January 23, 2025
Re: TRAN1-16907 - Hematopoietic Stem Cell Gene Therapy for MPSIIIB (Sanfilippo B) Syndrome

To the CIRM Application Review Subcommittee,

In response to the application review of **TRAN1-16907 - Hematopoietic Stem Cell Gene Therapy for MPSIIIB (Sanfilippo B) Syndrome,** which received an unexpected borderline score of 85, we write to point out erroneous information in the reviewer comments that likely negatively impacted the scoring. At the same time, we write to point out the key strengths of our critical study that merits funding.

Our proposal plans to develop an autologous, ex vivo lentiviral modified hematopoietic stem cell gene therapy for the treatment of MPSIIIB (or Sanfilippo Syndrome B). MPSIIIB is a fatal genetic neurodegenerative disease, referred to as "Childhood Alzheimer's". Children are affected at 2-4 years of age exhibiting a precipitous progressive loss of cognitive milestones and motor function, becoming visually and hearing impaired, nonverbal, wheelchair-bound and total care-dependent by adolescence and dying in the teen years.

Our proposed project has the potential for significant impact if funded:

1. The proposed product addresses a **devastating, fatal pediatric neurodegenerative condition,** closely aligned with CIRM's mission under the 2020 renewal to specifically research and develop treatments for diseases affecting the brain and central nervous system.

2. **There are currently no effective treatments for MPSIIIB**.

3. **Our proposed therapy has a high likelihood of providing a CURE.** This therapy builds on a platform approach which has utilized the same lentiviral vector backbone/promoter in a phase I/II clinical trial for the closely related disease MPSIIIA; clinical results have been remarkable in the 5 MPSIIIA patients treated to date with **4/5 patients gaining cognitive skills in line with normal development[1,2].** Co-I Dr. Bigger has recently seen one of these MPSIIIA trial patients in clinic and reports:

   "*Our 6-year-old patient with severe MPSIIIA rides a scooter, speaks two languages and spent last visit asking perspicacious questions about the assent form*."

   This picture of a healthy and thriving 6-year-old is in stark contrast to the expected disease natural history and highlights the clear efficacy of this approach in MPSIII syndromes. Encouragingly, MPSIIIB animal model data from our proposal have demonstrated **complete normalization of toxic heparan sulfate metabolites in the brain and complete functional correction of neurologic and behavioral phenotypes**, suggesting that our therapy is likely to be similarly clinically efficacious.

4. In 2024, the MPS community, including industry drug sponsors, reached alignment with FDA regarding the use of cerebrospinal fluid heparan sulfate measurement as an acceptable surrogate biomarker for regulatory purposes in the filing of drugs and biologics for accelerated approval. This milestone has opened the door to more efficient and successful development of therapies for neuropathic MPS diseases, including Sanfilippo B (MPS IIIB). Our team will utilize this surrogate biomarker and associated regulatory pathway to speed development of our proposed treatment.

In the four points below, we address incorrect information contained in our review summary from the GWG reviewers that likely lowered our overall score:

1. One reviewer was concerned about the potential impact of this project due to the rare incidence of this disease and incorrectly cited the incidence of MPSIIIB at 1:1,000,000, in contrast to the

many studies that have estimated the incidence between 1:100,000 and 1:200,000[3-10]. Notably, one study examining newborn screening results (the gold standard for incidence estimation) found a rate of 1: 24,581[11], suggesting MPSIIIB is highly underdiagnosed. We note that a rate of 1:25,000 is significantly more common than a number of diseases currently in CIRM's portfolio and **feel strongly that our grant should not be penalized for the mistaken rarity of the disease**.

2. One reviewer similarly expressed concerns over feasibility of patient recruitment: "*…given the ongoing studies for MPS IIIA, concentrating efforts on the even rarer MPS IIIB at a single site could affect patient recruitment".* We note that MPSIIIA and IIIB are genetically distinct diseases, thus recruitment for MPSIIIA should not impact recruitment for MPSIIIB as patients would only be eligible for the appropriate trial. We again reiterate the more accurate incidence estimates of ~1:25,000 above and note that Allievex successfully recruited 19 MPSIIIB patients for their trial of AX250, which was suspended due to loss of sponsor support. Already, we have identified 3 potentially eligible patients and would always offer worldwide recruitment for diseases of this nature (as we have done on our other trials) to ensure complete enrollment.

3. A reviewer commented that "*A new product, Tralesinidase Alfa (UK) [enzyme replacement therapy], shows promise ... It has demonstrated some clinical efficacy after intracerebroventricular (ICV) administration. The ongoing clinical trial is set to conclude in February 2025.*" While Allievex showed encouraging results with the above-described candidate AX 250, the trial has been halted and Allievex has gone out of business. Additionally, this therapy requires weekly administration of enzyme by the intracerebroventricular route, which is highly burdensome to patients and families, compared to our proposed **one-time curative treatment**. **Thus, MPSIIIB patients are still in dire need of a curative therapy**

4. One reviewer incorrectly commented that "*apart from correction of inflammation, no other functional neurological benefit associated with the product specifically have been shown by the applicant*." Quite the contrary, the data in our proposal clearly shows full functional correction of MPSIIIB behavioral phenotypes with treated animals appearing indistinguishable from wild-type controls (proposal pg. 21, figure 9).

In light of these factual inaccuracies, we urge the application review subcommittee to fund our grant application based on the urgency of getting a highly feasible cure for children with Sanfilippo B.

Sincerely,

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References

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