2020 ASGCT/FDA Liaison Meeting Summary

Recommendations for immunogenicity testing requirements for AAV gene therapy

Presented by Brian Long, PhD, Associate Director/Senior Scientist II at BioMarin Pharmaceutical

In this presentation, Dr. Long presented ASCGT's request for FDA to issue immunogenicity recommendations to provide developers with a clear risk-based framework. Recommendations could do the following:

- Employ a risk-based approach for immune monitoring that accounts for features of the therapy and the patient population (such as pre-existing immunity, innate/inflammatory immune activation, and adaptive immune responses).
- Include the circumstances under which analyses are required to determine if anti-gene therapy immunogenicity responses are impacting safety and/or efficacy.
- Include the circumstances under which immune monitoring in a temporal manner is required with respect to dose administration.
- Provide more detailed information pertaining to the appropriateness and utility of a companion diagnostic for assessing pre-existing immunity and requirements for product approval.

Recommendations for risk assessment requirements (safety and toxicology) for animal models and nonclinical data

Presented by Janet Benson, DVM, Senior Scientist at Lovelace Biomedical

D. Benson's suggestions for risk assessment requirements for animal models and nonclinical data included the following points:

- A qualified assay for product release should include PCR or ddPCR quantitation of vector, as well as microscopic examination of vector to assess integrity.
- Needed bridging data includes titer, purity, and potency (enhanced vector uptake by cells, enhanced gene expression, or improved full/empty capsid ratio).
- Clinical bridging studies are indicated when there is a change in vector serotype, promoter, or route of delivery to enhance efficacy or improve safety.
- An identified minimal effective dose is not essential to conduct preclinical pivotal toxicology and biodistribution studies, but at least two doses should be evaluated in early efficacy studies to help assess dose response for efficacy and potentially safety.
- ASGCT suggests an acceptable minimum of two euthanasia time points, with duration dependent on the specific therapy, disease indication, and potential for long-term effects.
- Clinical pathology endpoints should be limited to parameters relevant to the particular disease and therapy (e.g., coagulation parameters and CBC for hemophilia, CK when ROA is intramuscular), and basic liver and kidney endpoints in small animal models.
- Integration studies should not be required based on collective data that the frequency and level of AAV integration is very low and is considered non-integrating.

Gene therapy development challenges: A regulatory perspective
Presented by Wilson Bryan, MD, Director of OTAT

Dr. Bryan presented on topics such as preclinical study recommendations, trial design, INTERACT meetings, and COVID-19 effects on gene therapy development programs. Highlights included the following:

- Well-designed single-arm studies can support marketing approvals; four of the five gene therapies on the market used single-arm studies, but in order for FDA to have confidence in single-arm studies, it needs to have good knowledge of the natural history of the disease.
- OTAT has been encouraging the use of randomized studies in first-in-human studies, such as those used for Zolgensma, which used an open-label, two-dose design; the science of gene therapy products is so strong that it is possible for Phase I studies to support market access when using randomized studies.
- Because gene therapies are often for rare disorders, the data often does not yet exist on recommended endpoints, so FDA needs data from sponsors to support endpoint selection.
- Denials of INTERACT meetings (previously known as pre- pre-IND meetings) are typically because the trial is too early (e.g., insufficient CMC information) or too late in development (e.g., preclinical studies have been initiated or completed).
- To overcome COVID-19 disruptions in trials, sponsors are encouraged to talk to FDA on a case-by-case basis to determine whether the trial can be redesigned to obtain useful data.

Innovative clinical study design for gene and cell therapies
Presented by Jacob Elkins, MD, Senior Vice President, Head Clinical Sciences at Sarepta Therapeutics

Dr. Elkins presented ASGCT recommendations that included the following:

- ASGCT suggests utilizing three innovations—combined endpoints; blind-start study design with comparison to pre-treatment baseline; and greater standardization around the use of gene-expression biomarkers and/or intermediate clinical endpoints to enable accelerated approval when appropriate.
- The Society recommends using an approach of totality of evidence from multiple endpoints, which can be combined with statistical methods to quantify the chance of occurrence under the null hypothesis of no treatment effect.
- Demonstration that a gene therapy can restore a functional version of a native protein that is known to be causative for the target disease should be considered a surrogate endpoint that is reasonably likely to predict clinical benefit.
- Shorter-term improvement in clinical benefit should be considered sufficient to leverage as an intermediate clinical endpoint to support accelerated approval.
- We recommend that FDA adopt the use of tools such as modeling and simulation, and Bayesian Statistics in supporting the understanding of durability leveraging shorter term data, while continued clinical assessments can continue in the post-approval setting.
- Incorporate patient voice into the determination of unmet need, or unrealized unmet need, into benefit/risk decision making to support the decision to accelerate approval.
- ASGCT recommends the Agency develop a guidance document to provide clarity from the Agency regarding how to bridge clinical and CMC data across variants of rare, genetically heterogeneous disorders as described in Section 529A of the FFDCA.