



MEMORANDUM

To Administrative file for STN 125758/0

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Subject Quality Control Test Methods for atidarsagene autotemcel (OTL-200) drug product

Recommendation Approval

Summary of Review and Conclusion

On 19 July, 2023, a Biologics License Application (BLA) was submitted by Orchard therapeutics for atidarsagene autotemcel (OTL-200) drug product (STN 125758/0). This document constitutes the final review memo for the following analytical methods and their validations, as used for quality control lot release of the critical component and product:

1. ARSA Activity by (b) (4) for (b) (4) OTL-200 drug product
2. (b) (4)
3. (b) (4)
4. (b) (4)
5. (b) (4)
6. Appearance for OTL-200 drug product

Conclusion

All methods reviewed in this memo, except for the Appearance test, have been described and validated adequately, and are suitable as quality control tests for the product. The sponsor has committed to submitting data to support qualification of the appearance test method by July 31, 2024.

Background

Orchard therapeutics has submitted a new BLA for atidarsagene autotemcel (OTL-200), a gene therapy product containing autologous CD34+ hematopoietic stem and progenitor

cells (HSPC) transduced *ex vivo* with a replication-incompetent lentiviral vector (LVV) encoding the human arylsulfatase A (ARSA) gene. It is intended for the treatment of pediatric patients with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early juvenile (ESEJ) metachromatic leukodystrophy (MLD). The drug product is presented as a cell suspension for intravenous infusion. The treatment consists of a single dose containing a minimum of (b) (4) x 10⁶ CD34+ cells/kg of body weight, suspended in a cryopreservation solution in one or more infusion bags.

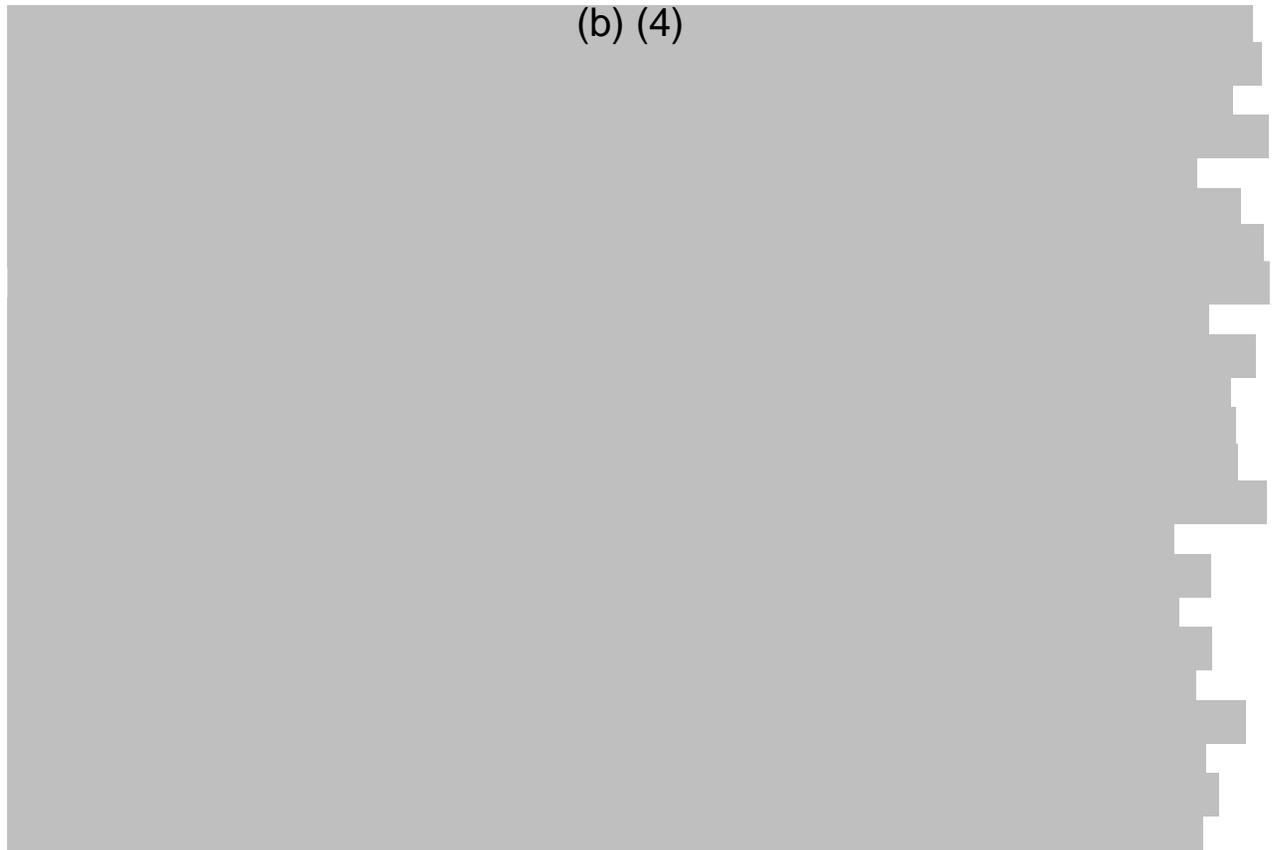
Information Reviewed

- 125758/0 — 1.2 Cover letters dated July 19, 2023
- 125758/0 — 2.3 Quality Overall Summary
- 125758/0 — 3.2.S.4.2 Analytical Procedures, (b) (4) Drug substance (critical component)
- 125758/0 — 3.2.P.5.2. Analytical Procedures, OTL 200 Drug Product
- 125758/0 — 3.2.S.4.3. Validation of Analytical Procedures, Drug Substance (critical component)
- 125758/0 — 3.2.P.5.3. Validation of Analytical Procedures, Drug Product

Review Narrative

1. ARSA Activity by (b) (4) for testing (b) (4) OTL-200
Method

(b) (4)



3 pages have been determined to be not releasable: (b)(4)

(b) (4)

6. Appearance of OTL-200

The specification for the appearance of OTL-200 DP is colorless to yellow or pink cell suspension. DP appearance in the (b) (4) bag is checked visually at (b) (4). The test sample container is (b) (4) to check that the appearance of the DP conforms to the specification (the color is due to the components like (b) (4) in the DP). The product office requested the standard operating procedure and data to support qualification of the method in an information request dated March 1, 2024. The firm responded in Amendment 53 by providing the SOP (MLN-ATT-000468) that includes images to guide the analysts' observations. The firm has committed to performing a qualification study of the appearance test method and will submit the data by July 31, 2024. The batch data for appearance test of (b) (4) DP lots manufactured by (b) (4) process for commercial use were acceptable.

Conclusion: The assay has not been qualified however, manufacturing personnel are trained to perform the visual inspection before (b) (4). Considering other tests that impact appearance (e.g., visible particulates, (b) (4) etc.) have been suitably verified or validated, it is acceptable to use the results of visual inspection of the OTL-200 drug product (b) (4), to support lot release. Data submitted for assay qualification by July 31, 2024, will provide additional assurance of method suitability.