



Our Reference: BLA 125610

Date: September 13, 2017

Spark Therapeutics, Inc.

ATTENTION: Jim Wang, M.B.A., Ph.D.

3737 Market Street, Suite 1100
Philadelphia, PA 19104

Dear Dr. Wang:

Attached is a copy of the agenda for your September 14, 2017 Mid-Cycle Communication Teleconference with CBER.

Please include a reference to Submission BLA # 125610 in your future submissions related to the subject product.

If you have any questions, please contact Nevitt Morris at [(240) 402-8269.

Sincerely,

Raj K. Puri, M.D., Ph.D.
Director
Division of Cellular and Gene Therapies
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

Mid-Cycle Communication Teleconference Agenda

Application type and number: BLA 125610/0

Product name: Voretigene neparvovec (LUXTURNA)

Proposed Indication: LUXTURNA is a gene therapy product indicated for treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy.

Applicant: Spark Therapeutics

Meeting date & time: September 14, 2017, 2:00 pm to 3:00 pm

Committee Chair: Lilia Bi, M.D., Ph.D.

RPM: Nevitt Morris, RN

Agenda:

To discuss the progress of the review.

Discussion Summary:

1. Any significant issues/major deficiencies identified by the review committee to date

CMC:

The following are significant issues regarding your drug product storage, packaging, distribution and shipping validations:

1. Storage and distribution of voretigene neparvovec following Drug Product (DP) labeling at (b) (4) must be established prior to November 15, 2017.
2. Shipping validation studies are incomplete and must be submitted to the BLA:
 - a. Drug Substance shipping validation from Spark Therapeutics, Philadelphia, PA to (b) (4).
 - b. Shipping validation studies for the Drug Product (DP) and Diluent from (b) (4) to (b) (4) (secondary package facility).
 - c. Shipping validation studies for the DP and Diluent from (b) (4) to the distribution site in the US.
 - d. Shipping validation studies for the DP and Diluent from the storage and distribution site(s) to clinical sites (worst case scenario expected).

- e. Procedures for packaging the DP and Diluent in shipping containers at each site.

3. DP Shipping validation studies do not include testing of actual samples of voretigene neparvovec shipped in the final container.

Please submit a plan for how to address the above issues by September 30, 2017. Please submit all shipping validation data to the BLA by October 30, 2017.

DMPQ: No major issues are noted from the information provided so far.

Clinical: No major issues are identified. There are no outstanding information requests.

Statistical: No major issues are identified.

Pharmacology/Toxicology: No major issues are identified.

2. Information regarding major safety concerns.

There are no major safety concerns identified at this time.

3. Preliminary review committee thinking regarding risk management:

The review committee acknowledges the applicant's proposed plan for risk management through use of specially trained centers for product administration. The safety data do not indicate the need for a required Risk Evaluation and Mitigation Strategy (REMS) or a safety post-marketing requirement (PMR) at this time.

The applicant's planned registry study is currently under review and could potentially be considered a postmarketing commitment (PMC), depending on the goals of the study after discussing with the applicant, and the outcome of the advisory committee meeting. FDA will provide more detailed comments and recommendations on the registry study after discussion with the applicant and the advisory committee meeting.

4. Any information requests sent and not received:

- a. DMPQ: Information Request submitted (requested on July 31, 2017) is substantial.

- b. Statistical Information Request submitted to Application on September 8, 2017. An information request will be submitted.

5. Any new information requests to be communicated

- a. Additional CMC information requests may be sent to the Applicant in the future to address remaining review issues, including but not limited to re-setting or tightening acceptance criteria for Drug Substance and Drug Product release specifications.
- b. Additional Clinical information requests may be sent to the Applicant in the future to address remaining review issues.

6. Proposed date(s) for the Late-Cycle Meeting and the Late-Cycle Meeting Materials

- a. Proposed date for Late-Cycle Meeting: November 7, 2017, 12:00 pm to 1:30 pm

- b. Proposed date for the Late-Cycle Meeting Materials: November 2, 2017.

If these timelines change we will communicate updates to you during the course of the review.

7. Updates regarding plans for the AC meeting:

- a. Proposed date for informal discussion of Advisory Committee (AC) meeting related issues: October 3, 2017

- b. Please send your AC presentation slides to us by 10/6/2017.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.

Advisory Committee Meeting: October 12, 2017