



Our STN: BL 125798/0

LATE-CYCLE
MEETING MEMORANDUM
October 25, 2024

Neurotech Pharmaceuticals, Inc.
Attention: (b) (4)

Dear Dr. (b) (4):

Attached is a copy of the memorandum summarizing your October 7, 2024, Late-Cycle Meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting 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 Crystal Melendez at (240) 772-6272 or Crystal.Melendez@fda.hhs.gov.

Sincerely,

Mara Miller, MA
Director
Division of Review Management and Regulatory Review 2
Office of Review Management and Regulatory Review
Office of Therapeutic Products
Center for Biologics Evaluation and Research

Late-Cycle Meeting Summary

Meeting Date and Time: October 7, 2024 12-1pm EST
Meeting Location: FDA, Building 71, Room 1206

Application Number: 125798/0
Product Name: revakinagene taroretcel (NT-501); ENCELTO
Proposed Indications: For the treatment of idiopathic macular telangiectasia type 2 (MacTel)
Applicant Name: Neurotech Pharmaceuticals, Inc.

Meeting Chair: Carolina Panico, MD, PhD
Meeting Recorder: Crystal Melendez, MT, RN, BSN, DCPM

FDA ATTENDEES:

Meghna Alimchandani, MD, CBER/OBPV/DPV
Natalya Ananyeva, PhD, CBER/OTP/OPPT
Marie Anderson, PhD, CBER/OCBQ/DBSQC
Mona Badawy, CBER/OTP/ORMRR
Michael Brony, PharmD, CBER/OCBQ/DCM/APLB
Sandip De, PhD, CBER/OTP/OCTHT
Maureen DeMar, CBER/OCBQ/DMPQ
'Lola Fashoyin-Aje, MD, MPH, CBER/OTP/OCE
Varsha Garnepudi, MS, RAC, CBER/OCBQ/DBSQC
Jin Sung Hong, PhD, CBER/OTP/OCTHT
Arlesa Hubbard, MS, CDRH/OPEQ/OHTIII/DHTIIIC
Christopher Jason, MD CBER/OBPV/DPV/PB
Xing Jing, PhD, CBER/OTP/OCE
Kathleen Jones, PhD, CBER/OCBQ/DMPQ
Alyssa Kitchel, PhD, CBER/OTP/OCTHT
Margaret Benny Klimek, PhD, CBER/OTP/OPT
Linda Le, MBA, CBER/OTP/ORMRR
Nicole Li, CBER/OCBQ/DMPQ
Jing Lin, PhD, CBER/OCBQ/DBSQC
Heather Lombardi, PhD, CBER/OTP/OCTHT
Rommel Maglalang, CBER/OTP/ORMRR
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Crystal Melendez, MT, RN, BSN, DCPM CBER/OTP/ORMRR
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Leyish Minie, MSN, RN, CBER/OTP/ORMRR
Victoria Moncada, MD, CBER/OBPV/DPV/PB2
Ernesto Moreira, MD, CBER/OTP/OPT
Miriam Ngundi, PhD, CBER/OCBQ/DMPQ
Steven Oh, PhD, CBER/OTP/OCTHT
Carolina Panico, MD, PhD, CBER/OTP/OCTHT
CDR Kenneth Phillips, CBER/OCBQ/DBSQC/LAC

Kanaeko Ravenell, MS, SBB (ASCP), CBER/OCBQ/DIS/BMB
Carolyn Renshaw, CBER/OCBQ/DMPQ
Andrey Sarafanov, PhD CBER/OTP/OPPT
John Scott, PhD, MA, CBER/OBPV/DB
Abigail Shearin, VMD, PhD, CBER/OTP/OPT
Rosa Sherafat-Kazemzadeh, MD, CBER/OTP/OCE
Svetlana Shestopal, PhD, CBER/OTP/OPPT
Edhriz Siraliev-Perez, PhD, CBER/OTP/OGT
Ramani Sista, PhD, CBER/OTP/ORMRR
Cinque Soto, PhD, CBER/OTP/OCTHT
Lisa Stockbridge, PhD, CBER/OCBQ/DCM/APLB
Kyung Sung, PhD, CBER/OTP/OCTHT
Edward Thompson, CBER/OTP/ORMRR
Ekaterini Tsilou, MD, CBER/OTP/OCE
Wojtek Tutak, PhD, CBER/OTP/OCTHT
Xiaoyu Zhang, PhD, CBER/OBPV/DB/TEB1
Tingting Zhou, PhD, CBER/OBPV/DB

APPLICANT ATTENDEES:

Richard Small, CEO, Neurotech Pharmaceuticals
Crystal Cortellessa, VP manufacturing and Facilities, Neurotech Pharmaceuticals
Thomas Aaberg, Chief Medical Officer, Neurotech Pharmaceuticals
Konrad Kauper, VP Research and Development, Neurotech Pharmaceuticals
Jacob Patterson, VP Quality Operations, Neurotech Pharmaceuticals
(b) (4), Regulatory and CMC consultant, (b) (4)
Patrica Davies, Clinical Operations, Neurotech Pharmaceuticals
Kevin Hibbert, VP regulatory Affairs, Neurotech Pharmaceuticals
(b) (4), Device Consultant

BACKGROUND

BLA 125798/0 was submitted on April 18, 2024, for revakinagene taroretcel.

Proposed indication: For the treatment of idiopathic macular telangiectasia type 2 (MacTel).

PDUFA goal date: December 17, 2024

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on September 27, 2024.

DISCUSSION

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.

Chemistry, Manufacturing and Controls

1. Identity testing of all raw materials for DS manufacturing
2. Cumulative leachables and extractables in the DP
3. Endotoxin spike and recovery study
4. (b) (4) testing on (b) (4)
5. Media fills studies

Summary of discussion of items 1-5:

1. Neurotech Pharmaceuticals, Inc. (Neurotech) summarized the identity tests proposed for the raw materials used in the manufacturing of the (b) (4) and stated the validation study results will be provided within 45 days or sooner, except the results for (b) (4) that might take longer because the related identity test (b) (4) analysis per (b) (4) was contracted to a third party.
FDA stated that Neurotech's proposed plan for reagent identity testing, including timeline and methods, is acceptable and asked Neurotech to clarify what activities will be conducted for the sample type validation Neurotech proposed for all tests. FDA also clarified that for compendial methods a full validation is not required, and qualification activities will be sufficient. FDA asked Neurotech to provide specific dates by which the validation study results will be provided and to submit any qualification data that Neurotech might already have collected as soon as possible.
Neurotech stated that qualification data that they already have, as well as specific completion dates, will be provided as soon as possible.
2. FDA stated the extractables/leachables (E&L) study submitted in the original BLA is insufficient as multiple deficiencies were identified, including Margin of Safety (MOS) levels above safety thresholds for some leachables (e.g., (b) (4) and Analytical Evaluation Threshold (AET) values and Limits of Quantitation (LOQ) not provided for any of the methods used to measure E&L. FDA acknowledged that Neurotech recently submitted results from a new E&L study and explained that three reports related to the new E&L study consist of a large amount of information (about 800 pages) and require time to review. FDA asked Neurotech to clarify whether the new study was intended to replace or to support the study submitted in the original submission.

Neurotech acknowledged the initial E&L study was performed poorly and some chemical compounds (e.g., (b) (4)) were likely erroneously identified because inadequate controls were used and also stated that the study did not include a robust risk analysis. Neurotech also stated that the new study included a more appropriate design, based on ISO 10993-18:2020 and ISO 10993-12:2021, and used appropriate controls and reference standards for each method and compounds. Neurotech stated the new study was intended to replace the study submitted in the original submission and stated that a schematic of the study will be provided to facilitate the review. FDA acknowledged the plan and found it acceptable.

3. Neurotech clarified the requested (b) (4) study is ongoing and results will be provided on or before October 30, 2024, as agreed during the interactive review. Neurotech also illustrated that the protocol was slightly changed from the one previously agreed upon with FDA based on preliminary results for short-term trends observed for the testing performed on Day 1. FDA acknowledged the changes to the protocol and stated the changes are acceptable. FDA asked Neurotech whether the preliminary data points presented during the meeting related to the average of multiple observations for each data point. Neurotech confirmed averages were provided.
4. Neurotech stated the requested (b) (4) testing on (b) (4) is ongoing and being conducted by (b) (4) and the results will be provided to FDA earlier than originally agreed (October 24, 2024, instead of November 15, 2024). FDA acknowledged Neurotech's effort to provide the study earlier.
5. Media fills: FDA stated the review is ongoing. However, FDA pointed out that there does not appear to be a comprehensive media fill study, and it appears that Neurotech is sourcing data from different noncomprehensive studies over the years to support the aseptic process. The initial studies did not include the (b) (4) process as the NT-501 PAC was (b) (4). FDA pointed out that based on a review of amendment 36, it appears that the (b) (4). Therefore, it appears that the (b) (4) is not tested for sterility. FDA stated that a follow up information request (IR) will be sent for details regarding the testing of the (b) (4). Neurotech explained that prior to 2020, the (b) (4) were tested, but after 2020, no testing was performed. FDA asked Neurotech to make a table of every step/process and interventions that were performed during the executed media fill studies. Neurotech presented a hard copy with summary information (study number, study designation, year study was performed, number of runs, lot size per run, and room number) for the media fills and PPQ lot history in rooms (b) (4). FDA pointed out that the hard copy was not available to all meeting attendees. Neurotech agreed to submit the document after the meeting. Neurotech stated that a linear list and interventions will be included in the

document. Neurotech explained that ISO (b) (4) are the same in the two rooms where media fills have been performed. Neurotech explained that the intervention performed included (b) (4) in the 2020 media fill study. Neurotech explained that operators stay on the floor from beginning until the end of the aseptic process.

FDA pointed out that Neurotech did not perform a risk assessment of the manufacturing process steps and interventions that should be included in the media fill program. FDA stated that a follow up IR regarding the risk assessment and interventions will be sent to Neurotech.

3. Discussion of Established Pharmacologic Class

Established Pharmacologic Class (EPC): Allogeneic encapsulated cell-based gene therapy product.

Summary of discussion:

Neurotech stated that including 'gene therapy' in the EPC may be confusing as gene therapy may indicate the genes of the patient receiving the product will be modified. FDA acknowledged Neurotech's concern and clarified that gene therapy products include cells that are genetically modified, like the cells in the drug product. FDA also stated that Neurotech's point of view will be discussed internally.

4. Additional Applicant Data – 10 minutes **(Applicant)**

Summary of discussion:

Neurotech indicated that they did not expect to submit additional data for review that was not previously mentioned.

5. Information Requests – 5 minutes

- a. An information request related to the toxicological risk assessment of cumulative extractables and leachables was sent on September 26, 2024. The response is expected by October 9, 2024.
- b. An additional information request related to the identity testing of the raw materials will be sent in the upcoming week.
- c. An additional information request related to elimination of periodic media fills, shipping validation, environmental monitoring, and equipment qualification and cleaning will be sent in the upcoming week.

6. Risk Management Actions (e.g., REMS, the ability of adverse event reporting and CBER's Sentinel Program to provide sufficient information about product risk).

- a. Will not be discussed, there is no anticipation of a REMS at this time.

7. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

- a. CMC PMC/PMR negotiations with the Applicant will start on November 5, 2024, if necessary.
- b. DPV does not anticipate safety-related studies such as PMR/PMC at this time.

8. Major labeling issues

- a. There are no major labeling issues identified at this time.

9. Review Plans

- a. Review of the BLA is on-going. We will continue sending IRs as necessary to get clarification on any submitted information. FDA plans to start label negotiations no later than November 15, 2024.

10. Applicant Questions –15 minutes

Summary of discussion:

There are no further questions from Neurotech.

11. Wrap-up and Action Items – 5 minutes

Summary of discussion:

Additional information requests will be sent to Neurotech and the open information requests will be submitted by their respective due dates.

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.