U.S. FOOD & DRUG ADMINISTRATION

Our STN: BL 125840/0

COMPLETE RESPONSE
February 7, 2026

REGENXBIO, Inc.
Attention: Steve Pakola, MD
9804 Medical Center Drive
Rockville, MD 20850

Dear Dr. Pakola:

Please refer to your Biologics License Application (b) (4), for clemidsogene lanparvovec, (b) (4)

We have completed our review of all the submissions you have made relating to this BLA. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

You submitted a BLA for clemidsogene lanparvovec, a gene therapy for the requested indication of treatment of patients with mucopolysaccharidosis type II (MPS II, Hunter syndrome). Your requested broad indication implies both neuronopathic and attenuated (non-neuronopathic) types of MPS II.

MPS II is a rare disorder of metabolism caused by mutations in the iduronate-2-sulfatase (*IDS*) gene. Deficiency of lysosomal enzyme results in progressive accumulation of glycosaminoglycans (GAGs) heparan sulfate (HS) and dermatan sulfate (DS) throughout body tissues and organs, leading to multi-organ dysfunction. The neuronopathic form of disease is distinguished from the attenuated form by presence of neurological impairment.

To support this BLA under the accelerated approval pathway, you submitted the results from a single study, RGX-121-101, an open-label, multi-part study; Part 1 focused on dose-finding and safety, and Part 2 served as the pivotal single-arm study which evaluated clemidsogene lanparvovec administered as a single intracerebroventricular (ICV) or intracisternal (IC) dose in 13 pediatric patients aged 4 to 56 months with protocol- defined neuronopathic MPS II. The Part 2 primary endpoint was the proportion of responders on a novel biomarker endpoint assessed in cerebrospinal fluid (CSF) at Week 16, compared to the patient's own baseline and informed by an external natural history control.

Although we agreed in principle to the study protocol, we expressed concerns throughout your development program at the Pre-IND, IND, and BLA meetings (b) (4)

(b) (4). Specifically, FDA expressed concerns regarding the uncertainty of the study eligibility criteria to adequately define a population with neuronopathic disease, comparability of the natural history external control to the study population, and the appropriateness of CSF HS D2S6 with the proposed performance threshold as a reasonably likely surrogate endpoint to predict clinical benefit on cognitive outcomes in support of a marketing application. FDA indicated that you could pursue an accelerated approval pathway, but the aforementioned concerns should be adequately addressed to provide substantial evidence of effectiveness and may be review issues at the time of BLA submission.

We continued to exercise applicable regulatory flexibilities by evaluating the totality of the data from one single arm study with a small sample size compared to limited external control data and utilizing a novel biomarker. The biomarker CSF HS D2S6 has not been used for any previous regulatory decision and is not routinely assessed as part of standard clinical practice. It lacks support from published literature as a biomarker for this disease and has no established performance threshold to differentiate neuronopathic from attenuated forms of MPS II, or to detect treatment response.

During our multidisciplinary review of your BLA, including consultation with FDA cross-center subject matter experts, we noted that the small, enrolled population of 13 patients had uncertain phenotype of the neuronopathic disease, an inadequate control, and insufficient support for a performance threshold for the novel CSF HS D2S6 biomarker. In addition, we considered the procedural and emergent safety risks of your gene therapy.

Despite exercising regulatory flexibility, given the breadth of uncertainties, we are unable to conclude that the RGX-121-101 study is an adequate and well-controlled study. As communicated during the Late Cycle Meeting (b) (4)), the data from the RGX-121-101 Part 2 study are insufficient to provide substantial evidence of effectiveness to support approval of clemidsogene lanparvovec for the proposed indication of treatment of patients with MPS II, or for the narrower indication of neuronopathic MPS II pursued during clinical development.

The specific deficiencies are explained in detail as follows:

1. Identification of a target population with neuronopathic MPS II

   Expert consensus is lacking to differentiate neuronopathic from attenuated disease in younger MPS II patients who have not yet reached the age at which cognitive plateau or decline is expected for the neuronopathic form. Patients were only required to meet one and not all four eligibility criteria (two based on *IDS* mutations and/or two based on neurodevelopmental scale scores) to define neuronopathic MPS II disease, leading to further heterogeneity and raising uncertainty that the enrolled population is representative of the target population.

Of the Part 2 pivotal study patients, 62% (8/13) were classified as having neuronopathic disease based on their specific *IDS* gene mutation, and 46% (6/13) based on a baseline Bayley Scales of Infant Development, 3rd Edition (BSID-III) cognitive score one standard deviation or more below the normative mean. One patient was classified by both.

The specific challenges with identification of a target population with neuronopathic MPS II are as follows:

a. Defining neuronopathic disease based on a specific genetic mutation is problematic because some mutations in the *IDS* gene contribute to a heterogenous disease presentation with a spectrum of severity inclusive of patients with and without cognitive impairment or have only been reported in a very small number of patients. Therefore, the genotype-phenotype correlation is not well-characterized.

   Among the 8 patients defined as having neuronopathic disease based on a specific *IDS* mutation, mutations generally associated with neuronopathic disease (e.g., large/whole gene deletions, inversions) were present in only 5 patients (63%), whereas the remaining 3 patients (38%) had a mutation with an unclear phenotypic correlation.

b. It is unclear if BSID-III cognitive scores one standard deviation (SD) or more below the normative mean identify cognitive impairment in study patients sufficiently to adjudicate their disease type (attenuated or neuronopathic) for study eligibility. This criterion encompasses a broad range of impairment, from at risk for developmental delay to severe cognitive impairment. Patients with attenuated disease may experience mild impairment, and there is no consensus on a threshold level of cognitive impairment that distinguishes attenuated from neuronopathic disease phenotypes. Additionally, limitations in performance-based testing in younger patients and those with hearing impairment challenge the interpretation of BSID-III results to accurately assess cognition for the purposes of phenotype determination.

   Among the 6 patients defined as having neuronopathic disease based on BSID-III cognitive scores (one SD or more below the normative mean), FDA confirmation of phenotype is challenging in very young patients less than one year of age (1/6, 17%), patients with mild cognitive impairment (3/6, 50%), and/or with concurrent hearing impairment (5/6, 85%).

2. Choice of control

   a. Lack of comparability between trial patients and external control population used to define the primary endpoint

The proposed threshold for CSF HS D2S6 is further compromised by lack of comparability between the Part 2 patients and the external control MPS II patients due to differences in patients' key characteristics such as age and varying definitions of cognitive impairment to distinguish attenuated from neuronopathic MPS II.

b. Using patients as their own control

During our review, we noted intra-patient variability in CSF HS D2S6 levels.

In response to a question raised during the Late Cycle Meeting discussion (b) (4), you later clarified that CSF was sampled by different routes, such as lumbar puncture vs. ICV, during the pre-treatment period, but all post-treatment samples were via lumbar puncture. This may have contributed to intra-patient variability.

We noted that 2 patients in Part 2 had pre-treatment CSF HS D2S6 level less than 100 ng/ml, which essentially made their data not evaluable to assess the treatment effect with clemidsogene lanparvovec.

These factors further complicate the interpretation of the surrogate endpoint.

3. Uncertainty that the primary endpoint of CSF HS D2S6 is reasonably likely to predict clinical benefit

You propose CSF HS D2S6 is a surrogate endpoint reasonably likely to predict cognitive outcomes. You defined "responders" as patients who at Week 16 achieved reduction in CSF HS D2S6 levels to at or below the upper limit detected in attenuated MPS II patients, which was subsequently clarified to mean less than 100 ng/ml and confirmed in the Statistical Analysis Plan dated (b) (4). This CSF HS D2S6 biomarker threshold has been proposed for the purposes of this application without external expert or scientific consensus. Specific deficiencies related to surrogate endpoint suitability are as follows:

a. Insufficient evidence for use of CSF HS D2S6 as a surrogate endpoint reasonably likely to predict clinical benefit

In your submission, you provided correlation analysis between CSF HS D2S6 level and cognitive function based on BSID-III scores. There was no natural history data provided for BSID-III scores to be able to model the expected timing of plateau and decline in untreated disease, and the timing of expected cognitive changes varies substantially in the published literature. Published analysis[1] from your natural history study (which evaluated neurodevelopment on a scale that

[1] Phillips, D., Cho, Y., Mulatya, C., Forsberg, M., Poe, M., & Escolar, M. (2024). Retrospective Natural History Study of neurodevelopment in neuronopathic Mucopolysaccharidosis Type II. *Medical Research Archives, 12*(11). doi:10.18103/mra.v12i11.5915

cannot be directly compared to BSID-III) suggests patients may acquire new skills until an inflection point (i.e., plateau period) which occurs between 66.1 to 74.6 months of age. Study patients were not followed to a sufficient age to evaluate for a deviation from the natural history. Additionally, cognitive changes were challenging to assess over a short duration of follow-up of only 52 weeks for most Part 2 patients. Therefore, the available data is not sufficient to support the correlation analysis between change in CSF HS D2S6 levels and cognitive outcomes.

b. Insufficient evidence to support the proposed threshold of CSF HS D2S6 and utility in differentiating disease phenotypes

   You did not provide sufficient evidence supporting the proposed threshold of reduction of CSF HS D2S6 levels to less than 100 ng/ml and its ability to predict a clinically meaningful benefit.

   This threshold was derived from a study which analyzed CSF samples from 51 patients; however, only 14% (7/51) were MPS II patients external to the RGX-121-101 study, including 6% (3/51) with neuronopathic disease and 8% (4/51) with attenuated disease. The proposed threshold's accuracy to differentiate between the two disease phenotypes is unclear. This was due to the small number of external patients with MPS II, including only 4 with attenuated disease to define the threshold, and no external validation of the threshold was provided.

   The threshold is further challenged by at least one pre-treatment CSF HS D2S6 level less than 100 ng/ml in 5 patients across all the clemidsogene lanparvovec interventional studies, including 2 patients characterized as having profound cognitive impairment at baseline.

We acknowledge the importance of early treatment and the need for therapies for patients with neuronopathic MPS II. We recognize the difficulties in providing robust efficacy data from the RGX-121-101 study, given that neuronopathic disease cannot be reliably identified during the presymptomatic stage, and the proposed biomarker of CSF HS D2S6 lacks sufficient evidence to support the proposed threshold to differentiate disease phenotypes and predict clinical outcomes.

Potential paths forward would be to demonstrate normalization of or a meaningful change in a relevant biomarker, or neurodevelopmental outcomes that deviate from the natural history of disease. You may choose to perform a new clinical study or enroll additional patients in your RGX-121-101 study and continue to follow patients with neuronopathic MPS II treated in study RGX-121-101, using stored CSF samples for biomarker analysis and longer neurodevelopmental follow-up. We recommend that you use an appropriate untreated control comparable to the study population on key factors such as age, stage of disease, and neurodevelopmental assessments, and an adjudication committee comprised of subject matter experts that selects the targeted

population based on multiple pre-defined factors to improve the interpretability of the study results.

We look forward to collaboratively working with you on a study design that adequately minimizes confounding from the above-mentioned factors.

We reserve comments on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed draft final labeling.

ADDITIONAL COMMENTS

In addition, we have the following comments that do not preclude approval.

4. In your future resubmission, consider addressing the following potential confounders to improve interpretability of study results:

    a. Concomitant treatments

        You did not provide sufficient evidence characterizing the potential effect of enzyme replacement therapy (ERT) on biomarkers and clinical outcomes in a younger population such as that of the Part 2 study. ERT was variably used amongst the Part 2 study patients, in that some patients were ERT-naïve (5/13), some continued ERT through the duration of follow-up (2/13), one patient started ERT during the study, and six patients discontinued ERT during the study (including 2 patients who later restarted). Given the uncertain effect of ERT on study outcomes and variable use of ERT amongst Part 2 study patients, study results may have been confounded by concomitant ERT use.

        The impact of immunosuppression on CSF HS D2S6 levels is uncertain since all study patients were still receiving immunosuppression at the time of the primary endpoint assessment. Additionally, we note that duration of follow up is insufficient to establish stabilization of CSF HS D2S6 levels following discontinuation of immunosuppression.

    b. Patient factors

        It is unclear if patient factors such as age and MPS II disease features and progression status (e.g., pre-symptomatic versus early symptomatic, symptoms such as seizures, MRI volumetric brain loss) are associated with differences in CSF HS D2S6 and other biomarker levels.

5. There was missing data for several key covariates such as hearing assessments and timing of ERT administration that challenged interpretability of study results. In your future resubmission, please include a discussion on how missing data potentially impacts interpretability of study results and the steps you have taken to mitigate issues related to missing data within your statistical analyses.

6. A case of a malignant brain tumor following treatment with a gene therapy product (RGX-111, under development for MPS I) with a similar viral vector, such as shared capsid and vector genome design, was reported. Because AAV vector integration was reported in the tumor tissue, potentially similar safety risks may exist for clemidsogene lanparvovec. This adverse event may lead to a requirement for a safety PMR for BLA 125840 in the future. In your future resubmission, include an updated safety summary and benefit-risk assessment incorporating your findings of vector integration analysis in MPS programs.

Your responses to our requests for additional information may be addressed in a separate amendment to the BLA.

Within one year after the date of this letter, you are required to resubmit or withdraw the application (21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a Type A post-action meeting within 3 months of the date of this letter. Please submit your meeting request as described in the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* at https://www.fda.gov/media/172311/download, and CBER's SOPP 8101.1 *Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm.

If you have any questions regarding the above, please contact the (b) (4)

Sincerely,

(b) (4)

Center for Biologics Evaluation and Research