



LATE-CYCLE MEETING MATERIALS

November 2, 2017

Our STN: BLA 125610/0

Spark Therapeutics, Inc.
Attention: Jim Wang, Ph.D.
3737 Market Street, Suite 1300
Philadelphia, PA 19104

Dear Dr. Wang:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for LUXTURNA, voretigene neparvovec.

Attached are our meeting materials, including our agenda, for the Late-Cycle Meeting (LCM) scheduled for November 7, 2017.

If you have any questions, please contact the Regulatory Project Manager, 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

ENCLOSURE:
Late-Cycle Meeting Materials

Late-Cycle Meeting Materials

Meeting Date and Time: November 7, 2017 2:00 PM – 3:30 PM
Meeting Location: Teleconference
White Oak, Building 71, Room 1206
Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Application Number: BLA 125610/0
Product Name: voretigene neparvovec
Indication: For the treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy.
Sponsor/Applicant Name: Spark Therapeutics, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authorities, division directors, and application Chair. Therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that could be submitted to address any identified issues. We may also discuss whether the submission of such information would be expected to trigger an extension of the PDUFA goal date if the Review Committee should decide, upon receipt of the information, to review it during the current review cycle.

Please note: if you submit any new information in response to the issues identified in this background package prior to this LCM we may not be prepared to discuss that information at this meeting.

1. Substantive Review Issues to be discussed during the LCM

The following substantive review issues have been identified to date:

Chemistry, Manufacturing, and Controls (CMC) Issues

- a. Regarding the substantive CMC issues discussed at the September 14, 2017 mid-cycle meeting:

- i. The major deficiency issues discussed with the applicant at the midcycle meeting regarding drug substance and drug product shipping validations and establishment of a distributor for the commercial product have not been resolved.
 - ii. Please provide updates on when the data from the shipping validation studies and the establishment of the distributor for voretigene neparvovec distribution will be provided to the BLA.
- b. Regarding the CMC information requests:
- i. Please note that some of your recent responses to the CMC information requests (e.g. Amendment 36 received on October 30, 2017) are still under review.
 - ii. Please be reminded some responses to the recent CMC information requests (sent during the week of October 23-27, 2017) are still pending. Please provide updates on the when responses will be submitted to the BLA.
 - iii. We note that in Amendment 36 received on October 30, 2017, the data for qualification studies for the (b) (4) [REDACTED] will not be available until mid-December.
- c. Any potential requirements for post marketing commitment for CMC studies will be discussed with the applicant once we have a clear understanding of when outstanding CMC requirements can be met. Agreement on the scope and timing of potential post marketing commitments for CMC are expected to be achieved by December 1, 2017.

CMC/Facilities Issues

- a. There are no substantive issues for discussion. However, there are two outstanding amendments in response to the following information requests (IR):
 - i. September 5, 2017 Information Request due November 12, 2017: Please provide data (results of EM and media fill) from the media fill run being executed September 26 through October 10, 2017. Please ensure that nonviable particle monitoring in operation (as agreed in your August 29 - August 31, 2017 emails) will be performed during this media fill run.
 - ii. October 27, 2017 IR due November 12, 2017: You indicated in your October 25, 2017 email that the sealable foil pouch is utilized to prevent (b) (4) [REDACTED] during product shipments. However, this intended use is not indicated in the original BLA submission and any of its amendments. Please provide a clear

description of your intended use for the pouch along with associated validation information (including validation protocol summary and data). If the intended use is not validated, please provide your plans and a timeframe for validating.

Labeling

- a. The PDUFA goal date for the start of labeling discussions with the applicant is December 12, 2017. However, we anticipate that we will communicate with you on labeling in November.

For inspections: Inspections are complete. A final recommendation is pending at this time.

2. Advisory Committee Meeting

The Advisory Committee Meeting was held on October 12, 2017. We do not plan to discuss at this meeting.

3. Risk Management Actions (e.g., REMS)

We have not identified issues related to risk management. We do not believe that a risk management action (e.g., REMS) is needed at this time.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/Chair)
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues – 15 minutes. Each issue will be introduced by FDA and followed by a discussion.
 - a. Discussion of drug substance and drug product shipping validations.
 - b. Discussion of establishment of distributor for the commercial product.
3. Discussion of Minor Review Issues – 00 minutes
4. Additional Applicant Data – 5 minutes (Applicant)
5. Information Requests – 10 minutes
 - a. CMC-Recent responses to information requests currently under review.
 - b. CMC- Pending information requests sent the week of October 23, 2017.

- c. CMC- Discussion of data for qualification studies will not available until Mid-December.
 - d. CMC/Facilities-Information request dated September 5, 2017 is due on November 12, 2017.
 - e. CMC/Facilities-Information request dated October 27, 2017 is due on November 12, 2017.
6. Postmarketing Requirements/Postmarketing Commitments – 00 minutes
- a. Do not plan to discuss at this meeting.
7. Major labeling issues – 00 minutes
- a. Do not plan to discuss at this meeting.
8. Review Plans –00 minutes
- b. Do not plan to discuss at this meeting.
9. Applicant Questions –5 minutes
10. Wrap-up and Action Items – 5 minutes