Brain Neurotherapy Bio, Inc.
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California Institute for Regenerative Medicine
1999 Harrison Street, Suite 1650
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10th October 2019

RE: CLIN2-11661: A Phase 1b safety study for MRI guided delivery of AAV2-GDNF for the treatment of Parkinson's disease

Dear ICOC Members,

We are very grateful for CIRM's support of our Parkinson's disease (PD) clinical study testing the safety, tolerability and preliminary efficacy of AAV2-GDNF delivered to the bilateral putamen, and the opportunity to provide an update on progress made towards initiation of that trial.

PD remains the second most common human neurodegenerative disorder, a debilitating illness where the neuronal pathway that produces the neurotransmitter dopamine undergoes an exponential degeneration leading to disability and death. Based on our vast preclinical and clinical experiences we believe that gene therapy treatment that delivers the trophic factor GDNF will slow down or even reverse this degenerative process. An initial clinical safety study in 13 patients with advanced PD showed safety over the 3+ years after GDNF gene delivery, with trial data analyses suggesting that the approach slowed down or halted the progression of PD in these advanced patients. With this in mind, we approached FDA and were granted permission to test a higher dose of our gene therapy not only to patients with advanced PD, but also in subjects during the earlier stages of the disease, where more profound therapeutic efficacy may be noted.

Our new **Phase 1b PD gene therapy study was approved by The Ohio State University (OSU) Biomedical Investigational Review Board (IRB) on October 4, 2019**, and we are in the process of finalizing the site initiation visit (SIV). The OSU investigators expect to start screening for eligible PD patients by early November, and the study remains on track to enroll the first subject prior to the end of 2019.

The experienced medical and surgical movement disorder gene therapy study team at the University of California San Francisco (UCSF) is also poised to initiate their startup activities, including but not limited to IRB approval and SIV, and look forward to beginning recruitment for this investigation. With support from this CLIN2-11661 award, the UCSF site will be opened for recruitment of subjects in California, as early as the spring (Q2) of 2020, with a projected full study enrollment completed by early 2021. We anticipate recruitment of approximately equal numbers of subjects at each of the two clinical sites (OSU and UCSF).

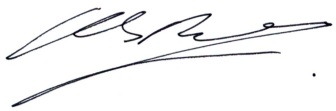
In August 2019, The Cure Parkinson's Trust organized a meeting of key opinion leaders (KOL) in Grand Rapids, MI, specifically to discuss the lessons learned from prior clinical studies related to GDNF and associated growth factors for treating PD. Key issues raised at this meeting included (i) the need to target early stage PD for therapeutic intervention, compared to the later disease stages that have previously been investigated, (ii) optimization of delivery parameters and the poor pharmacokinetics associated with current intermittent protein delivery methods, both of which can be addressed using a gene therapy approach, and (iii) exploration of more appropriate clinical endpoints to reflect the multifaceted clinical features being impacted by growth factor therapeutics. Despite the disappointing results associated with earlier clinical investigations, there continues to be immense support amongst KOL for additional testing of GDNF therapeutics in PD, provided that the key issues are adequately addressed. We share this view and had considered each of the issues identified by the KOLs in designing our Phase 1b GDNF gene therapy trial. In particular, the clinical optimization of our gene delivery approach, tested by our team in a parallel Phase 2/3 gene therapy program, under clinical development by Voyager Therapeutics Inc., has demonstrated safe and reproducible therapeutic distribution within the target brain volume using precise image-guided neurosurgical methods.

In preparation for the next stage of development, we are working closely with a contract manufacturer specializing in gene therapy products to produce a new batch of our AAV2-GDNF investigational product using commercial-ready processes and release testing. Given that the manufacturing process planning and execution, along with verification of comparability to our current product is expected to take up to 2 years, we are requesting CIRM's funding support for undertaking these activities in parallel with the proposed Phase 1b clinical trial. This strategy is expected to ensure that we are positioned to initiate a Phase 2/3 efficacy study with minimal delay following supportive early data from the Phase 1b safety study.

Complete funding of our CLIN2-11661 proposal will, therefore, enable us to accelerate the Phase 1b safety study, with the activation of the UCSF study site, and allow for simultaneous activation of product manufacturing required for Phase 2/3 clinical development and implementation. These two parallel activities are essential components of our GDNF gene therapy product development for PD. Together they significantly increase the likelihood of efficiently advancing our GDNF gene therapy program into multi-center Phase2/3 efficacy studies. In contrast to other gene therapies currently in clinical development, GDNF gene therapy provides a truly disease-modifying potential, with efficacy measures likely to disclose a mitigation or stoppage of the progressive deterioration, and even reversal of specific impairments associated with PD.

We look forward to collaborating with CIRM on this important project.

Sincerely,



Krystof S. Bankiewicz, MD, PhD
CEO and President

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

Californian Institute for Regenerative Medicine
Independent Citizens Oversight Committee

Re: Support of clinical study of GDNF Gene Therapy for the treatment of Parkinson's Disease

Dear Members of the CIRM Independent Citizens Oversight Committee,

On behalf of the MJFF, I am pleased to extend our support for Brain Neurotherapy Bio's AAV2-GDNF clinical development program.

Over the years, the MJFF has supported a number of research efforts related to central nervous system (CNS) gene therapy and the development of novel brain delivery methods, including those pioneered and clinically translated by Dr Krystof Bankiewicz and colleagues. MJFF supported the AAV2-AADC gene therapy program for Parkinson's disease, in which we partnered with Dr Bankiewicz to advance clinical evolution. As a result, positive Phase 1 trial data utilizing AAV2-AADC gene therapy has now being brought forward by Voyager Therapeutics, and most recently Neurocrine Biosciences in registration trials assessing clinical efficacy in advanced Parkinson's disease.

Research efforts advanced by Dr Bankiewicz's group have contributed to the way that the clinical neurosciences are approaching direct brain delivery. Such approaches and methods have helped the field to overcome major limitations to therapeutic distribution within the CNS, especially related to the delivery of neurotrophic factors. Through optimized neurosurgical delivery platforms, it is now possible to achieve targeted, constant, constitutive expression of GDNF within the brain and test potential efficacy. The proposed clinical investigation, submitted to CIRM by Dr Bankiewicz, provides a clinical opportunity for directly testing the safety and preliminary efficacy of GDNF gene therapy for the treatment of Parkinson's disease.

We are esupportive of the current Phase 1b study's plan to prospectively assess the effects of putaminal AAV2-GDNF gene therapy in early stages of Parkinson's disease. Retrospective analysis of prior clinical gene therapy studies, some of which we had supported, suggest that subjects within a few years of their Parkinson's disease diagnosis likely have a better chance of responding to neurotrophic factor gene therapy treatment than those treated during later disease stages. This is also consistent with the underlying pace of neurodegeneration in Parkinson's disease, with earlier stage patients more likely to have to respond to the administered trophic factors, capacity that is lost or significantly limited in more advanced disease stages. The proposed study could help the field to understand the potential of this approach to achieve a disease modifying option for Parkinson's disease.

In conclusion, I strongly endorse the GDNF gene therapy clinical development program submitted to CIRM by Dr Bankiewicz and his experienced team at Brain Neurotherapy Bio.

Sincerely,

Todd Sherer

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