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January 20, 2019

Ms. Maria Bonneville
Vice President of Administration
Executive Director of the ICOC
California Institute for Regenerative Medicine
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Re: CLIN1-10953: An hESC-derived hNSC Therapeutic for Huntington's Disease

Dear Members of the Independent Citizen's Oversight Committee,

Huntington's disease (HD) is a devastating dominantly inherited neurodegenerative disease that strikes individuals in the prime of life, typically beginning between the ages of 35 and 50, although in severe cases it can begin in children as young as age two and in young adults. The disease is caused by a mutation that creates an expansion of a repeating DNA unit (CAG repeat) within the HD gene (*HTT*); the length of the repeat expansion correlates with the age of onset and severity of the disease. The disease leads to widespread neuronal dysfunction and death in multiple brain regions, primarily in the striatum and cortex. Symptoms are unrelenting and progressive and include inability to control body movements (most often chorea), declining cognition leading to dementia, and a profound effect on an individual's psychiatric and emotional well-being and personality. Affected individuals eventually lose employment and ability to take care of a family, and usually die within 15-20 years of diagnosis.

Given the relatively slow progression of HD, care-giving stretches over 10 years or more after the patient loses independence. Patients become completely dependent on family and caregivers, who in turn have an emotional and debilitating economic burden managing the physical, cognitive and psychiatric manifestations of the disease. HD can lead to catastrophic events such as homelessness, prolonged hospitalization awaiting placement, or long-term psychiatric placement. The length and severity of the disease has a profound financial and emotional impact on families and health systems. The direct medical costs and costs of disability and care giving for each patient are substantial and pass from one generation to the next.

Currently, there are *no FDA approved treatments available that alter onset or progression of HD*. There are no small molecules with disease-modifying efficacy. Approaches to reduce expression of the mutant

HTT protein as a strategy to prevent disease are in various stages of clinical development, however the efficacy of those approaches is not yet known.

In our CLIN1 application, we propose to carry out IND-enabling safety studies for a cell therapeutic approach to HD. Using CIRM funding from prior Early Translation and Preclinical Development awards, we have identified and shown proof of concept for a therapeutic candidate consisting of ESC-derived Neural Stem Cells (ESI-017 NSC). We have also worked with the UC Davis GMP manufacturing facility to develop a reproducible manufacturing process for these cells. In our preclinical studies, these cells durably engraft and show signs of differentiation. There are increased levels of BDNF (a growth factor that is diminished in the brains of HD patients), decreased levels of mutant HTT protein accumulation, and significant improvements in multiple behavioral assessments (some approaching restoration to normal). Thus, the preponderance of the evidence suggests there is reason to believe that transplant of these cells might similarly ameliorate the disease in patients.

We are very appreciative of the GWG Tier 1 score and to CIRM for their recommendation to fund our CLIN1-10953 application. Below, we address some of the remaining reviewer concerns from the resubmission. We hope that the ICOC will support further funding of our work toward developing a stem cell based therapeutic for Huntington's disease (HD). If successful, we will be able to address a severe unmet need. Use of standard medical and neurosurgical procedures and practices for delivery of ESI-017 hNSCs would enable widespread use of this therapy.

First, the reviewers agreed that there is an unmet medical need and that if the proposed therapy slows progression, it will represent an improvement over the standard of care for HD. Reviewers disagreed on whether the potential for a clinically meaningful benefit would be worth pursuing given the risk of surgery and immunosuppression in patients and thought that prior failures in trials with different cells did not support moving forward with the therapy. We point out that our proposed stem cell product is a significant improvement over previously tested cell therapies given that the candidate is a defined cell type that can be reproducibly manufactured and has shown robust efficacy in preclinical studies. This is very different than previous cell therapies using cells from different donors, non-standardized manufacturing methods and minimal characterization of the composition of cells being injected.

Second, some reviewers felt that ongoing clinical testing of promising, non-cellular approaches to HD reduced enthusiasm for further development of this therapy. At this time, there is no proven disease-modifying treatment for HD; other investigational approaches that target the gene and its product have not yet proven their efficacy. A therapy, such as our stem cell approach, that could potentially slow down the disease process remains desperately needed and should be considered. As stated by some GWG reviewers, despite the stated risks, any treatment that can potentially slow down the disease progression is worth pursuing as current alternative therapeutic approaches are still many years away from commercial use.

Third, reviewers generally agreed that there was evidence that the cells were producing brain-derived neurotrophic factor (BDNF) in the animal models. However, reviewers disagreed on whether the delivery of BDNF would have clinically meaningful benefit. HD mice and patients have decreased levels of striatal BDNF and preclinical studies that produce beneficial effects often display increases in BDNF. Further, there is growing literature showing that communication between the cortex and the striatum is disrupted as disease progresses. This results in loss of cortical-mediated support for the striatum, in particular by BDNF, which is synthesized in cortical neurons and transported to the striatum and released. This lack of communication and trophic support may be one of the major contributors to abnormal

movements as well as to impaired cognition. Recent literature also suggests that the lack of BDNF may also impact psychiatric features of HD, including depressive behaviors. We propose that BDNF is one of the factors that contributes to beneficial effects in mice, and it is possible that other trophic factors provided by our product may also be beneficial. We do not yet have mechanistic data to define how cells are improving outcomes in HD modeled mice, but have proposed additional studies in the CLIN1 application to identify mechanisms of action and additional cell characterization. We agree that the possible connections formed by the cells, based on both electrophysiological data and electron microscopy, does not indicate that cells are actively signaling or responsible for the preclinical efficacy, but it does provide evidence that the cells are maturing over time and could have additional benefit beyond trophic support.

Thank you for considering funding our proposed studies.

Sincerely,

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