

Our STN: BL 125610

December 10, 2017
LATE-CYCLE
MEETING MEMORANDUM

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

Dear Dr. Wang:

Attached is a copy of the memorandum summarizing your November 7, 2017 Late-Cycle teleconference with CBER. This memorandum constitutes the official record of the teleconference. If your understanding of the teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in 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 Regulatory Project Management
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

Late-Cycle Meeting Summary

Meeting Date and Time: November 7, 2017 2:00 pm
Meeting Location: White Oak, Building 71, Room 1206

Application Number: BLA 125610/0
Product Name: voretigene neparovec
Proposed Indications: For the treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy.

Applicant Name: Spark Therapeutics, Inc.

Meeting Chair: Lilia Bi, MD, Ph.D.
Meeting Recorder: Nevitt Morris, RN, BSN, BS

FDA ATTENDEES

Nevitt Morris, RN, DRPM/OTAT/CBER
Lilia Bi, MD, PhD, CBER/OTAT/DCGT/GTB
Robert Aksamit, PhD, CBER/OTAT/ DCGT/GTB
Dana C. Jones, BS, OCBQ, DCM/APBL/CBER
Ramani Sista, PhD, Director, DRPM, OTAT
Angela Whatley, PhD, CBER/OTAT/ DCGT/GTB
Rabia Ballica, PhD, OCBQ/DMPQ/CBER
Bethany Baer, MD, OBE/CBER
Wiley Chambers, MD, CDER,/OND/DTOP
Yao-Yao Zhu, MD, DCEPT/OTAT/CBER
Annie Lin, PhD, OBE/DB/CBER
Patrick Riggins, PhD, Chief, DRPM, OTAT/CBER
John A. Eltermann Jr., RPh, MS, Director, CBER/OCBQ/DMPQ
Deborah Trout, BS, OCBQ/DMPQ/CBER
Steven Oh, PhD, Deputy Director, DCGT/ CBER/OTAT
Shiowjen Lee, PhD, OBE/DB/CBER
Wilson Bryan, MD, Director, CBER/OTAT/IOD
Rachael Anatol, PhD, Deputy Director, OTAT/IOD
Denise Gavin, PhD, Chief, CBER/OTAT/ DCGT/GTB
Raj Puri, MD, PhD, Director, DCGT/IOD/CBER
Kimberly Benton, PhD ADRM, IOD/ OTAT
Carla Jordan, BIMO/OCBQ/CBER
Adamma Mba-Jones, MD, OBE/CBER

APPLICANT ATTENDEES

Michael Cowan, Head of QA
Mark Galbraith, Head of Quality Control and Analytical Sciences
Diane Blumenthal, Head of Tech Ops

Christopher Klem, Drug Product Manufacturing Lead
Paul Gil, Regulatory CMC lead
Kathy High, President and Head of R&D
Jim Wang, Head of Regulatory Affairs Strategy

BACKGROUND

BLA 125610/0 was submitted on May 16, 2017, for voretigen neparvovec.

Proposed indication: For the treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy.

PDUFA goal date: January 12, 2018

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on November 2, 2017.

DISCUSSION

1. Discussion of Substantive Review Issues - 15 minutes:

Each issue will be introduced by FDA and followed by a discussion.

- 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.

Additional Discussion:

Spark stated the distributor for voretigene neparvovec has been established and the BLA will be updated accordingly. The physical address of the distributor is:

(b) (4)

- 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.

Additional Discussion:

According to Spark, the Drug Product shipping validation protocol was initiated on October 17, 2017 and is currently ongoing. Associated samples are currently on test. Spark is on track for providing a final report for this validation to the FDA on or before November 30, 2017.

The third and final run of the Drug Substance shipping validation protocol has also been completed and associated samples are also currently on test. Spark will provide a final report for the Drug Substance shipping validation to the FDA on or before November 30, 2017.

- 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.

Additional Discussion: Spark acknowledged and provided status updates to the items listed:

Date Received	Topic	Status
23 Oct	(b) (4)	RPM checking with Reviewer
27 Oct	Foil Pouch Validation	Response Sequence 0038
27 Oct	(b) (4) Test Data November 20	Response Sequence 0040*
	RPE65 Gene Source	

Other CMC Info Requests:

Date Received	Topic	Status
13 Oct	Known EM Isolates	Response Sequence 0039 Submission Target TBD
27 Sep	(b) (4) Potency Validation	Submission Target November 10
03 Nov	Specifications and Hold Times	Submission Target November 10

- iii. We note that in Amendment 36 received on October 30, 2017, the data for qualification studies for the (b) (4) [redacted] [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.

Additional Discussion:

According to Spark, non-viable particle monitoring in operation was performed during the media fill on October 5, 2017 at (b) (4) [REDACTED]. Data from this media fill will be provided in the IR response due on November 12, 2017.

- 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.

Additional Discussion: Spark stated an additional IR response on intended use of the foil pouch as a secondary packaging component was provided to the FDA on November 2, 2017. (Sequence 0038).

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.

Additional Discussion: The FDA stated labeling discussions would be toward the later part of November and FDA acknowledged receiving Spark's revised labels and will provide feedback to the Spark in the near future.

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.

4. Discussion of Minor Review Issues – 00 minutes

5. Additional Applicant Data – 5 minutes (Applicant)

6. 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.

7. Postmarketing Requirements/Postmarketing Commitments – 00 minutes

- a. Do not plan to discuss at this meeting.

8. Major labeling issues – 00 minutes

- a. Do not plan to discuss at this meeting.

9. Review Plans – 00 minutes

- a. Do not plan to discuss at this meeting.

10. Applicant Questions – 5 minutes

Spark Therapeutics indicated that data qualifications information would be ready for FDA by middle of Decembr 2017.

Spark indicated additional discussion on expiration dating and Lot Release Protocol (LRP) as topics for future discussion.

11. Wrap-up and Action Items – 5 minutes

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.