



Center for Biologics Evaluation and Research (CBER)
Office of Therapeutic Products (OTP)
Office of Plasma Protein Therapeutics CMC (OPPT)
Division of Hemostasis (DH)
Hemostasis Branch 2 (HB2)

MEMORANDUM

To: Administrative file for BLA STN 125722/0 (eCTD Sequence #0001)
From: Andrey Sarafanov, PhD; CBER/OTP/OPPT/DH/HB2
Through: Natalya Ananyeva, PhD; Branch Chief; CBER/OTP/OPPT/DH/HB2
Applicant: PTC Therapeutics
Product: Eladocogene exuparvovec [KEBILIDI]
Indication Treatment of patients with aromatic L-amino acid decarboxylase (AADC) deficiency
Subject: Extractables and Leachables assessment in Drug Product
CC: Tolani Ishola, CBER/OTP/ORMRR/DRMRR1/RMSB1
Bo Liang, PhD, Chair, CBER/OTP/OGT/DGT1/GTB2
Mondona McCann, PhD, CBER/OTP/OPT/DPT1/PTB3
Zuben Sauna, PhD; CBER/OTP/OPPT/DH
Mahmood Farshid, PhD; CBER/OTP/OPPT
Basil Golding, MD; CBER/OTP/OPPT

EXECUTIVE SUMMARY

The Drug Product (DP), International Nonproprietary Name (INN) and US Adopted Name (USAN): eladocogene exuparvovec, proprietary name [KEBILIDI], is a gene therapy product based on a recombinant adeno-associated virus serotype 2 (AAV2) vector comprising a human dopa decarboxylase (DDC, also referred to as AADC) cDNA transcript, which encodes human AADC. Following patient treatment, expression of this enzyme corrects its deficiency and normalizes phenotype. The BLA was received by FDA on March 15, 2024, and my review assignment was to review information on analytical assessment of leachables in DP. To identify the manufacturing process step from which leachables accumulate in DP, I also reviewed the process description. During my review, I requested additional information from the Applicant that was provided. Upon review of all information, I found that the scope of assessment and the obtained analytical data are acceptable. Review of toxicological assessment of the analytical data was performed by Dr. Mondona McCann, (CBER/OTP/OPT/DPT1/PTB3) who found the data acceptable and reflecting low risk of leachables. Thus, from the perspective of the leachables safety, **approval** of this BLA was recommended.

REVIEW SUMMARY

1. Identification of process step from which leachables accumulate in drug product and respective high-risk materials

The Drug Substance is manufactured by (b) (4)

The DP is further produced upon (b) (4), sterilizing filtration, and filling into Container Closure System (CCS). The resulting DP (b) (4) is comprised of (b) (4) excipients including potassium chloride, sodium chloride, potassium phosphate, disodium hydrogen phosphate, and poloxamer 188 in Water for Injection (WFI) (b) (4). The CCS is a single-dose 2-mL glass vial; stoppered with a siliconized, chlorobutyl stopper with (b) (4) sealed with an aluminum/plastic (b) (4) cap (Section 3.2.P.2.4).

Upon filling, the DP vials are frozen to -65 °C (Section 3.2.P.3.3) and stored for up to 48 months (DP shelf life) (Section 3.2.P.8.1). In clinical use, the thawed DP (0.32 mL) is administered by dripping directly into the putamen of the brain using a cannula via a neurosurgical procedure.

Reviewer Comment 1

The major high-risk for leachables materials are (b) (4)

2. Extractables and leachables assessment

The initial assessment was performed by assigning risk scores for the process materials. This identified the above listed materials as high-risk (Section 3.2.P.2.3). These materials were further studied in extractables and leachables (E&L) studies. These studies used conventional (b) (4) based methods for organic compounds detection and (b) (4) based methods for elemental compounds detection. Identification and quantitation of the compounds was performed using (b) (4)

For Extractables assessment, the Applicant used data from the components' manufacturers, which were generated using relevant (b) (4) conditions. Based on evaluation of these extractables data, the Applicant performed studies, termed "simulated extractable", on each of individual components: DP CCS (Section 3.2.P.2.4), and (b) (4)

In these studies, they used (b) (4)

In analytical assessment, they applied Analytical Evaluation Threshold (AET, reporting limit) (b) (4) corresponding to Safety Concern Threshold (SCT) of (b) (4) for organic compounds per (b) (4) and element-specific AETs per (b) (4)

The highest levels were found for (b) (4); and cumulative levels of each compound were considered safe. In addition, from DP CCS, (b) (4) specific organic and (b) (4) elemental compounds were found above AET. Among these, (b) (4)

organic compounds (b) (4)

(b) (4)) were found with Margins of Safety (MOSs) of (b) (4) Based on toxicological assessment of these data, the Applicant concluded that DP is safe in regard to leachables.

Reviewer Comment 2

The initial assessment of leachables missed a real-time study through the high-risk process steps starting from the (b) (4) step, and instead, was based on limited assessment. This approach may result in errors in actual levels of leachables in DP, considering closeness of MOS values for several organic compounds to risk levels. Furthermore, as the DP is administered onto two small areas of tissue (brain), the local burden of these leachables can be much higher compared to other routes of administration. Thus, additional information to support the safety was requested.

COMMUNICATION FOR ADDITIONAL INFORMATION

I. An Information Request (IR) was sent to the Applicant on May 22, 2024 (Question (Q) 9 within a combined IR, corresponding to Issue 1 from the Filing Notification Letter of FDA sent on May 13, 2024) as follows.

Your assessment of leachables in final drug product (DP) is insufficient as the actual study was performed only for (b) (4) process components (DP Container Closure System (CCS), (b) (4) (b) (4) . For each of them, you performed a separate study termed “simulated extractables”, which rather corresponds to a “simulated accelerated leachables” study.

Even each study results were acceptable, your overall assessment still misses an evaluation of cumulative leachables that appear in final DP from other (b) (4) process components including and (b) (4) the high-risk for leachables process step (b) (4) , in particular, involving such high-risk materials as (b) (4) (b) (4) etc. Please note that even low levels of leachables from individual components (such as scored low- or medium-risk), upon accumulation in final DP, may altogether exceed safety thresholds. Thus, for a BLA submission, a real-time study through the manufacturing process, shelf-life and in-use conditions is required, as in particular, reflected in (b) (4) and such study cannot be substituted with only (b) (4) based assessments and/or performing an actual leachables study only for selected components. Please also consider that upon your product administration, all leachables will be absorbed on a small area of the brain tissue due to lipophilic chemical nature of majority of these compounds - by this, the local biochemical burden of them could be significant.

Therefore, please perform a real-time study to assess overall leachables in DP as described above. Considering complexity of the DP matrix that may interfere with leachables analytical detection, and your already performed simulation study on the DP CCS, you may choose performing a simulated study that mimics your manufacturing process segment from the (b) (4) step and through the (b) (4) step, using respective (b) (4) leachables profile from that study to that already determined in your simulated study with CCS; in this case, the Analytical Evaluation Thresholds in each study should be (b) (4) (implying reassessment of your CCS study results).

The **Response** was provided on May 31, 2024 (Amendment 6, eCTD Sequence #0007). The Applicant acknowledged the Agency's request and committed to perform (i) a real-time study to assess overall leachables in DP accumulated from the (b) (4) process step through (b) (4) step, and (ii) re-evaluate the CCS leachables profile using AETs in each of the two studies appropriate for (b) (4) the reported compounds. They informed that this work had been initiated with the manufacturer (b) (4) to design and execute the protocol for the requested real-time process simulation, and with (b) (4) to test the real-time process simulation samples, as well as to reevaluate the CCS study results with appropriate AET. The Applicant anticipated to complete these studies by the middle of September 2024.

Reviewer Comment 3

The response is acceptable.

II. A follow-up IR (Q1 within a combined IR from other reviewers) was sent to Applicant on July 7, 2024, as follows.

In your May 31, 2024 response to the potential CMC review issue # 1 in the May 13, 2024 Filling Notification Letter, you committed to i) conduct a real-time process simulation study for leachables from (b) (4) through the (b) (4), ii) re-assess the container closure system leachable study results using appropriate Analytical Evaluation Threshold, and iii) conduct safety risk assessment upon merging analytical data from these two studies (i.e., reconstructing overall leachables profile in final DP). You also committed to submit the data from these studies by the middle of September 2024. Please address our following additional comments:

- a. Please provide an update on the progress of these studies and whether you will be able to submit the data by the timeline you committed or earlier, if possible, for us to coordinate our review.
- b. In the planned leachables study (i), please assess extractables from the respective high-risk materials for targeting respective leachables and submit the data along with the data from the other studies by the middle of September 2024.
- c. Please also include a toxicological risk assessment for any identified compounds from your leachable studies.

The **Response** was provided on July 22, 2024 (Amendment 20, eCTD Sequence #0021). The Applicant confirmed that they are working to get the results and submit them to FDA by mid-September 2024.

Reviewer Comment 4

The response is acceptable.

On September 27, 2024, the Applicant provided further **Response** to IRs dated May 22, 2024 (Q9) and July 7, 2024 (Q1) (Amendment 45, eCTD #0046).

The Applicant performed the simulated leachables study (b) (4) step through the (b) (4) step with maximal operational times at (b) (4) (Reports *PD-SD651-24-05 Rev 0* and *PD-SD651-24-06 Rev 2*). The samples were analyzed with respective methods in a (b) (4) with the appropriate standards chosen based on the extractables study results. The AET was (b) (4) to assure that final (cumulative) AET of (b) (4) will remain unchanged when combining the new results with the re-processed

leachables data for the CCS). The used analytical methods were (b) (4)

(b) (4) for detection of organic leachables and (b) (4) for detection of elemental leachables.

(b) (4) organic leachables were found above the AET, (b) (4) and (b) (4) elemental leachables, (b) (4) were found above respective AETs by (b) (4) (Report *Screening Study Report-1686-SCR Rev 0.0*).

2. For CCS leachables reevaluation, the extractables study results (as worst-case leachables) were reassessed using the (b) (4) AETs (b) (4) for organics, and respective element-specific values for elemental leachables). No new compounds were identified above respective AETs in addition to previously identified (b) (4) since the vial is made from borosilicate glass (Report *Simulated Extractable Study Report-1157-SCR Rev 1.0*).

Upon summing up the leachables profiles from both studies (with the resulting AET of (b) (4) (b) (4), no compounds were found that were identified in both studies (i.e., no increase of any leachable level was observed). Toxicological assessment of the data showed the margins of safety (MOS) (b) (4) and the Applicant concluded that the risk of leachables in DP is low (Report *Toxicological Hazard Assessment Report*).

Reviewer's Comment 5.

Based on my review, the analytical data are acceptable. Toxicological assessment of these data was found acceptable by Dr. McCann.

REVIEW CONCLUSION AND RECOMMENDATION

The assessments of leachables in DP indicate its safety. From my review scope, I recommend **approval** of this BLA.