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Summary Basis for Regulatory Action

Date:	November 24, 2025
From:	Tania Rosen-Cheriyan, PhD, Review Committee Chair, Division of Gene Therapy 1 (DGT1) Office of Gene Therapy (OGT) Office of Therapeutic Products (OTP)
BLA STN:	BLA 125856/0
Applicant:	Novartis Gene Therapies, Inc.
Submission Receipt Date:	March 28, 2025
PDUFA Action Due Date:	November 26, 2025
Proper Name:	onasemnogene abeparvovec-brve
Proprietary Name:	ITVISMA
Indication:	Treatment of spinal muscular atrophy (SMA) in adult and pediatric patients 2 years of age and older with confirmed mutations in *survival motor neuron 1 (SMN1)* gene.

***** PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

Acting Director, Office of Clinical Evaluation, Office of Therapeutic Products.

Discipline Reviews	Reviewer / Consultant - Office/Division
Regulatory	Crystal Melendez Regulatory Project Manager CBER/OTP/ORMRR/DRMRR2/RMSB2
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC) • FONSI	Tania Rosen-Cheriyan, PhD CMC Reviewer/Committee Chair CBER/OTP/OGT/DGT1/GTB2 Sharmila Shrestha, DMPQ, CBER/OCBQ/DMPQ/MRB3 Marie Anderson, OCBQ Lot Release, CBER/OCBQ/DBSQC/QAB
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DPV) • BIMO	Mike Singer, CBER/OTP/OCE/DCEGM/GMB2 Ning Hu, CBER/OTP/OCE/DCEGM/GMB2 Douglas Rouse, CBER/OBPV/DPV/PB2 Char-Dell Edwards, BIMO, CBER/OCBQ/DIS/BMB
Statistical • Clinical data (OBPV/DB) • Non-clinical data	Boyang Tang, CBER/OBPV/DB/TEB1
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Gregory Salimando, CBER/OTP/OPT/DPT1/PTB1
Clinical Pharmacology	Yang Chang, PhD CBER/OTP/OCE/DCEGM/GMB1

Discipline Reviews	Reviewer / Consultant - Office/Division
Labeling • Promotional (OCBQ/APLB) • USPI Review	Benajmin Cyge, CBER/OCBQ/DCM/APLB Afsah Amin, CBER/OTP/OCE
Other Review(s) not captured above categories, for example: • Consults • Devices • Software • Human Factors	Johnny Lam, Device, CBER/OTP/PSPS Najat Bouchkouj, Pediatrics, CBER/OTP/OCE Melvyn Okeke, Clinical Analyst, CBER/OBPV/DB Osman Yogurtcu, Benefit risk assessment, CBER/OBPV/DABRA/BRAB

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1. Introduction

Novartis Gene Therapies, Inc. submitted Biologics License Application (BLA) STN 125856, for licensure of onasemnogene abeparvovec-brve with the proprietary name ITVISMA. ITVISMA is indicated for the treatment of spinal muscular atrophy (SMA) in adult and pediatric patients 2 years of age or older with confirmed mutations in the *survival motor neuron 1* (*SMN1*) gene.

ITVISMA is an AAV-based gene therapy utilizing a non-replicating, recombinant AAV9 vector to deliver a gene encoding the human survival motor neuron (SMN) protein. The product, which was designated as OAV101B in clinical studies, received Orphan Drug designation and Breakthrough Therapy designation during development.

Novartis currently markets ZOLGENSMA (onasemnogene abeparvovec-xioi, BLA 125694), which contains the same active ingredient (drug substance) as ITVISMA, that is, both ZOLGENSMA and ITVISMA utilize the same AAV9-based vector and deliver the same DNA sequence. ZOLGENSMA received FDA approval on May 24, 2019, for treatment in pediatric patients less than 2 years of age with SMA and bi-allelic mutations in *SMN1* gene. ZOLGENSMA is administered as a single intravenous infusion with weight-based dosing. In contrast, ITVISMA is a twofold-concentrated formulation of the same drug substance, and is administered as a fixed dose independent of patient weight, directly to the central nervous system via a single intrathecal injection.

SMA is a serious and life-threatening neurodegenerative disorder caused by mutations in the *SMN1* gene. SMA is inherited in an autosomal recessive manner. Insufficient levels of SMN protein in motor neurons in the brainstem and spinal cord leads to death of those cells, resulting in progressive atrophy and weakness of skeletal muscles. Depending on the severity of disease, patients may be unable to achieve fundamental motor milestones, including sitting, standing, and walking. In severe forms of SMA, critical functions such as breathing and swallowing are impaired, which can be fatal without intervention. SMA has an incidence of 4-10 per 100,000 live births.

Three FDA-approved therapies currently are available for SMA: the gene therapy onasemnogene abeparvovec-xioi (ZOLGENSMA), and the small-molecule drugs nusinersen (SPINRAZA) and risdiplam (Evrysdi). However, an unmet medical need remains, which ITVISMA can help address:

- ZOLGENSMA is indicated only for patients less than 2 years of age; ITVISMA would expand the patient population to include those over 2 years of age.

- Because ITVISMA is delivered intrathecally at a lower total dose than ZOLGENSMA, it reduces systemic exposure and potential adverse reactions associated with intravenous administration.

- Unlike nusinersen and risdiplam, which require lifelong treatment, ITVISMA provides as an alternative one-time therapy.

This document summarizes the basis for the regulatory action for traditional approval of ITVISMA. The BLA is supported by three clinical studies: Phase 3 study (B12301,

NCT05089656), Phase 1/2 study (CL-102, A12102, NCT03381729), and Phase 3b study (B12302, NCT05386680).

ITVISMA demonstrated substantial evidence of effectiveness for the treatment of SMA in pediatric patients 2 years of age or older with confirmed mutation in *SMN1* gene based on primary evidence of effectiveness from the adequate and well controlled Phase 3 study, B12301, and the confirmatory evidence of effectiveness from data characterizing the mechanism of the product for delivering a gene encoding SMN protein, as well as efficacy findings from Zolgensma, which as noted above, contains the same active ingredient but in an intravenous formulation.

The primary evidence of efficacy was established based on the data from Period 1 of Study B12301, a Phase 3, randomized, double-blind, and sham-procedure controlled pivotal trial. The prespecified primary efficacy endpoint was the change from baseline to Week 52 in motor function, as measured by the Hammersmith Functional Motor Scale-Expanded (HFMSE). Patients who received ITVISMA demonstrated a statistically significant and clinically meaningful improvement on the HFMSE compared to patients who received sham treatment. Although the five prespecified secondary efficacy endpoints did not reach statistical significance, all showed numerical improvements in favoring the ITVISMA group, providing supportive evidence for efficacy.

The safety profile of ITVISMA was evaluated through the safety database of 167 patients across three clinical studies who received ITVISMA at a fixed dose of 1.2×10^{14} vector genomes via a single intrathecal injection. Safety was further characterized based on data from Period 1 of Study B12301 and was described in Section 6 of the label. The adverse events of special interest (AESI)s included hepatotoxicity, transient thrombocytopenia, DRG toxicity signs/symptoms, and cardiac AEs, observed in ITVISMA clinical program, were consistent with identified risks associated with ZOLGENSMA.

The hepatotoxicity boxed warning from the ZOLGENSMA label is retained in the ITVISMA label with modified language as hepatic biodistribution following intrathecal administration still occurs following intrathecal administration, despite reduced systemic exposure compared to the intravenous delivery. This approach is supported by clinical data showing hepatotoxicity in 18 (11%) of 167 patients in ITVISMA clinical studies, with two patients experiencing severe ALT elevations (20× ULN). Additionally, fatal acute liver failure cases have been reported in ZOLGENSMA's postmarketing experience, further supporting the need for this warning.

Acknowledging the rarity and serious and life-threatening nature of SMA, the Agency exercised regulatory flexibility in the review of this BLA. Since the product received Breakthrough Therapy designation for the indication, the BLA was granted priority review.

Clinical Regulatory Flexibility
The Agency agreed with the Applicant's proposal to extend the indication beyond the age range of the pivotal study population (pediatric patients 2.1 to 16.6 years of age) to include adult patients with SMA. The key justifications for including adult patients in the proposed indication include:

- The OAV101B clinical program enrolled patients across a broad range of ages and functional levels to represent the heterogeneous SMA patient population.
- Adult-onset SMA patients typically present with the mildest disease course and slowest progression, making them clinically comparable to the study population with highest-functioning patients. The subgroup with the highest motor milestone of "able to walk with assistance" (n=24), which represents the mildest form of SMA typically seen in adult-onset cases, demonstrated a robust improvement compared to sham treatment (least square [LS]-means difference of 4.25 in change from Baseline in HFMSE, 95% CI: 1.07 to 7.42).
- While the safety profile in adults is not expected to differ significantly from the studied pediatric population, warnings and precautions are warranted due to the potentially increased risks of adverse events of special interest (e.g., hepatotoxicity and cardiotoxicity) in adult patients with preexisting chronic medical conditions. Accordingly, a cardiotoxicity warning and a hepatotoxicity boxed warning have been incorporated into the USPI.

CMC Regulatory Flexibility
Additional regulatory flexibility was exercised in this approval process by leveraging information from the manufacturing and quality assessment history for ZOLGENSMA. This was possible because ZOLGENSMA and ITVISMA are manufactured from the identical drug substance (DS, active ingredient) and utilize the same manufacturing facility. The major difference between the two products is the concentration of the active ingredient and the route of administration (ROA). Regulatory flexibilities included leveraging DS process validation and analytical method validation studies for tests that are used to evaluate the quality of both products. For any post-approval manufacturing change that is identical between ZOLGENSMA and ITVISMA, FDA will accept a single submission as a trans-BLA supplement to streamline submission and review of such a change.

In summary, ITVISMA demonstrated a favorable benefit-risk profile for treating SMA in pediatric patients aged 2 years and older with confirmed *SMN1* gene mutations, based on efficacy and safety findings submitted in the BLA. The review teams recommend approval of ITVISMA for treating SMA in adult and pediatric patients aged 2 years and older with confirmed *SMN1* gene mutations, and retention of the hepatotoxicity boxed warning with modified language based on the justification stated above.

2. Background

SMA is a serious autosomal recessive neurodegenerative disorder caused by mutations in the *survival motor neuron 1* (*SMN1*) gene. In healthy individuals, the *SMN1* gene serves as the primary source of functional SMN protein, which is essential for motor neuron survival. When this gene is defective, it leads to progressive muscle weakness and atrophy, making SMA a serious and life-threatening disease. The progressive muscle weakness affects fundamental motor functions, including sitting, standing, and walking. In severe cases, weakness extends to critical functions such as breathing and swallowing, which can be fatal without intervention.

Loss or mutation of *SMN1* gene leads to SMN protein deficiency in motor neurons of the brainstem and spinal cord. The clinical phenotype and severity of SMA are influenced by the nearby *SMN2* gene, which acts as a disease modifier. Higher *SMN2* copy numbers provide partial compensation for *SMN1* loss, with increased copy numbers associated with milder disease severity.

SMA is traditionally classified into several types (Type 0 to 4) based on age of onset and maximum motor function achieved. The classification ranges from Type 0, the most severe form with prenatal/neonatal onset, to Type 4, which presents in adulthood (typically after age 30 years) with the mildest course and slow progression.

The study population in the clinical studies of OAV101B represents patients with SMA Type 2. This intermediate form has onset between 6 month -18 years of age and encompasses a spectrum of functional capabilities, ranging from patients who can sit independently to those who are unable to achieve unassisted ambulation.

SMA has an incidence of 4-10 per 100,000 live births. In the United States, SMA type II accounts for approximately half of all SMA cases, with an estimated incidence of 1 in 24,000 live births.

Three FDA-approved therapies currently are available for SMA. However, an unmet medical need remains. Please refer to the available therpies and unmet medical need in Section 1.

ITVISMA was developed under an Investigational New Drug submission (IND 15699). FDA engaged and corresponded with the Applicant on multiple occasions before and after the BLA submission. Major regulatory milestones for BLA) are summarized in Table 1.

Table 1: Major Regulatory Milestones

Regulatory Events / Milestones	Date
1. IND 15699 submission	08/06/2013
2. Fast Track designation granted	09/27/2013
3. Orphan Drug designation granted	09/30/2014
4. Breakthrough Therapy designation granted	07/15/2016
5. Rare Pediatric Disease designation granted	07/02/2018
6. Pre-BLA meeting	02/12/2025
7. BLA 125856/0 submission	03/28/2025
8. BLA filed	05/27/2025
9. Mid-Cycle communication	07/22/2025
10. Late-Cycle meeting	09/11/2025-Canceled by Applicant
11. Action Due Date	11/26/2025

Source: CBER regulatory systems.

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

The CMC review concludes that the manufacturing process for ITVISMA (onasemnogene abeparvovec-brve, OAV101B) yields a product with consistent quality characteristics, and the CMC review team recommends approval.

ITVISMA is a suspension of an AAV vector-based gene therapy, intended for intrathecal infusion, to treat spinal muscular atrophy (SMA) in adult and pediatric patients 2 years of age or older with confirmed mutation in SMN1 gene. The drug substance (DS, active ingredient) consists of a non-replicating, recombinant AAV9 vector containing the human survival motor neuron (SMN) cDNA. The drug product (DP) has a nominal concentration of 4×10^{13} vector genomes (vg)/mL and is delivered as a 3 mL flat dose containing 1.2×10^{14} vg (not dependent on patient weight). It is formulated in 20 mM Tris (pH 8.0), 1 mM magnesium chloride ($MgCl_2$), 200 mM sodium chloride (NaCl) and 0.005% poloxamer 188. The DP is sterile and contains no preservative. The DP is packaged in a carton which contains one DP vial and the prescribing information sheet. The carton is shipped frozen (b) (4) and after receipt the carton should be stored in a refrigerator (2-8°C) for no more than 14 days.

Novartis has an approved product, ZOLGENSMA (onasemnogene abeparvovec-xioi, OAV101) under BLA 125694 containing the identical DS (active ingredient) at a lower concentration ($2x10^{13}$ vg/mL), which is delivered via intravenous infusion (IV) to treat patients < 2 years old. Therefore, the applicant was able to leverage much of the CMC information from the ZOLGENSMA BLA to support the quality of ITVISMA.

Considering the high degree of similarity between the current BLA application for ITVISMA and the previously approved BLA 125694 for ZOLGENSMA, Table 2 highlights the differences between the products:

Table 2: Differences between ZOLGENSMA and ITVISMA

Parameter	ZOLGENSMA	ITVISMA
Regulatory history:	BLA 125694 Approved May 24, 2019	BLA 125856 (current)
Dose:	Dose-specific kits containing required #vials – based on patient weight (1.1×10^{14} vg/ kg)	Single dose of 1.2×10^{14} vg (flat dose)
Route of administration:	Intravenous (IV)	Intrathecal (IT)
Concentration:	2×10^{13} vg/mL	4×10^{13} vg/mL (formulation buffer remains the same)
Volume:	5.5 mL, 8.3 mL kits	Single dose: 3 mL volume
Container closure:	10 mL vial	5 mL vial
Endotoxin:	(b) (4)	(b) (4)

Parameter	ZOLGENSMA	ITVISMA
Highlighted Mfg. differences:	(b) (4)	Same current DS process, modified DP process for dilution to meet a higher DP target titer. Same facility.
Delivery device[a]:	IV needle and apparatus	Spinal needle & syringe (not a combination product)
Packaging & label:	Aluminum seal button is light green. Trade name on label is purple.	Aluminum seal button is violet. Trade name on label is purple and green.

Source: BLA 125856 & BLA 125694.
[a] No specific devices are indicated, general label.

Manufacturing:
(b) (4)
For forward processing, the DS (b) (4) and adjusted to the desired target concentration of $4x10^{13}$ vg/mL and filled into 5 ml vials, which are labelled and stored at ≤-60°C. The DP manufacturing steps do not include any further process- or product-related impurity removal steps.

Manufacturing Validation:
(b) (4)

Comparability:
The ITVISMA and ZOLGENSMA (b) (4) manufacturing process is identical. Since product comparability was already demonstrated under the approved BLA 125694 for ZOLGENSMA, and no additional process changes were made, additional comparability assessment was not needed for ITVISMA.

Quality:
The analytical control strategy for ITVISMA includes testing of (b) (4) includes using validated/verified assays for lot release of (b) (4) (b) (4) drug product for microbial and viral contaminants, identity, purity and strength. (b) (4) The release assays for DP include strength, potency, identity, product-related impurities including (b) (4) and safety. There are general tests for appearance, pH (b) (4) performed on (b) (4) DP. The potency assay to confirm the activity of the product consists of a matrix approach, consisting of (b) (4)

Stability:
ITVISMA DS is stable at (b) (4) The stability of the ITVISMA DP is demonstrated for at (b) (4) representative, comparable lots at ≤-60°C for 24 months. Stability updates for the registrational ITVISMA lots will be submitted to the BLA when available. This was acceptable due to the extensive manufacturing experience with ZOLGENSMA. The applicant eventually plans to request a DP shelf life extension to (b) (4) when sufficient data is collected. Once thawed, the DP is stable for 14 days at refrigerated temperature (2-8°C), and 24 hours in syringes at room temperature. The drug product is not light-sensitive.

b. Testing Specifications

The majority of the DP specifications were reviewed under the ZOLGENSMA BLA (STN 125694). For some tests the lot release acceptance criteria were unique to ITVISMA due to the route of administration. All specifications are outlined below, those unique to ITVISMA are bold.

Table 3: Drug product specifications

Test	Acceptance Criteria	Test for Release	Test for Stability
Appearance by Visual Inspection	Clear to slightly opaque, colorless to faint white solution, free of visible particulates	(b) (4)	
pH	(b) (4)		
(b) (4)	(b) (4)		

Test	Acceptance Criteria	Test for Release	Test for Stability
(b) (4)		+	+
		+	-
Total Protein (b) (4) (b) (4)	(b) (4)	+	-
(b) (4)		+	-
In vitro Relative Potency by (b) (4)		+	+
(b) (4)		+	-
Identity (b) (4)		+	-
Identity (b) (4)		+	-
(b) (4)		+	+[b]
% Total Purity by (b) (4)		+	+
% Total Impurities by (b) (4)		+	+
(b) (4)		+	-
Endotoxin[a]		+	-
Sterility	No Growth	+	-
(b) (4)		+	-
Container Closure Integrity Testing	Pass	+	+

Source: Module 3.2.P.5.1 in BLA 125856.
[a] Mandatory; -: Not required
[b] (b) (4) will be tested, and (b) (4) results will be reported.
[b] Stability doesn't have established acceptance criteria. Release specification will be used for comparison with stability results.

The analytical methods and their validations and/or qualifications reviewed for the ITVISMA (b) (4) DP were found to be adequate for their intended use at the time of approval.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release. In-house CBER testing will not be required since this product is used to treat a rare disease, requiring infrequent production in small batches.

d. Facilities Review / Inspection

Facility information and data provided in the BLA STN 125856/0 were reviewed by CBER and found to be sufficient and acceptable. The activities and inspectional history for the facilities involved in the manufacture of ITVISMA are summarized in the table below.

Table *4*: Manufacturing Facilities Table for ITVISMA

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
Novartis Gene Therapies, Inc. (b) (4) DS & DP manufacturing, DP release testing	(b) (4)	(b) (4)	Waiver	(b) (4) Surveillance Inspection ORA VAI
(b) (4) DP release testing	(b) (4)	(b) (4)	Waiver	(b) (4) PAI ORA VAI
Novartis (b) (4) DP release testing	(b) (4)	(b) (4)	Waiver	(b) (4) PLI CDER VAI

Source: Modules 3.2.S.2.1 and 3.2.P.3.1 in BLA 125856.
Acronym key: DS – drug substance; DP – drug product; CBER – Center for Biologics Evaluation and Research; CDER – Center for Drug Evaluation and Research; ORA – Office of Regulatory Affairs; PAI – Pre-Approval Inspection; PLI – Pre-License Inspection; VAI – Voluntary Action Indicated; DMPQ – Division of Manufacturing and Product Quality

In (b) (4) ORA performed a routine surveillance inspection at Novartis Gene Therapies, Inc. covering ZOLGENSMA DS and DP manufacturing process, including review of Quality System, Facilities and Equipment, Material, Packaging and Labeling and Laboratory Control. All Form FDA-483 issues were resolved, and the inspection was classified as VAI.

In (b) (4) ORA conducted a PAI at (b) (4) LP. All FDA Form-483 issues were resolved. The inspection was classified as VAI.

In (b) (4) the Division of Biotechnology Manufacturing/CDER performed a PLI at Novartis (b) (4) covering quality, production, materials, facilities and equipment, laboratory controls and packaging and labeling systems. All Form FDA-483 issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

The ITVISMA drug product is filled into a sterile, ready-to-use, clear 5mL (b) (4) cyclic olefin polymer vial (b) (4) that is capped with a sterile, ready to use, gray 20 mm, (b) (4) chlorobutyl elastomeric stopper (b) (4) (b) (4) A sterile, 20 mm flip-off, aluminum seal with a colored plastic button cap (b) (4) is used as the final seal for the vial and stopper.

Container-closure integrity was tested by (b) (4) method at the Novartis Gene Therapies, Inc. manufacturing facility and all acceptance criteria were met.

f. Environmental Assessment

The Applicant submitted an environmental assessment (EA) pursuant to 21 CFR part 25. The Agency determined that approval of ITVISMA will not result in any significant environmental impact. A Finding of No Significant Impact memorandum has been prepared.

4. Nonclinical Pharmacology/Toxicology

The nonclinical development program for ITVISMA evaluated research grade lots, referred to as scAAV9.CBA.SMN, OAV101, and OAV101B, to inform the safety and activity of ITVISMA. Among the research lots, OAV101B is the vector that is with specifications the most comparable to ITVISMA. In a piglet model of SMA, scAAV9.CBA.SMN administered by the IT ROA prevented the development of hindlimb muscle weakness and slowed overall disease progression. Pharmacology studies were conducted in both healthy nonhuman primate (NHP) cynomolgus monkeys and a mouse model of SMA (SMNΔ7). IT administration of scAAV9.CBA.SMN demonstrated a 55-79% transduction efficiency of choline acetyltransferase (ChAT) positive motor neurons in NHP spinal cords. Single intracerebroventricular (ICV) administration of scAAV9.CBA.SMN to SMNΔ7 mice demonstrated improvements in survival, motor function, and neuromuscular transmission compared to uninjected control animals.

In vivo toxicology/safety studies conducted in NHPs utilized a single IT administration of OAV101 at 1.2 x 10^{13} vg/animal, considered equivalent to the proposed starting clinical dose level for ITVISMA of 1.2x10^{14} vg/patient based on a 10-fold difference in CSF volume between NHP and human. These studies demonstrated that OAV101 was well tolerated at this dose level up to 12 months post injection, with minor microscopic findings reported 6 weeks post-administration in the dorsal root ganglia (DRG), spinal cord, peripheral nerves, and brain that did not increase in severity or incidence over the 12 month study. These toxicity findings precluded the determination of a no-observed-

adverse-effect level. Biodistribution (BD) of OAV101 demonstrated the highest titers in the liver, DRG, and spinal cord, with lower levels reported in the periphery, including gonads. Additional single-dose studies in the newborn Friend Virus B (FVB) mouse strain and NHPs further demonstrated high tolerability to OAV101 or scAAV9.CBA.SMN following ICV or IT administration, respectively, with no major safety signals. .

Fertility and early embryonic development (FEED) studies were conducted in healthy male and female FVB mice administered a single intravenous injection of OAV101B. There were no reported adverse effects on fertility, fecundity, or mating behaviors in either sex. Additionally, there was no evidence of germ cell transduction or germline transmission. No carcinogenicity, genotoxicity, or repeat dosing were conducted for OAV101B. These studies are not necessary based on the intended ROA, dosing regimen (i.e., single infusion), known product characteristics, and overall safety profile for this class of product.

The nonclinical program for ITVISMA demonstrated: (1) in vivo activity commensurate with the proposed mechanism of action (MOA) of the product; (2) BD primarily to the intended target tissues and neuronal cell populations; and (3) an acceptable safety profile following administration of the product at dose levels comparable to or exceeding the intended clinical starting dose administered via the clinical ROA.

5. Clinical Pharmacology

The clinical pharmacology of ITVISMA was evaluated in three studies: a phase 1/2 study (CL-102), a pivotal phase 3 study (B12301), and a supportive phase 3b study (B12302). The clinical pharmacology assessment of ITVISMAincludes vector shedding and immunogenicity evaluations.

ITVISMA is a non-replicating recombinant AAV9 vector that delivers a functional copy of the human survival motor neuron gene (*SMN1*) to transduced cells. The transgene is expressed under a constitutive promoter, resulting in continuous and sustained SMN protein expression. By providing an alternative source of SMN protein in motor neurons, ITVISMA is expected to promote the survival and function of transduced motor neurons in patients with SMA, which is caused by bi-allelic mutations in the *SMN1* gene resulting in insufficient SMN protein expression.

a. Pharmacokinetics (PK) : Vector Shedding

Vector shedding studies assessed the elimination of vector DNA through saliva, urine, feces, and nasal secretions following intrathecal administration in 134 patients across the three studies. Vector DNA was detectable in shedding samples from all 134 patients. Shedding of ITVISMA DNA occurred primarily via feces. Peak shedding was observed within 10, 3, 2, and 8 days post-dose for stool, urine, saliva, and nasal secretions, respectively. The majority of vector DNA (>90%) was excreted within 2 weeks after dose administration. Vector DNA was below the limit of quantification (BLQ) in most participants by 4 weeks (stool), 1 week (urine), 3 weeks (saliva), and 10 weeks (nasal secretions).

b. Pharmacodynamics (PD)

There are no available clinically relevant pharmacodynamic data for ITVISMA.

c. Immunogenicity

Anti-AAV9 antibody responses were consistent and robust across all studies, with all participants developing high titers that remained elevated through study completion. In Studies B12301 and B12302, anti-AAV9 antibody titers were evaluated in 102 patients following a single intrathecal injection of ITVISMA. Patients were required to have baseline anti-AAV9 antibody titers <1:50. Despite a course of immunosuppression with oral prednisolone 1 mg/kg/day (or equivalent) started 24 hours before ITVISMA infusion and tapered after 30 days, an increases from baseline in anti-AAV9 antibody titers were reported in all patients, with median anti-AAV9 antibody titers of ≥1:819,200 reported in both studies. During the 12-month period following ITVISMA injection in Studies B12301 and B12302, positive anti-SMN antibodies were observed in 5/75 (6.7%) and 2/27 (7.4%) of ITVISMA-treated patients, respectively. No clinical effects of anti-SMN or anti-AAV9 antibodies on the pharmacodynamics, pharmacokinetics, safety, or efficacy of ITVISMA were identified over the 12-month follow-up period.

6. Clinical/Statistical

a. Clinical Program

The approval of ITVISMA for treatment for SMA in pediatric patients 2 years of age and older is based on clinical data from three studies:

- Phase 3 Study B12301, in treatment-naïve patients with SMA aged 2 to <18 years,
- Dose-ranging, Phase 1/2 Study CL-102, in treatment-naïve patients with SMA aged 6 to <60 months
- Phase 3b Safety Study B12302 in patients with SMA aged 2 to <18 years who were previously treated with nusinersen or risdiplam.

The efficacy data supporting the use of ITVISMA are primarily derived from the primary analysis of the Phase 3 study B12301 through Period 1 (52 weeks).

All three studies contributed to the overall safety database for ITVISMA.

Patients who received ITVISMA in clinical trials were to be enrolled in the 5 year long term follow up (LTFU) study A12308 (NCT05335876) that was initiated for ZOLGENSMA (IV).

Phase 3 Study B12301

Study B12301 is a multicenter, randomized, sham-controlled, double-blind study in patients with SMA, 2 to less than 18 years of age, who were treatment-naive, and able to sit but never able to walk independently. Patients with elevated (reference to > 1:50) baseline serum anti-AAV9 antibody titer were excluded from the study.

The study comprised two periods:

- Period 1: A randomized, double blinded, sham controlled period through Week 52. Patients received either ITVISMA at a fixed dose of 1.2×10^{14} vg by single lumbar intrathecal injection or sham procedure, at a randomization ratio of 3:2. Randomization was stratified by age and pre-treatment HFMSE score.

  Sedation/anesthesia (per institutional guidelines) was administered for all patients receiving ITVISMA and sham procedure. The intrathecal infusion was performed by unblinded interventional radiologist or a qualified specialist (e.g., neurologist) as detailed in the Pharmacy Manual.

  The sham procedure consisted of a small needle prick on the lower back at the LP injection site without needle insertion. The sham procedure mimicked ITVISMA dosing procedure as closely as possible.

- Period 2: After completing Period 1, eligible patients enrolled in Period 2. The patients who received a sham procedure in Period 1 received ITVISMA, and patients who received ITVISMA in Period 1 received the sham procedure. The primary purpose of Period 2 was to allow participants who received a sham procedure in Period 1 to receive ITVISMA in Period 2 while maintaining the blind.

Patients treated in the study received a course of oral corticosteroid, equivalent to oral prednisolone at 1 mg per kg of body weight per day (mg/kg/day) for a total of 30 days, starting one day prior to ITVISMA administration. The corticosteroid dose was tapered after the 30-day period, based on the clinical status and liver function testing.

Efficacy Endpoints

The primary endpoint was change from baseline in HFMSE total score at the end of Follow-up Period 1 in the overall study population (≥ 2 to < 18 years age group). The end of Follow-up Period 1 was defined as the average of the Week 48 and Week 52 assessments. If just one of the assessments was valid/available, it was defined as the end of Follow-up Period 1 value.

The HFMSE evaluates motor function in patients with SMA who have limited ambulation, comprising of 33 graded items that assesses various motor skills movements ranging from sitting to using the stairs. Each item is scored from 0-2, with a total score of 66. Higher scores indicate better motor function.

Secondary efficacy endpoints:

1. Change from baseline in HFMSE total score at the end of Follow-up Period 1 in the ≥ 2 to < 5 years age group.
2. Achievement of at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1 in the overall study population.
3. Achievement of at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1 in the ≥ 2 to < 5 years age group.
4. Change from baseline in RULM at the end of Follow-up Period 1 in the overall study population.

5. Change from baseline in RULM at the end of Follow-up Period 1 in the ≥ 2 to < 5 years age group.

The RULM assesses upper limb functional abilities in patients with SMA. The test consists of 19 scorable items: 18 items scored on a 0 (unable) to 2 (full achievement) scale, as with the HFMSE, and one item that is scored from 0 (unable) to 1 (able). The total score ranging from 0 to 37 points; higher scores correspond to better function.

The primary and secondary efficacy analyses were prespecified and controlled for multiplicity.

Clinical Efficacy Findings

A total of 136 patients were randomized in a 3:2 ratio. Ten randomized patients were excluded from the efficacy analysis because they did not receive their assigned treatment for various reasons. The analysis population (e.g., Full Analysis Set, FAS) included 126 patients who received either ITVISMA (n = 75) or sham procedure (n = 51), with 71 patients in the 2 to <5 years age group (42 in ITVISMA and 29 in Sham), and 55 patients in the 5 to <18 age group (33 in ITVISMA and 22 in Sham).

Patient ages ranged from 2.1 to 16.6 years (mean 5.9 years) at dosing. Sixty-two patients (49%) were male. Seventy-four patients (59%) were Asian, 14 patients (11%) were White, 9 patients (7%) were Black or African American, and 7 patients (6%) were American Indian or Alaska Native, 22 patients (18%) were of “unknown” race.

The majority of patients (122/126, 96.8%) presented with confirmed biallelic deletion of *SMN1* gene (0 copies), while the remaining 4 patients (3.2%) retained 1 copy. *SMN2* copy number was consistent across the cohort, with nearly all patients (119/126, 94.4%) carrying 3 copies. All patients met the eligibility criterion of baseline anti-AAV9 antibody titers ≤1:50, as measured by (b) (4) Caregiver reports of patients' highest motor milestone ever achieved revealed a spectrum of functional capabilities across the study population. Just over half of patients (66/126, 52.4%) had achieved sitting without support as their peak milestone, while approximately one-quarter (33 patients, 26.2%) had progressed to standing with assistance. Nearly one-fifth of patients (24/126, 19.0%) had reached walking with assistance, and a small subset (3 patients, 2.4%) had achieved independent standing. Baseline HFMSE scores demonstrated well-balanced treatment groups, with mean scores of 17.97 in the ITVISMA-treated group and 18.17 in the sham-control group.

Table 5 summarizes the primary efficacy endpoint analysis result. The least square (LS) mean (standard error of the mean, SEM) of change from baseline in HFMSE total score to the end of Follow-up Period 1 was 2.39 (0.44) points in ITVISMA arm compared to 0.51 (0.53) points in the Sham arm. The LS mean difference of 1.88 points between ITVISMA arm and the Sham arm was statistically significant [95% confident interval (CI): 0.51, 3.25; p-value: 0.0074] which demonstrates the efficacy of ITVISMA to improve motor function in patients with SMA aged 2 to <18 years (Table 5). The observed treatment effect exceeded the minimal clinically important difference (MCID) of 1.46

points for HFMSE improvement in patients with type 2 SMA, which represents the target population per the study eligibility criteria. This MCID was established by Coratti et al. (2024)[1] using an anchor-based methodology in accordance with FDA guidance (2023)[2].

Table 5. Primary Efficacy Results as Measured by HFMSE from Study B12301, period 1 (n=126)

Time Point	Statistics	ITVISMA	Sham
Baseline	N	75	51
	Mean (SD)	17.97(10.11)	18.17(9.76)
	Median	16.50	19.00
	Min, Max	1.0, 41.0	2.0, 42.5
End of Follow-up Period 1	N	74	50
	Mean(SD)	20.49(11.36)	19.05(10.13)
	Median	18.00	20.75
	Min, Max	2.0, 50.5	2.5, 41.5
Change from baseline at End of Follow-up Period 1*	N	74	50
	Mean (SD)	2.38(3.83)	0.56(3.87)
	Median	2.00	1.00
	Min, Max	-5.5, 15.0	-8.5, 10.5
	LS-Means (SEM)	2.39(0.44)	0.51(0.53)
	95% CI	1.52, 3.26	-0.55, 1.56

Source: Adapted from BLA 125856/0; Module 5.3.5.1 COAV101B12301 Week 52 Study Report, p68.
Abbreviations: SD: standard deviation; LS-Means: Least squares (LS) means; SEM: standard error of the mean; CI: confident interval
*Estimated using a linear mixed model repeated measures (MMRM) model with the observed change from Baseline in HFMSE total score at all post-baseline visits as the dependent variable. The fixed effects included treatment, visit, treatment by visit interaction, randomization strata, and the baseline HFMSE total score as covariate. An unstructured covariance matrix was used. The end of Follow-up Period 1 was defined as the average of the Week 48 and Week 52 assessments. If just one of the assessments was valid/available, it was defined as the end of Follow-up Period 1.
Treatment Difference ITVISMA-Sham (95% CI): 1.88 (0.51 – 3.25) [p-value: 0.0074].

Table 6 summarizes the secondary efficacy endpoint analysis results. None of the five secondary efficacy endpoints achieved statistical significance according to the prespecified multiple testing strategy; all showed numerical improvement in favor of the ITVISMA group compared to the Sham group.

[1] https://doi.org/10.1111/ene.16309
[2] Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making | FDA

Table 6. Secondary Efficacy Results from Study B12301, period 1 (n=126)

Endpoint	ITVISMA OVA101B LS-Means (95% CI)	Sham LS-Means (95% CI)	Treatment Difference ITVISMA-Sham (95% CI)	Nominal P-value[5]
Change from baseline in HFMSE score at end of Follow up Period 1 for ≥ 2 to < 5 age group[1,4]	3.00 (1.86, 4.13)	1.56 (-0.19, 4.13)	1.44 (-0.33, 3.22)	0.11
Change from baseline in RULM score at end of Follow up Period 1 for ≥ 2 to < 18 age group[1,4]	2.44 (1.60, 3.19)	0.92 (0.00, 1.83)	1.52 (0.34, 2.71)	0.012
Change from baseline in RULM score at end of Follow up Period 1 for ≥ 2 to < 5 age group[1,4]	3.27 (2.20, 4.33)	1.82 (0.53, 3.10)	1.45 (-0.22, 3.12)	0.087
Endpoint	**ITVISMA Proportion (%) (95% CI)**	**Sham Proportion (%) (95%CI)**	**Odds ratio (95% CI)**	**Nominal P-value[5]**
Proportion of 3-point HFMSE improvement at end of Follow up Period 1 in ≥ 2 to <18 age group[2,4]	39.2 (28.1, 50.3)	26 (13.8, 38.2)	2.03 (0.90, 4.57)	0.088
Proportion of 3-point HFMSE improvement at end of Follow up Period 1 in ≥ 2 to <5 age group[3,4]	48.8 (33.5, 64.1)	37.9 (20.3, 55.6)	1.27 (0.46, 3.56)	0.64

Source: Adapted from BLA 125856/0; Module 5.3.5.1 COAV101B12301 Week 52 Study Report, Table 11-2, Table 11-3, Table 11-4, Table 11-5, Table 11-6, p70-76.
Abbreviations: LS-Means: Least squares (LS) mean; CI: confident interval
[1]LS-Means estimated using a linear mixed model repeated measures (MMRM) model with the observed change from Baseline in the corresponding score at all post-baseline visits as the dependent variable. The fixed effects included treatment, visit, treatment by visit interaction, randomization strata, and the baseline score as covariate. An unstructured covariance matrix was used.
[2]Odds ratio computed using Logistic Regression Model with firth correction including treatment, randomization strata, and baseline HFMSE total score as covariate
[3]Odds ratio computed using Generalized Linear Mixed Effects Model including treatment, visit, treatment by visit interaction, randomization strata, and baseline HFMSE total score as covariate. The model included “logistic” as the link function. A compound symmetry variance-covariance structure was used.
[4]The end of Follow-up Period 1 was defined as the average of the Week 48 and Week 52 assessments. If just one of the assessments was valid/available, it was defined as the end of Follow-up Period 1.
[5]None of the 5 secondary efficacy endpoints achieved statistical significance according to the prespecified multiple testing strategy. All P values (two-sided) are nominal.

Additionally, the Applicant conducted subgroup analyses to support extending the indication to include adult patients with SMA. In Study B12301, the subgroup with the highest motor milestone of "able to walk with assistance" (n=24), representing the mildest form of SMA typically observed in adult-onset cases, demonstrated a robust

improvement with the LSM difference of 4.25 points (CI: 1.07, 7.42) between the ITVISM arm and sham treatment. The efficacy results and age information for this subgroup are summarized in Table 7.

Table 7. Subgroup Analysis of Patients Who Were "Able to Walk with Assistance," as Measured by HFMSE from Study B12301, Period 1

Characteristic/ Outcome	Statistics	ITVISMA (n = 15)	Sham (n = 9)
Age (Years)	Mean (SD)	6.72 (4.44)	5.42 (2.89)
Age (Years)	Minimum, Maximum	2.33, 16.5	2.33, 10.9
Change from baseline in HFMSE at end of Follow up Period 1 score [1]	LS-Means (SEM) [95% CI]	3.88 (0.988) [1.92, 5.84]	-0.37 (1.273) [-2.89 2.15]

Source: Adapted based on data from the Applicant's response to the clinical information request submitted on October 20, 2025.
Abbreviations: SD: standard deviation; LS-Means: Least squares (LS) mean; SEM: standard error of the mean; CI: confident interval; n=number of subjects
[1]LS-Means estimated using a linear mixed model repeated measures (MMRM) model with the observed change from Baseline in HFMSE total score at all post-baseline visits as the dependent variable. The fixed effects included treatment, visit, treatment by visit interaction, randomization strata, and the baseline score as covariate. An unstructured covariance matrix was used. The end of Follow-up Period 1 was defined as the average of the Week 48 and Week 52 assessments. If just one of the assessments was valid/available, it was defined as the end of Follow-up Period 1.
Treatment difference ITVISMA-Sham (95% CI): 4.25 (1.07, 7.42).

Efficacy was established in the Phase 3 study B12301 (Period 1) based on the prespecified primary efficacy endpoint of improved motor function, as measured by the HFMSE at the end of period 1 (e.g., 52 weeks), in patients receiving ITVISMA compared to sham procedure. Efficacy was supported by numerical improvement in favor of the ITVISMA group compared to the Sham group in all five prespecified secondary efficacy endpoints.

Efficacy Conclusions
ITVISMA demonstrated substantial evidence of effectiveness for the treatment of SMA in pediatric patients 2 years of age or older with confirmed mutation in *SMN1* gene based on primary evidence of effectiveness from the adequate and well controlled Phase 3 Study B12301, and the confirmatory evidence of effectiveness including data characterizing the product's mechanism for delivering a gene encoding SMN protein and efficacy findings from ZOLGENSMA, which contains the same active ingredient in an intravenous formulation.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) Clinical Investigator (CI) inspection assignments were issued for three foreign clinical study sites that participated in the conduct of study protocol COAV101B12301.The inspections did not reveal substantive issues that impact the data submitted in this original BLA.

c. Pediatrics

The Pediatric Research Equity Act (PREA) is not applicable to ITVISMA because the product was studied in the pediatric population aged 2 years and older and the program was granted orphan drug designation.

d. Other Special Populations

Efficacy and safety findings from pediatric patients aged 2 years and older were extrapolated to support inclusion of adults with SMA in the proposed indication. The primary justifications for including adult patients are:

- ITVISMA clinical program enrolled patients across a broad range of ages and functional levels to represent the heterogeneous SMA patient population.

- Adult-onset SMA patients typically present with the mildest disease course and slowest progression, making them clinically comparable to the study population with highest-functioning patients. The subgroup with the highest motor milestone of "able to walk with assistance" (n=24), which represents the mildest form of SMA typically seen in adult-onset cases, demonstrated the greatest improvement compared to sham treatment (LS-mean change in HFMSE of 4.25 points, 95% CI: 1.07 to 7.42).

- While the safety profile in adults is not expected to differ significantly from the studied pediatric population, warnings and precautions are warranted due to the potentially increased risks of adverse events of special interest (e.g., hepatotoxicity and cardiotoxicity) in adult patients with preexisting chronic medical conditions. Accordingly, a cardiotoxicity warning and a hepatotoxicity boxed warning have been incorporated into the USPI.

7. Safety and Pharmacovigilance

The safety population included 167 patients who received ITVISMA at a fixed dose of 1.2×10^{14} vg via a single intrathecal injection in the following three studies:

- **Phase 3 Study B12301**: The Study is described in Section 6a. 115 patients contributed to the safety database: 75 patients treated in Period 1 and 40 patients who received sham in Period 1, then ITVISMA in Period 2.

- **Phase 1/2 Study CL-102:** A Phase 1/2, open-label, dose-ranging study in treatment-naïve patients with SMA who were between six and 60 months of age. The study population consisted of patients with a genetic diagnosis of SMA with bi-allelic deletion of *SMN1* and 3 copies of *SMN2*, all of whom were able to sit independently but could not stand or walk independently.

- **Phase 3b Study B12302:** A Phase 3b, open-label, single-arm, multi-center study to evaluate the safety and tolerability of ITVISMA in patients aged 2 to <18 years with SMA who had previously received treatment with approved SMN-targeted

therapies. This study enrolled patients who had discontinued treatment with either nusinersen (washout period of at least 4 months) or risdiplam (washout period of at least 14 days), representing a population of treatment-experienced SMA patients.

The overall median follow-up duration was 13.83 months (range: 0.2-74.5 months) post ITVISMA administration. All 167 patients received a course of oral corticosteroid prior to and following ITVISMA administration. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) scale Version 5.0 was used for grading of AEs per protocol.

Table 8 summarizes the safety database and breakdowns of adverse events (AEs), follow-up durations, severity grades, serious adverse events (SAEs), and AEs leading to discontinuation across the three studies.

Table 8. Summary of ITVISMA Safety Data (n=167)

Parameters	**Study B12301 (Period 1) N=75 (%)**	**Study B12301 (Period 2) N=40 (%)**	**Study B12302 N=27 (%)**	**Study CL-102 N=25 (%)**
Follow up duration	52 weeks	12 weeks	52 weeks	12-15 months
Patients with AEs	73 (97.3%)	26 (65.0%)	27 (100%)	25 (100%)
Total AEs	387	74	341	284
Deaths	0	0	0	0
Patients with SAEs	21 (28%)	10 (25%)	4 (15%)	6 (24%)
Total SAEs	50	14	19	11
Patients with AE ≥Grade 3	8 (11%)	2 (5%)	1 (4%)	8 (32%)
Patient with mild/moderate AEs	65 (87%)	24 (60%)	26 (96%)	17 (68%)
AEs Leading to Discontinuation	1*	0	0	0

Source: Clinical reviewers adapted based on data from the Applicant's response to the clinical information request submitted on October 20, 2025.
* The patient discontinued the study due to ineligibility for Period 2 in Study B12301 because of peripheral sensory neuropathy that occurred in Period 1 was not resolved.
Abbreviations: AE: Adverse Event.

There were no deaths. Five SAEs were assessed as possibly related to ITVISMA and/or administrative procedure. One hundred fifty-one (151) patients experienced at least one AE. Majority (79%) of AEs were mild to moderate in severity according to CTCAE, version 5. The most common AEs by preferred term include upper respiratory tract infection, pyrexia, vomiting, and cough.

Serious Adverse Events (SAEs)
A total of 41 patients experienced 94 SAEs across the three studies. Five SAEs were assessed as possibly related to OAV101 and/or administrative procedure (Table 9).

Table 9. SAEs, Possibly Related to ITVISMA, Safety Population (n=167)

SAE (Study)	Onset/ duration (days)	Severity	Description/Resolution Status
Liver enzyme increased (Study B12301)	27/750+	Moderate	3-year-old male; maximum ALT 408 U/L (8X ULN) and AST 234 (4X ULN) U/L at Week 6; resolved
Signs and symptoms related to DRG toxicity (Study B12301)	17/766 ongoing	Moderate	16-year-old female; peripheral sensory neuropathy (paresthesia on both feet); unresolved despite multiple treatment interventions
Signs and symptoms related to DRG (Study B12301)	20/750+	Moderate	16-year-old female; hypoesthesia (numbness in both legs); unresolved at the end of Period 1
Vomiting (Study B12301)	6/6	Severe	3-year-old female; hospitalized for IV fluid due to severe vomiting; resolved
Elevated ALT/AST (Study CL-102)	16/77	Severe	14-month-old male; hepatomegaly and elevated ALT 461 IU/L and AST of 229 IU/L; resolved

Source: Clinical reviewers adapted based on data from the Applicant's response to the clinical information request submitted on October 24, 2025.
Abbreviations: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ALP: Alkaline Phosphatase; ULN: Upper Limit of Normal; IU/L: International Units per Liter.

Adverse Events of Special Interest (AESI)
The adverse events of special interest (AESI) have been determined on a program level based on the important identified or potential risks associated with onasemnogene abeparvovec-xioi (ZOLGENSMA) as listed below.

- Hepatotoxicity
- Transient Thrombocytopenia
- DRG Toxicity Signs/Symptoms
- Cardiac Adverse Events
- New Malignancies
- Thrombotic Microangiopathy (TMA)

Table 10 and Table 11 provide summaries of AESIs that were assessed at least possibly related to ITVISMA treatment for studies B12301 Periods 1 and 2, B12302, and CL-102.

A total 53 AESIs occurred in 36 patients. Most of the AESIs were mild to moderate in severity.

The AESIs of hepatotoxicity, transient thrombocytopenia, DRG toxicity signs/symptoms, and cardiac AEs were also observed in the ITVISMA clinical program, consistent with identified potential risks associated with onasemnogene abeparvovec-xioi (ZOLGENSMA).

Hepatotoxicity was observed in 18 (11%) of 167 patients in ITVISMA clinical studies.

No new malignancies or TMA events were reported.

Table 10. AESI Categories across Studies of ITVISMA in Safety Population (n=167)

AESI Category	CL-102 (N=25) n (%) E	B12301 P1 (N=75) n (%) E	B12301 P2 (N=40) n (%) E	B12302 (N=27) n (%) E
Hepatotoxicity	5 (20.0) 7	7 (9.3) 7	2 (5.0) 2	4 (14.8) 4
Transient Thrombocytopenia	4 (16.0) 4	4 (5.3) 4	1 (2.5) 2	8 (29.6) 12
DRG toxicity	0	2 (2.7) 5	1 (2.5) 1	2 (7.4) 4
Cardiac Adverse Events	1 (4.0) 1	0	0	0

Source: Reviewer adapted based on data from the Applicant's response to the clinical information request submitted on October 24, 2025.

Table 11. Frequency and Severity of AESIs across Studies of ITVISMA in Safety Population (n=167)

Study	AESI Reports	Patients	Mild n (%)	Moderate n (%)	Severe n (%)
B12301 Period 1 (n=75)	16	12	9 (56.2%)	7 (43.7%)	0 (0%)
B12301 Period 2 (n=40)	5	4	4 (80.0%)	1 (20.0%)	0 (0%)
B12302 (n=27)	20	13	18 (90.0%)	2 (10.0%)	0 (0%)
CL-102 (n=25)	12	7	7 (58.3%)	1 (8.3%)	4 (33.3%)
Total	53	36	38 (71.6%)	9 (17.0%)	4 (7.5%)

Source: Reviewer adapted based on data from the Applicant's response to the clinical information request submitted on October 24, 2025.

Among the three studies, Study CL-102 reported four severe adverse events involving hepatic enzyme elevation. The Applicant confirmed that no patients developed clinical

signs and symptoms such as jaundice associated with these laboratory findings. The overall safety findings did not reveal additional safety signals.

Study B12301 Period 1

Safety of ITVISMA was further characterized based on data from the Phase 3, randomized, double-blind, sham-controlled trial through Week 52 (Study B12301, Period 1). The study compared safety between 75 patients who received a single intrathecal injection of ITVISMA at a fixed dose of 1.2 x 10^14 vg and 51 patients who received a sham procedure. The comparative safety information in Study B12301 (Period 1) are described in Section 6 of the USPI.

Among 75 subjects who received ITVISMA, 73 subjects (97.3%) reported 387 AEs. Most patients (65/75, 86.6%) experienced AEs that were mild or moderate in severity. There were no deaths reported. The four SAEs that possibly related to the ITVISMA treatment in Study B12301 Period 1 were discussed above. The most common AEs (Table 12, frequency > 2%) were upper respiratory tract infection, pyrexia, upper gastrointestinal symptoms, hepatic enzyme increased, headache, dizziness, pain in extremity, thrombocytopenia, sensory disturbance. Table 12 is included in the USPI.

Table 12. Most Common ARs (> 2%) in Study B12301 (Period 1)

Adverse reactions	**ITVISMA (N = 75), n (%)**	**Sham (N = 51), n (%)**
Upper respiratory tract infection*	31 (41)	15 (29)
Pyrexia	19 (25)	12 (24)
Upper gastrointestinal symptoms*	20 (27)	8 (16)
Hepatic enzyme increased*	6 (8)[a]	5 (10)
Headache	8 (11)	2 (4)
Dizziness	4 (5)	1 (2)
Pain in extremity	3 (4)	1 (2)
Thrombocytopenia*	3 (4)	0
Sensory disturbance*	2 (3)[b]	1 (2)[c]

Source: Section 6 of USPI
* Is a composite that includes multiple related term
[a)] Two patients had ALT elevations of 20 times the upper limit of normal (ULN)
[b)] Signs and symptoms that may be suggestive of dorsal root ganglion (DRG) toxicity occurred within 3 weeks of ITVISMA injection and stabilized but remained unresolved at the end of study period.
[c)] Occurred 154 days after the sham procedure and resolved after 15 days without intervention.

Hepatotoxicity in Study B12301 Period 1

As shown in Table 13, OAV101-treated patients experienced higher peak transaminase values, with 2 patients developing ALT elevations >20x ULN. The events in these two patients were assessed as mild in intensity and non-serious by investigators despite the significant laboratory elevations. Although no transaminase increases were accompanied

by bilirubin elevations or clinical signs of hepatic insufficiency, this finding supports including a boxed warning in the label.

Table 13. Liver Function Tests (LFTs) through the End of Follow-up Period 1 in Study B12301

Parameter	Treatment Arm	>3x ULN n (%)	>5x ULN n (%)	>10x ULN n (%)	>20x ULN n (%)
AST	OAV101 (N=75)	3 (4.0%)	2 (2.7%)	1 (1.3%)	0 (0%)
	Sham (N=51)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ALT	OAV101 (N=75)	4 (5.3%)	3 (4.0%)	3 (4.0%)	2 (2.7%)
	Sham (N=51)	3 (5.9%)	1 (2.0%)	0 (0%)	0 (0%)
ALP	OAV101 (N=75)	2 (2.7%)	1 (1.3%)	0 (0%)	0 (0%)
	Sham (N=51)	1 (2.0%)	0 (0%)	0 (0%)	0 (0%)
Total Bilirubin	OAV101 (N=75)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Sham (N=51)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: Reviewer adapted based on data from the Applicant's response to the clinical information request submitted on November 4, 2025.
Abbreviations: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ALP: Alkaline Phosphatase; ULN: Upper Limit of Normal

Safety Conclusion:

The safety profile of ITVISMA was evaluated in a safety database of 167 patients who received ITVISMA at a fixed dose of 1.2×10^{14} vg via single intrathecal injection across three clinical studies. Safety was further characterized based on the data from the Phase 3 Study B12301 (Period 1), which compared 75 patients receiving a single intrathecal injection of OAV101B at the fixed dose versus 51 patients who received a sham procedure. In Study B12301 (Period 1), no deaths were reported. Four SAEs were assessed as possibly related to ITVISMA and/or the administration procedure, including increased liver enzymes (1), signs and symptoms related to DRG toxicity (2), and vomiting (1). The most common AEs (Table 12, frequency > 2%) were upper respiratory tract infection, pyrexia, upper gastrointestinal symptoms, hepatic enzyme increased, headache, dizziness, pain in extremity, thrombocytopenia, sensory disturbance.

The AESIs of hepatotoxicity, transient thrombocytopenia, DRG toxicity signs/symptoms, and cardiac AEs were also observed in the ITVISMA clinical program, consistent with identified potential risks associated with onasemnogene abeparvovec-xioi (ZOLGENSMA). The overall safety findings in an open label phase 1/2 study (CL-102) did not reveal additional safety concerns. In Study B12302, an open label, single arm, Phase 3b study, patients who had discontinued treatment with either nusinersen

(washout period of at least 4 months) or risdiplam (washout period of at least 14 days) were enrolled. The safety profile was comparable to that observed in the Phase 3 Study B12301.

Pharmacovigilance Plan

The Pharmacovigilance Plan (PVP) for ITVISMA (received July 25, 2025) includes the Applicant's assessment of important identified risks, important potential risks, and missing information. Important identified risks include hepatotoxicity, transient thrombocytopenia, and TMA. Important potential risks include cardiac adverse events, dorsal root ganglia toxicity, and tumorigenicity due to chromosomal integration. Missing information includes long-term efficacy and safety of onasemnogene abeparvovec-brve therapy.

The Applicant will conduct routine pharmacovigilance, which includes adverse event reporting, in accordance with 21 CFR 600.80. Expedited reporting of adverse events of special interest (hepatic failure, thrombotic microangiopathy, and peripheral sensory neuropathy) described in 11.c. will also be required for three years following product licensure. The proposed pharmacovigilance plan for ITVISMA is adequate for the labeled indication.

The available data do not indicate a safety signal which would require a Risk Evaluation and Mitigation Strategy (REMS). There is no safety-related study as a postmarketing requirement (PMR) or as an agreed upon postmarketing commitment (PMC) at this time.

8. Labeling

A new proposed Proprietary Name Request to be submitted by the sponsor was requested from the Agency on October 29, 2025. The review team expressed concerns about the safety of intrathecal administration of this product due to the similarity between this proposed name and the already-approved ZOLGENSMA (onasemnogene abeparvovec-xioi) for intravenous administration. The previous acceptable proprietary naming convention (b) (4) presented a substantial risk of medication errors, specifically where healthcare providers may inadvertently administer product by an incorrect route (intrathecal vs. intravenous) and incorrect product concentration with the potential for exposure to subtherapeutic or toxic dose. It is important to note that unlike conventional medications, gene therapy products can only be administered once in a patient's lifetime, and any administration error could permanently disqualify the patient from receiving the correct treatment, representing an irreversible clinical outcome with potentially devastating consequences for the patient.

We strongly recommended the proposal include a distinctly different proprietary name from the intrathecal formulation that clearly differentiates it from the approved intravenous formulation, ZOLGENSMA. The new name should eliminate any potential for confusion between the two products and be sufficiently distinct to prevent look-alike/sound-alike errors in clinical and pharmacy settings.

The proposed proprietary name, ITVISMA, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on November 12, 2025, and was found acceptable.

CBER communicated the acceptability of the proprietary name to the Applicant on November 13, 2025.

APLB reviewed the proposed prescribing information and package and container labels on October 31, 2025 and found them acceptable from a comprehension, readability, and promotional perspective.

The Office of Clinical Evaluation (OCE) labeling review team, together with the relevant discipline review teams, reviewed and revised the proposed prescribing information to ensure that it meets regulatory/statutory requirements, is consistent with current labeling practice, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the product, and provides clear and concise information for the healthcare providers. With the agreed revisions, the prescribing information is acceptable.

Several significant labeling changes were made to enhance safety and clarity. A hepatotoxicity boxed warning was added (retained from ZOLGENSMA with modified language), and the indication was revised to specify that ITVISMA is indicated for SMA patients 2 years and older with confirmed SMN1 gene mutations. As discussed in Section 1, the indication was extended beyond the age range of the pivotal study population (pediatric patients 2.1 to 16.6 years of age) to include adult patients with SMA. Critical dosing information and detailed administration steps were added to Section 2, while Section 5 was expanded to include a new warning about elevated cardiac troponin risk. The adverse reactions section was restructured to reflect current labeling practices and include post-marketing experience from ZOLGENSMA, while non-informative study data was removed. Additional revisions included clarifying the mechanism of action, updating immunogenicity data and refining clinical studies descriptions to focus on pre-specified and clinically meaningful endpoints.

9. Advisory Committee Meeting

The submitted information, including clinical study design and trial results, did not raise unresolved scientific or regulatory questions that would benefit from advisory committee discussion. Therefore, this BLA was not referred to the Cellular, Tissue, and Gene Therapies Advisory Committee.

10. Other Relevant Regulatory Issues

The Applicant requested a rare pediatric disease priority review voucher, which has been denied. The active ingredient (drug substance) in BLA 125856 (onasemnogene abeparvovec-brve) is identical to the active ingredient in the approved BLA 125694 (onasemnogene abeparvovec-xioi). Since the active ingredient has already been approved in BLA 125694 under Section 351(a) of the Public Health Service Act, BLA 125856 does not meet the criteria for granting a rare pediatric disease priority review voucher.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant has provided substantial evidence of effectiveness from an adequate and well controlled (AWC) study based on the change from baseline in HFMSE total score to Week 52 in treatment group compared to the sham-control arm. The demonstrated benefits on motor function outweigh the important identified risks of hepatotoxicity, transient thrombocytopenia, and TMA, and important potential risks of cardiac adverse events, dorsal root ganglia toxicity, and tumorigenicity due to chromosomal integrationand. The risks can be mitigated through labeling and post-marketing pharmacovigilance activities. Based on the favorable benefit-risk assessment of ITVISMA for treating SMA in pediatric patients 2 years of age and older with confirmed *SMN1* gene mutations, the review team recommends approval of ITVISMA via traditional regulatory pathway.

b. Benefit/Risk Assessment

Overall, ITVISMA demonstrated a favorable benefit/risk profile for treating spinal muscular atrophy (SMA) in pediatric patients 2 years of age or older with confirmed *SMN1* gene mutations.

The primary evidence of effectiveness of ITVISMA to improve motor function in patients with SMA aged 2 to <18 years, was provided from the single AWC study which demonstrated the LS mean change from baseline (SEM) in HFMSE total score to Week 52 of 2.39 (0.44) points in ITVISMA arm compared to 0.51 (0.53) points in the sham arm. The LS mean difference of 1.88 points between ITVISMA arm and the sham arm was statistically significant [95% CI: 0.51, 3.25; p-value: 0.0074]. The confirmatory evidence of effectiveness is based on, (i) mechanistic evidence of ITVISMA, designed to deliver a gene encoding the human SMN protein, and (ii) efficacy findings from ZOLGENSMA (onasemnogene abeparvovec-xioi), a product that contains the same active ingredient for intravenous administration. The Applicant provided adequate justification to support expanding the indication beyond the pivotal study population to include adult patients with SMA.

The safety profile of ITVISMA was evaluated in a safety database of 167 patients who received ITVISMA at a fixed dose of 1.2×10^{14} vg via single intrathecal injection across three clinical studies. The observed safety risks of hepatotoxicity, transient thrombocytopenia, DRG toxicity, and cardiac AEs, and common adverse reactions (e.g., upper respiratory tract infection, pyrexia, upper gastrointestinal symptoms, hepatic enzyme increased, headache, dizziness, pain in extremity, thrombocytopenia, sensory disturbance) were consistent with the risks reported with ZOLGENSMA. These risks can be mitigated by routine medical management, appropriate labeling of Prescribing Information (PI), and expedited pharmacovigilance plan proposed by the Applicant. In addition, the ongoing 5-year LTFU safety study will provide additional long-term data on the potential safety risks, such as tumorigenicity.

c. Recommendation for Postmarketing Activities

Routine pharmacovigilance activities will be conducted for postmarketing safety monitoring of ITVISMA, with adverse event reporting as required under 21 CFR 600.80.

Expedited reporting to the FDA Adverse Event Reporting System (FAERS) for the following adverse events (AEs) of special interest following use of ITVISMA, regardless of seriousness or expectedness, will be required:

a. Cases of hepatic failure
b. Cases of thrombotic microangiopathy
c. Cases of peripheral sensory neuropathy

These reports must be submitted to FAERS as soon as possible but no later than 15 calendar days from initial receipt of the information by Novartis. Expedited reporting of these AEs will be required for three years following the date of product licensure.

In addition, a narrative summary and aggregate analysis for each of these AEs will be included in periodic safety reports for three years following the date of product licensure.

Long-term follow up studies of subjects treated in clinical trials (voluntary observational postmarketing studies: Study AVXS-101-LT-002 [COAV101A12103], NCT 04042025; and Study COAV101A12308, NCT 05335876) will provide additional follow-up data regarding safety and effectiveness of ITVISMA.

The Review Committee has determined that ITVISMA the identified risks can be adequately mitigated through product labeling and the Applicant's proposed post-marketing pharmacovigilance activities. A Risk Evaluation and Mitigation Strategy (REMS) or post-marketing safety studies through PMR or PMC are not warranted.

12. References

FDA Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC) Meeting #70, Toxicity Risks of Adeno-associated Virus Vectors for Gene Therapy, September 2-3, 2021.

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