Gene Therapy: Nonclinical and Regulatory Strategy

Module 4, Part 1 Abstract: Approved Gene Therapy Products: Case Studies

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Development of Luxturna, The First Approved Gene Therapy for Ocular Disease – Challenges and Lessons Learned

In December 2017, the US FDA approved for marketing in the US Luxturna (voretigene neparvovec), the first Adeno-Associated Virus (AAV) gene therapy for patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. It was also the first AAV gene therapy approved anywhere in the world. The story of how Luxturna became a therapy goes back many years before this date, with a complex journey into routes of administration, relevant animal models, viral vector design, appropriate clinical trial design and several other aspects. From the beginning of collaborative work across a handful of academic labs, models needed to be identified that replicated the genetic, anatomical, and electrophysiological aspects of the disease. While some safety aspects were obtained from these models, other species were used to supplement this data set to obtain information with ocular anatomies closest to humans. The subretinal route of administration, while employed in various ophthalmologic settings on rare occasions, was required to be optimized for Luxturna delivery in this case owing to the need for maximal transduction of RPE cells and photoreceptors. This highlighted the need for an evaluation of safety as well as questions regarding distribution beyond this space and impact of the immune response (?). Finally, the clinical trial required thorough evaluations of safety and, most importantly, novel endpoints for measurement of efficacy. This presentation will provide an overview of the early to late stages of development that covers many of these challenges outlined above.