QUESTIONS FOR THE ADVISORY COMMITTEE

Discussion Question 1

The primary efficacy endpoint of Study 301 was improvement in MLMT. At the one-year evaluation, eleven (11) of the 21 (11/21, 52%) subjects using both-treated eyes and fifteen (15) of the 21 (15/21, 71%) subjects using the first-treated eye had 2-light level or more improvement in MLMT (i.e., an MLMT score improvement of ≥2). The difference in the median MLMT score change between the treatment and control groups is statistically significant.

FDA review of this BLA identified the following issues regarding the use of MLMT to assess the functional vision, including:

- The limited data on this novel outcome measure; and
- The relationship of the MLMT score change to activities of daily living

Please discuss whether a 2-light level improvement in MLMT is clinically meaningful in "patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy."

Discussion Question 2

Because of the safety concerns related to the subretinal injection procedure, only subjects who had significant vision loss were enrolled into the clinical studies. The youngest subject treated was 4 years old. Additionally, individuals with more advanced disease did not appear to benefit from study agent administration. Considering that patients carrying disease-causing *RPE65* mutations would be expected to have progressive vision loss, please discuss the optimal time to treat patients, especially,

a. At what stage of clinical presentation do the benefits of therapy outweigh the risks?
b. How can the data from subjects with advanced vision loss be extrapolated to patients with earlier stages of disease, with or without measurable vision loss prior to treatment?
c. Considering the adverse events associated with the subretinal injection of voretigene neparvovec and the concomitant use of oral prednisone, what are your concerns for treating pediatric patients at a young age?
d. What is the reasonable minimal age, if any, that you would recommend for treatment?

Discussion Question 3

In the clinical studies supporting the BLA, each eye received a one-time subretinal injection of voretigene neparvovec. The median MLMT score change of 2 in the treatment group of Study 301 was observed at the Day 30 visit following voretigene neparvovec administration, and was maintained throughout the 1-year follow-up period. However, there is no available long term follow up data to address whether the effect decays over time. Therefore, the duration of AAV2-mediated transgene expression leading to sustained clinical benefits beyond one year is unclear.

As such, repeat administration of voretigene neparvovec may be indicated to maintain vision or delay vision loss. However, as repeat administration of voretigene neparvovec in any eye was not evaluated in the clinical studies, there are no clinical data addressing potential benefit and risk of re-administration.

a. Please discuss the potential benefits and risks of repeat administration of voretigene neparvovec into one eye.

b. What additional data, if any, would be necessary to support such repeat administration?

Discussion Question 4 (voting question)

Considering the efficacy and safety information provided in the briefing document, as well as the presentations and discussions during the AC meeting**,** does voretigene neparvovec have an overall favorable benefit-risk profile for the treatment of patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy?