Memorandum

Date: December 26, 2017

Subject: Critical Path Innovation Meeting: Genetic Prion Disease

Date of meeting: November 14, 2017

Requestor: Broad Institute

Note: Discussions at Critical Path Innovation Meetings are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants.

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1. BACKGROUND

Prion disease is a fatal, rare neurodegenerative disease caused by the misfolding of the prion protein (PrP). Familial prion disease accounts for approximately 15% of all human occurrences of the disease. Scientists from the Broad Institute of MIT and Harvard requested a CPIM to discuss their preliminary work to develop a therapeutic strategy for genetic prion disease.

2. DISCUSSION

The research team from the Broad Institute presented data on the pathogenesis of prion disease. All cases of prion disease in humans and animals are due to the same causative factor, a gain-of-function mutation in the prion protein gene (*PRNP)* which produces a misfolded version of the prion protein (PrP) known as a "prion". The prion acts as an infectious agent that can interact with normal prion proteins leading to the aberrant form known as PrP Scrapie (PrP^{SC}) and can spread across the brain. The research team indicated that less than 1% of prion disease cases are acquired through infection and that 85% of cases occur spontaneously, with no known environmental or genetic cause. They further noted that the remaining 15% of prion disease cases are due to a genetic cause — protein-altering variants in *PRNP*, with three high-

penetrance mutations comprising the majority of genetic cases. Prion disease progression is extremely rapid, with death occurring approximately 6 months from onset of initial symptoms of disease. The age of onset in genetic prion disease is highly variable for any given allele. Previously published biochemical and human and animal genetic data support a central role for PrP in prion disease. The research team presented data from mouse models showing that PrP knockout mice are resistant to prion disease, and postnatal suppression of PrP can delay or prevent prion disease. The adverse effects of PrP loss appeared to be minimal. These results indicate that therapeutic strategies which turn off or substantially reduce PrP expression by targeting *PRNP*, RNA or PrP in the brain may provide protection against the disease. Preclinical studies of compounds shown to extend survival in mouse models, but not effective against human prion disease stains, suggest that treatment can be highly effective before disease symptoms occur.

Broad Institute team proposed antisense oligonucleotides (ASOs) against PrP RNA as therapeutic candidates for prion disease. Results from preclinical and clinical studies of ASO targets against other diseases can be leveraged to support the safety, tolerability, and pharmacodynamics and pharmacokinetics of ASOs in humans (i.e. Huntington's disease model). The Broad Institute is collaborating with a pharmaceutical company on proof-of-concept studies in mice to assess the effectiveness of ASOs in reducing PrP mRNA levels in mouse cortex and spinal cord. Preliminary data in mice show that the ASOs are capable of reducing PrP RNA levels in the brain by 50%. Survival studies in mice intracerebrally infected with prions and treated with ASOs are ongoing. The Broad Institute team anticipates preliminary results from these studies in January 2018. FDA recommended that the Broad Institute team conduct natural history, safety and pharmacokinetics studies in non-human primates before moving to human studies.

The Broad Institute research team provided rationale for the use of cerebrospinal fluid (CSF) PrP measurement as a surrogate endpoint for evaluating efficacy of ASOs in lowering PrP levels in humans. CSF PrP levels can be quantified with ELISA in presymptomatic individuals who are more likely to benefit from therapy than symptomatic individuals. Studies indicate that CSF PrP measurement is stable over time. In addition, the Broad Institute team is exploring the use of mass spectrometry to quantify PrP in CSF. FDA recommended the conduct of studies to assess the distribution of PrP in different cell types in the brain, and how effective ASOs are in reducing PrP expression in these different cell types. The FDA also recommended evaluating knockdown of PrP in NHPs to assess pharmacodynamics and the impact of loss of PrP in a primate model, as well as evaluation of candidate ASOs in symptomatic human individuals. The Broad Institute team and their commercial partner are working to identify ASO candidates for human studies. FDA expressed support of the evaluation of CSF PrP as a surrogate endpoint and recommend the use of registries to identify prion disease kindreds. The Broad Institute team noted that the National Prion Disease Surveillance Center can be a resource to identify potential patients for clinical trials.

NEXT STEPS

- Broad Institute will share results of their survival studies in mice with FDA.

- Broad Institute will share information on data being collected in current or planned patient registries. Chris Leptak in OND will help to coordinate feedback on general registry design elements.
- FDA encourages subsequent communication with the Broad Institute around targeted topics to advance development of ASOs for treatment of prion disease. Topics include preclinical studies, assay validation, pharmtox, and registries/databases. The Division of Neurology Products will serve as the point of contact for additional discussions with the Broad Institute.
- FDA will share information on a bioinformatic tool to assist with ASO candidate selection.

Bioinformatics Analysis of ASO Targets

To characterize the potential off-targets of antisense oligonucleotides (ASO), we request that the following analyses be performed in a bioinformatics study using BLAST or other tools that compare the ASO target to genes in an appropriate database:

1. Please provide a list of all potential off-target matches in the human transcriptome, including those matches identified for the sense and antisense strands of each ASO with relaxed matching criteria. For each of these, describe available information on mouse knockouts and human genetic disease. Please comment on how any significant off-target effects would be monitored.
2. Please provide a list of potential off-target matches in the human mitochondrial transcriptome (example: https://www.mitomap.org/foswiki/bin/view/MITOMAP/WebHome).
3. Please determine the variation within the off-target matches in the transcriptomes of different populations in the US. Are different populations more susceptible to off-target effects than others?
4. Please determine the conservation among the candidate off-target human genes with their respective mouse and nonhuman primate genes. Are these sites sufficiently different in mouse and nonhuman primate such that toxicities related to off-target matches would not be present in these animals?