Food and Drug Administration (FDA)

Cellular, Tissue, and Gene Therapies Advisory Committee

(CTGTAC) Advisory Committee Meeting

Toxicity Risks of Adeno-associated Virus (AAV) Vectors for Gene Therapy (GT)

September 2-3, 2021

Advisory Committee FINAL Discussion Questions

Day 1: September 2nd, 2021

Session 1: Vector Integration and Oncogenicity Risk

1. Please discuss the merits and limitations of animal studies to characterize the risk of AAV vector-mediated oncogenicity, and provide recommendations on specific preclinical study design elements, to include:
    a. Animal species; healthy vs. disease models; and animal age
    b. In-life and post-mortem assessments, including methods for integration analysis
    c. Duration of follow-up, post-dose.

2. Current literature suggests that various factors may affect AAV-mediated vector genome persistence, vector integration, and the risk of oncogenesis. Please discuss benefit-risk considerations for AAV vector-mediated oncogenesis, such as patient's age at the time of treatment, pre-existing liver conditions (e.g., infection with hepatitis B and C virus), and high vector dose.

3. Considering the risk of oncogenesis,
    a. Please provide recommendations on safety monitoring measures that should be included in clinical trials.
    b. Please provide recommendations on duration, frequency, and method of long-term follow-up (LTFU) for recipients of AAV vectors.

4. Please discuss whether some vector designs may enhance the frequency of vector-mediated integration and the risk of oncogenesis. For example, how is the risk affected by promoter-enhancer elements, genome-targeted nucleases, or novel AAV vector designs for which there is limited clinical experience. Because AAV vectors can carry significant levels of co-packaged DNA impurities from the manufacturing process, is the risk of oncogenesis increased due to potential integration of non-vector DNA, and what types of studies should be performed to assess this risk?

Session 2: Hepatotoxicity

1. Please discuss the merits and limitations of animal studies to characterize the risk of hepatotoxicity, and provide recommendations on preclinical study design elements, such as animal species / disease models, and in-life and post-mortem assessments.

2. How should patients be screened and categorized based on their risk for developing liver injury before AAV vector administration? Please discuss whether pre-existing hepatic conditions may predict the risk of serious liver injury.

3. What additional strategies could be implemented before and / or after AAV vector administration to prevent or mitigate the risk of liver injury?

4. What factors (e.g., level of disease severity) other than weight should be considered to determine the vector dose for systemic administration?

5. Considering the risk of hepatotoxicity observed in clinical trials with high doses of AAV vectors,
    a. Please discuss whether an upper limit should be set for the total vector genome dose per subject.
    b. Given that many AAV products contain significant amounts of empty capsids, please discuss whether an upper limit should be set on the total capsid dose.

Day 2: September 3rd, 2021

Session 3: Thrombotic Microangiopathy (TMA)

1. Please discuss factors that may increase the risk of TMA following AAV vector administration.

2. Please provide recommendations on strategies that could be implemented before and / or after AAV vector administration to prevent or mitigate the risk of AAV vector-mediated TMA.

3. Considering the risk of TMA observed in clinical trials with high doses of AAV vectors,
    a. Please discuss whether an upper limit should be set for the total vector genome dose per subject.
    b. Given that many AAV products contain significant amounts of empty capsids, please discuss whether an upper limit should be set on the total capsid dose.

Session 4: Neurotoxicity: Dorsal Root Ganglion (DRG) Toxicities

1. Based on the published data, please discuss the relevance of the non-human primate cases of DRG toxicity to human subjects.

2. Please provide recommendations on preclinical study design elements, such as animal species / disease models, age, in-life and post-mortem assessments, and duration of follow-up, post-dose, that may contribute to further characterization of DRG toxicity.

3. In addition to periodic neurological examinations, please provide recommendations on other methods to mitigate the risk of DRG toxicity in clinical trials.

Session 5: Neurotoxicity: Brain Magnetic Resonance Imaging (MRI) Findings

1. Please provide recommendations for any preclinical in-life and post-mortem assessments (e.g., behavioral and neuropathological assessments) and duration of follow-up, post-dose, to

identify and further characterize the risk of neurotoxicity following intraparenchymal administration of AAV vectors.

2. Please discuss the clinical significance, if any, of brain MRI abnormalities observed in clinical trials of AAV vector gene therapies. Please discuss whether the delivery procedure vs. AAV vector may have contributed to the abnormal brain MRI findings.

3. Please provide recommendations on strategies that could be implemented before and after vector administration to prevent or mitigate the risk of central nervous system injury.

4. Please recommend a duration of monitoring for subjects who have abnormal brain MRI findings, or factors to consider for the determination of an appropriate duration of monitoring.