.10.8.
Saliva, Urine, and Stool Samples (for viral shedding)	X			(X)	(X)	X	X	X	X								See Section 12.1.10.9. (X): Collected within 24 and 48 hours post dose.
Prophylactic Prednisolone		X	X	X	X	X	X	X	X	(X)	(X)						See Section 9.2.1. (X): After 30 days, prednisolone (or equivalent glucocorticoid) can be tapered for patients whose GGT, ALT, and AST values are below the threshold.
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 13.
Prior and Concomitant Medications	Collected from 2 weeks before gene replacement therapy until End of Trial visit																

Ab = antibody; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSIDv03 = Bayley Scales of Infant and Toddler Development version 3; CBC = complete blood count; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; ET = early termination; GGT = gamma glutamyl transferase; IRB = Institutional Review Board; LFT = liver function tests; WHO = World Health Organization

APPENDIX 2. POST-MORTEM TISSUE AND ORGAN COLLECTION PLAN

Post-mortem tissue/organ collection and autopsy, where possible, will be requested for any patient who receives gene replacement therapy. The autopsy and tissue collection will be performed by the clinical site local pathologist or a contracted vendor who may deploy a pathology assistant to the funeral home, hospital, or other applicable location to perform the tissue and organ collection. Standard autopsy incisions will be used to perform the procedures.

During the procedure, multiple tissues along with the entire spinal cord will be collected for research purposes, including up to 7 sections or pieces from each organ and each region of the spinal cord. Upon collection, these tissue samples will be provided to Novartis Gene Therapies for analysis.

Tissue analysis will be done to determine whether the vector transduced the expected motor neurons and if the SMN gene was expressed. These results will demonstrate whether the vector delivered the therapeutic gene as expected. Tissue samples collected will also be available for histology and immunohistochemistry, allowing the state of the motor neurons and muscles to be examined.

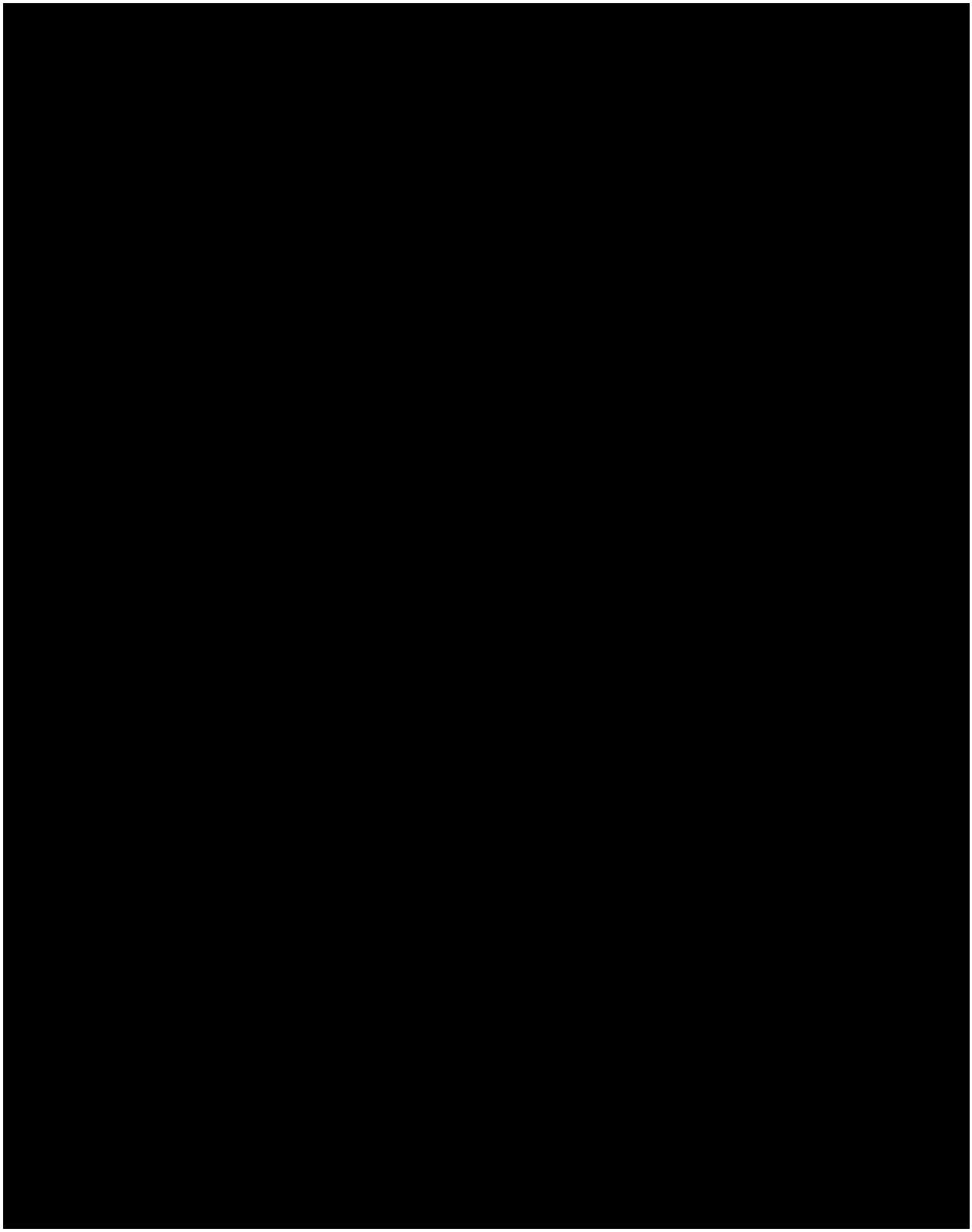
Specifically, tissue samples from the spinal cord, muscles, and organs will be collected as indicated in Table 5. Tissue samples will be frozen or fixed (e.g., 2% paraformaldehyde) for appropriate analysis.

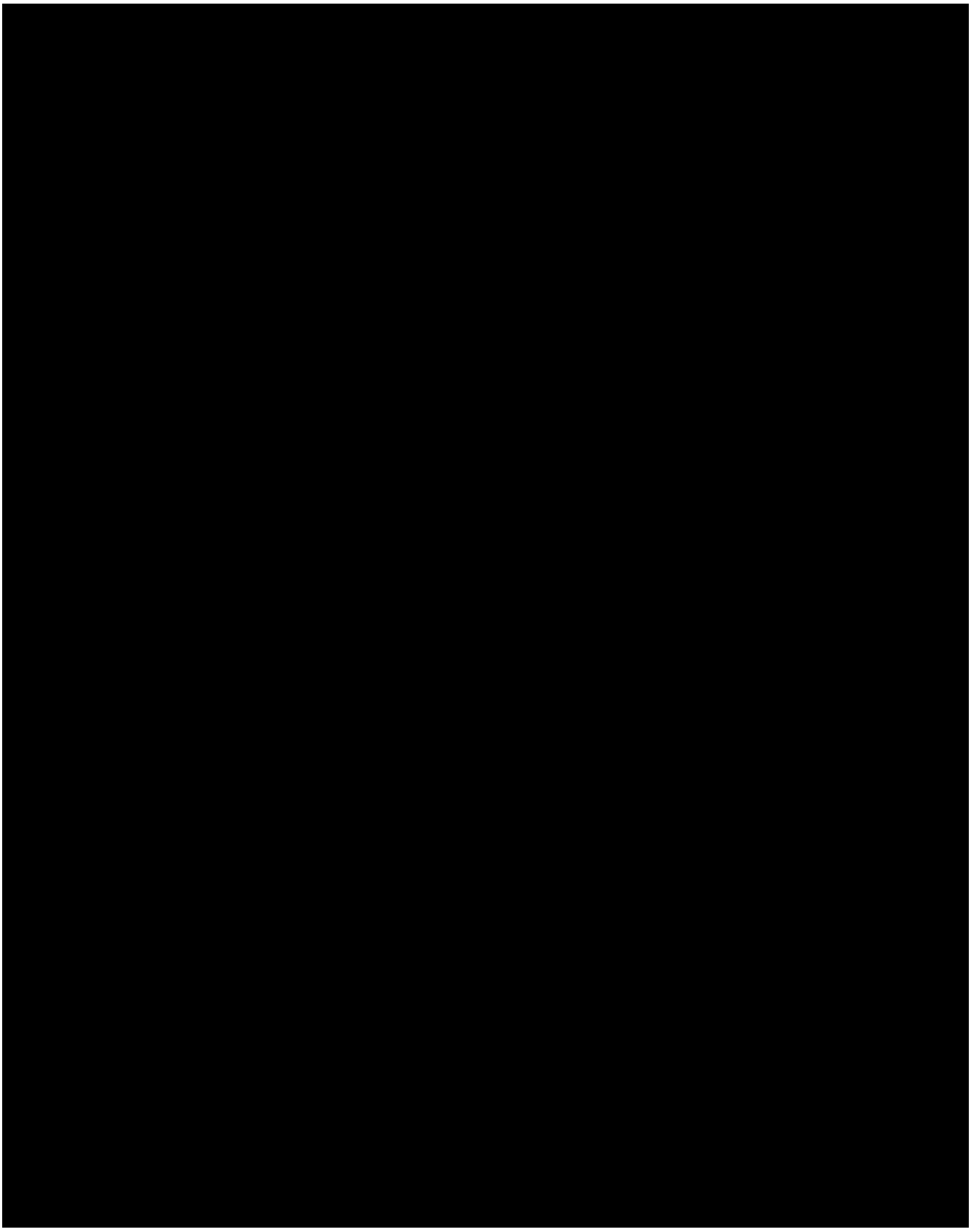
Families may be asked to consent to authorize tissue collection prior to any sign of moribund or death by the clinical team conducting the trial. Declining the post-mortem tissue and organ collection will not prevent patients from participating in the trial.

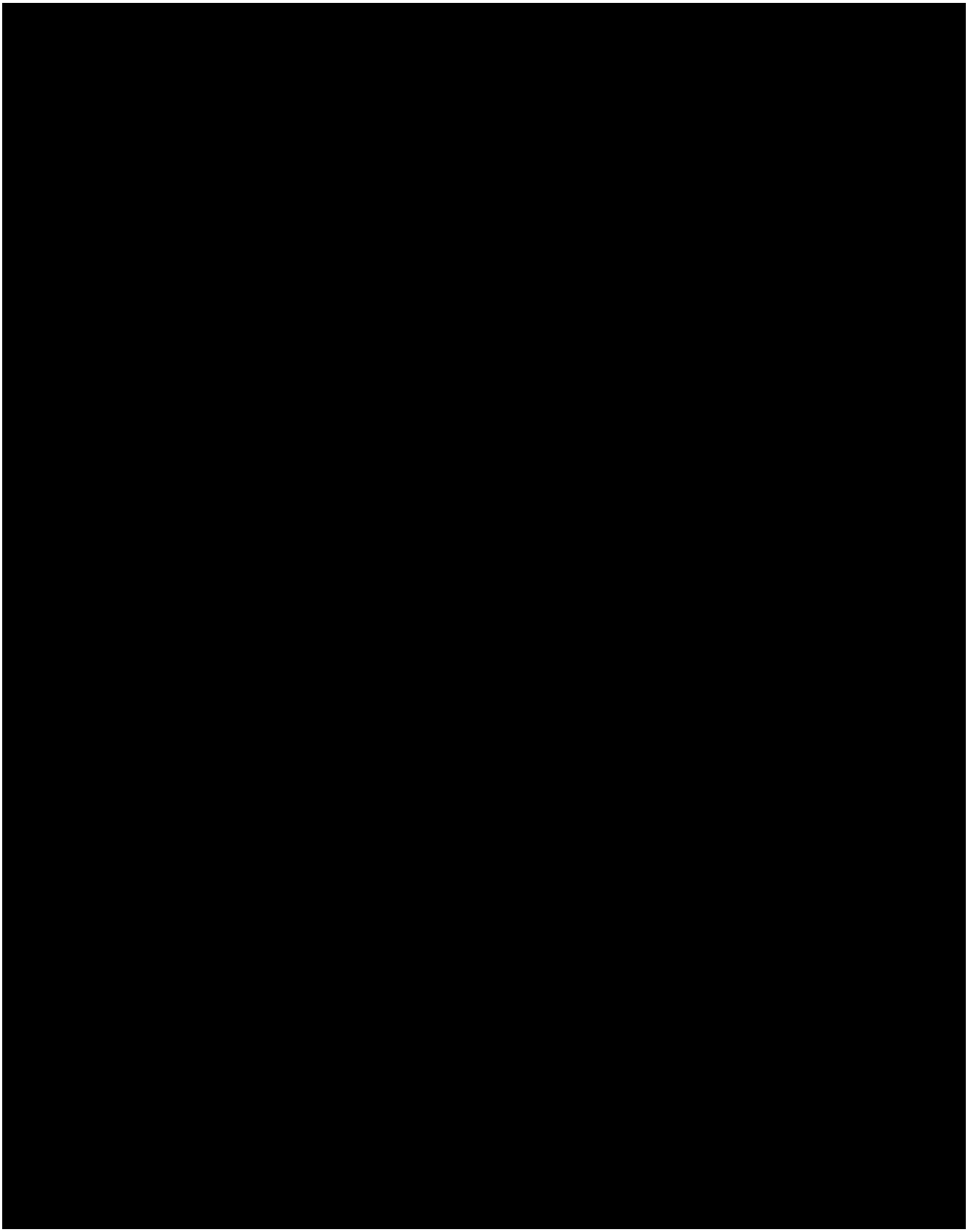
Table 5 - Tissue Sample for Analysis

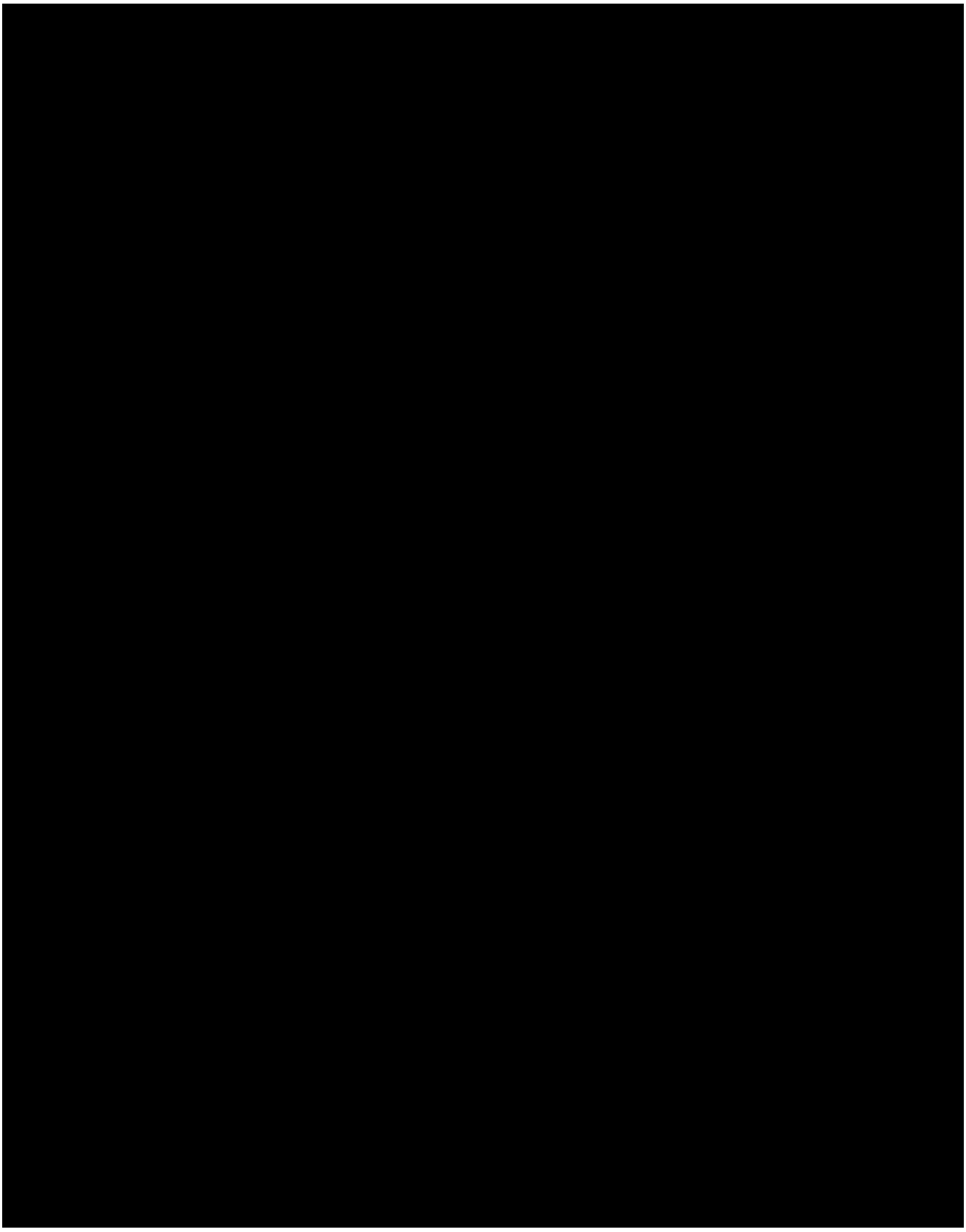
Brain	Spinal Cord	Muscles	Organs
Motor cortex	Cervical spinal cord	Diaphragm	Spleen
Layer 5 motor cortex	Thoracic spinal cord	#6/#7 Rib with intercostal muscle and nerve	Kidney
Brain stem	Lumbar spinal cord	Psoas muscle	Small intestine
	Sacral spinal cord		Large intestine
	Dorsal root		Pancreas
	Cervical level		Stomach
	Ventral root		Lung
	Cervical level		Heart
	DRG root		Liver
	Cervical level		Inguinal lymph node
	Cerebrospinal fluid		Gonads

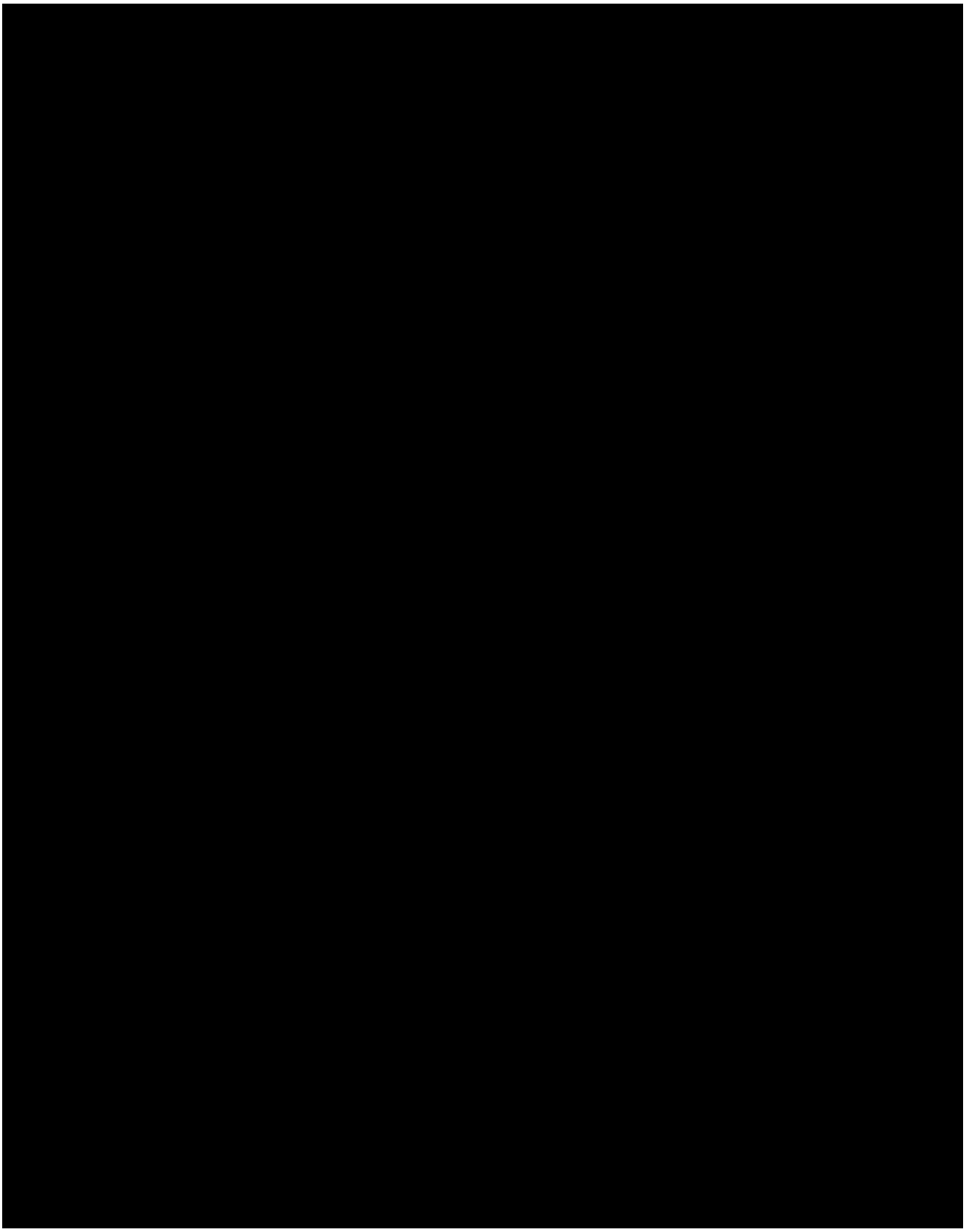
APPENDIX 3. BAYLEY SCALES OF INFANT AND TODDLER DEVELOPMENT (VERSION 3)

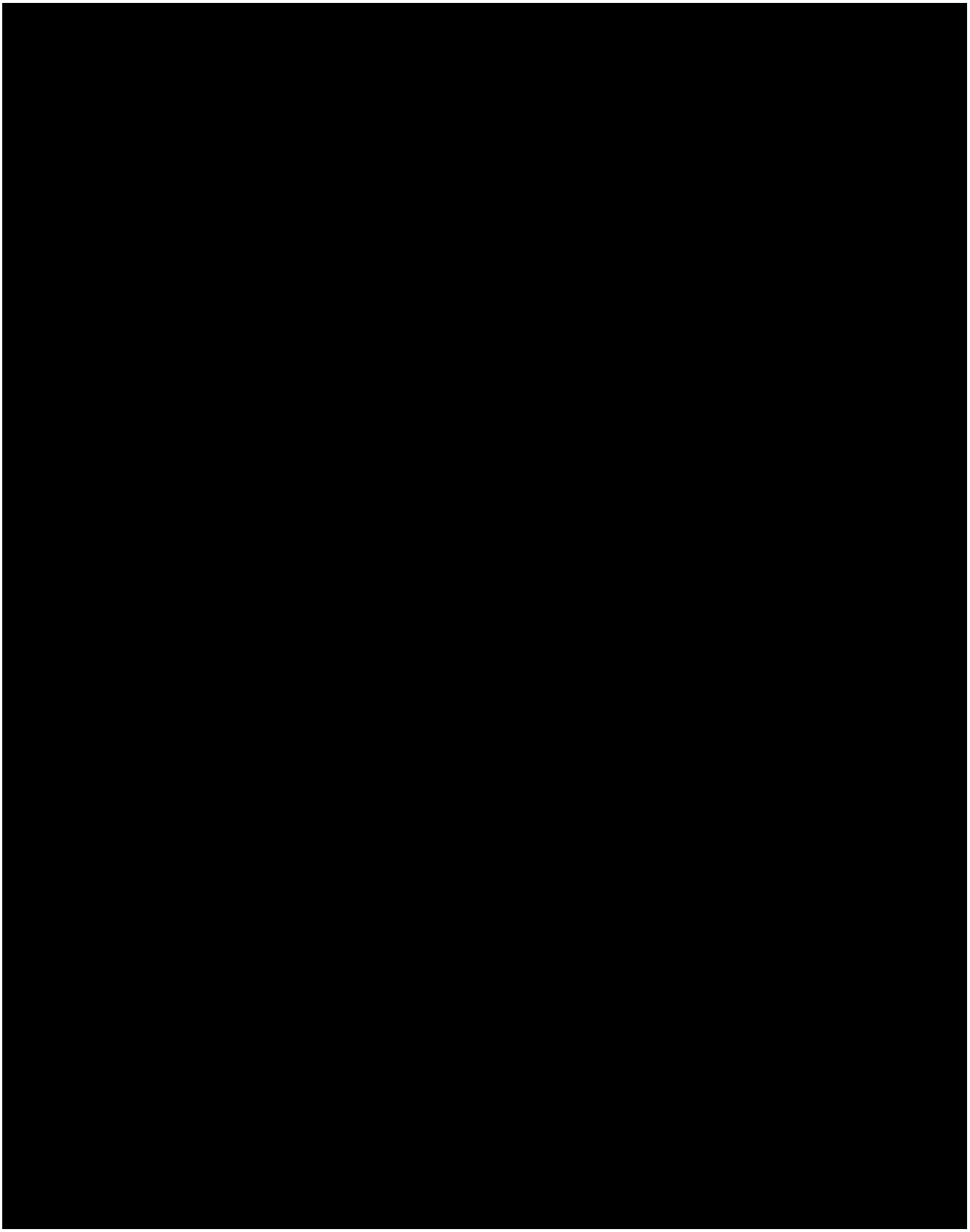


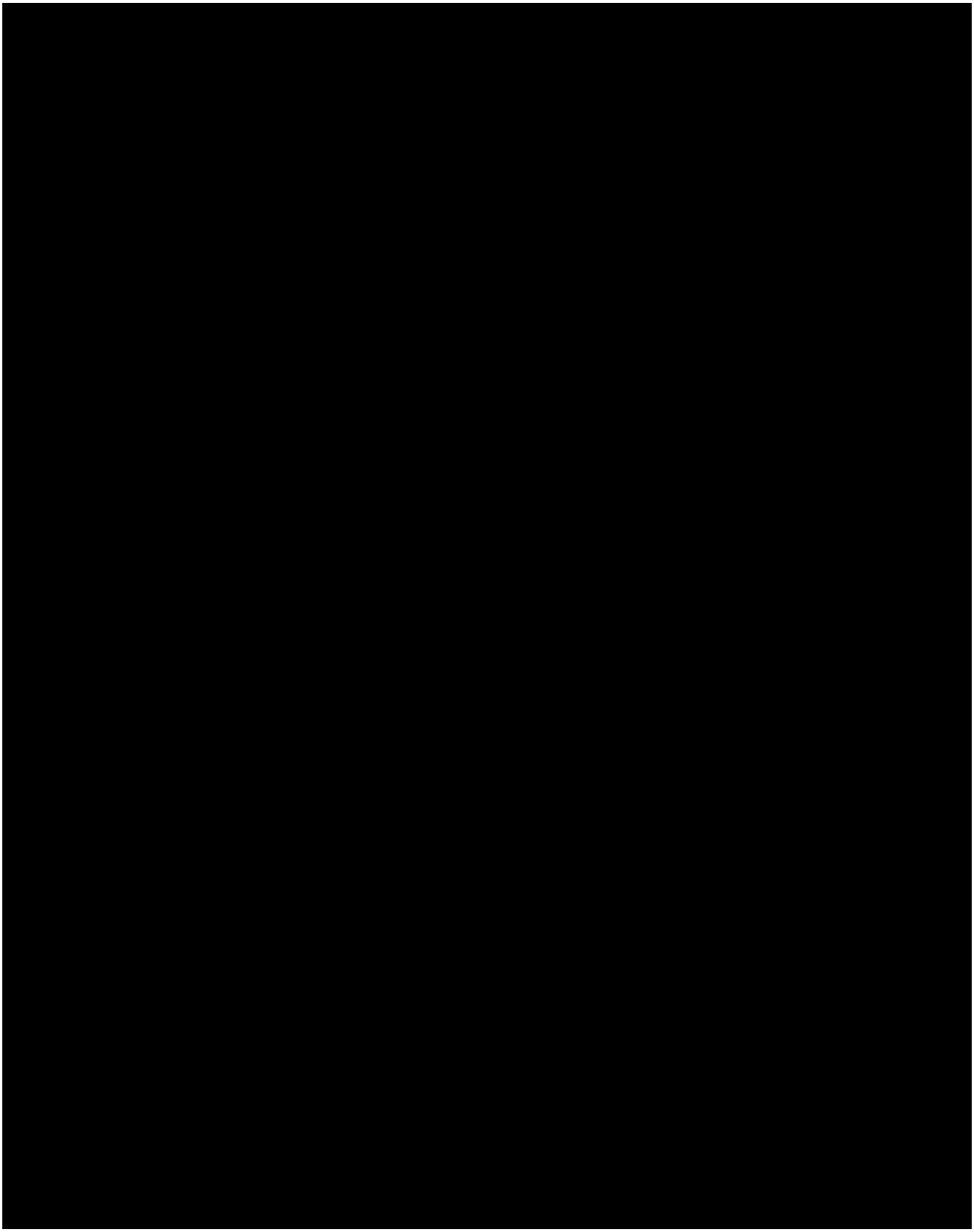


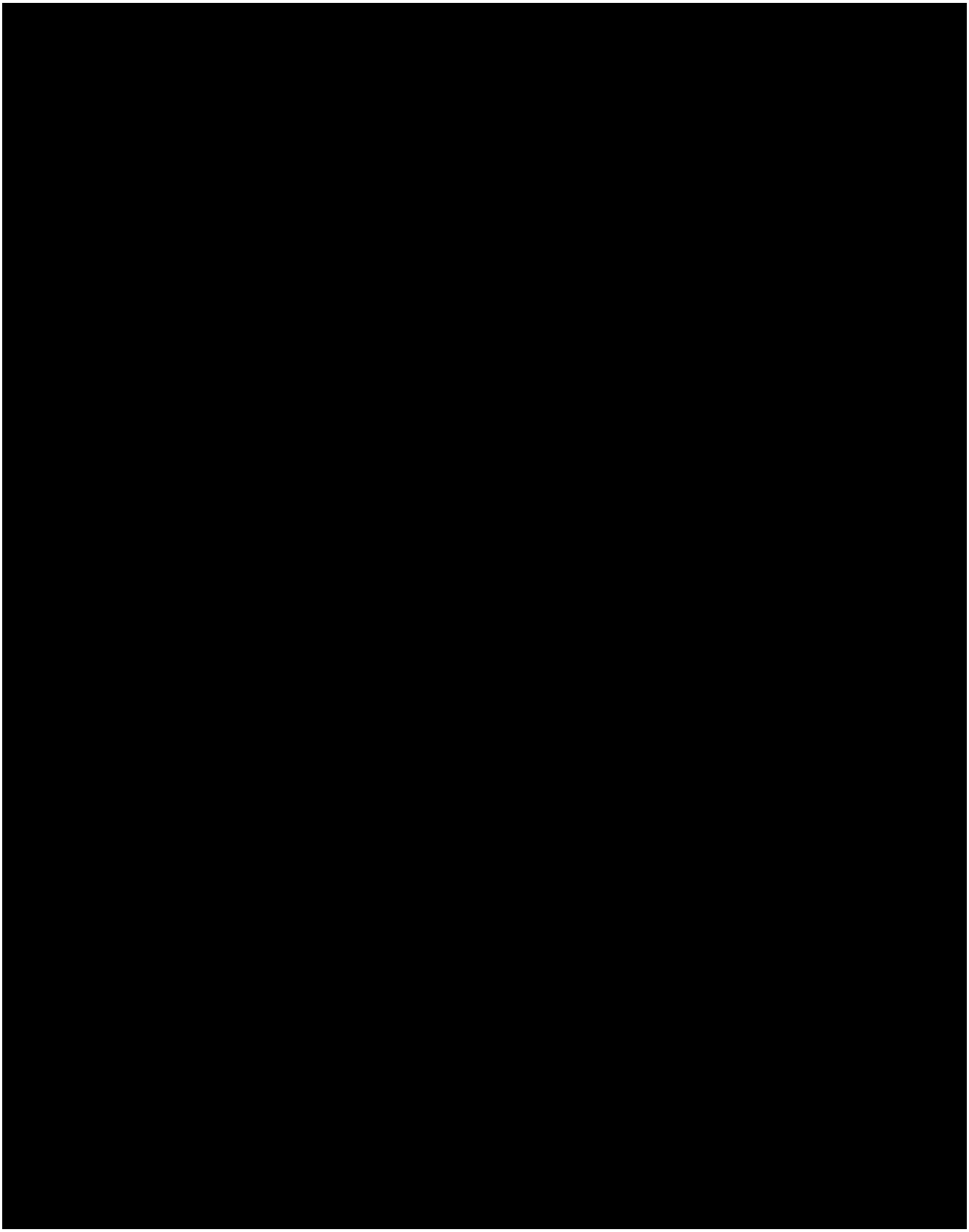


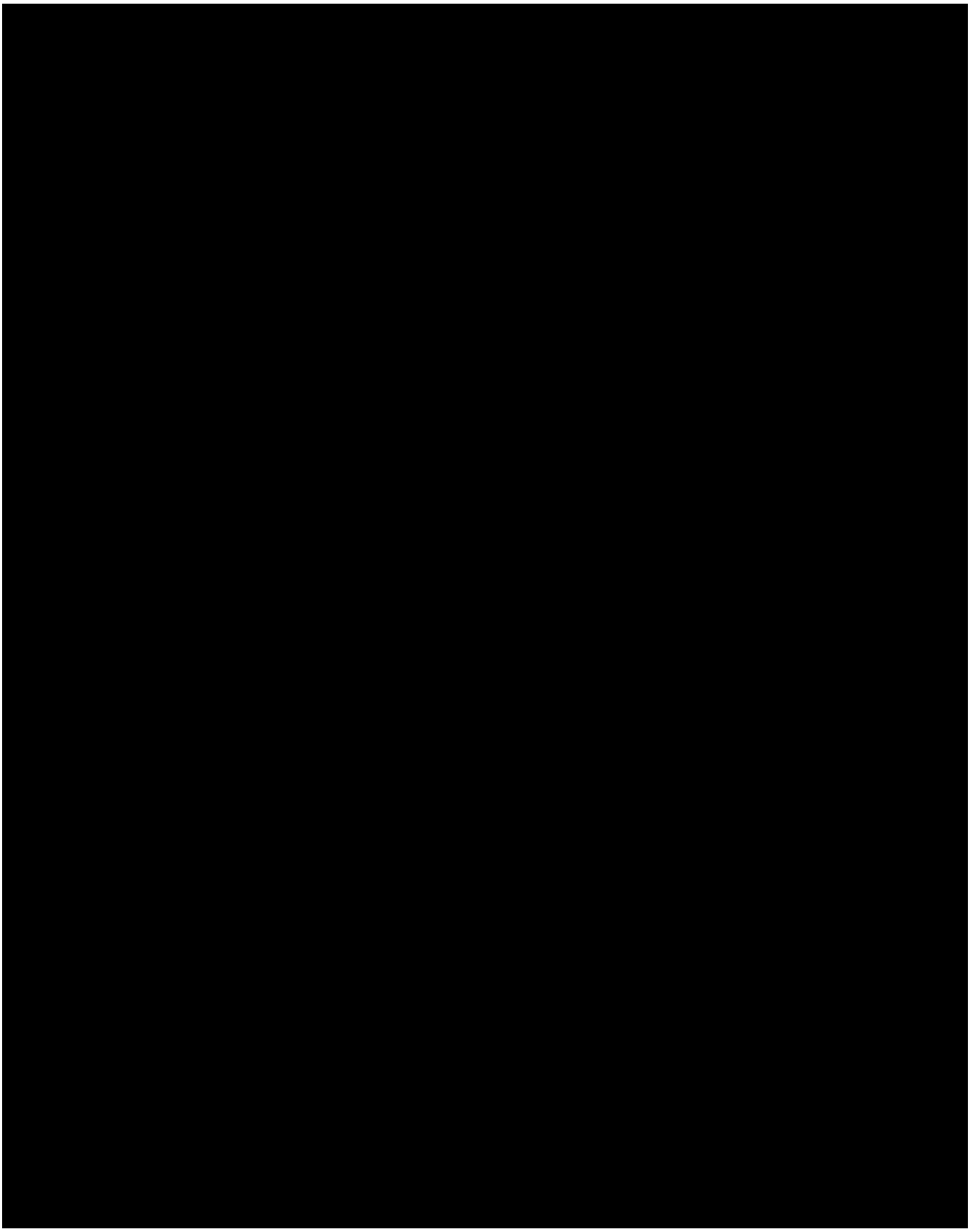


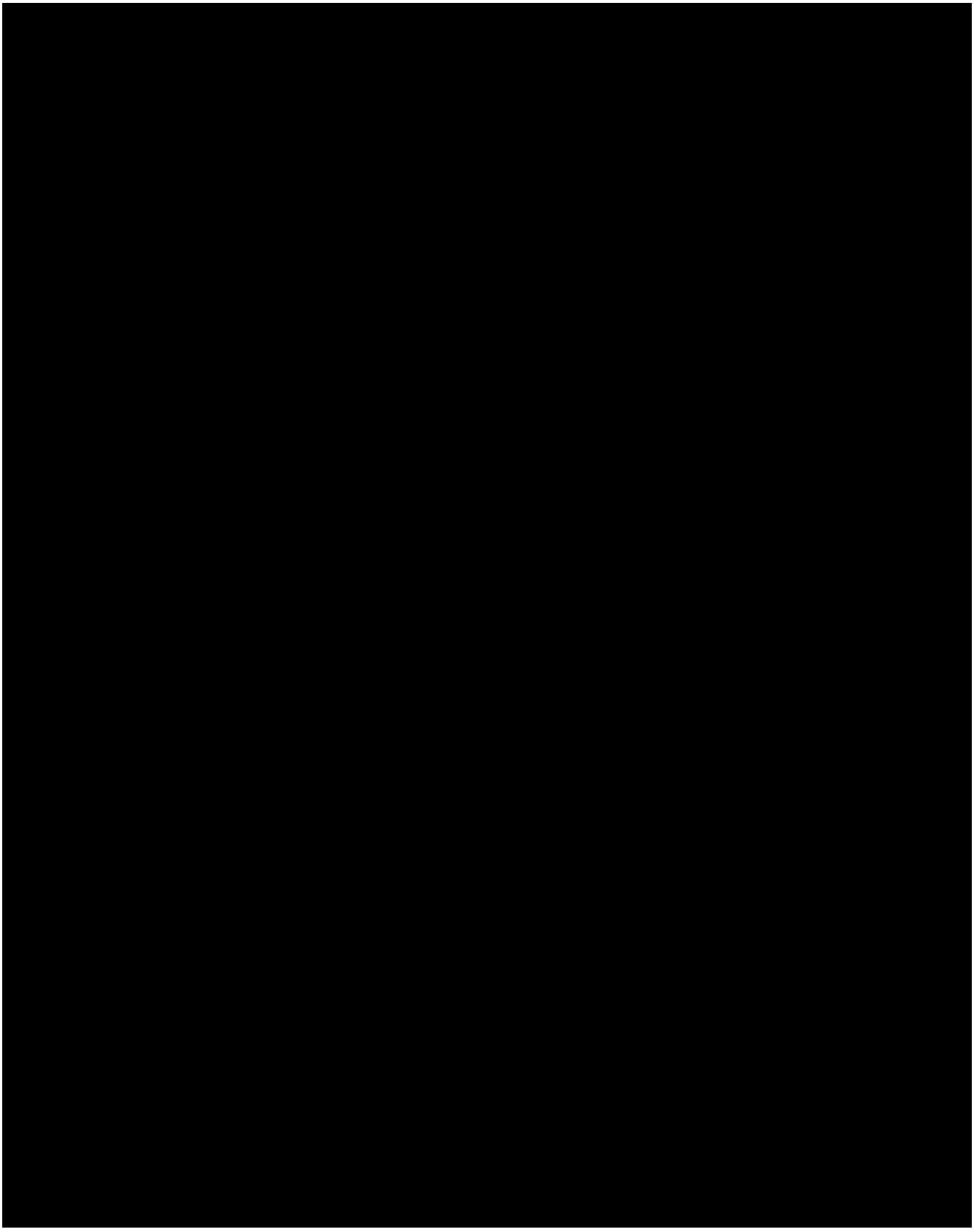


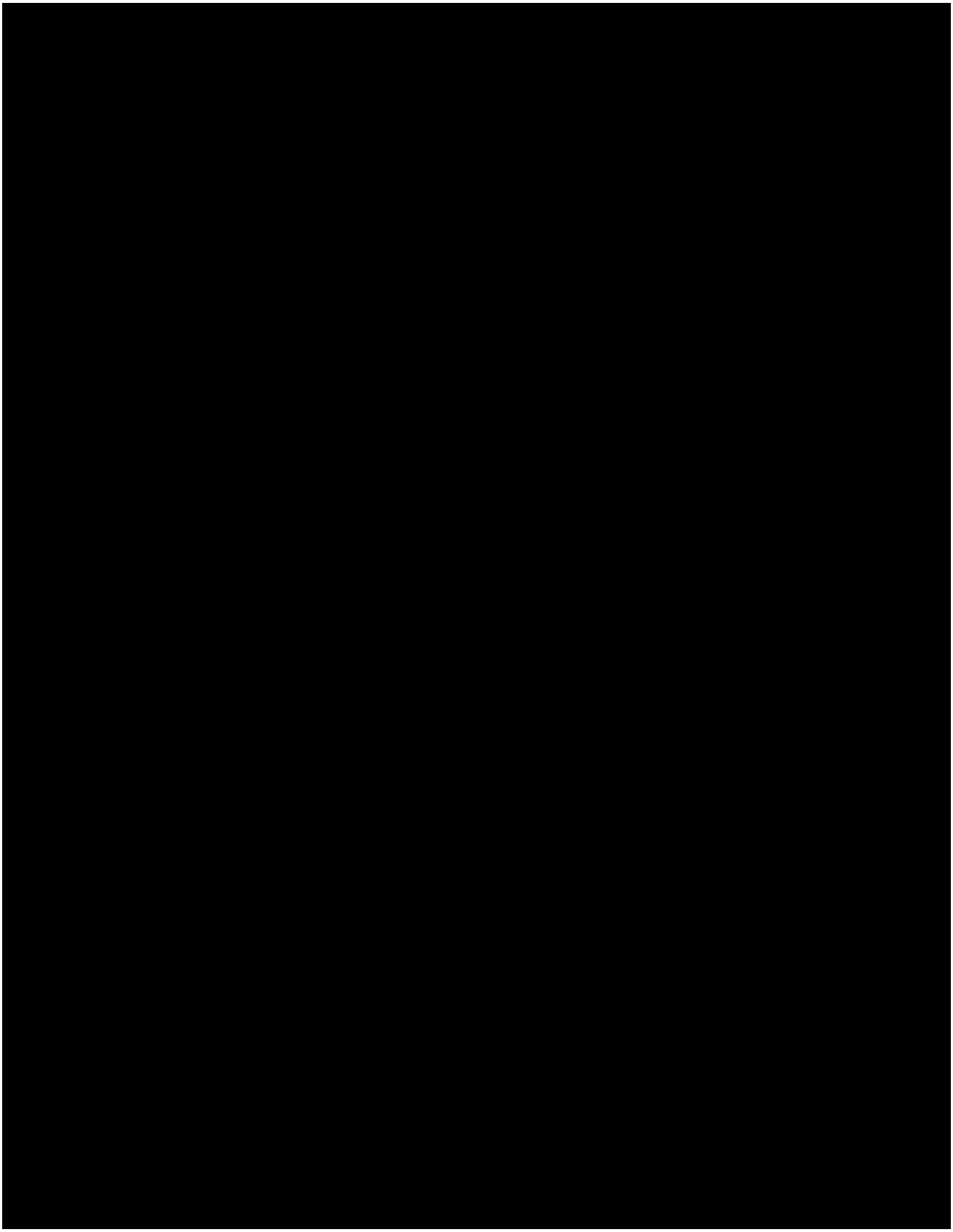


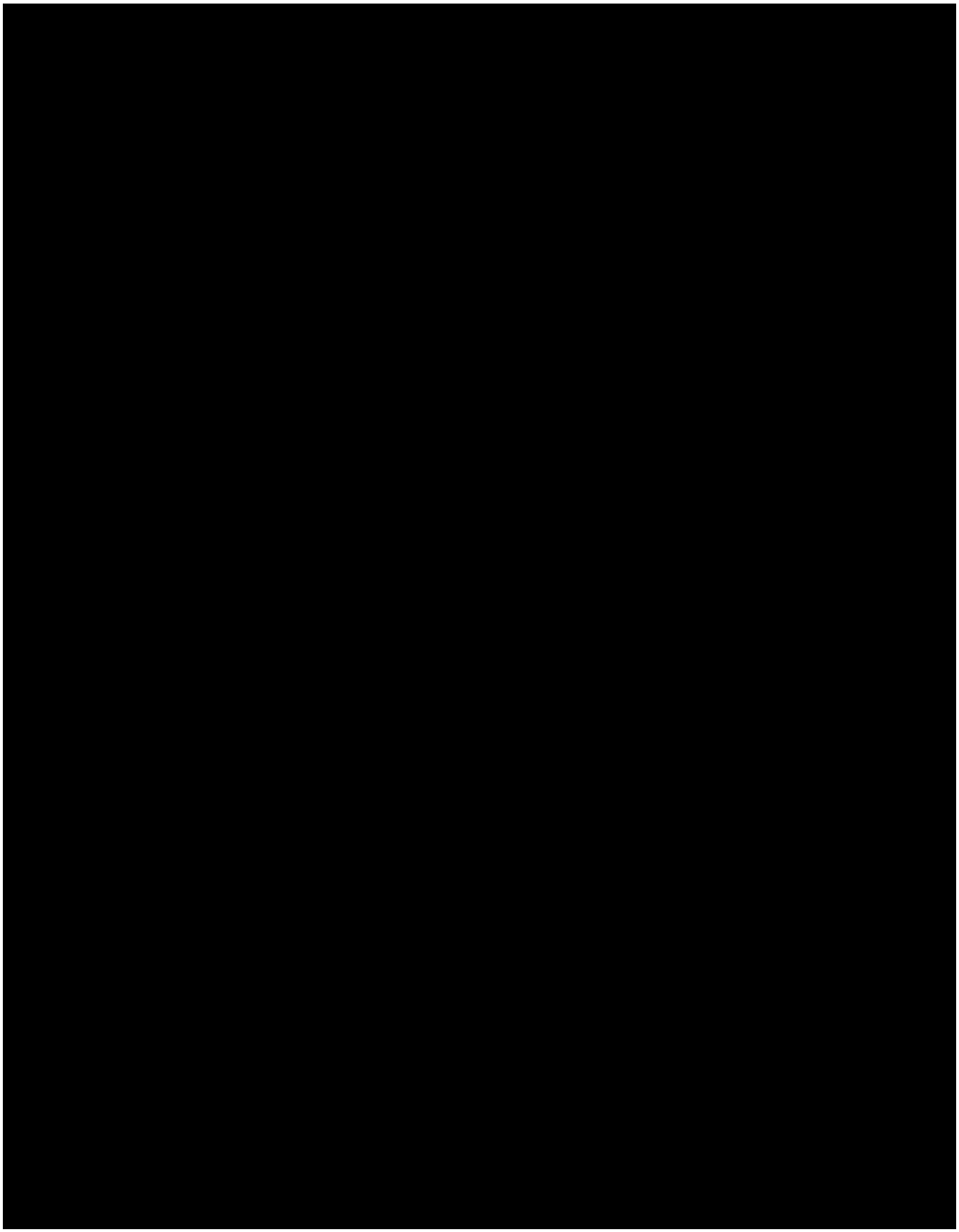


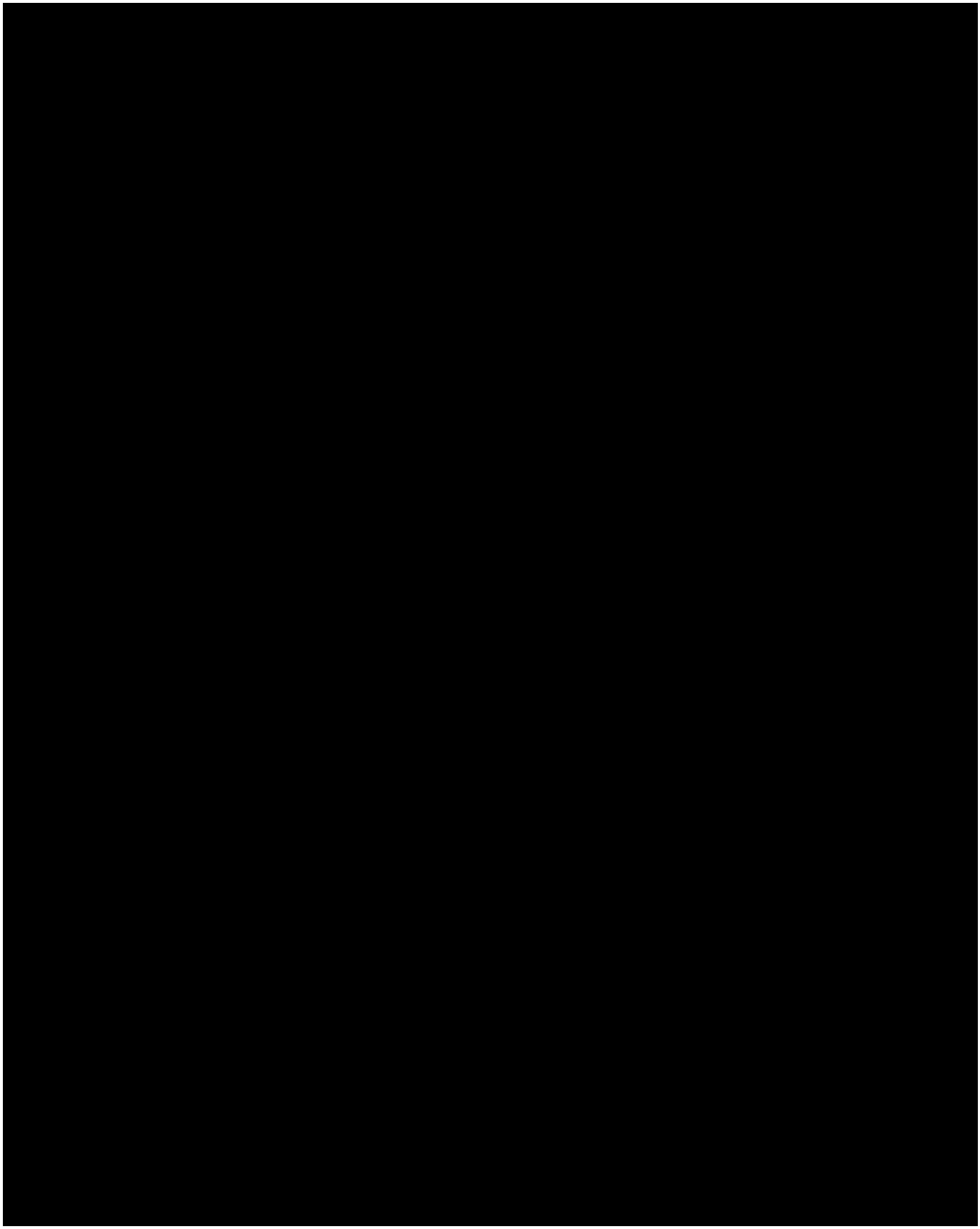


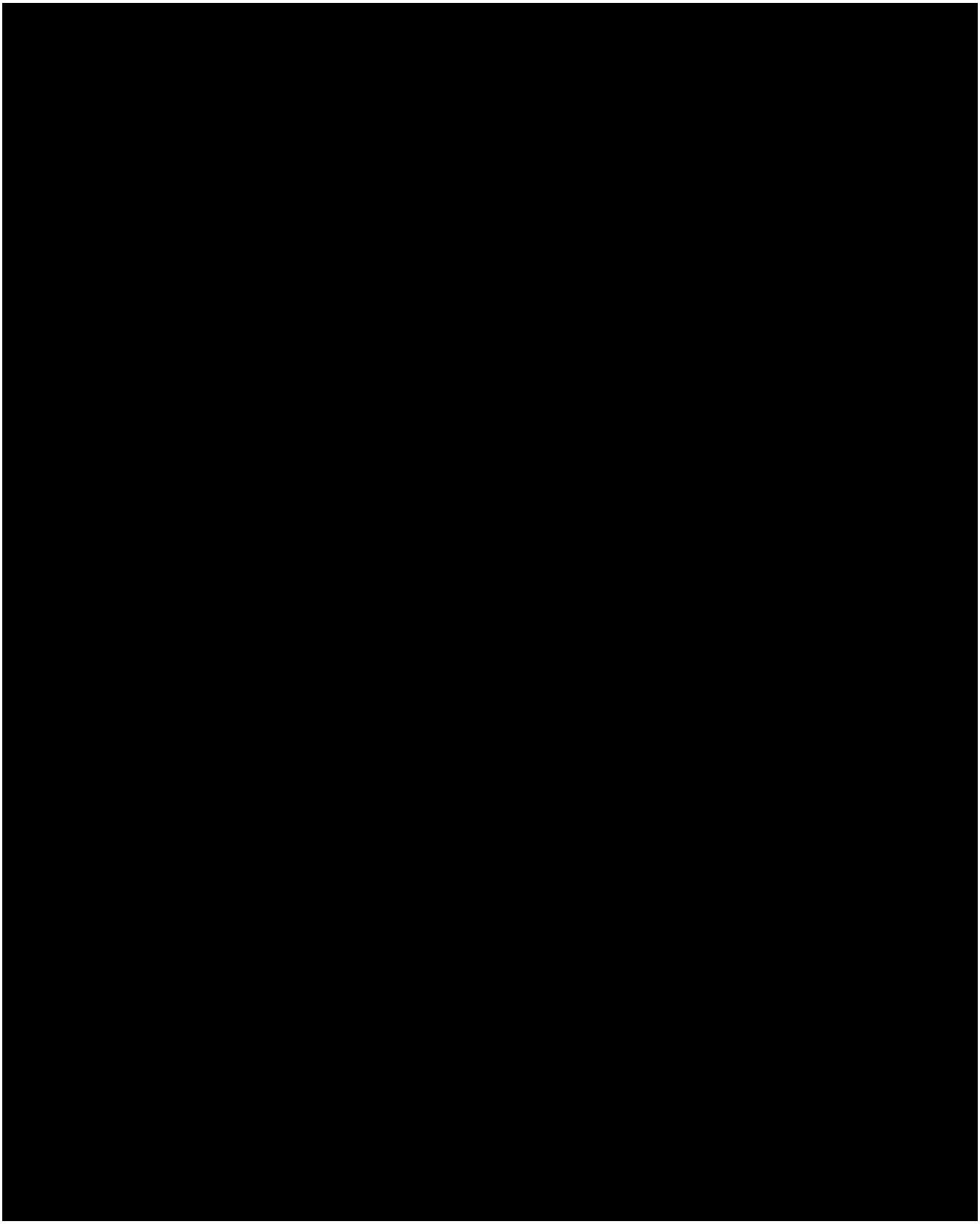


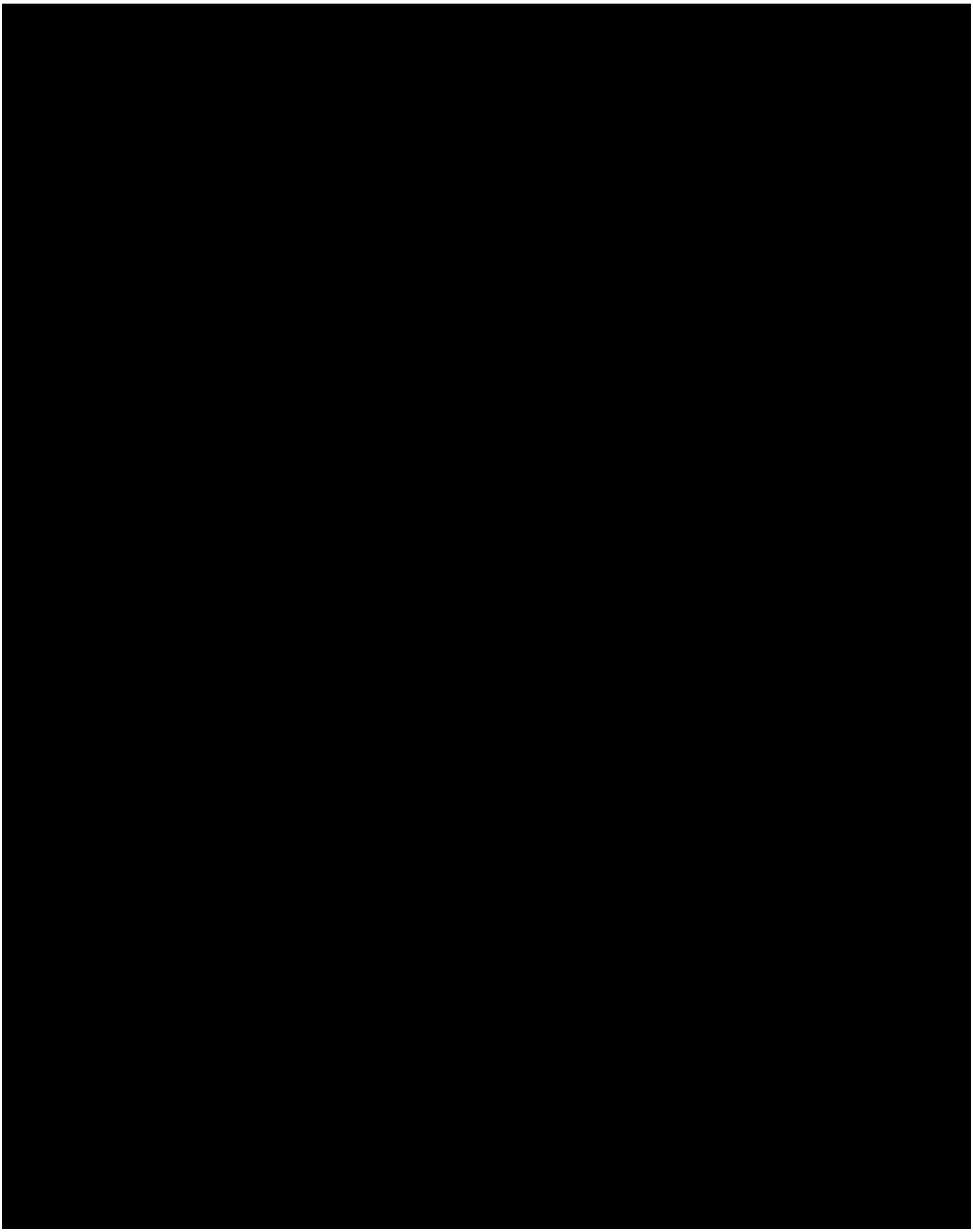


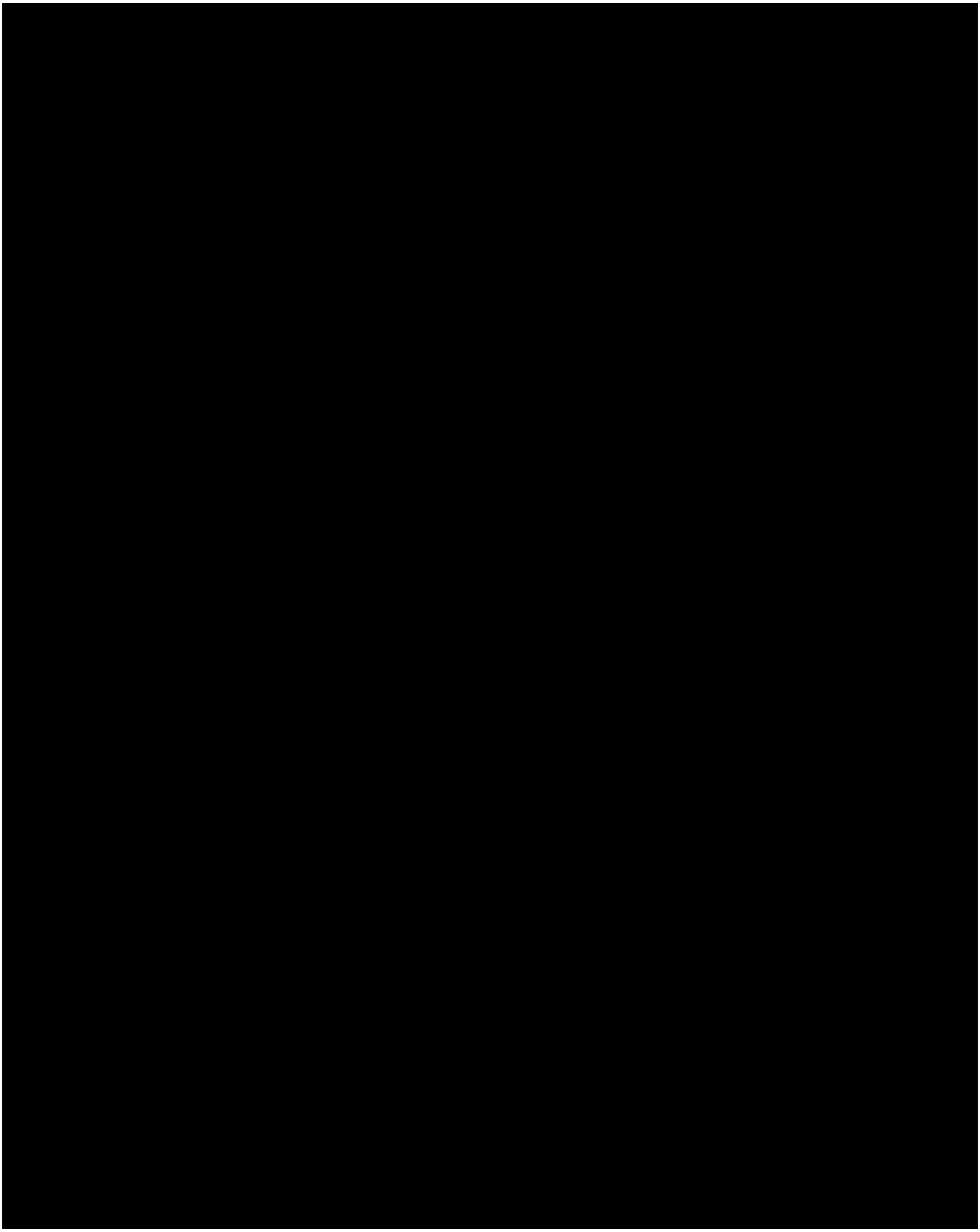












APPENDIX 4. PERFORMANCE CRITERIA FOR BAYLEY SCALES INFANT AND TODDLER DEVELOPMENT (VERSION 3) DEVELOPMENTAL MILESTONES

Developmental Milestone	Performance Criteria
Head Control – Gross Motor Subtest Item #4	[redacted]
Rolls from Back to Sides – Gross Motor Subtest Item #20	
Sits Without Support – Gross Motor Subtest Item #26	
Stands With Assistance - Gross Motor Subtest Item #33	
Crawls – Gross Motor Subtest Item #34	
Pulls to Stand – Gross Motor Subtest Item #35	
Walks With Assistance – Gross Motor Subtest Item #37	
Stands Alone – Gross Motor Subtest Item #40	
Walks Alone – Gross Motor Subtest Item #42	

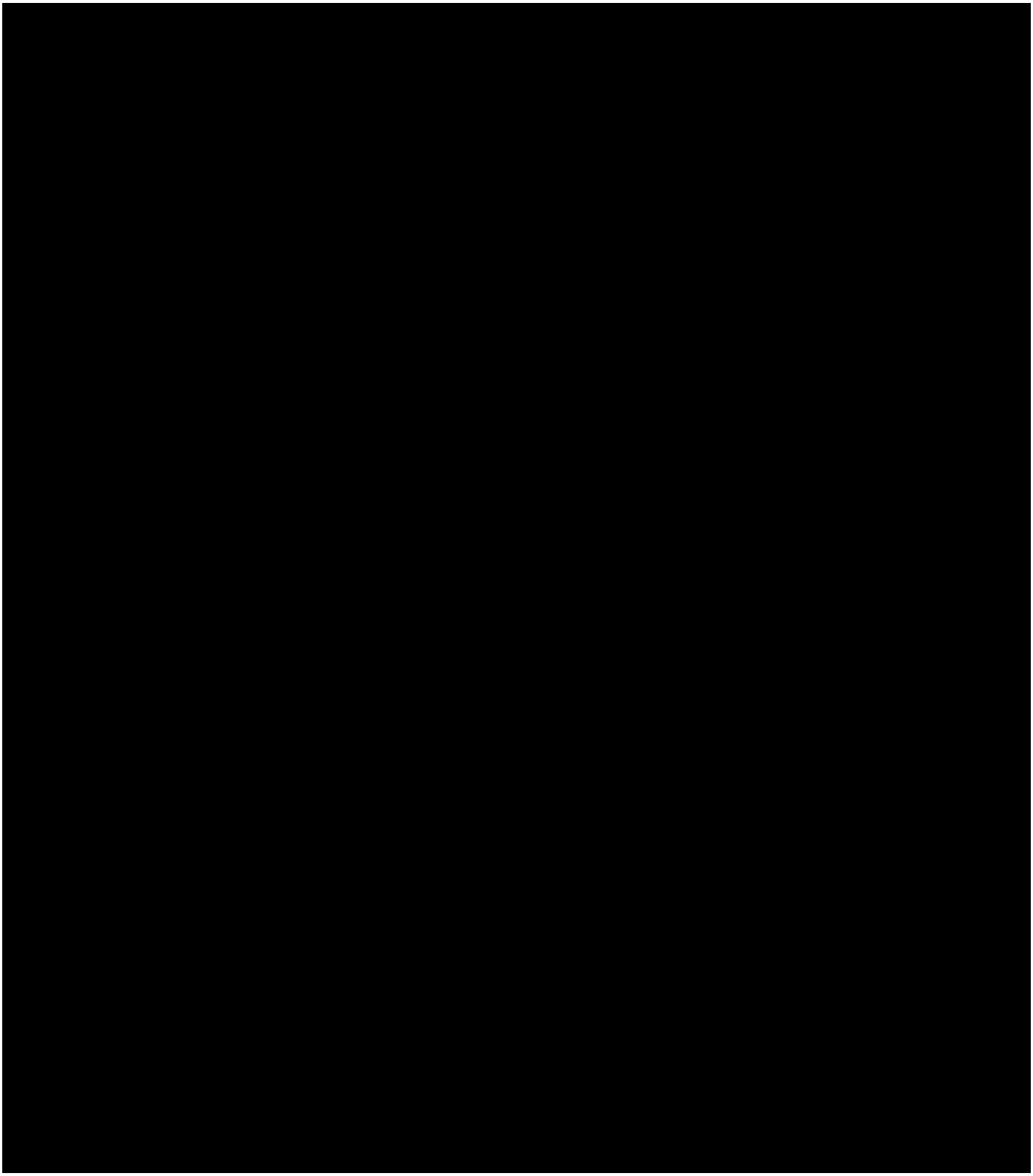
Source: Bayley, N. (2006). Bayley Scales of Infant and Toddler Development. Third ed. San Antonio, TX: Harcourt Assessment; 2007.

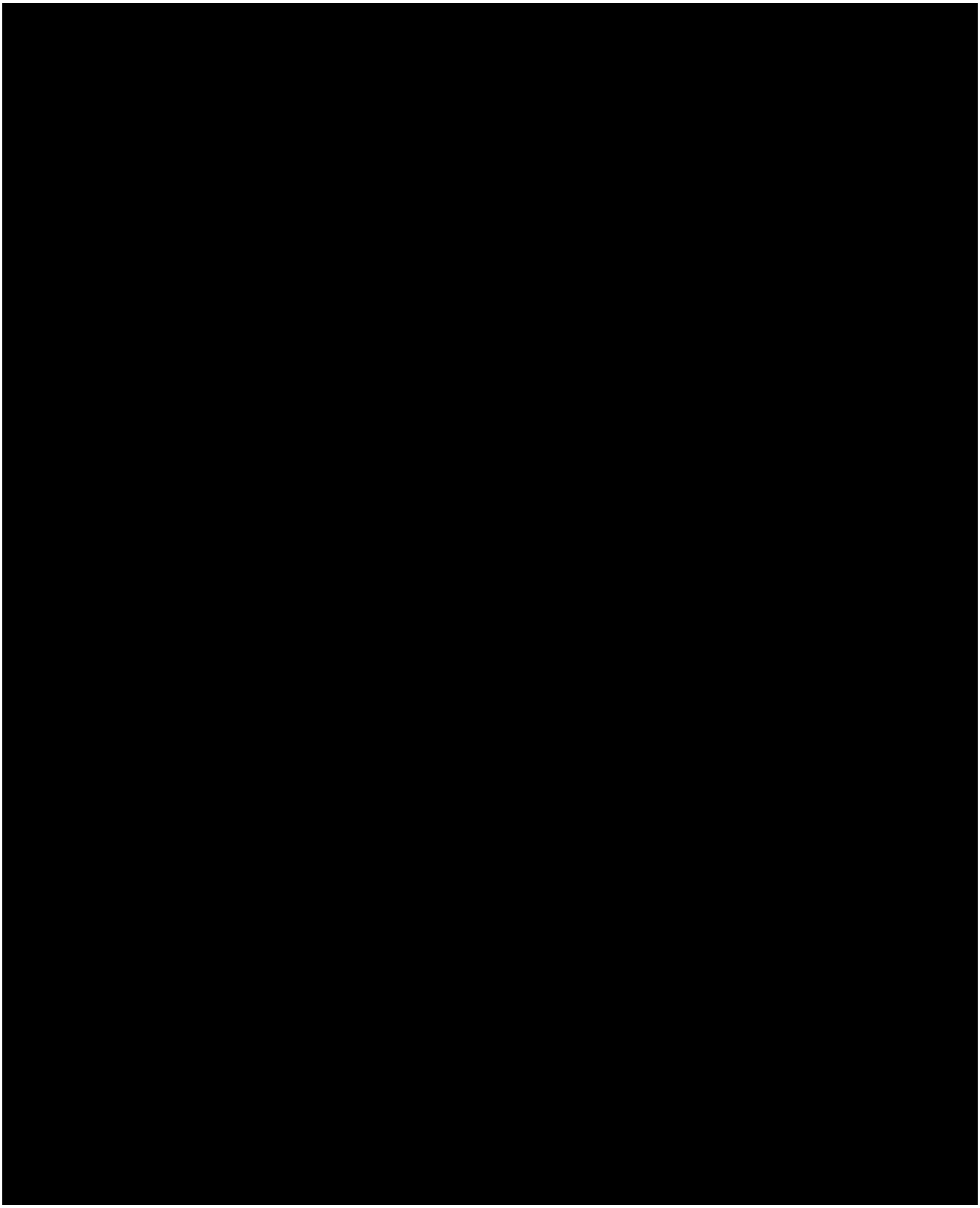
APPENDIX 5. PERFORMANCE CRITERIA FOR WORLD HEALTH ORGANIZATION (WHO) DEVELOPMENTAL MILESTONES

Gross Motor Milestone	Performance Criteria
Sitting without support	[redacted]
Hands-and-knees crawling	
Standing with assistance	
Walking with assistance	
Standing alone	
Walking alone	

WHO = World Health Organization
Source: WHO Multicentre Growth Reference Study Group. WHO Motor Development Study: windows of achievement for six gross motor development milestones. Acta Paediatr Suppl. 2006;450:86-95 and Wijnhoven TMA, de Onis M, Onyango AW, et al. Assessment of gross motor development in the WHO Multicentre Growth Reference Study. Food Nutr Bull. 2004;25(1 Suppl):S37-45

APPENDIX 6. CHOP INTEND





APPENDIX 7. DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008 64th WMA General Assembly, Fortaleza, Brazil, October 2013

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving Human subjects, including research on identifiable human material and data.
2. The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
3. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving Human subjects to adopt these principles.

General Principles

1. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”
2. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3. Medical progress is based on research that ultimately must include studies involving Human subjects.
4. The primary purpose of medical research involving Human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
5. Medical research is subject to ethical standards that promote and ensure respect for all Human subjects and protect their health and rights.
6. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research patients.
7. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research patients. The responsibility for the protection of research patients must always rest with the physician or other health care professionals and never with the research patients, even though they have given consent.

8. Physicians must consider the ethical, legal and regulatory norms and standards for research involving Human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research patients set forth in this Declaration.
9. Medical research should be conducted in a manner that minimizes possible harm to the environment.
10. Medical research involving Human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
11. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
12. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research trial will not adversely affect the health of the patients who serve as research patients.
13. Appropriate compensation and treatment for patients who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

1. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving Human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research patients.
2. All medical research involving Human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

   Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
3. Physicians may not be involved in a research trial involving Human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

   When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the trial.

Vulnerable Groups and Individuals

1. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

   All vulnerable groups and individuals should receive specifically considered protection.
2. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

1. Medical research involving Human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
2. The design and performance of each research trial involving Human subjects must be clearly described and justified in a research protocol.

   The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, Sponsors, institutional affiliations, potential conflicts of interest, incentives for patients and information regarding provisions for treating and/or compensating patients who are harmed as a consequence of participation in the research trial.

   In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

1. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the trial begins. This committee must be transparent in its functioning, must be independent of the researcher, the Sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research patients set forth in this Declaration.

   The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the trial, the researchers must submit a final report to the committee containing a summary of the trial's findings and conclusions.

Privacy and Confidentiality

1. Every precaution must be taken to protect the privacy of research patients and the confidentiality of their personal information.

Informed Consent

1. Participation by individuals capable of giving informed consent as patients in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research trial unless he or she freely agrees.
2. In medical research involving Human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the trial and the discomfort it may entail, post-trial provisions and any other relevant aspects of the trial. The potential subject must be informed of the right to refuse to participate in the trial or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential patients as well as to the methods used to deliver the information.

   After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research patients should be given the option of being informed about the general outcome and results of the trial.

3. When seeking informed consent for participation in a research trial the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
4. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research trial that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
5. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
6. Research involving patients who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the trial may proceed without informed consent provided that the specific reasons for involving patients with a condition that renders them unable to give informed consent have been stated in the research protocol and the trial has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.
7. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a trial or the patient's decision to withdraw from the trial must never adversely affect the patient-physician relationship.
8. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

1. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

   Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

1. In advance of a clinical trial, Sponsors, researchers and host country governments should make provisions for post-trial access for all patients who still need an intervention identified as beneficial in the trial. This information must also be disclosed to patients during the informed consent process.

Research Registration and Publication and Dissemination of Results

1. Every research trial involving Human subjects must be registered in a publicly accessible database before recruitment of the first subject.
2. Researchers, authors, Sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on Human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

1. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX 8. SUMMARY OF CHANGES

The section below describes the changes incorporated into this version of the protocol.

AVXS-101
AVXS-101-CL-306

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

Summary of Changes: Protocol Version 6.0, Amendment 5, 11 Nov 2020

SUMMARY AND JUSTIFICATION OF CHANGES

This protocol amendment was required in order to:

- Update to reflect current non-clinical, clinical, and risk information
- adjust trial sample size
- update statistical methods to align with the changes
- address COVID-19 related impact on trial conduct
- apply consistent definitions of the primary endpoint and exploratory endpoints
- clarify the collection and central review of videos of efficacy parameters
- update the schedule of assessments to align protocol changes for consistency
- address specific requests from Competent Authorities regarding Safety Reporting timelines and Hy's Law Criteria
- make administrative changes
- make minor changes and edits for error correction, clarification, and overall consistency.

The following changes were made to the Protocol from Version 5.0 Amendment 4 dated 26 Nov 2019 to Version 6.0 Amendment 5 dated 11 Nov 2020.

SUMMARY OF CHANGES:

The section below describes the changes incorporated into this version of the protocol.

Protocol Version 6.0 Incorporating Amendment 5 includes the following changes

Description of Change	Location(s)	Rationale for Change
Replaced AveXis with Novartis Gene Therapies	Overall	To update per company name change
Replaced [redacted] with [redacted], [redacted] with [redacted]. [redacted] with [redacted], and [redacted] r with [redacted]	Signature page	To update per company administrative changes
Updated to reflect current nonclinical, clinical, and risk information	Section 5: Introduction	To include new information
Modified language associated with enrollment as at least 6 patients was originally planned to be enrolled, the enrollment was closed with 2 patients actually enrolled.	Section 2: Synopsis Section 7.2: Number of Patients Section 14.3: Sample Size Calculation	Enrollment is discontinued due to the changes in the scope of study and related data analysis. Combining analysis with Study AVXS-101-CL-302 data will no longer be performed.
Text for exploratory objectives/endpoints was revised [redacted]	Synopsis: Exploratory Objectives Sections 6.3: Exploratory Objectives Section 14.1.3: Exploratory Endpoints	To align with Appendix 4
Updated text to include that safety monitoring for AESIs and all visits will be scheduled based on a 30-day month calendar	Synopsis: Methodology, Statistical Methods Section 7.1: Overall Trial Design Figure 4 footnotes	To align with Section 13.3 for consistency and for clarification
Text added to allow changes in study conduct during the COVID-19 pandemic (or other similar catastrophic event): - change to the conduct of study visits - when a patient may be considered withdrawn due these factors, versus withdrawn consent - change to the manner in which efficacy and safety assessments are performed - change to the manner in which monitoring visits are performed - the process of obtaining remote informed consent	Section 7.1: Overall Trial Design Section 8.3: Patient Withdrawal Criteria Section 11: Assessment of Efficacy Section 12: Assessment of Safety Section 16.1: Trial Monitoring Section 18.3: Written Informed Consent	To address the impact of the COVID-19 pandemic (or other similar catastrophic event) on: - a site's ability to conduct on-site study visits and efficacy and safety assessments per protocol - a subject's willingness or ability to continue participating in the study - a monitor's ability to perform on-site monitoring visits - a site's ability to follow the usual process of obtaining written informed consent
Text was added to state that all developmental milestones should be assessed, documented and video recorded regardless of previous attainment	Section 11.1: Developmental Milestones	For clarification
Text added to state that additional information on contractures will also be collected, as described in the Physical Assessments Manual	Section 11.2.3: CHOP INTEND	Collection of contractures data was included in the scoring sheet provided in Appendix 6 of previous protocol versions, but is not included in the new scoring sheet provided by CHOP. The Physical Assessment Manual contains a supplemental CHOP-INTEND contractures data collection sheet for use by investigator sites, to ensure consistency in the data collected throughout the study

Description of Change	Location(s)	Rationale for Change
Text added to include examples of electrolytes to be collected in the protocol	Section 12.1.10.2: Blood Chemistry	To provide clarity
"30 days after last visit" was removed from SAE Reporting; language SAE Reporting was reverted back to protocol version 4.0/amendment 3	Section 13.1.2 Serious Adverse Event	"30 days after last visit" is unnecessary for a single dose treatment of gene therapy. SAEs will be collected through the end of study visit.
"Within 24 hour" was removed for AESI Reporting and the AESIs Reporting requirements was reverted back to language in protocol version 4.0	Section 13.1.3 Adverse Events of Special Interest	AESI reporting within 24 hour is not feasible as AESIs are coded after Investigator reporting of AEs and SAEs. Investigators are made aware of AESIs categories for increased surveillance of reporting.
Revised statistical analysis methods to align with the adjustment of study: - Efficacy Analysis Population removed. - Removed text for sample size calculation	Section 14: Statistics Section 14.2: Section 14.3: Sample Size Calculation	- Study CL-306 will no longer be considered a secondary efficacy population with the European counterpart, AVXS-101-CL-302. - Data for Study CL-306 study will be presented as data listings descriptively. Sample size calculation based on hypothesis combined with Study CL-302 study is no longer applicable for Study CL-306.
Section 14.5.1 Hy's Law Criteria and definition inserted, with a link in Section 5.5	Section 14.5: Safety Analysis	At the request of the Belgium FAMPH
Video Manual changed to Physical Assessments Manual	Throughout	The Physical Assessments Manual is the new reference document for Clinical Evaluators
Schedule of Assessments was updated with minor editing and to specify the schedule of BSIDv03 Gross and Fine Motor Subtests (with video), to include the cross-link sections	Appendix 1: Schedule of Assessments	To align with protocol changes and for clarification
Addition of copyright information at the bottom of each page of the Bayley record	Appendix 3: Bayley Scales of Infant and Toddler Development (Version 3)	Per copyright requirements
Scoring sheet has been replaced with an updated version	Appendix 6: CHOP INTEND	A new scoring sheet was provided by CHOP