Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)

SUMMARY MINUTES
67th CELLULAR, TISSUE, AND GENE THERAPIES ADVISORY COMMITTEE MEETING
October 12, 2017

Cellular, Tissue, and Gene Therapies Advisory Committee Members (Voting)
Dale Ando, M.D. ** (Non-Voting Industry Representative)
David Bartlett, M.D. +
Bollard, Catherine, M.D., MBChB+
Butterfield, Lisa, Ph.D.
Barry Byrne, M.D., Ph.D. (Temporary Chair)
Hawkins, Randy, M.D.* (Consumer Representative)
Longo, Daniel, M.D. +
Grace E. Pluhar, D.V.M, Ph.D.
Roos, Raymond, M.D. +
Wu, Joseph, M.D., Ph.D.
Wittes, Janet, Ph.D. +
Ann C. Zovein, M.D.

Temporary Members (Voting)
Brooks, Brian, M.D. Ph.D.
Marcia Carney, M.D.
Chiorini, John (Jay) Ph.D.
Emerson, Jeffrey , M.D.Ph.D.
Flotte, Terrence, M.D.
Humsberger, Sally, Ph.D.
Lai, Michael, M.D. Ph.D.
Lee, Brendan, M.D. Ph.D.
Massof, Robert, W., M.D.
Raasch, Thomas, W., M.D.
West, Constance, M.D.

Sponsor Presentation Speakers
High, Katherine, M.D. Spark Therapeutics
Kelley, Deborah, M.D. Spark Therapeutics
Maguire, Albert, M.D. Children's Hospital of Philadelphia (CHOP)
Pennesi, Mark, M.D., Ph.D. Oregon Health and Science University (OHSU)
Reape, Kathleen, M.D. Spark Therapeutics

FDA Participants (Speakers)
Bryan, Wilson, M.D., Director, Office of Tissues and Advanced Therapies (OTAT), CBER, FDA
Zhu, Yao-Yao, M.D., Ph.D., Medical Officer, OTAT, CBER, FDA
Chambers, Wiley A., M.D., Supervisory Medical Officer, CDER, FDA

Designated Federal Officer Prabhakara L. Atreya, Ph.D., DSAC, CBER, FDA

Committee Management Specialists
Joanne Lipkind, M.S., DSAC, CBER, FDA
Denise Royster, DSAC, CBER, FDA

+ Not in attendance
* Consumer Representative
** Industry Representative

These summary minutes for the 67th meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) that took place on October 12, 2017 were approved on March 22, 2018

I certify that I participated in the 67th meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee on October 12, 2017 and that these minutes accurately reflect what transpired.

/S/
Barry Byrne, M.D., Ph.D.
Acting Chair, CTGTAC

/S/
Prabhakara L. Atreya, Ph.D.
Designated Federal Officer, CTGTAC

The CTGTAC meeting to discuss the safety and efficacy of Biologics License Application (BLA) 125610, voretigene neparvovec, Spark Therapeutics, for the treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy was called to order at 8:30 a.m. Eastern Standard Time on October 12, 2017 by the CTGTAC ACTING Chair, Dr. Barry Byrne.

The Chair invited the members and temporary members seated at the table to introduce themselves. The Designated Federal Office (DFO) made administrative remarks and read the conflict of interest statement into the public record.

An introduction and overview of the topic for the meeting were presented by Dr. Wilson Bryan, the Director of the Office of Tissues and Advanced Therapies (OTAT), Center for Biologics Evaluation and Research (CBER), FDA. Dr. Bryan's presentation was followed by five (5) presentations from the Applicant, Spark Therapeutic, Inc., on the unmet medical need, clinical program, efficacy, safety, and clinical perspective for voretigene neparvovec, Spark Therapeutics, BLA 125610, for the treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy. The Applicant's presentations were followed by an FDA presentation on BLA 125610 for voretigene neparvovec, submitted by Spark Therapeutics, Inc.

The Open Public Hearing (OPH) began after the questions and answers portion of the meeting. During the OPH, several clinical trial participants, their family members and other professionals familiar with these trials provided oral comments on their experience with the disease and the trials. They are listed as follows and their statements are in Transcripts available on FDA website for this meeting under the meeting materials (https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/ucm574396.htm).

OPEN PUBLIC HEARING SPEAKERS

LAURA MANFRE
Co-Founder/President, Sofia Sees Hope

ERIC PIERCE, M.D., Ph.D.
Director, Ocular Genomics Institute and
Inherited Retinal Disorders Clinical Service
Massachusetts Eye and Ear Infirmary
Harvard Medical School

KATELYN COREY
Study Participant

CHRISTOPHER COREY
Father of Study Participant

KRISTIN SMEDLEY
President, Curing Retinal Blindness Foundation

ASHLEY CARPER
Mother of Study Participant

COLE CARPER
Study Participant

EUGENE DE JUAN, M.D.
Department of Ophthalmology
University of California, San Francisco

MISTY LOVELACE
Study Participant

BART LEROY, M.D., Ph.D.
Chairman and Head of Department of Ophthalmology
Director, Ophthalmic Genetics Clinics
Children's Hospital of Philadelphia

JOAN O'BRIEN, M.D.
Chairman, Department of Ophthalmology
University of Pennsylvania

Director, Scheie Eye Institute

LAURA GATT
Mother of Study Participant

ANGELINA GATT
Study Participant

ELIZABETH GUARDINO
Mother of Study Participant

CHRISTIAN GUARDINO
Study Participant

CHRISTINE KAY, M.D.
Ophthalmologist/Vitreoretinal Surgeon

STEPHEN ROSE, Ph.D.
Chief Research Officer
Foundation Fighting Blindness

There were two sessions for Questions and Answers (Q & A), one before the OPH and one after the OPH and lunch break. During the Q & A, the AC members asked questions mainly to the Applicant regarding the AC presentations. The main discussions are summarized below:

- There was no clear correlation between the outcomes and the types of RPE65 mutations (e.g., nonsense, small deletion or insertions). There was also no clear correlation between the immune response to voretigene neparvovec and the types of RPE65 mutations.

- Applicant did not consider using sham control (e.g., surgical prep, a needle injecting into the vitreous body) in the Phase 3 trial because the sham procedure involves more than minimal risks and provides no prospect of direct benefit to children.

- There was no clear correlation between the age of a subject and improvement in his / her MLMT in the trial.

- Subjects whose subretinal injection went into the macular area were more likely to have macular thinning.

- The success rate of subretinal injections for all five surgeons in the trials was 100%. Training for subretinal injection is recommended even though it involves only standard maneuvers of retinal surgery.

- The surgeons in the trials did not experience additional surgical difficulties or complications when operating on adult patients with more retinal scarring or gliosis.

- All cases of increased intraocular pressure were resolved. Sixteen eyes developed cataracts. Seven of them had cataract extraction. Nine cataracts are ongoing and considered clinically insignificant.

- FDA considered several factors in order to determine the clinical meaningfulness of the product. For example, the amount of change in visual acuity was expected to reach a certain degree (e.g., a doubling of the visual angle or 0.3 LogMAR) to be considered clinically meaningful. Other factors such as improvement in conducting activities of daily living that involve multiple different aspects were considered important, e.g., the patient could see in dim light.

Final Discussion Questions (clinical) for the Advisory Committee (AC)

Discussion Question 1

The primary efficacy endpoint of Study 301 was a score change of 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, comparing the treatment and control groups, is statistically significant. This endpoint is new and has not been used to support prior applications.

a. 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."

b. If you consider that the 2-light level improvement in MLMT is not clinically meaningful, please discuss,

i. whether a larger change in MLMT would be clinically meaningful;

ii. whether any other endpoint used in the clinical trial is clinically meaningful.

The discussion of Question 1 is summarized below:

- A two-light level improvement in MLMT (i.e., an MLMT score change of 2) is clinically meaningful although the design of MLMT is not perfect.

- The overall design of MLMT achieves its goal of evaluating functional vision although MLMT is performed in a compact navigation course of 5 by 10 feet, which is much smaller than many of the tasks patients have to deal with daily.

- The intervals (measured in log luminance) between consecutive light levels of the seven light levels used in MLMT is not evenly distributed. Therefore, depending on a patient's baseline, a two-light level change may mean something different.

- The change in FST (Full-Field Light Sensitivity Threshold), a secondary endpoint, which showed a 2-log increase in white light sensitivity, supports the MLMT results.

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 minimal age, if any, that you would recommend for treatment?

The discussion of Question 2 is summarized below:

- The benefits of voretigene neparvovec include an increase in the ability to perform activities of daily living under varying levels of low luminance. The risks of treatment are largely associated with delivery procedures, including cataract, elevated intraocular pressure (IOP), retinal tears and holes, inflammation, and endophthalmitis.

- Similar short term corticosteroid regimens are commonly used to treat children with serious illnesses. The safety profile is known and acceptable.

- Vitrectomy in young children may introduce media opacities and refractive errors, which could lead to amblyopia. However, there is a window around 3 or 4 years of age where the risk of introducing amblyopia would be low and benefits from voretigene neparvovec could be substantial.

- Although there are no clinical trial data for patients younger than four years of age, there is a need to treat these patients as natural history suggests that they don't improve without intervention. There was a suggestion of treating patients before they become symptomatic to prevent cell death of retinal pigment epithelium (RPE).

- The appropriate age to treat patients should be based on when most of the terminally differentiated retinal cells complete proliferation, which occurs around 8 months of age, as AAV, a non-replicating vector is going to be lost to the dividing cells.

- Instead of recommending a minimum age for treatment, it may be preferable to leave the decision as to the optimal time for treatment to the discretion of the treating physician. The level of comfort, the training, and the ability to operate on patients of very young ages vary among the treating physicians. Some may be comfortable operating on a 3-year-old eyeball that is close to adult eyeball size. Others may be comfortable operating on eyes of very young patients, such as infants in the intensive care units who are much younger and fragile, and who undergo much riskier procedures to preserve eyesight.

- Compared to older children's eyes, younger children's eyes are harder to operate on because the posterior hyaloid is very adherent and needs more manipulations and maneuvers. It is reasonable to wait until patients are over 3 or even 6 years of age. In addition, it is easier to assess visual function in older children.

- Considering the risks associated with delivery procedures, after treating the first eye, it may be beneficial to wait for 30 days before treating the second eye for children younger than 4 years of age.

- Potential risks of subretinal injection can be minimized by relying on the expertise of qualified pediatric retinal surgeons and pediatric anesthesiologists who are comfortable with young patients.

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, 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, repeat administration of voretigene neparvovec in any eye was not evaluated in the clinical studies. Therefore, there are no clinical data that address the potential benefits and risks of repeat administration of voretigene neparvovec.

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?

The discussion of Question 3 is summarized below:

- The following general reasons for repeat administration of voretigene neparvovec to the same eye were considered:

    a. a decrease in gene expression following initial administration;

    b. progressive disease that may overwhelm the therapeutic effect of the initial administration and requiring repeat administration to maintain efficacy;

    c. only one-fifth of the retina may be exposed to voretigene neparvovec with the initial administration; a repeat administration to the same eye may extend the treatment to additional parts of the retina for additional effect.

- In the clinical trials, the immune response to AAV vector and RPE65 protein was low following voretigene neparvovec administration to both eyes. However, the immune response following repeat administration of voretigene neparvovec to one eye may be different from what was noted following initial administration to both eyes. Therefore, additional careful studies will be necessary to ensure the safety of repeat administration to a single eye.

- The human cellular immune response to AAV vectors are not well-predicted by animal studies. Therefore, human studies will be required to understand the cellular immune response to AAV vector following repeat administration.

- There was no clinical information available as to whether repeat administration to one eye would be safe from a surgical perspective.

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, do you conclude that voretigene neparvovec has an overall favorable benefit-risk profile for the treatment of patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy?

There were further discussions regarding Question 4 before the voting process.

- It is important to consider that a drug for any disease, and especially for a rare disease, should be available for use in a wider population following marketing approval.

- It is important for the Applicant to implement the proposed risk mitigation plan to ensure safe administration of voretigene neparvovec.

- Outcome measures used in the studies were not able to fully capture and quantitate the impact of voretigene neparvovec on developmental aspects that accompany visual impairment, such as learning and socialization.

- Statistical analyses methods are sound, and the results are consistent and reassuring. Both FDA and Applicant presented their statistical analyses and results well.

The committee participates in simultaneous electronic voting. The results of the CTGTAC Committee voting were as follows: 16 Yes, 0 No, and 0 Abstention. It is a 16/16 votes, a unanimous vote with regards to voretigene neparvovec having an overall favorable benefit-risk profile for the treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy.

After the individual member votes were read by the DFO for the public record, the meeting was adjourned at 3:20 p.m.