July 23, 2025

U.S. Food and Drug Administration
Dockets Management Staff (HFA-305)
Fishers Lane, Rm. 1061
Rockville, MD 20852

Sent via electronic delivery

Re: FDA-2025-N-1559 – Rare Disease Innovation, Science, and Exploration Public Workshop Series

To Whom It May Concern,

Please accept our proposal for a **Rare Disease Innovation, Science, and Exploration (RISE) Workshop to collectively optimize risk assessment and mitigation strategies including rapid exchange of shared learning across the durable cell and gene therapy community.** The objective is to develop a process for real-time exchange of shared information across the cell and gene therapy community that is pre-competitive and benefits patients. The expected outcome of the meeting is to advance the field of cell and gene therapy in a way that establishes genetic medicine as a reliable modality for the management of a wide variety of conditions amenable to this approach.

Gene therapy holds significant promise for treating a wide range of genetic and acquired diseases. To date, AAV vectors are the predominant delivery vehicle for gene therapy and have been a breakthrough intervention for rare, monogenic diseases, often with significant unmet need. Of the 10,000 rare disorders impacting 10% of the US population, fewer than 5% have FDA approved therapies. Among available viral and non-viral gene delivery approaches, AAV vectors remain the most efficient means for in vivo delivery of DNA to the nucleus.[i] Over 250 therapies are in the development pipeline of 180 companies working to develop disease modifying therapies[ii]. AAV vectors now constitute a bona fide novel therapeutic delivery platform for seven US Food and Drug Administration-approved products with over 10-fold more in clinical development for an expanding number of disease indications. The real-world experience with these products has led to the identification of a variety of clinical problems to overcome to enable more widespread and safe use.[iii] In particular, the risk profiles of viral vectors have become more evident and warrant more systemic, shared data to enable trend analyses and communication of findings to all stakeholders.

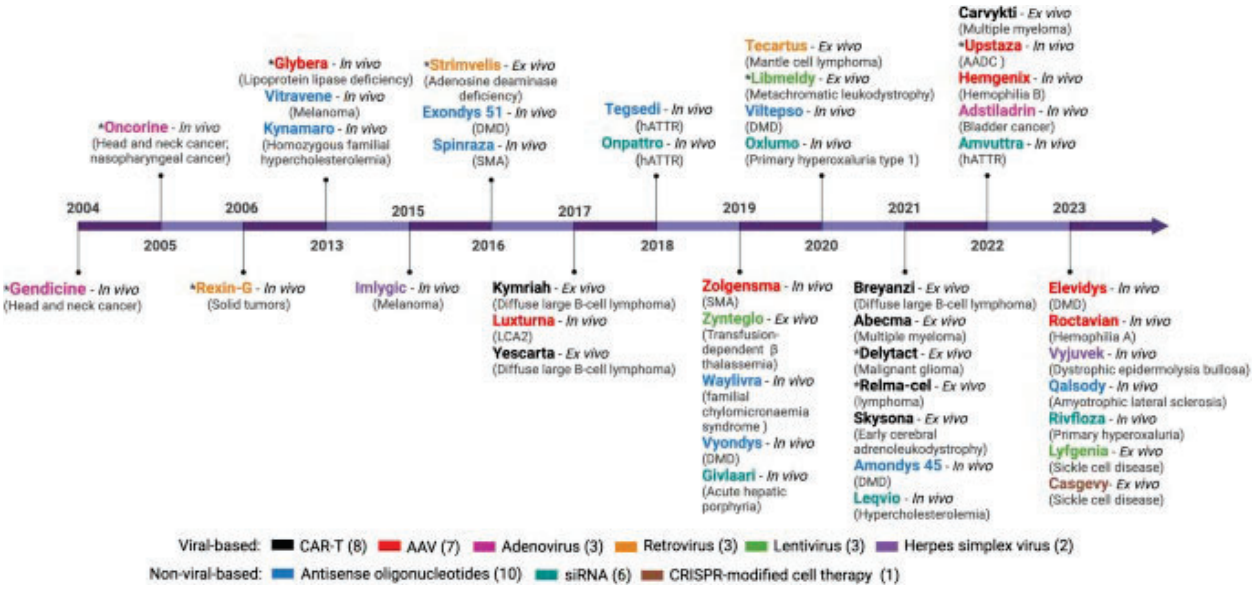
Studies in rare disease and small populations are complex and underscoring the need for innovative trial design and risk mitigation strategies as well as novel immune management approaches that would benefit rapid exchange of best practices established between clinicians, drug developers, regulators, and patient communities. Such risk mitigation strategies include, but are not limited to, expert consensus on pre-treatment regimen recommendations, enhancements to the FDA FAERS reporting system, opportunities for best practice communication exchange across clinical communities, and more.

As scientific advances in gene therapy yield significant clinical gains for patients with life threatening diseases, improved outcomes can be weighed against the therapeutic risks.

As one critical example, liver toxicity is one of the most significant safety concerns associated with AAV gene therapies, particularly at high doses. For the current generation of AAV products, the liver is the primary site of AAV vector exposure, which can lead to immune-mediated liver inflammation and hepatocellular injury. Biomarkers of liver injury have been identified at varying degrees in all systemically delivered AAV products. Findings in patient populations have resulted in transient liver injury and in rare cases, liver failure and several fatalities due to the associated morbidity of loss of liver synthetic function. These adverse events are believed to result from both innate and adaptive immune responses to the AAV capsid, as well as from the direct effects of high vector doses, especially if further confounded by the presence of process impurity in the active product. The variability in patient response and the unpredictability of toxicity have led to increased regulator and clinician oversight. Such instances of liver toxicity have occurred across the gene therapy field, yet current monitoring strategies have not yet been standardized, and the need exists for mechanisms for real-time information dissemination. New approaches in risk programs that bridge across compartmentalized safety data practices could further inform patient management protocols.

Traditional models of data analyses and exchanges between developers and clinical experts must be transformed to provide insights that inform experimental and commercial programs. With collaboration, those insights could include extensive formalized interactions that extend across time and product specific learnings.

A RISE Workshop provides a forum for developers, regulators, and patient organizations to discuss and take actions to address cross-cutting challenges and opportunities that advance scientific and regulatory benefit risk approaches that can realize the full promise of the AAV gene therapy pipeline while mitigating current and future safety concerns.



Approved Gene therapy products with delivery platforms - https://www.nature.com/articles/s41392-024-01780-w

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[i] https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(25)00365-X

[ii] https://www.barchart.com/story/news/33472853/aav-vectors-in-gene-therapy-pipeline-appears-promising-with-180-leading-biotech-and-pharma-companies-driving-innovation-in-the-therapeutics-segment-delveinsight

[iii] https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(25)00365-X