Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) Meeting
September 2-3, 2021
Erratum – FDA Briefing Document

1. Page 21, Section 3.1, Sentence #6: "Notably, there are also no reports of oncogenesis associated with AAV integration in non-hepatic tissues." Revised to read: "Notably, the majority of the reports of oncogenesis to date appear to be associated with AAV integration in hepatic tissues (55, 72, 128, 186)."

2. Pages 24, Section 3.2.1, Sentence #1: "For example, a recent study conducted in neonatal Twitcher mice demonstrated HCC development following administration of AAV9 vector into the CNS, while a similar study using an AAV5 vector did not find any HCC development (12, 102)."

   Page 27, Section 3.3.1, Sentence #4: "Because AAV vectors are thought to integrate randomly into transcriptionally active regions of the genome, it is not surprising that integration events have also been observed outside of the *Rian* locus and near proto-oncogenes (7, 12, 104, 129)."

   Page 28, Section 3.3.2, Sentence #2: "Various approaches to evaluate AAV vector-mediated oncogenesis have been reported, including: 1) histopathological assessments to characterize the type of lesion, 2) potential markers associated with HCC (e.g., elevated serum alpha-fetoprotein (AFP)), and 3) gene expression profile and vector integration analysis of healthy and tumor tissue (7, 12, 47)."

   > Reference **#12**: Li C, Samulski RJ. 2020. Engineering adeno-associated virus vectors for gene therapy. Nat Rev Genet 21:255-272.

   This reference citation is replaced with:

   > New reference #**186**: Li Y, et al. 2021. Enhanced Efficacy and Increased Long-Term Toxicity of CNS-Directed, AAV-Based Combination Therapy for Krabbe Disease. Mol Ther 29(2):691-701.

3. Page 27, Section 3.3.1, Sentence #4: "Because AAV vectors are thought to integrate randomly into transcriptionally active regions of the genome, it is not surprising that integration events have also been observed outside of the Rian locus and near proto-oncogenes (7, 12, 104, 129)."
   Removal of reference citation **#129**: Wang PR, et al. 2012. Induction of hepatocellular carcinoma by in vivo gene targeting. Proc Natl Acad Sci U S A 109:11264-9.

4. Page 29, Section 3.3.2, Sentence #4: "In nonrodent species, follow-up durations of 8-10 years in various canine disease models (7, 132, 133)…" Revised to read: "In nonrodent species, follow-up durations of more than 10 years in various canine disease models (7, 132, 133)…" and include a new reference:

New reference **#187**: Batty P, et al. 2020. Frequency, location and nature of AAV vector insertions after long-term follow up of FVIII transgene delivery in a hemophilia A dog model. Res Pract Thromb Haemost. 4S1:550.

5. Page 51, Section 7.3, last sentence of the page: “Over time, the severity of some findings increased (in rats), while others decreased (in NHPs), and new abnormalities were evident.” Revise to read: “Over time, the incidence and/or severity of some findings increased (e.g., perivascular cuffing, swollen microvesiculated neurons, gliosis), while others decreased (e.g., hemosiderin-laden macrophages) to variable degrees in these animals.”