Our STN: BL 125694/452

PROPOSED PEDIATRIC STUDY REQUEST
WRITTEN REQUEST
June 28, 2024

Novartis Gene Therapies, Inc.
ATTENTION: Lisa Krueger, PharmD
2275 Half Day Road, Suite 200
Bannockburn, IL 60015

Dear Dr. Krueger:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for onasemnogene abeparvovec-xioi.

Please also refer to your Proposed Pediatric Study Request received March 1, 2024, submitted under Section 505A of the Food, Drug, and Cosmetic Act (FDCA) for onasemnogene abeparvovec-xioi suspension for intrathecal infusion.

This study investigates the potential use of onasemnogene abeparvovec-xioi in the treatment of late onset type 2 spinal muscular atrophy (SMA) in patients 2 years to less than 18 years of age who are treatment naive, sitting, and never ambulatory.

Background:
SMA is an autosomal recessive, early childhood disease with an incidence of approximately 1:10,000 live births, of which approximately 45% to 60% of cases are SMA Type 1. SMA is classified into four phenotypes on the basis of age of onset and highest motor function achieved, with an additional phenotype (Type 0) to describe the severe forms of antenatal onset. Table 1 summarizes the classification of SMA types. Similar to SMA Type 1, individuals with SMA Type 2 present before age 2 years with severe motor developmental delay and shortened life expectancy. Therefore, this pediatric population may benefit from this treatment.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Table 1. Classification of SMA Types

Type	Age at Symptom Onset		Maximum Motor Function	Life Expectancy	*SMN2* Copy Number
0	Fetal		Nil	Days–Weeks	1
1	< 6 months	1A: birth – 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

bold = predominant *SMN2* copy number that defines the SMA type, the other copy numbers represent a small percentage of the designated SMA type.
Source: Adapted from Kolb and Kissel 2011 and Mercuri et al 2012

The most common form of SMA results from biallelic pathogenic variants in the survival motor neuron 1 gene (*SMN1*) on chromosome 5q13 (5q SMA); of these 5q SMA cases, 95% are due to biallelic deletions, with the remainder being hemizygous deletions with a point mutation on the other chromosome. In humans, two forms of the survival motor neuron gene (*SMN*) exist: a telomeric form (*SMN1*) and a centromeric form (survival motor neuron 2 [*SMN2*] gene). Transcription of *SMN1* produces full-length messenger RNA (mRNA) transcripts that encode the SMN protein, necessary for motor neuron survival. The *SMN2* gene is nearly identical to the *SMN1* gene. A C to T substitution at position 840 results in the preferential exclusion of exon 7 from most of the transcriptional product. The resultant truncated protein is not functional. Approximately 10% to 15% of the protein product of *SMN2* is the full length, functional SMN protein. Pathogenic variants in both copies of *SMN1* cause a decreased expression of the SMN protein. Individuals with SMA lack a normally functioning *SMN1* gene and rely on functional protein produced by the *SMN2* gene for motor neuron survival. The normal population carries 0 to 4 copies of *SMN2*. In patients with SMA who lack functional *SMN1* genes, higher *SMN2* copy numbers are associated with less severe disease.

Although the primary pathology of SMA is neurodegeneration at the level of the spinal motor neurons, some clinical reports indicate the involvement of other organs to include the heart, liver, pancreas, and intestine. In addition, metabolic deficiencies including hyperglycemia and hypoglycemia have been reported. SMA is therefore best described as a motor neuron disease for which the root cause is SMN1 protein deficiency. Deficiency of SMN protein correlates directly with death of the individual's motor neurons. Loss of motor neurons leads to muscle weakness and muscle atrophy. Progressive loss of muscle control, swallowing, and breathing can lead to death in the most severe forms of the disease. Proximal muscles are preferentially affected in SMA with greater effects in lower extremities compared to the upper extremities[1,2].

[1] Kolb SJ, Kissel JT (2011). Spinal muscular atrophy: a timely review. Arch Neurol p. 979-84.
[2] Mercuri E, Bertini E, Iannaccone ST (2012). Childhood spinal muscular atrophy: controversies and challenges. Lancet Neurol p. 443-52.

Treatment approaches to SMA include the use of both gene therapy and splicing modulators. Onasemnogene abeparvovec-xioi is an adeno-associated virus (AAV) vector-based gene therapy which is administered intravenously (IV). Onasemnogene abeparvovec-xioi is currently the only approved gene therapy treatment and directly corrects the SMN protein deficiency which is the root cause for all phenotypic variants of SMA, by providing a functional copy of the *SMN1* gene. Onasemnogene abeparvovec-xioi IV is approved for use in patients less than 2 years of age with SMA with bi-allelic mutations in the SMN1 gene.

Additionally, two splicing modulator therapies have been approved: nusinersen[3], and risdiplam[4]. Splicing modulators increase production of SMN protein by modifying splicing in the available back-up *SMN2* gene and require life-long administration. Gene replacement therapy has not been studied in patients with later-onset SMA. While chronically administered therapies have become available in recent years, there is little well controlled clinical data in this population. Data to support the use of nusinersen in later-onset SMA was from a limited study population that only allowed for inclusion of patients up to 12 years of age with baseline Hammersmith Functional Motor Scale–Expanded (HFMSE) scores ≥ 10 [2]. Despite representation across a range of ages in the risdiplam pivotal study, no statistical improvement in HFMSE score was demonstrated with only a 0.58-point treatment effect observed. Therefore, there is an unmet medical need for the patients with later onset SMA, ≥ 2 to < 18 years of age. Because onasemnogene abeparvovec-xioi is currently approved for patients <2 years of age, a pediatric study in neonates is not warranted.[5]

Representation of Ethnic and Racial Minorities: The study must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

To obtain needed pediatric information on onasemnogene abeparvovec-xioi, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, and pursuant to section 351(m) of the Public Health Service Act (the PHS Act), as amended by the Biologics Price Competition and Innovation Act of 2009, that you submit information from the studies described below.

Nonclinical studies:

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this Written Request.

[3] Spinraza USPI 2023
[4] Evrysdi USPI 2023
[5] Zolgensma USPI 2023

Clinical study:

Study 1: A randomized, sham-controlled, double-blind study to evaluate the efficacy and safety of onasemnogene abeparvovec-xioi intrathecal (IT) in patients ≥ 2 years to less than 18 years of age with later onset type 2 SMA who are treatment naive, sitting, and never ambulatory

- **Study Objectives:**

Primary objective: To evaluate the efficacy and safety of onasemnogene abeparvovec-xioi IT in patients ≥ 2 years to less than 18 years of age with later onset type 2 SMA who are treatment naive, sitting, and never ambulatory.

Secondary objectives:

1. To compare the efficacy of onasemnogene abeparvovec-xioi IT, vs. sham control in two patient age groups: ≥ 2 years to < 5 years (HFMSE[6], RULM[7]); ≥ 2 years to < 18 years (RULM)

2. To evaluate the safety and tolerability of onasemnogene abeparvovec-xioi IT vs. sham control in patients ≥ 2 years to < 18 years

- **Patients to be studied:**

Age groups: late onset type 2 SMA in patients ≥ 2 years to less than 18 years of age who are treatment naive, sitting, and never ambulatory.

Number to be studied: A minimum of 125 patients must be enrolled and randomized in a 3:2 ratio to receive onasemnogene abeparvovec-xioi by lumbar IT injection or to receive a sham procedure**.**

- **Study endpoints:**

Efficacy Endpoints:

The primary efficacy endpoint must include change from baseline in HFMSE total score at the end of follow-up Period 1 (Week 52) in the overall study population (≥ 2 to < 18 years age group)

Safety Endpoints:

Safety monitoring that must be included in the protocol and described in the final study report:

a. Incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs)
b. Number of patients with adverse events of special interest (AESIs)

[6] Hammersmith Functional Motor Scale–Expanded
[7] RULM: Revised upper limb module

c. Evaluation of changes from baseline in vital signs, physical/neurological examinations, laboratories (chemistry, hematology, liver functions tests), echocardiogram, ECG, anthropometry, and Columbia-Suicide Severity Rating Scale (C-SSRS)
d. Number (and percentage) of patients with intracardiac thrombi
e. Number (and percentage) of patients with low cardiac function
f. Evaluation of vector shedding in treated patients

Adverse Events of Special Interest (AESIs): The protocol must include plans for the monitoring of the following AESIs and the study report must include a summary of these adverse events:

a. Hepatotoxicity: Acute Serious Liver Injury, Acute Liver Failure or Elevated Aminotransferases
b. Systemic immune response
c. Thrombocytopenia
d. Thrombotic microangiopathy
e. Increased troponin-I
f. Tumorigenicity

A Data Monitoring Committee (DMC) must be included because of the potential risks associated with intrathecal administration of AAV-vector based gene therapy.

- **Known safety concerns and monitoring:**

The protocol will include plans for the monitoring of all AEs until symptom resolution or until the condition stabilizes.

Extraordinary results:

In the course of conducting this study, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

Biological product information:

1. *Dosage form: AAV-vector based gene therapy*
2. *Route of administration: intrathecal*
3. *Regimen per protocol: one-time, single IT injection of a fixed dose of onasemnogene abeparvovec-xioi*

Statistical information, including power of Study 1 and statistical assessments:

The primary efficacy analysis will be performed by testing the null hypothesis of no difference in the change from baseline in HFMSE total at the end of Follow-up Period 1 between the treatment and sham procedure against the alternative hypothesis that there is a difference at an overall two-sided 5% level of significance. The primary efficacy endpoint will be analyzed using a mixed model with repeated measurements (MMRM), with treatment, scheduled visit, treatment by visit interaction, the stratification variable, and the pre-treatment HFMSE total score as covariates. The primary efficacy endpoint will be analyzed based on the full analysis set. A hierarchical gate-keeping procedure and the Hochberg method will be used to control the overall Type 1 error rate of two-sided 5%.

Assuming a true treatment difference in the change from Baseline in HFMSE of 3 points and a standard deviation of 5 points, a sample size of 125 subjects (75 in the treatment group and 50 in the sham procedure) provides more than 90% power to demonstrate statistical significance at a two-sided 5% level of significance.

Labeling that may result from the study:

You must submit proposed pediatric labeling to incorporate the findings of the study. Under section 505A(j) of the FDCA, regardless of whether the study demonstrate that onasemnogene abeparvovec-xioi is safe, pure, and potent, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study. Under section 505A(k)(2) of the FDCA, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study.

Format and types of reports to be submitted:

You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain Agency agreement.

Under section 505A(d)(2)(B) of the FDCA, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this product that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 600.80 should include adverse events occurring in an adult or a pediatric patient.

In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the guidance for industry *Providing Postmarketing Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report)* at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346564. You are encouraged to contact the reviewing Division for further guidance.

For studies started after December 17, 2017, study data must be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document *Study Data Technical Conformance Guide* at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf and referenced in the FDA guidance for industry *Providing Regulatory Submissions in Electronic Format - Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf. For more information, please visit http://www.fda.gov/ectd.

Timeframe for submitting reports of Study 1:

Reports of the above study must be submitted to the Agency on or before June 30, 2025. Please keep in mind that pediatric exclusivity can attach only to existing exclusivity, if any, that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, if there is unexpired exclusivity that is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such exclusivity is otherwise due to expire.

If FDA has not determined whether onasemnogene abeparvovec-xioi is eligible for reference product exclusivity under section 351(k)(7) of the PHS Act, you may submit a request for reference product exclusivity with supporting data and information to the Agency. Note that neither the issuance of this formal Pediatric Written Request, nor any request for exclusivity made by you confers or otherwise implies that you are eligible for reference product exclusivity under section 351(k)(7) of the PHS Act.

Response to Written Request:

Under section 505A(d)(2)(A)(i) of the FDCA, within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric study complete study report will be submitted. If you do not agree to the request, you must indicate why you are declining to conduct the study. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Submit protocols for the above study to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC WRITTEN REQUEST STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study must be submitted as a supplement to your approved Biologics License Application (BLA) with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the FDCA, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e., complete or partial response);
2. the status of the application (i.e., withdrawn after the supplement has been filed or pending);
3. the action taken (i.e., approval, complete response); or
4. the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at https://www.fda.gov/about-fda/about-center-biologics-evaluation-and-research-cber/list-determinations-made-cber-including-written-request.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the PHS Act, you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, please contact the Regulatory Project Manager, Crystal Melendez, at (240) 772-6272 or by email at Crystal.Melendez@fda.hhs.gov.

Sincerely,

Lola Fashoyin-Aje, MD, MPH
Acting Director
Division of Clinical Evaluation General Medicine
Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics Evaluation and Research