

CBER CMC BLA Review Memorandum

BLA STN 125758

Product Name: atidarsagene autotemcel

Reviewer/Title/Affiliation

Tiffany Lucas, PhD / Chair, Reviewer / OTP/DGT/GTB4

Jacob Bitterman, PhD / Reviewer / OTP/DGT/GTB2

Maitreyi Chattopadhyay, PhD / Reviewer / OTP/DGT/GTB4

Christelle Mbondji, PhD / Reviewer / OTP/DGT/GTB5

Timothy Kamaldinov, PhD / Reviewer / OTP/DGT/GTB4

1. BLA#: STN 125758

2. APPLICANT NAME AND LICENSE NUMBER

Orchard Therapeutics (Europe) Limited

License Number: 2263

DUNS: 221097235

3. PRODUCT NAME/PRODUCT TYPE

Non-Proprietary/Proper/USAN: atidarsagene autotemcel

Proprietary Name: LENMELDY

UNII: EPP8G99QG4

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

- a. Pharmacological category: Autologous hematopoietic stem cell-based gene therapy
- b. Dosage form: Suspension
- c. Strength/Potency: 2E6 – 11.8E6 cells per mL and Potency of a minimum dose of 4.2E6 CD34+ cells/kg for pre-symptomatic late infantile (PSLI) metachromatic leukodystrophy (MLD), 9.0E6 CD34+ cells/kg for pre-symptomatic late infantile (PSEJ), and 6.6E6 CD34+ cells/kg for early symptomatic early juvenile (ESEJ) MLD. The minimum arylsulfatase-A (ARSA) enzyme expression is (b) (4) in transduced cells. The maximum dose is 30E6 CD34+ cells/kg body weight.
- d. Route of administration: Intravenous infusion
- e. Indication(s): Treatment of pediatric patients with PSLI, PSEJ, or ESEJ MLD.

5. MAJOR MILESTONES

Event	Date
DCC Receipt	07/19/2023
Filing Meeting	Internal: 09/05/2023 External communication: 09/15/2023
Application Orientation Meeting (AOM)	Clinical focus: 09/15/2023 CMC focus: 09/18/2023
Inspections	11/07/2023- 11/20/2023 AGC Biologics Facilities (b) (4) Bresso, Milan, Italy
Midcycle Meeting	Internal 11/02/23 External 11/17/23
Latecycle Meeting	Internal: 12/15/2023 External applicant: 01/08/2024

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Tiffany Lucas, PhD / OTP/DGT/GTB4	Cellular drug substance and drug product manufacturing, controls, drug product acceptance criteria
Jacob Bitterman, PhD / OTP/DGT/GTB2	Potency assay, extractables and leachables, chemistry, excipients, container closure
Maitreyi Chattopadhyay, PhD / OTP/DGT/GTB4	Lentiviral vector and cellular drug product testing and assay validations for safety, (b) (4), stability
Christelle Mbondji, PhD / OTP/DGT/GTB5	Lentiviral vector manufacturing, manufacturing controls, replication competent lentivirus testing, replication competent lentivirus testing, lentivirus specifications, characterization
Timothy Kamaldinov, PhD / OTP/DGT/GTB4	Control of materials, assays for adventitious agent, (b) (4)
Andrey Sarafanov, PhD / OTP/OPPT/DH/HB2	Extractables and Leachables Assessment for DP Manufacturing Process (Section 3.2.P.3.5)
Rukmini Bhardwaj, PhD / OTP/OPT/DPT2/PTB2	Safety assessment for DP (b) (4) leachables for DP Manufacturing Process (Section 3.2.P.3.5)

7. INTER-CENTER CONSULTS REQUESTED

Not applicable

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
07/18/2023	STN 125758/0	Filed
09/12/2023	STN 125758/4 (response to IR #1) Sent 09/01/2023	Translated COAs, certificates, lentiviral vector (LVV)/drug substance (DS)/ drug product (DP) contact materials list, (b) (4), testing of low-risk DP contact components, validation tests for (b) (4) methods
10/26/2023	STN 125758/10 (response to IR #2) Sent 10/10/2023	Control materials (b) (4) bags), CD34, hold time DP, adventitious agent safety, ARSA assay and validation, (b) (4) raw validation data, (b) (4) assay and validation, (b) (4) assay and validation, apheresis stability and shipping, DP batch analysis/process valid., OTL200 data table updates, DP PPQ lot clarification, use of (b) (4) to support OTL-200 LVV.
11/22/2023	STN 125758/14 (response to IR #3, Part 1, comments 1,3,5,8,10-15) Sent 11/07/2023	LVV CQA/MA, LVV PSQ, (b) (4) MF LVV testing, (b) (4) composition, (b) (4) testing, multi-lot reagent qualification/bridging, resuspend apheresis handling, vendor qualification, apheresis, and DP shipping, shipper changes, packing failures in validation ship, scaled-down model use

Date Received	Submission	Comments/ Status
11/29/2023	STN 125758/16 (response to IR #3, Part 2, comments 2,4,6,7,9) Sent 11/07/2023	Transduction Assay, incoming reagents (b) (4) E&L
01/16/2024	STN 125758/29(response to IR #4 Part 1/2) Sent 01/04/2024	E&L, Validation assays, shipping, max bags, (b) (4) LVV lots in manufacturing 1 DP lot
01/20/2024	STN 125758/30 (response to IR #4 Part 2/2) Sent 01/04/2024	Cell concentration and viability, extractables and leachables, (b) (4) validation, transduction efficiency assay and validation, VCN assay
01/24/2024	STN 125758/33 (response to IR #5) Sent 01/10/2024	(b) (4)
02/07/2024	STN 125758/39 (response to IR #6) Sent 02/01/2024	Cell count/viability robustness for Clinical study data, (b) (4) (timeline related to PMC/Feb. 28th response anticipated).
02/15/2024	STN 125758/41 (follow-up to IRs #4, #5, #6)	ARSA activity, Adventitious Agent testing
02/20/2024	STN 125758/43 (response to IR #7) Part 1 response Sent 02/13/2024	Human ARSA antibody clinical assay, ASRA assay validation, LVV (b) (4) robustness, "or equivalent" language in assays and manufacturing, transportation DP times, adventitious agent testing SOP and validation information, (b) (4) SOP and validation information, DP lots used to support Commercial (b) (4) DP sterility testing, DP appearance testing, COI generation, number of DP lots a patient can receive, CPP targets for (b) (4) DP
02/22/2024	STN 125758/44	PMC response
02/22/2024	STN 125758/45	PMR response
02/23/2024	STN 125758/46 (response to IR #7) Part 2 response Sent 02/13/2024	(b) (4) updated MF to adventitious agent, (b) (4), and (b) (4) testing

Date Received	Submission	Comments/ Status
02/28/2024	STN 125758/50 (response to IR #8 Sent 02/13/2024	(b) (4) assay, (b) (4) assay
02/29/2024	STN 125758/52	Orchard follow-up to CMC IRs #3, #6, #7
03/06/2024	STN 125758/53 (response to IR #9) Sent 03/01/2024	Negotiate acceptance criteria for LVV and DP release. Clarification of PMCs
03/08/2024	STN 125758/55 (response to IR #9 Part 2) Sent 03/01/2024	LVV acceptance criteria negotiation
03/08/2024	STN 125758/56	Updates to DP labels
03/11/2024	STN 125758/57 (response to IR #10) Sent 03/08/2024	Final LVV commercial acceptance criteria, confirmation of stability for DP and LVV, PMC negotiation of (b) (4) and appearance testing
03/12/2024	STN 125758/58	Final PMC agreement response
03/13/2024	STN 125758/59 (response to IR #11) Sent 03/11/2024	Final DP commercial acceptance criteria
03/15/2024	STN 125758/60 (response to IR #12) Sent 03/13/2023	Label updates based on final cell concentration specifications, revised PI

9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type & #	Holder	Referenced Item	Use in BLA (LVV or DP)	Letter of Cross-Reference Provided	Comments/Status
MF (b) (4)	(b) (4)	(b) (4)	DP	Yes	Suitable for commercial manufacturing. CMC: Heba Degheidy (CBER/OTP/OCTHT/DCT 1/CTTB)
DMF (b) (4)	(b) (4)	(b) (4)	DP	Yes	Suitable for commercial manufacturing. CMC: Iain Farrance (CBER/OTP/OCTHT/DCT 1/CTB1)
MF (b) (4)	(b) (4)	(b) (4)	DP	Yes	Suitable for commercial manufacturing. CMC: Wojtek Tutak (CBER/OTAT/DCGT/TEB)
MF (b) (4)	(b) (4)	(b) (4)	DP	Yes	Suitable for commercial manufacturing. CMC: Jin Sung Hong (CBER/OTP/OCTHT/DCT 2/TEB1)

Submission Type & #	Holder	Referenced Item	Use in BLA (LVV or DP)	Letter of Cross-Reference Provided	Comments/Status
MF (b) (4)	(b) (4)	(b) (4)	DP	Yes	Suitable for commercial manufacturing. CMC: Andrew Timmons (CBER/OTP/OGT/DGT2/ GTB5)
MF (b) (4) Module 3.2.S. and specific media related modules	(b) (4)	(b) (4)	LVV	Yes	Suitable for commercial manufacturing. CMC: Elizabeth Lessey-Morillon (CBER/OTP/OCTHT/DCT 1/CTB1)
MF (b) (4)	(b) (4)	the Production of (b) (4) Drug Master File (DMF)	LVV	Yes	The relevant sections of MF were reviewed by Timothy Kamaldinov.
MF (b) (4)	(b) (4)	Analytical Methods for LVV release testing and LVV MCB/WCB	LVV	Yes	The relevant sections of MF were reviewed by Timothy Kamaldinov
MF (b) (4)	(b) (4)	(b) (4)	DP	Yes	Suitable for commercial manufacturing. CMC: Guo-Chiuan Hung (CBER/OTP/OGT/DGT1/ GTB3)
MF (b) (4)	(b) (4)	(b) (4)	DP	Yes	Suitable for commercial manufacturing. CMC: Archana Devi Siddam (CBER/OTP/OCTHT/DCT 1/CTB1)
MF (b) (4)	(b) (4)	(b) (4)	DP	Yes	Suitable for commercial manufacturing. CMC: Elena Gubina (CBER/OTP/OGT/DGT1/ GTB3)
MF (b) (4)	(b) (4)	(b) (4)	DP	Yes	Suitable for commercial manufacturing. CMC: Guo-Chiuan Hung (CBER/OTP/OGT/DGT1/ GTB3)

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Written by TML

The FDA CMC Review Team concludes that the manufacturing process, test methods, and control measures for atidarsagene autotemcel (LENMELDY) are capable of yielding autologous products with consistent quality attributes determined acceptable for commercial manufacturing under this BLA for Orchard Therapeutics (Europe) Limited (herein Applicant or Orchard).

Atidarsagene autotemcel is for treatment of metachromatic leukodystrophy (MLD) for specific MLD forms characterized by age of onset: pre-symptomatic late infantile (PSLI, 0-2.5 years), pre-symptomatic early juvenile (PSEJ, 2.5-16 years), or early symptomatic early juvenile (ESEJ, 2.5-16 years) MLD. MLD is a fatal, lysosomal storage disease that leads to progressive neurodegenerative disease. Atidarsagene autotemcel is an autologous CD34+ cell enriched population, originating from hematopoietic stem and progenitor cells (HSPCs), transduced with a lentiviral vector (LVV) encoding the human arylsulfatase (ARSA) gene (ARSA LVV). ARSA is a lysosomal enzyme required for degradation of sulfatides. Sulfatide accumulation leads to myelin damage and MLD disease manifestation.

During atidarsagene autotemcel manufacturing, the ARSA gene is transferred into the patient's CD34+ cells by the ARSA LVV. The proposed atidarsagene autotemcel mechanism of action is that, following engraftment, these transduced CD34+ cells, which encode ARSA, differentiate into macrophage and/or microglial populations that are capable of functional ARSA expression. However, the actual mechanism of action is not fully elucidated, as 1) the migration and replacement, as well as residency, of macrophages and microglia in the CNS and other tissues is not fully understood, 2) the scientific literature has documented people with low ARSA expression (due to other mutations) who not develop MLD or who do not have excess levels of sulfatides in urinalysis, 3) some data suggests that ARSA may be able to cross the blood-brain-barrier to some degree, and 4) ARSA enzymes may also hydrolyze the sulfated glycolipids seminolipid and lactosylceramide sulfate, suggesting more than one role for ARSA. ARSA, like most lysosomal enzymes, has mannose 6-phosphate (Man-6-P) residues, which allows for transport of extracellular ARSA into cells by binding to cellular mannose 6-phosphate receptors (MPRs).

The ARSA LVV is manufactured at a contract manufacturing facility (b) (4). ARSA LVV is a nonreplicating, self-inactivated lentivirus, based on a (b) (4) HIV-1-derived vector, (b) (4)

For ARSA LVV production, (b) (4)

The ARSA LVV stability at (b) (4) was supported up to (b) (4).

To manufacture atidarsagene autotemcel, autologous hematopoietic stem and progenitor cells (HSPC) are obtained from up to two apheresis collections from each patient at a Qualified Treatment Center (QTC), following HSPC mobilization with granulocyte-colony stimulating factor (G-CSF) and plerixafor. The apheresis material is then shipped to the AGC Biologics drug substance (DS)/drug product (DP) manufacturing facility (Bresso, Milan, Italy). (b) (4) of manufacturing, the apheresis material is enriched for cells expressing CD34+ by (b) (4)

(b) (4)

, the CD34+ cells are transduced (b) (4) with ARSA LVV in (b) (4). On the (b) (4) day of manufacturing, the DS is subjected to a (b) (4) wash before becoming the DP, which is formulated in cryopreservation formulation medium (5% v/v DMSO, (b) (4)) and filled into (b) (4) bag(s) and cryopreserved for administration. The CD34+ cells are resuspended at a target concentration of 1.8E6 to 11.8E6 cells per mL (total cells 2E6 to 11.8E6 viable cells per mL) in a volume of 10 to 20 mL of cryopreservation formulation medium per (b) (4) bag, for up to a total of 8 bags of DP.

Each DP lot may be comprised of between one to eight 50 mL (b) (4) -bags, depending upon the number of cells produced at the end of manufacture. Filled bags are visually inspected and examined for integrity, placed in individual metal cassettes, then cryopreserved using a (b) (4), and stored at $\leq -130^{\circ}\text{C}$ in vapor phase liquid nitrogen until lot release testing is complete. There are no hold steps between DS and DP manufacture, which takes place over a (b) (4) period. Atidarsagene autotemcel stability in vapor phase liquid nitrogen ($\leq -130^{\circ}\text{C}$) was supported up to 6 months.

Atidarsagene autotemcel DP is supplied as a frozen suspension of cells for intravenous infusion.

The minimum dose is dependent on MLD subtype and patient weight.

- 4.2E6 CD34+ cells/kg for PSLI MLD
- 9E6 CD34+ cells/kg for PSEJ MLD
- 6.6E6 CD34+ cells/kg for ESEJ MLD

Other than the samples taken for lot release testing and retain samples, each patient receives the entire DP manufactured. No additional lots are manufactured for an individual patient.

Atidarsagene autotemcel is shipped frozen in a vapor phase liquid nitrogen shipper to the administration site once patient administration has been scheduled. Up to 4 DP bag(s), contained within individual cassettes, are secured in a metal rack within the shipper. Up to 2 shippers may be used, for up to a total of 8 bags. Following receipt at the administration site, atidarsagene autotemcel is stored in vapor phase liquid nitrogen ($\leq -130^{\circ}\text{C}$) until the scheduled treatment time, when it is thawed and infused within 2 hours. Patients receive atidarsagene autotemcel after myeloablative conditioning, which occurs after the product is released by Quality Assurance.

Manufacturing process consistency is assured through 1) raw material and reagent qualification programs, 2) in-process monitoring, 3) in-process control testing, and 4) lot release and stability testing. Raw materials derived from animals and humans are appropriately controlled to ensure the absence of microbial contaminants and adventitious agents. Lot release test methods are suitably validated or verified, and product specifications are adequate to ensure product quality and consistency with DP used in the clinical study. The manufacturing process has been adequately validated and continuous process verification is in place. Because of the autologous nature of the product, Chain of Identity/Chain of Custody (COI/COC) is established at the

collection site and maintained through the manufacturing process and administration by conducting label checks at specified times throughout the process.

B. RECOMMENDATION

I. APPROVAL

This biological license application (BLA) provides an adequate description of the manufacturing process and characterization of atidarsagene autotemcel (LENMELDY). The CMC review team has concluded that the manufacturing process, along with associated test methods and control measures, are capable of yielding a product with consistent quality characteristics. This information along with post-marketing commitments and requirements listed below satisfy the CMC requirements for biological product licensure per the provisions of section 351(a) of the Public Health Service (PHS) Act controlling the manufacture and sale of biological products. Based on the information provided in the BLA submission, subsequent amendments, and the information gathered during the pre-license inspection of the AGC Biologics Facilities in (b) (4) Bresso, Milan, Italy sites and the FDA/ORA inspection of Ospedale San Raffaele - Telethon Institute for Gene Therapy (SR-TIGET) Milan, Italy facility (Site ID 212141) in November 2023, the CMC review team recommends approval of BLA 125758.

Drug Substance and Drug Product Manufacturing Facilities:

FEI: (b) (4), DUNS: (b) (4) for two facilities:

Lentiviral Vector: (b) (4)

Drug Product: AGC Biologics S.p.A.; Via Meucci 3 Openzone 20091 Bresso (Milan) Italy

Post-Marketing Commitments (PMCs):

Responses were received in Amendment 44 (received 02/22/2024)

1. Orchard Therapeutics (Europe) Limited commits to provide additional sterility validation data evaluating the test sample handling manipulation. The final report will be submitted as a "Postmarketing Commitment - Final Study Report" by October 31, 2024.

Final Report Submission: October 31, 2024

2. Orchard Therapeutics (Europe) Limited commits to validate the appearance testing assay and reassess the lot release criterion. The final report will be submitted as a "Postmarketing Commitment - Final Study Report" by July 31, 2024.

Final Report Submission: July 31, 2024

3. Orchard Therapeutics (Europe) Limited commits to revalidate the (b) (4) assay to include the range of the commercial lot release criterion. The final report will be submitted as a "Postmarketing Commitment - Final Study Report" by October 31, 2024.

Final Report Submission: October 31, 2024

4. Orchard Therapeutics (Europe) Limited, commits to perform an additional validation study to assess the performance of the (b) (4) assay in the clinically relevant range. The final report will be submitted as a "Postmarketing Commitment - Final Study Report" by July 31, 2024.

Final Report Submission: July 31, 2024

5. Orchard Therapeutics (Europe) Limited commits to perform additional robustness assessments of the (b) (4) assays. The final report will be submitted as a "Postmarketing Commitment - Final Study Report" by May 31, 2024.

Final Report Submission: May 31, 2024

6. Orchard Therapeutics (Europe) Limited commits to perform additional robustness assessments of the (b) (4) assay. The final report will be submitted as a "Postmarketing Commitment - Final Study Report" by October 31, 2024.

Final Report Submission: October 31, 2024

7. Orchard Therapeutics (Europe) Limited commits to perform additional robustness assessments of the (b) (4). The final report will be submitted as a "Postmarketing Commitment - Final Study Report" by October 31, 2024.

Final Report Submission: October 31, 2024

8. Orchard Therapeutics (Europe) Limited commits to perform additional robustness assessments of the (b) (4) assay used to (b) (4). The final report will be submitted as a "Postmarketing Commitment - Final Study Report" by October 31, 2024.

Final Report Submission: October 31, 2024

Post-Marketing Requirements (PMRs):

1. An adequate leachables safety assessment for the OTL-200 drug product (DP) through its manufacturing process, storage, and in-use conditions. This assessment must include the following:
 - a. Assessment of elemental extractables from relevant DP manufacturing/storage components, and both elemental and organic leachables (i.e., cumulative) in the final DP.
 - b. The leachables study can be conducted by simulating the DP manufacturing process from the step with high-risk for leachables components (b) (4), may include simulation of respective (b) (4), should be conducted with all operations performed using maximal hold times and temperatures at respective steps, and continue through the product freezing, shelf-life storage, thawing, and in-use processing.
 - c. This evaluation will also include a full toxicological risk assessment for the identified leachables.

Confirmed proposed study milestone dates:

- Final Protocol Submission: June 30, 2024
- Study Completion Date: June 30, 2025
- Final Study Report Submission: August 31, 2025

Lot release requirements (Yes/No): No

II. COMPLETE RESPONSE (CR)

Not Applicable

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Tiffany Lucas, PhD, Chair, CMC Reviewer, OTP/DGT/GTB4	Concur	
Jacob Bitterman, PhD, CMC Reviewer, OTP/DGT/GTB3	Concur	
Maitreyi Chattopadhyay, PhD, CMC Reviewer, OTP/DGT/GTB4	Concur	
Timothy Kamalidinov, PhD, CMC Reviewer, OTP/DGT/GTB4	Concur	
Christelle Mbondji, PhD, CMC Reviewer, OTP/DGT/GTB5	Concur	
Secondary Level Review Kimberly Schultz, PhD, Director, OTP/OGT/Division 2	Concur	
Tertiary Level Review Denise Gavin, PhD, Director, OTP/Office of Gene Therapy	Concur	

Review of CTD

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Module 3

3.2.S DRUG SUBSTANCE – (b) (4)

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

Reviewed by CMW

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

3.2.P DRUG PRODUCT - atidarsagene autotemcel (herein OTL-200 DP)

3.2.P.1 Description and Composition of the Drug Product

Reviewed by TML

OTL-200 DP is a cryopreserved product supplied in single use 50 mL nominal volume (b) (4) bag(s) for administration and is formulated in cryopreservation formulation medium (5% v/v DMSO, (b) (4) Infusion). Autologous CD34+ cells transduced with ARSA LVV are resuspended at a target concentration of 2E6 to (b) (4) E6 viable cells per mL in a volume of 10 to 20 mL of cryopreservation formulation medium per (b) (4) bag, for up to a total of 8 bags of DP. The cryopreserved, autologous DP is infused to the patient after thawing and no modification of the DP occurs at the clinical site. As confirmed in Amendment 43 (received 02/20/2024), a patient will only receive a single commercial DP lot (i.e., a patient will not receive two manufactured DP lots).

Reviewer Comment: The description is acceptable for the proposed DP.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

Reviewed by JLB

OTL-200 Drug Substance (DS) consists of an autologous CD34+ cell enriched population that contains hematopoietic stem and progenitor cells (HSPCs) transduced ex vivo using a lentiviral vector encoding the human ARSA gene.

3.2.P.2.1.2 Excipients

The excipients used in the formulation of OTL-200 Dispersion for Infusion are dimethyl sulfoxide (DMSO), (b) (4) solution, and Sodium Chloride Infusion (saline solution).

A list of the OTL-200 excipients, their function, and quality standards are outlined in [Table 58](#).

Table 58. Excipients Present in OTL-200

Material	Purpose	Concentration	Grade
0.9% w/v Sodium Chloride Infusion	Cell resuspension and to provide tonicity	0.9% w/v	Medicinal product ¹
Dimethyl Sulfoxide	Cryoprotectant	5% v/v	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

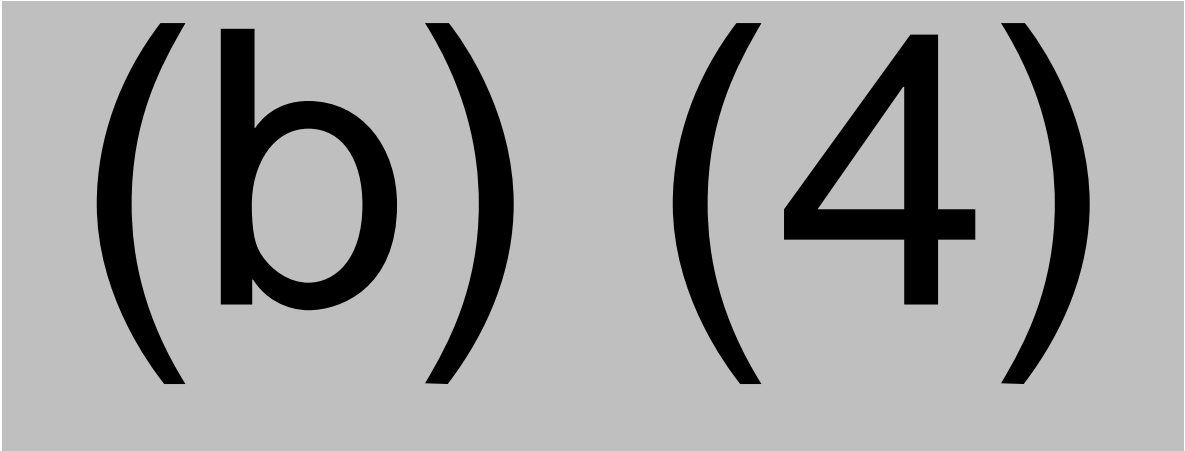

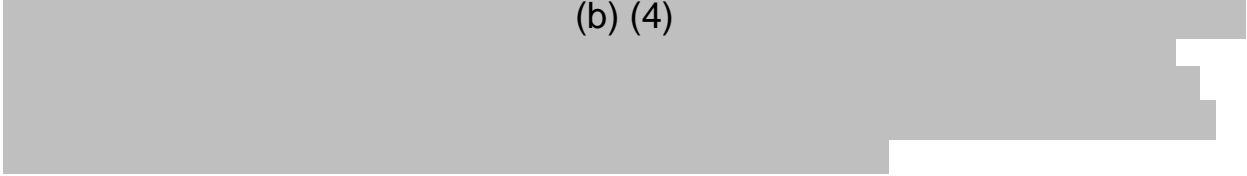
¹Registered as a medicinal product in Europe

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

Reviewed by JLB

(b) (4)



Reviewer Comment: *The information provided on formulation development to support the use of the 5% DMSO cryopreservation formulation is acceptable.*

3.2.P.2.2.2 Overages

Reviewed by TML

There are no overages of the OTL-200 DP.

Reviewer Comment: *This is acceptable.*

3.2.P.2.2.3 Physicochemical and Biological Properties

Reviewed by TML

The atidarsagene autotemcel DP contains a function human arylsulfatase A (ARSA) gene, which has been added ex vivo into the patient's autologous CD34+ cells (hematopoietic stem and progenitor cells [HSPCs]) with a lentiviral vector encoding ARSA. Patients receive myeloablative conditioning to eliminate existing ARSA-deficient CD34+ cells and to generate space for the DP cells to engraft in the bone marrow. Engrafted OTL-200 cells function as the progenitor cell for downstream macrophages, which are thought to be the cells most critical for expression of the ARSA enzyme into the tissue microenvironment. While the mechanism is unknown, MLD disease progression is generally attributed to inadequate ARSA expression by macrophages, microglia, and/or resident macrophages, which leads to the accumulation of toxic aryl-sulfatides, and neuronal degradation and death. It is speculated that macrophages and/or microglia can repopulate the CNS and provide adequate enzyme levels to protect the CNS.

The physiochemical and biological properties are described in [3.2.S.1.1 Nomenclature](#), [3.2.S.1.2 Structure](#), [3.2.S.3.1 Elucidation of Structure and Other Characteristics](#), and [3.2.P.1 Description and Composition of the Drug Product](#). Attributes critical to the performance of the DP are monitored for each batch as part of release testing and are described in [3.2.P.5.1 and 3.2.P.5.6 Specification\(s\) and Justification of Specification\(s\)](#).

***Reviewer Comment:** The description and understanding of the OTL-200 product's physiochemical and biological properties is acceptable.*

3.2.P.2.3 Manufacturing Process Development

Reviewed by TML

(b) (4)

(b) (4)

(b) (4)

Filling of (b) (4) Bag

For processes (b) (4), OTL-200 DP was filled into a (b) (4). The (b) (4)

Orchard performed additional suitability studies to support the (b) (4) bag for OTL-200 use:

- (b) (4)
- DP stability was evaluated by (b) (4)

Reviewer Comment: The (b) (4) bag is suitable for the OTL-200 DP. Data provided by Orchard demonstrated that the (b) (4)

These are not the representative commercial conditions for the DP but are similar and provide added assurance that there is nothing implicitly incompatible between the DP and the (b) (4) bag.

(b) (4) **Bag for Filling**

(b) (4)

(b) (4)

In-use Stability in (b) (4) Bag

The in-use stability of the (b) (4) bag for the OTL-200 product is reviewed in [3.2.P.8 Stability](#).

Reviewer Comment: *The stability of the cellular starting material, DS, and DP is adequately supported by data reviewed in [Control of Starting \(i.e., Source\) Material\(s\), Filling of \(b\) \(4\) Bag](#), and [3.2.P.8.1 Stability Summary and Conclusion](#) and [3.2.P.8.3 Stability Data](#). There are not additional concerns with the stability of the cellular DP.*

3.2.P.2.4 Container Closure System

Reviewed by JLB

The primary container closure system for OTL-200 DP ((b) (4) 50 mL (b) (4) bags [(b) (4)]) is described in detail in Section [3.2.P.7 Container Closure System](#). The choice of packaging is deemed by Orchard to be suitable because the bag is designed specifically for the manipulation and storage of cellular material. The (b) (4) bags are cleared for frozen donor tissue storage (510(k) No. (b) (4)).

Container Closure Integrity Testing

Container closure integrity testing has been performed by the bag supplier as well as at AGC Biologics as described in the following sections.

Supplier Container Closure Integrity Testing

The bag supplier, (b) (4) , performed container closure integrity testing, including

(b) (4)

, following procedures specified in (b) (4) . The study demonstrated that the bags could withstand at (b) (4) freeze thaw cycle without loss of integrity. The supplier also tested (b) (4) integrity after (b) (4)

The bags were shown to be resistant to this challenge.

AGC Biologics Container Closure Integrity Testing

A container closure integrity test was performed at AGC biologics to confirm the suitability of the 50 mL (b) (4) bags as primary packaging for OTL-200. Bags were (b) (4)

(b) (4)

The integrity of the bags was maintained for the entire (b) (4) storage duration.

Reviewer Comment: This information is acceptable to support container closure integrity.

Extractables and Leachables Testing

Extractables and leachables testing covering the entire OTL-200 DP manufacturing process is discussed in [3.2.P.3.5 Process Validation and/or Evaluation Extractables and Leachables](#). As part of the risk assessment, the DP bag was identified as a high-risk material. As a result, extractables and leachables testing was performed on the (b) (4) cryobag. Simulated leachable studies were performed using a (b) (4)

(b) (4). The bags were tested in several extractable and leachable conditions as described in [Extractables and Leachables](#). From the bags, (b) (4), were above the 120 µg reporting threshold. As described in [3.2.P.3.5 Process Validation and/or Evaluation](#), Orchard performed a safety assessment for these compounds and concluded that they do not pose a risk to patients.

Reviewer Comment: The information provided on leachables for the container closure was not sufficient as it did not assess cumulative leachables in the DP manufacturing process through freezing, thawing, and preparation at the clinical site. Additional information on leachables for the entire DP manufacturing process has been included as a PMR, as discussed in Section 3.2.P.3.5 Process Validation and/or Evaluation.

3.2.P.2.5 Microbiological Attributes

Reviewed by TML

OTL-200 is a cellular drug product, which cannot be terminally sterilized, and is manufactured under aseptic conditions. The final product is considered sterile, based the entirety of the sterility assurance strategy including sterility, mycoplasma, and endotoxin testing of the final DP. All container-closure components, reagents, excipients, and product contact materials are sterile. The DP bags are integrity tested by the manufacturer prior to release. Testing by Orchard's DP manufacturer (AGC Biologics) has demonstrated container closure integrity through all DP conditions, including freezing, shipping, and thawing.

Reviewer Comment: The materials, reagents, and process are adequate to support microbial control and final product sterility assurance. Acceptable.

3.2.P.2.6 Compatibility

Reviewed by JLB

The cryopreserved OTL-200 DP is administered at qualified treatment centers (QTCs) via an intravenous blood delivery set. Once the patient has been conditioned to receive the DP, OTL-200 is thawed and administered by an approved infusion set within 2 hours of thawing. In-use stability studies to confirm the stability of OTL-200 in the (b) (4) bag after thawing are described in Section [3.2.P.8.1 Stability Summary and Conclusion](#) and [3.2.P.8.3 Stability Data](#). The data support the stability of the OTL-200 DP up to 120 minutes at room temperature after thawing at 37°C and support the maximum time of two hours from thaw to end of administration as described in the product manual and label.

The first clinical study used the (b) (4) device for product administration. A compatibility study was performed to assess recovery of cells when DP manufactured from healthy donor material was thawed and passed through the device. In this study, (b) (4) of cells were recovered after passage through the infusion device. During clinical studies, two additional 510(k) cleared infusion sets were used. These were accepted for use based on an Orchard assessment which compared the infusion sets attributes compared to those of the (b) (4) set used for the compatibility study. For commercial use, Orchard outlines a risk-based

approach for assessing potential new infusion sets for use with OTL-200. The BLA contains a table outlining the output of the risk assessment and desired attributes of infusion sets used in the commercial setting. Infusion sets used during clinical development are considered compatible with OTL-200 and are cleared for commercial use ([Table 61](#)). Other infusion sets for commercial use will be cleared by Orchard prior to use following this risk assessment. Only 510(k) cleared devices are acceptable as part of this risk assessment. QTCs must notify Orchard of the infusion set to be used prior to scheduling a patient cell collection.

Table 61. Infusion Sets Used in Clinical Studies and Cleared for Commercial Use

Infusion Set	Manufacturer (Part)	Device Clearance
(b) (4)		

Reviewer Comment: The information provided supports the compatibility of the OTL-200 DP with the infusion sets used at the clinical site. This is acceptable.

Overall Reviewer’s Assessment of Section 3.2.P.2:

- Orchard provided suitable data to support the drug substance components, excipients, formulation, container closure, microbiological attributes, and compatibility for all contact materials for the DP.
- FDA CMC evaluation of the extractables and leachables studies determined that Orchard’s study was inadequate to address elemental leachables and cumulative leachables in the DP through processing and storage: In Amendment 30, Orchard committed to conduct a new leachables study, which was included in the PMR notification letter sent to Orchard on 02/05/2024. Additional information is included in [Section 3.2.P.3.5 Process Validation and/or Evaluation](#).

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Reviewed by TML

The OTL-200 DP is manufactured at and tested by the parties as described in [Table 62](#).

Table 62. Manufacturing and Testing Facilities for OTL-200 Drug Product

Facility	Address	FEI	DUNS	Responsibilities
AGC Biologics S.p.A.	Via Meucci 3 Openzone 20091 Bresso (Milan) Italy	3020270660	428486752	Drug product manufacture In-process testing Drug product primary, secondary, and tertiary packaging and storage; Release and stability testing for the following test methods: • Cell concentration • Total volume • Viability • Vector copy number • Vector copy number (b) (4) • Transduction efficiency • (b) (4) • (b) (4) • (b) (4) CD34+ • (b) (4) • Bacterial endotoxins • Mycoplasma Drug product release
(b) (4)	(b) (4)	(b) (4)	(b) (4)	Release and stability testing for the following test methods : • Transgene function (ARSA Activity)

3.2.P.3.2 Batch Formula*Reviewed by TML*

The OTL-200 batch formulation is described in [Table 63](#). (b) (4) of OTL-200 DS is processed into the OTL-200 DP. The OTL-200 DP formula may be provided in up to 8 bags for infusion, depending on the total number of cells harvested, and is determined by the (b) (4) range of each bag and the cell concentration range (Amendment 29, received 01/16/2024). The minimum recommended dose is dependent upon indication: 4.2E6 CD34+ cells/kg for PSLI MLD, 9.0E6 CD34+ cells/kg for PSEJ MLD, and 6.6E6 CD34+ cells/kg for ESEJ MLD. There are no overages. All available DP is administered to the patient and each bag is flushed with saline at the end of infusion to ensure the patient receives as many cells as possible.

Table 63. Drug Product Batch Formulation

Component	Quantity	Reference to Standard
Autologous CD34+ enriched hematopoietic stem and progenitor cells transduced <i>ex vivo</i> with a replication-incompetent lentiviral vector encoding human arylsulfatase A (LVV ARSA) gene	2E6 - 11.8E6 viable cells/mL ¹	Internal Orchard
0.9% w/v Sodium chloride Infusion	0.9% w/v	Medicinal product ²
Dimethyl sulfoxide (DMSO)	5% v/v	(b) (4)
(b) (4)	(b) (4)	(b) (4)

¹ The target concentration at time of cryopreservation is 2-^{(b) (4)} E6 viable cells/mL. The final DP must meet the minimum recommended dose of CD34+ cells/kg dependent on the MLD subtype and a minimum transduction efficiency of ^{(b) (4)}

² Registered as medicinal drug product in US and EU

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:

The description of site responsibilities for the OTL-200 DP and the batch formulation description are acceptable. There are no outstanding concerns.

3.2.P.3.3 Description of Manufacturing Process

Reviewed by TML

Overview of Drug Product Manufacturing Process

(b) (4)

(b) (4)

(b) (4)

Manufacturing Process

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Step (b) (4) (Day (b) (4)): Formulation and fill

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The filled (b) (4) cryobags are then moved from the (b) (4). A final visual inspection is performed to ensure the correct sealing (b) (4). Lastly, the filled (b) (4) cryobags are labelled.

Each primary 50 mL (b) (4) cryobag is placed in a secondary (b) (4) overwrap bag and labelled; the secondary overwrap bag is sealed. Lastly, the DP and QC samples are transferred out of the manufacturing production area to the (b) (4) and cryopreserved using the (b) (4). After cryopreservation, each frozen DP bag is placed into a labelled metal cassette and stored at <-130°C in the vapor phase of liquid nitrogen. After formulation, QC samples for batch release are collected (b) (4) filling the DP into 50 mL (b) (4) cryobags.

Chain of Identity and Chain of Custody

Reviewed by TML

Orchard has implemented a controlled chain from the initiation of apheresis through patient administration. The documentation plan is outlined in [Table 64](#). Representative labels with identifiers are shown in [B. Labeling Review](#). Assignment of initial identifiers at the time of apheresis through receipt at AGC Biologics is described in [Table 40](#) and [Control of Starting \(i.e., Source\) Material\(s\)](#).

The COI and COC is a paper-based, chronological documentation that supports identity and traceability. The traceability ensures the DP and raw materials, which includes all substance that may contact the cells, can be traced through sourcing, manufacturing, packaging, storage, transport, delivery, treatment site custody, and patient administration ([Figure 14](#)). Orchard's Distribution and Logistics department within the Technical Operations function are responsible for all COI and COC procedures.

Each patient is identified via their unique Chain of Identity Identifier (COI ID). For the DP, there are two interchangeable types of nomenclature (referred to as batch numbers and lot numbers). Orchard uses the 'Lot Number' identifier in place of the 'Batch Number' in a subset of the COC and COI documents. 'Lot Number' is referenced on certain documents including the labels. Importantly, the batch number and the lot number are identical, and the terms can be considered interchangeable; both refer to the same unique identifier.

Traceability of COI Documents: COI is tracked via the Patient Journey Form and the Product Journey Form. Detailed instructions for completion of these two forms is provided in the Product Manual. The purpose of the Patient Journey Form is to document:

- Patient-specific information including name, date of birth (DoB), patient weight, planned date of apheresis, and QTC information.
- Product-specific information including dates and times of collections, technical details pertaining to apheresis, expiry dates and times for the collected mPB, and timings of product handling throughout the product journey.

Traceability of COC Documents: COC is tracked via the Chain of Custody Cooled Form and the Chain of Custody Cryopreserved Form. The purpose of the COC cooled and cryopreserved forms are to document:

- For the COC Cooled Form to document the transport and handling of the patient cellular source material.
- For the COC Cryopreserved Form to document the transport and handling of the patient drug product.

Manufacturing Chain: From receipt of cellular source material until completion of manufacture, the COI ID is maintained throughout the manufacturing process together with the manufacturing batch number at AGC Biologics. The COI ID is recorded in the Manufacturing Batch Record and is then recorded throughout the GMP manufacturing process along with the batch number.

Labeling: The primary DP label, secondary overwrap bag label, and tertiary cassette label are described in [B. Labeling Review](#).

Storage and Batch Release: Following manufacture, the OTL-200 DP is stored at AGC Biologics until release testing and batch review activities have been completed. As part of batch review activities, the COI ID and batch number are reviewed and confirmed as correct. The batch is then certified by the Qualified Person at AGC Biologics and then dispositioned by Orchard. The DP batch is then released and transported to the QTC.

Packaging for Transportation: The DP is prepared for shipment to the QTC. COI ID, batch number and (b) (4) number are all recorded and verified by the CMO before releasing to the transport provider. The transport provider verifies the (b) (4) upon pickup. A Lot Information Sheet detailing the batch specific information is provided with each shipment. COC handover is recorded on the Chain of Custody Cryopreserved Form and maintained by Orchard.

Table 64. Chain of Identity (COI) Example of Identifiers and Labels

Document/Label	COI ID	Patient Initials or Name	Date of Birth	Patient Weight (kg)	ISBT 128 Donation ID Number (DIN)	Manufacturing Batch Number
Identifier format	XX- YYYYY A ¹	JD Doe, John	DD- MMM- YYYY	XX	A9999 YY 123456 ^{B 2 3}	XXYYY/Z ^{C 4}
Patient Journey Form	Y	Y	Y	Y ⁵	N/A	N/A
Product Journey Form	Y	N/A	N/A	Y ^{6 7}	Y	Y
OTL Cell Source Label	Y	Y	Y	N/A	N/A	N/A
QTC Cell Source Label	N/A	N/A	N/A	N/A	Y	N/A
Primary DP bag Label	Y	Y	Y	N/A	Y	Y
Secondary Overwrap Label	Y	Y	Y	N/A	Y	Y
Tertiary Cassette Label	Y	Y	Y	N/A	Y	Y
Lot Information Sheet	Y	Y	Y	Y ⁶	Y	Y
Chain of Custody Cooled Form	Y	N/A	N/A	N/A	Y	N/A
Chain of Custody Cryopreserved Form	Y	N/A	N/A	N/A	Y	Y

^A Issued by Orchard ^B Issued by QTC ^C Issued by the CMO

¹ XX= (b) (4)

² A9999 22 123456 where A9999 = (b) (4).

³ DIN is recorded on a QTC-generated label (DIN is not available when Orchard labels are generated).

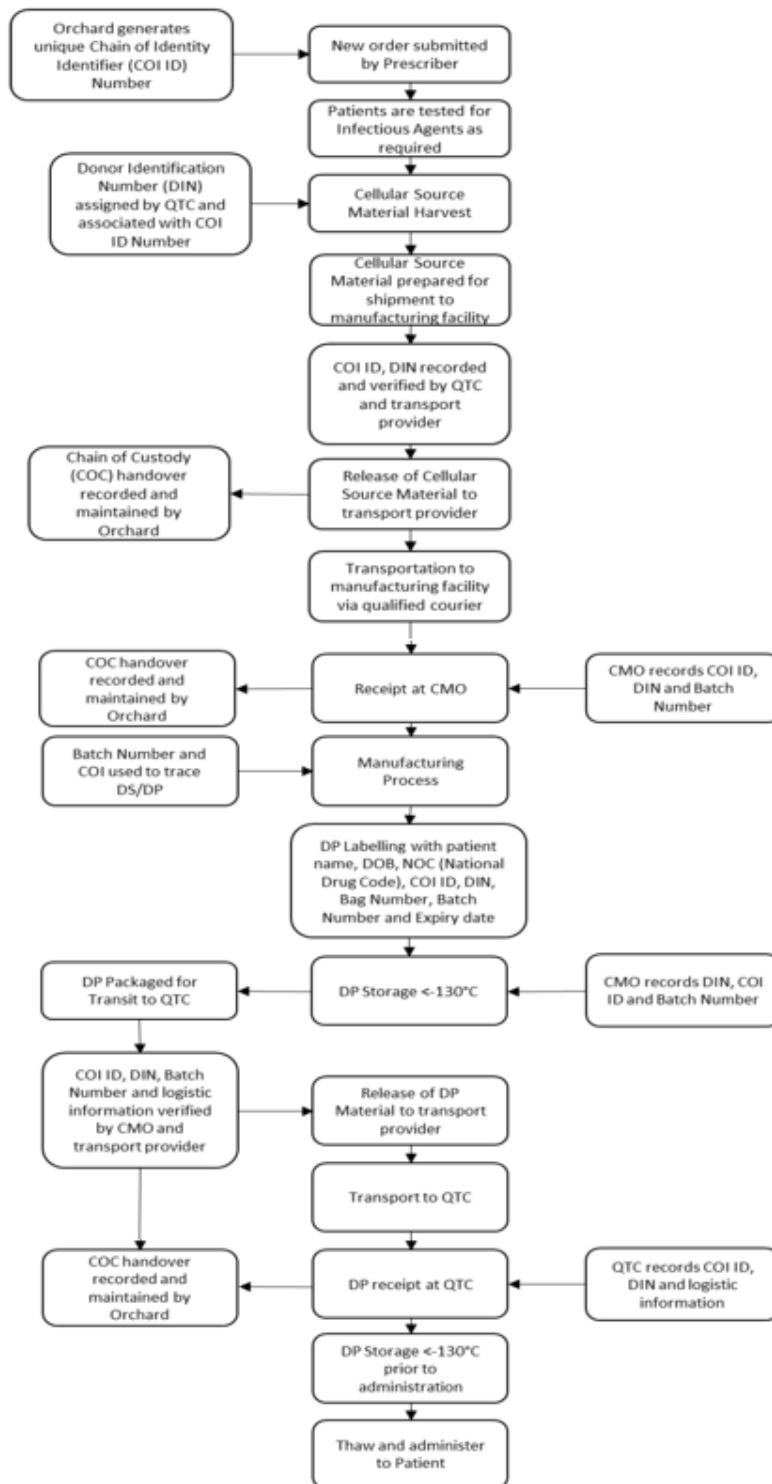
⁴ XXYYY/Z where XX = (b) (4)

⁵ Patient weight (pre-treatment)

⁶ Patient weight (at first collection)

⁷ Patient weight (at infusion)

Figure 14. Overview of the OTL-200 Chain of Custody and Chain of Identity from Apheresis Through Administration



Overall Reviewer's Assessment of Section 3.2.P.3.3:

No concerns are noted for the general manufacturing plan. The proposed commercial OTL-200 DP manufacturing plan is acceptable.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Reviewed by TML

Parameters and controls are defined in [Table 65](#) (b) (4), and no reprocessing is allowed. The control of critical steps in the manufacturing process is assured through defined process parameter CPPs and IPCs ([Table 65](#)). Action limits were set based on instrument limitations, previous manufacturing knowledge, and data from clinical historical batches. Select IPCs and CPPs were experimentally confirmed.

IPCs and CPPs for DP Manufacturing

Table 65. In-Process Controls and Critical Process Parameters for OTL-200 Manufacturing

Step	Manufacturing Process Step	Material	Classification	Parameter (CPPs) or Attribute (CQAs)	Target or Range
(b) (4)					

Reviewer Comment: The CPP ranges are supported by manufacturing experience and in risk assessment studies for CPPs. However, during review FDA CMC notes that several media components are provided as targets and not ranges. Therefore, Orchard is required to use the exact quantities/volumes listed as targets and no variation is permitted around the target, as these are established conditions.

Overall Reviewer's Assessment of Section 3.2.P.3.4:

The target values or ranges defined for Steps (b) (4) are based on experience and data collected to date. The controls and classifications are acceptable to support manufacturing process control of the DP. FDA CMC communicated with Orchard that all Target CPPs must be met exactly as described because of a lack of characterized ranges for these attributes (Amendment 43, received 02/20/2024). There are no additional concerns.

3.2.P.3.5 Process Validation and/or Evaluation

Reviewed by TML

Process Validation

Overview:

Process terms are defined in Section [3.2.S.2.4 Controls of Critical Steps and Intermediates](#) (e.g., AC, IPC, CPP, CQA, Acceptable Range)

The OTL-200 manufacturing process validation was performed in 2017 at the AGC Biologics S.p.A. (previously MolMed S.p.A.) facility in Bresso, Milan, Italy. The study was sponsored by Glaxo-Smith-Klein (GSK) (OTL-200 referred to as GSK269274).

The validation protocol was developed from validation master protocol CQAs and CPPs, which are based on small-scale development studies and clinical manufacturing data outcomes. The process is currently part of the continuous process verification (CPV) cycle. Three consecutive full-scale PPQ batches were manufactured with healthy donor (HD) mPB (obtained from (b) (4)) using the (b) (4) process at a single site ([Table 66](#)). Healthy donors were pre-treated with G-CSF to reflect the patient starting material. Validation included the following studies: PPQ production batches, aseptic processing, hold times, extractable and leachable risk for DP contact materials, residual process impurity risk and clearance, and transport validation.

Orchard intends to use (b) (4) Bresso GMP suites for OTL-200 manufacturing, based on supporting (b) (4) mPB PPQ runs: (b) (4). Orchard implemented a global manufacturing program for the (b) (4) suites to ensure identical design in terms of qualified personnel, environmental control, and facility systems. Orchard confirmed that (b) (4) will not be used to manufacture the commercial DP, as it was not qualified with mPB (Amendment 10, received 10/26/2023). As BM is not a proposed source starting material for this BLA DP, the suite (b) (4) data is not reviewed.

(b) (4)

PPQ Acceptance Criteria and Results:

The CPP and CQAs along with results for DS step (b) (4) are presented in [Table 67](#) and for step (b) (4) are presented in [Table 68](#).

(b) (4)

One page has been determined to be not releasable: (b)(4)

(b) (4)

***Reviewer Comment:** The process validation is appropriate to support the proposed commercial manufacturing process.*

Continuous Process Validation (CPV)

A CPV program is in place for OTL-200, which monitors the proposed commercial manufacturing process. The CPV is based on monitoring of in-process controls and additional tests. It includes assessment of incoming starting material and release testing based on specifications. The verification of operational ranges for input parameters is performed during manufacturing and is also performed during the batch record review process for each manufactured batch. Any deviations from the established ranges will be investigated through the standard deviation process. Orchard tracks and trends the manufacturing process over time to ensure adequate control. Trending attributes will be performed through control charts, process capability metrics, and signal analysis for trend variation. Orchard established statistical process control limits by collecting data to determine the general trend. In the initial phase, historical data ranges from clinical batches are used to understand the behavior of the data, which may also be used to inform investigations. In the second phase, which is the long term CPV monitoring, assessment is conducted by using the established statistical process variability and compared against new data. As part of CPV, Orchard is establishing trend analysis programs for the following characterization parameters based on the first (b) (4) lots manufactured with the (b) (4) process: DP (b) (4). In Amendment 53 (received 03/06/2024), Orchard moved (b) (4) testing from the DP release tests to CPV testing.

***Reviewer Comment:** The CPV is acceptable. FDA CMC noted to Orchard removed the (b) (4) testing from DP release testing and agreed to incorporate testing into CPV testing. As testing for (b) (4) is performed on the LVV and no additional (b) (4) would be introduced into the DP manufacturing process, the test provides no additional benefit to impurities testing.*

Aseptic Process Validation

Reviewed by TML

Orchard evaluated sterility assurance using a combination Failure Modes, Effects and Criticality Analysis (FMECA) and process simulations ([Table 69](#)). The suites are identical in terms of qualified personnel, equipment control, layout, documentation, and environmental monitoring and controls. An ongoing requalification program is in place. APS is reviewed in detail by DMPQ; please refer to the DMPQ memo for details of the APS validation.

Reviewer Comment: *The APS validation is acceptable.*

Table 69. Orchard's Assessment of Sterility Assurance Overview

Validation Element	Description	Additional Assessment Performed
Process simulation	Media fills have been performed to assess the cumulative impact of aseptic activities and enclosed processes on sterility assurance. Simulations were based on a highly similar Orchard manufacturing process with more open manipulations	Yes- manipulation and handling of (b) (4) (simulated similar manufacturing process) and (b) (4) runs with (b) (4).
Filtration efficacy	As the OTL-200 manufacturing process does not include a final sterilizing filtration prior to DP fill, no validation of sterilizing filter is required. (b) (4)	No
Sterilization of equipment, containers, closures	All equipment, containers and closures are pre-sterilized by the respective vendors. Low risk.	No

Media Hold Time Validations

Orchard performed media hold-time challenges for the (b) (4)

(b) (4) Held media components were then tested on a run with (b) (4) HD cells. Results of the study were evaluated with the defined PPQ acceptance criteria. All acceptance criteria were met; no differences were observed between the (b) (4) HD cells.

Reviewer Comment: *The commercial media hold times are adequately supported by the data. Acceptable.*

Shipper Qualification and Quality Attribute Assessment

❑ Final Drug Product Shipping to Patient Site

Information for DP shipping to the administration site was incomplete. Additional information to support shipping was provided in Amendment 14 and 29 (received 11/22/2023 and 01/16/2024, respectively).

Control of Shipping Records- data logger and site responsibilities: A data logger is used to record shipping temperature conditions. The DP Administration Site is responsible for review and compliance of the shipping conditions; review (to ensure required shipping conditions were met) is required for administration to the patient. Temperature excursions or transport deviations are investigated and documented per a quality assurance (QA) procedure prior to infusion. Mock shipments were performed as part of Qualified Treatment Center qualification.

Description of Shipper: (b) (4) manufactures the (b) (4) shippers. (b) (4)

The shipper is qualified to ship up to 4 bags; if more than 4 bags are produced during manufacturing, a second shipper will be used. The commercial OTL-200 DP will be shipped at a temperature of $< -130^{\circ}\text{C}$ from the CDMO, AGC Biologics, to the DP Administration Site with the (b) (4) shipper. Operational qualification, (b) (4) shippers, was performed by (b) (4) and Orchard performed the product-specific qualification with the (b) (4) shipper ((b) (4)).

Testing Methods and Study Design:

(b) (4)

One page has been determined to be not releasable: (b)(4)

(b) (4)

This is acceptable.

Production Capacity

A single DP lot is generally manufactured at a time, due to the rarity of the disease. (b) (4) manufacturing suites within AGC Biologics Bresso site are capable of manufacturing OTL-200.

Review Comment: *This is acceptable given the exceedingly rare prevalence of the disease. The manufacturing process is completed in less than (b) (4) , including room changeover.*

Extractables and Leachables

Reviewed by JLB

Orchard performed a risk assessment of the materials used to produce ARSA LVV and OTL-200 to assess the risk to product safety, identity, strength, purity, and quality. The product contact materials were evaluated for several factors including contact time, composition of the fluid in contact with each material, the product contact surface area exposure temperature, material compatibility, and reduction potential. These factors were used to consider the likelihood of generation or retention of leachables in the DS and DP through a failure modes and effects analysis (FMEA). The outcome of the FMEA was the identification of (b) (4) high risk components used during the DP manufacturing process. These included the cryobag used as container closure for the DP, the (b) (4) used for (b) (4)

during the washing step, (b) (4) used to transfer DP from the (b) (4) to the cryobags. Product contact materials from upstream processes before the final formulation were considered low risk due to the number of (b) (4) steps prior to the final formulation.

The materials identified as high risk were subjected to extractable and simulated leachable studies under representative and exaggerated conditions ([Table 71](#)). The extractable conditions were used to understand the extractable profile for each component and to demonstrate the suitability of the analytical methods employed. The leachables conditions were slightly exaggerated from the DP manufacturing conditions to simulate a worst-case condition of use. The final product formulation contains (b) (4) . The (b) (4) solution was not included in the simulated leachables studies as it was expected to interfere with the analysis and not expected to increase the amount of leachables.

Table 71. Summary of Conditions Used for Extractable and Simulated Leachables Studies

Component	Non-Volatile Extractables	Non-Volatile Leachables	Semi-Volatile Extractables	Semi-Volatile Leachables	Volatile Extractables	Volatile Leachables
(b) (4)						

Component	Non-Volatile Extractables	Non-Volatile Leachables	Semi-Volatile Extractables	Semi-Volatile Leachables	Volatile Extractables	Volatile Leachables
	(b) (4)					
Bag	(b) (4)					

Non-volatile extractables and leachables were identified using (b) (4) in the presence of an internal standard solution to aid in quantitation. Semi-volatile extractables and leachables were identified after (b) (4) in the presence of an internal standard. Volatile extractables and leachables were identified using (b) (4) in the presence of an internal standard.

For the extractable studies, an analytical evaluation threshold (AET) of (b) (4) was used. A reporting threshold of (b) (4) was calculated based using (b) (4) of this AET and an assumed 60 mL dose of DP. In some conditions many compounds were extracted. In these cases, the reporting threshold was raised to focus on major extractables. The extractables results were used to aid in identifying leachable compounds in the simulated leachables conditions. Compounds that were above a threshold of toxicological concern of 120 µg/day (based on Table 2 of ICH M7) were identified for further safety assessment. The safety assessment was based on toxicological evaluations, and for some compounds calculated permissible daily exposure (PDE) limits based on the toxicological evaluations. The identified compounds, their maximum exposure, and the PDE are summarized in [Table 72](#). All identified compounds were determined to be below the PDE or not considered high risk.

Table 72. Compounds Identified in the Simulated Leachables Study That Are Above the 120 µg/day Threshold and Required Additional Safety Assessment

Component	Identified Compound	Estimated Exposure (µg/day)	Safety Assessment
(b) (4)	(b) (4)		
Bag			
(b) (4)			
(b) (4)			
(b) (4)			

Component	Identified Compound	Estimated Exposure (µg/day)	Safety Assessment
Tubing of Bag (b) (4)	(b) (4)		Total exposure is significantly below toxic levels reported in the literature.

Reviewer Comment: In the original BLA submission, the sponsor provided additional analytical data for (b) (4) that was analyzed in samples collected from (b) (4) PPQ runs of the DP manufacturing process. In CMC IR #3, we requested additional information about the collection and analysis of the samples. Orchard provided a response in Amendment 16 (received 11/29/2023) where they confirmed that samples were taken from the (b) (4) to the final formulation in (b) (4), 5% DMSO, (b) (4). We concluded that these samples were not representative of the concentration of (b) (4) in the final drug product, and the results could not be used to justify Orchard's original conclusion that concentrations of (b) (4) are likely to be lower than the concentration reported in the extractables and leachables assessment. The maximum exposure for (b) (4) of (b) (4) is based on the data collected from the simulated leachables study, and use of the maximum 8 bags for a single patient. This exposure is representative of a worst-case patient exposure.

The extractables and leachables assessment was reviewed in consultation with Andrey Sarafanov (OTP/OPPT/DH/HB2). Together, we requested additional information on how the extractables and leachables assessment was performed in CMC IR#4. We also identified that Orchard did not evaluate elemental leachables, did not include (b) (4) in their extractables and leachables assessment, and did not perform their calculations for the correct maximum possible dose. We also noted that the study did not assess cumulative leachables through DP storage, thawing, and preparation at the clinical site. Orchard provided a response in Amendment 30 (received 01/18/2024). Based on the additional information included in the response about the conduct of the extractables study, we concluded that the extractables study performed for the identified high-risk components was acceptable. However, the leachables study was not sufficient. We concluded that Orchard should perform an additional leachables study that evaluates leachables through the high-risk manufacturing steps beginning from the (b) (4) step through the formulation, storage, and in-use processing. Following this additional study, a full toxicological risk assessment should be performed. Elemental extractables and leachables should also be assessed. Orchard agreed to conduct an additional study in the Amendment, and this study was included in the PMR letter sent on 02/05/2024.

Amendment 30 also included updated calculations of the maximum estimated exposure based on a maximum of 8 bags being administered to a patient. This updated data is reflected in [Table 72](#). The amendment included additional safety risk assessments considering the new exposure estimates. We consulted with Rukmini Bhardwaj (OTP/OPT/DPT2/PTB2) on the safety assessments and together concluded that the compounds identified in [Table 72](#) do not pose a safety risk to patients being treated with OTL-200 at the identified maximum exposures.

Overall Reviewer's Assessment of Section 3.2.P.3.5:

The overall Process Validation is acceptable to support the BLA approval. The process validation was acceptable based on the results of 3 PPQ runs. Media hold times and shipper validations were acceptable to support in-use times, as applicable for commercial plans.

The APS validation was adequate to support that the DP can be produced without introduction of microbial contaminants during handling.

FDA CMC evaluation, in consultation with Andrey Sarafanov (CBER/OTP/OPPT/DH/HB2), of the extractables and leachables studies determined that Orchard's study was inadequate to

address elemental extractables and leachables and cumulative organic leachables in the DP through processing and storage. Additional information on extractables and leachables was requested in CMC IR #3 and #4. In Amendment 30 (received 01/18/2024), Orchard committed to conduct a new leachables study, which was included in the PMR notification letter sent to Orchard on 02/05/2024.

3.2.P.4 Control of Excipients

Reviewed by JLB

3.2.P.4.1 Specifications

The list of excipients used in OTL-200 is described in Section [3.2.P.2.1.2 Excipients](#). DMSO and (b) (4) have (b) (4) specifications. Sodium chloride solution is purchased as a medicinal product in the EU. The specifications for the medicinal product align with the (b) (4) specifications. Additional in-house testing is performed on 0.9% w/v sodium chloride as described in [Table 73](#).

Table 73. In-House Testing of 0.9% w/v Sodium Chloride

Test	Acceptance Criteria	Method Reference
(b) (4)		

Reviewer Comment: This is acceptable.

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

The analytical procedures are stated as compliant with (b) (4) methods. Method validation was considered unnecessary by Orchard.

Reviewer Comment: This is acceptable.

3.2.P.4.4 Justification of Specifications

The specifications are all (b) (4).

Reviewer Comment: This is acceptable.

3.2.P.4.5 Excipients of Human or Animal Origin

(b) (4) is used as an excipient for product manufacture. (b) (4) is sourced from (b) (4) and is (b) (4) grade. (b) (4) has certified this (b) (4) as the same source and quality as that released as the product approved under BLA (b) (4)

Reviewer Comment: This is acceptable.

3.2.P.4.6 Novel Excipient

Not applicable.

Overall Reviewer's Assessment of Section 3.2.P.4:

The information provided on the excipients is acceptable to support their use in the final formulation of OTL-200.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Reviewed by TML

Patient lot data was provided, analyzed in, and reviewed from multiple amendments (Amendments 4, 10, 39, 43, 53, 59, received 09/12/2024, 10/26/2023, 02/07/2024, 02/20/2024, 03/06/2024, 03/13/2023, respectively).

The commercial release acceptance criteria for the commercial DP release are provided below and are based on (b) (4) clinical, commercial, and compassionate DP lots, which demonstrated efficacy (as determined by FDA Clinical): lots (b) (4), (b) (6) . (b) (4) patients presented as PSLI, (b) (4) patient presented as PSEJ, and no patient DP lots were available for ESEJ patients.

Table 74. Release Specifications for OTL-200 Drug Product

Attribute	Test	Method	Acceptance Criteria	Justification
General	Cell Concentration (cells/mL)	(b) (4)	2.0E6 to 11.8E6 cells/mL	Based on range tested for stability and to reach a minimum fill volume of 10 mL, which may occur with small patients. Upper limit based on experience.
	Total Volume (mL)	N/A	FIO	Range 10-20
	Appearance ^a	Visual inspection	A colorless to yellow or pink cell suspension	Based on clinical “abnormal appearance” and (b) (4) formulation. See PMC
Identity	Transgene Function (ARSA activity)	(b) (4)	Detected	ARSA expression is detected relative to non-transduced patient cells.
Potency	Viability (%)	(b) (4)	(b) (4)	Based on experiential range
	Vector Copy Number (b) (4)	(b) (4)	(b) (4)	Based on experiential range
	Vector Copy Number in transduced cells (b) (4)	Calculation	(b) (4)	Based on experiential range
	Transduction Efficiency (%)	(b) (4)	(b) (4)	Based on experiential range
	Transgene Function (ARSA Activity) (b) (4)	(b) (4)	(b) (4)	Based on experiential range
	(b) (4)	(b) (4)	(b) (4)	Based on experiential range, while accounting for assay variability
	(b) (4)	Calculation	(b) (4)	Based on experiential range and quantitative detection limits of assay

Attribute	Test	Method	Acceptance Criteria	Justification
Identity/ Purity	(b) (4) CD34 ⁺ (%)	(b) (4)	(b) (4)	Based on experiential range, while accounting for assay variability
Safety	Sterility ^c	(b) (4)	Negative	Requirement
	Endotoxin (EU/mL)	(b) (4)	(b) (4)	Based on experience
	Mycoplasma	(b) (4)	Not detectable	Requirement

^a Appearance testing requires additional validation studies, as outlined in PMC (Amendment 58, received 03/12/2024)

^b (b) (4) is defined by a numerical threshold (b) (4)

^c Sterility testing is performed on (b) (4) the Drug Product (b) (4)

FDA CMC analyzed the (b) (4) lots efficacious DP lots with the (b) (4) manufacturing process that demonstrated efficacy ([Table 75](#)). This data was used to support justification of specifications.

Table 75. Results of Efficacious Patient Lots Manufactured with the (b) (4) process to Establish Commercial Drug Product Specifications

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:

The overall DP release specifications are acceptable and reflective of experience in manufacturing and efficacious lots. The final release specifications were agreed upon and updated, along with justification for specifications in Amendment 59 (received 03/13/2024). The PMC for the Appearance assay, including additional assessment of the specification was agreed to as a PMC (Amendment 58, received 03/12/2024). The justification for the commercial release criteria is acceptable.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

(b) (4)

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

(b) (4)

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

Assays are suitable for the intended use and were adequately validated.

Orchard committed to several PMCs (Amendment 44, received 02/22/2024) related to lot release testing. A PMC was added to address the (b) (4) of sterility test articles prior to sterility testing and Orchard has committed to validating the assay to demonstrate that (b) (4) does not impact the assay's ability to detect microbial contamination. Orchard agreed to a PMC with DBSQC for validation of the (b) (4)-based mycoplasma, which requires the use of (b) (4) positive controls. Orchard committed to two PMCs regarding (b) (4) analytical method: (1) a study to evaluate inclusion of additional controls, such as (b) (4) controls and (2) additional validation study to further evaluate method's performance in the clinically relevant range of CD34+ cells. Orchard committed to perform additional robustness study for the (b) (4) testing, and for (b) (4), committed to revalidate the assay range to include the commercial lot release range of (b) (4). Additionally, Orchard committed to validate their appearance test in Amendments 53 and 57 (received 03/06/2024 and 3/11/2024, respectively). As written, the protocol does not contain sufficient information or instruction to the operators on the test colors that meet the acceptance criterion of colorless to pink or yellow. The assay has not been validated to demonstrate that it is suitable for use. Furthermore, Orchard implemented the assay only for commercial DP release; it was not available during clinical studies. Therefore, the AC is not based on experience with actual DP, but rather was established based on the appearance of (b) (4). The PMC will be sufficient to address the appearance testing and validation issues identified. This is not considered a safety issue. There are no additional concerns.

3.2.P.5.4 Batch Analyses

Reviewed by TML

DP lot data was updated in Amendments 10, 29, 43, received 10/26/2024, 01/16/2024, 02/20/2024, respectively). FDA Clinical reclassified three patients following review of patient records (no patients in the (b) (4) group were reclassified)

Across all manufacturing methods, starting CD34+ cell sources, and patient indications, a total of (b) (4) OTL-200 DP lots were manufactured for multiple patient indications ([Table 83](#)). Four patients received two lots, as the first lot had insufficient CD34+ cells per patient kg (n=8 lots total).

Commercial specifications were established using data from (b) (4) lots demonstrating patient efficacy, based on several potential endpoints determined by FDA Clinical reviewers. Of the (b) (4) lots administered, 12 lots did not have efficacy data available. Comparability was established for mPB-sourced CD34+ DP that was produced with the (b) (4) process (n=(b) (4) lots). Comparability was not established for DP produced from either mPB vs BM across multiple manufacturing methods (b) (4).

The following indications were included for analysis: PSEJ, ESEJ, PSLJ.

The following indications were excluded from analysis: (b) (4).

Due to both the recent treatment of some patients and the potentially slower juvenile form, 13 of the patients had inadequate follow-up to determine efficacy resulting in 13 patients without supporting data. 5 lots showed no efficacy and of these, 3 patients died, most likely due to disease progression (ESEJ lots = 4, 2 deaths; PSEJ lots = 1, 1 death)

Table 83. All OTL-200 Drug Product Lots by Indication, Source of CD34 Cells, Manufacturing Site, and Method.

(b) (4)

^a (b) (4) were not included in Orchard's requested indications within the BLA submission.

*Four patients received two lots to produce sufficient cells to meet infusion minimums. No products manufactured with the method, which uses mPB-sourced material failed to meet dosing minimums. For the 4 patients who received two lots, each lot was manufactured with a different method.

Reviewer Comment: *The approximately 10-year DP development and DP improvement, and changes in clinical practice, resulted in multiple method changes. Furthermore, (b) (4) possible indication types were identified in patients by treating clinicians, with only 3 forms being commonly recognized and included in the BLA assessment and evaluation of approval of indications (as applied for by Orchard). The commercial specifications were based on lots manufactured with the (b) (4) process and demonstrated efficacy in patient outcomes, as determined by FDA Clinical.*

3.2.P.5.5 Characterization of Impurities

During OTL-200 DP process development, levels of impurities were monitored. During OTL-200 DP process validation, the clearance of impurities was determined. The impurities from excipients are reviewed in Section [3.2.P.4 Control of Excipients](#).

Process Related Impurities: The impurity profile from OTL-200 was evaluated based on product-related impurities, specifically (b) (4).

Cellular Impurities: The impurity profile from manufacturing process was based on process-related impurities or residuals, and impurities that are derived from or introduced during the manufacturing process.

3.2.P.5.5.1 Process Related Impurities

Orchard provided data and justification for continued or discontinuation of impurity testing based on data collected from clinical, PPQ, and (b) (4) manufacturing process lots ([Table 84](#)). The process (b) (4) introduced (b) (4) of the DP to further reduce process impurities. Impurity levels were measured (b) (4)

(b) (4) (during the formulation process). Most process related impurities were at or below the LLOQ after the (b) (4) .

(b) (4)

One page has been determined to be not releasable: (b)(4)

(b) (4)

3.2.P.6 Reference Standards or Materials
Reviewed by TML

There are no reference standards or materials for the DP. Some DP release assays use material as positive controls, however no release testing results are normalized to a references standard and each positive control must meet system suitability controls for each assay to be valid. The assay level control was deemed acceptable for use as positive controls.

3.2.P.7 Container Closure System

Reviewed by JLB

The primary container closure for OTL-200 DP is the 50 mL (b) (4) Freezing Bag supplied by (b) (4). The bags are 510(k) cleared by the FDA (No. (b) (4)). The composition of the bag and components are described in [Table 85](#), and a diagram of the primary and secondary container closures is shown in [Figure 16](#). Manufacturer specifications for the freezing bag are shown in [Table 86](#). Following loading of the DP, the filling assembly is removed, and the (b) (4) tubing is sealed. The primary bag is placed in a secondary overwrap bag and sealed.

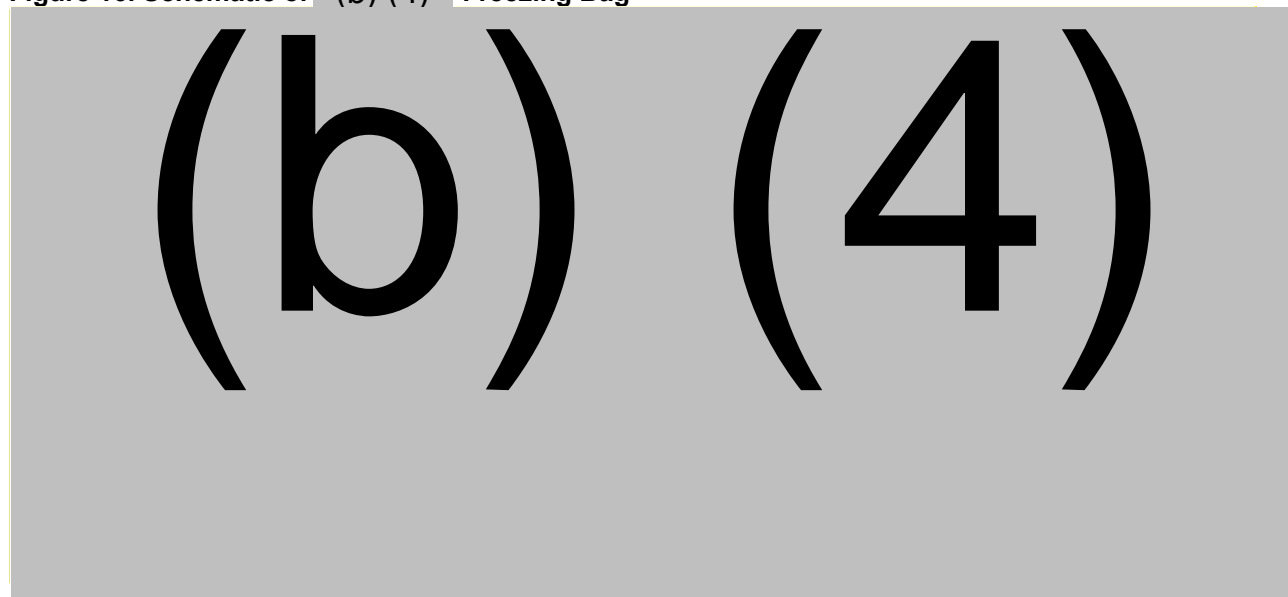
Table 85. Components of the Primary Container Closure System

Part Description	Raw Material
Filling Assembly	
Injection Port: Y-piece/Injection port	(b) (4)
Tubing	
Y-connectors	
Roller clamps: housing/wheel	
Luer lock connectors	
Luer lock caps	
Freezing Bag	
Tubular foil	(b) (4)
Spike ports	
Tubing	

Abbreviations:

(b) (4)

Figure 16. Schematic of (b) (4) Freezing Bag



(b) (4)

After OTL-200 DP is filled and sealed into the primary packaging, and sealed in the secondary package, it is cryopreserved using a (b) (4). The cryopreserved (b) (4) bag(s) is placed within a metal cassette for transportation. Each cassette can hold one (b) (4) bag with its overwrap bag. This tertiary packaging is used to protect the bags during storage and transportation.

The (b) (4) LN2 model (b) (4) shipper is used to transport the DP from the AGC Biologics (CMO) to the clinical treatment site. The shipper has an (b) (4) which monitors shipping conditions in transit. The shipper is reviewed in [Final Drug Product Shipping to Patient Site](#).

Overall Reviewer's Assessment of Section 3.2.P.7:

The information on the container closure system is acceptable. Suitability of the container closure, extractables and leachables, and in-use stability are discussed in Section [3.2.P.2.4 Container Closure System](#).

3.2.P.8 Stability

Reviewed by MC

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

(b) (4) bag and in final formulation containing either (b) (4). Two different cell concentrations (2E6 cells/mL and (b) (4) E6 cells/mL) were tested to demonstrate stability of the DP bracketed across the allowable product concentration range. Two different fill volumes (b) (4) and 10mL) were tested. All 3 PPQ batches, and (b) (4), (b) (6) have fill volume of (b) (4), while (b) (4), (b) (6) have 10 mL. For the (b) (4) fill volume, the intended DP container closure (50 mL nominal volume cryobags) was (b) (4) sealed to reduce the nominal volume to (b) (4), to mimic the volume to surface area expected for DP with the lowest fill volume of (b) (4)/10mL.

Long-Term stability protocol and results:

The long-term stability studies have been completed for all batches and up to 6 months data are provided. Stability study plan is outlined in [Table 87](#). The specifications used in the stability monitoring program are provided in [Table 88](#).

Table 87. Long-Term and in-use Stability Plan

Table of Long Term and In-use Stability Plan					
Designation	Site and Date of Manufacture	Batch	Proposed Time points (months) for Long-term (LT) stability	Storage condition	Status
Process development ^a	(b) (4)	(b) (4), (b) (6)	T0, T6M	LT <- 130°C	Complete (6 months)
Tech transfer batch			T0, T1M, T2M, T3M, T6M	LT <- 130°C	Complete (6 months)
				In-use RT*	Complete (2 hours)
PPQ			T0, T1M, T2M, T3M, T6M	LT <- 130°C	Complete (6 months)
				In-use RT	Complete (2 hours)
PPQ			T0, T1M, T2M, T3M, T6M	LT <- 130°C	Complete (6 months)
				In-use RT	Complete (2 hours)
PPQ			T0, T1M, T2M, T3M, T6M	LT <- 130°C	Complete (6 months)
Process development ^a			T0, T3M, T6M	LT <- 130°C	Complete (6 months)
				In-use RT	Complete (2 hours)
Process development ^a			T0, T3M, T6M	LT <- 130°C	Complete (6 months)
				In-use RT	Complete (2 hours)
Process development ^a			T0, T3M, T6M	LT <- 130°C	Complete (6 months)

^a Manufactured for comparability studies.

^b Used (b) (4) in final formulation.

^c Used (b) (4) In the final formulation

^d Tested at a Target Concentration of $(b)(4) \times 10^6$ cells/mL

^e Tested at a Target Concentration of 2×10^6 cells/mL

^f Tested in 10 mL fill volume

^g Tested in (b) (4) fill volume

* RT samples are the same LT samples stored at <-130 that were after thawing were held at RT for 45 mins and 2 hrs.

Table 88. Test Parameters and Acceptance Criteria for Stability Study

Stability Test	Method Number	Test Method	Stability Study Acceptance Criteria
Viability and Viable Cell Concentration	CRE002	(b) (4)	(4)
(b) (4)	IFT018		
	IFT020 ^a		
(b) (4)	CRE005		
Transduction Efficiency	ETR012		
Vector Copy Number	DOS026		
ARSA Activity	EST021	(b) (4)	Negative
Microbiological Control	STE008		

^a IFT020 is a characterization method only, for analysis of (b) (4).

Stability data analysis:

In-use stability study:

In-use stability data are collected after thawing the DP stored at different intervals for up to 6 months and then thawed at 37°C and held for 45 mins and 2 hours at room temperature (RT). The data generated from batches (b) (4), demonstrated that except for lot (b) (4) which didn't meet the AC after thaw (T0), all lots met AC after thawing and holding at RT for 45 mins and 2 hrs. Although the lot (b) (4) did not meet the AC after thaw (T0), the values from other timepoints of this lot demonstrated similar trend compared to T=0, which is almost horizontal to the X-axis, demonstrating no obvious trends when ASRA activity is plotted as a function of time. The total (b) (4) remained well above the AC for all lots at all time points tested when held the samples at RT (b) (4) 2 hrs. The % change in (b) (4) compared to T0 for lots (b) (4), (b) (6) respectively, demonstrating a variable downward trend for all lots (b) (4) 2 hrs. of the storage time. The 40-minute timepoint showed similar variability. [Figure 17](#) below shows the trend analysis for ASRA activity and (b) (4) for all lots.

(b) (4)

Long-Term stability:

Data provided for all batches with 2 cell concentrations demonstrated that the DP remains stable over the 6 months of storage. Sterility is maintained throughout the storage time. Viability

remains 88% to 97% and without any trend. %CD34+ cells remain 99.4% to 100% without any trend as well. All lots for the (b) (4), remained well above the DP release criteria over the time points tested except for (b) (4) lot which didn't meet the AC at higher concentration at 2 months timepoint. %TE remained above established AC over the time points tested with batch (b) (4), (b) (6) showed a downward trend at 2E6 cells/mL concentration and batch (b) (4), (b) (6) at (b) (4) E6 cells/mL concentration. VCN remains stable over the storage. Similarly, ASRA activity remains stable and above AC for all batches over the time points tested. A trend analysis for ASRA activity and (b) (4) for long-term storage is shown in the figure below:

(b) (4)

The ASRA activity and the (b) (4) as function of storage time at <- 130°C for determining the shelf-life of the DP. Acceptance criteria (AC) is the DP lot release criteria.

Reviewer Comment: An OOS result for batch (b) (4), (b) (6) at T0 is probably due to the variable nature of the ASRA assay, as the data generated from all other lots at all time points at RT storage remained above the AC. The trend line analysis of the (b) (4) the 2 hrs. of storage at RT demonstrated OTL-200 DP is stable for up to 2 hours at room temperature.

Orchard proposes a DP shelf life of 6 months at $\leq -130^{\circ}\text{C}$ based on the 6 months stability data available for the (b) (4) PPQ batches and (b) (4) process development batches and (b) (4) tech transfer batch. The long-term stability study test results of all test parameters for all batches were within acceptance criteria. Sterility was maintained for all lots for time points tested. For some lots, variability is seen in viability, %TE, the (b) (4), and ASRA activity, however, no apparent trends were observed in these test parameters. Additionally, it was found that different cells concentrations had no effect on these trends. Therefore, the proposed shelf-life of 6 months under long term storage conditions ($\leq -130^{\circ}\text{C}$) is acceptable.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

Not applicable as all stability studies in support of the commercial shelf life have been completed. As the product is an autologous cell product, no annual stability testing is planned.

Overall Reviewer's Assessment of Section 3.2.P.8:

The stability data from PPQ and process development support the proposed 6 months long-term storage shelf-life for OTL-200 DP. The data also support a post-thaw stability of up to 2 hours at ambient temperature, and once thawed, product should be administered immediately to the patient for completion within 2 hours.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Reviewed by TML

A pre-license inspection of AGC Biologics manufacturing facilities were conducted between November 9-20, 2023. The LVV is manufactured at (b) (4) site located at (b) (4) (also called (b) (4) site; FEI: (b) (4) ; DUNS: (b) (4)). The (b) (4) facility is located in the (b) (4) building of (b) (4) . The DP is manufactured at AGC Biologics site located at AGC Biologics S.p.A, Via Meucci 3, 20091 Bresso (Milan), Italy (also called Bresso site). Both facility sites are used by AGC Biologics to manufacture viral vectors and cellular DPs for commercial, clinical, and pre-clinical programs. Both sites have similar QC capabilities, with a few exceptions, such as the OTL-200 potency assay. AGC Biologics (b) (4)

FDA 483s were issued during inspection and discussion items were presented. Please see the Establishment Inspection Report for additional information.

Overall Reviewer's Assessment of Section 3.2.A.1:

The facilities and equipment information were reviewed in detail during inspection and is documented in the EIR. The material provided is acceptable. No deficiencies were identified after reviewing Orchard's responses to the 483.

3.2.A.2 Adventitious Agents Safety Evaluation

Information in this section is integrated into [3.2.S.2.3 Control of Materials](#) – ARSA LVV, [3.2.S.2.4 Controls of Critical Steps and Intermediates](#) – ARSA LVV, [3.2.S.2.3 Control of Materials](#) – OTL-200, and [3.2.P.5 Control of Drug Product](#).

❑ Viral Clearance Studies

Since it is not feasible to incorporate viral clearance steps into vector or cellular drug substance manufacturing without vector or cell inactivation/destruction, viral clearance studies were not conducted on (b) (4) or OTL-200 (b) (4) DP. Clearance and control of (b) (4) impurities was evaluated in Section [3.2.S.2.5 Process Validation and/or Evaluation](#), [3.2.S.2.6 Manufacturing Process Development](#), and [3.2.S.3.2 Impurities](#).

Overall Reviewer's Assessment of Section 3.2.A.2:

- The risk mitigation is appropriate for the OTL-200 DP. Appropriate sourcing and testing is performed for all materials of human or animal origin. Testing of the (b) (4) for adventitious agents, sterility, and mycoplasma is performed. The DP is tested for sterility and mycoplasma testing to determine whether any agents were introduced during the manufacturing process. The use of commercial (b) (4) provides further assurance that no human pathogens have been introduced to the DP.*
- During inspection it was observed that AGC stores QC samples at (b) (4) °C. During review (Amendment 43, received 02//202024) testing of (b) (4) DP samples was discussed with Orchard. FDA CMC notified Orchard that (b) (4) of QC samples may impact the viability, and thus the ability to detect, microorganisms presented in the samples. This information is necessary to support the validated process. Orchard agreed with FDA CMC and stated that they do not have data to support the impact of (b) (4) on microorganisms and that validation was performed with (b) (4) samples. FDA CMC, with discussions with DBSQC, determined that the overall risk is low.*

Therefore, Orchard agreed to a PMC to determine the impact of (b) (4) on microbes in QC samples.

- No additional deficiencies were identified.

3.2.A.3 Novel Excipients

No novel excipients are used in the OTL-200 DP.

3.2.R Regional Information (USA)

❑ Executed Batch Records

Reviewed by TML

Batch records were translated from Italian to English by Orchard. All records are maintained by AGC Biologics as paper documents.

For the LVV, a commercial blank master batch record (MBR) (b) (4) and two executed batch records were supplied for a PPQ batch ((b) (4), (b) (6)) and a Confirmatory batch with the Commercial record ((b) (4), (b) (6)). An additional executed batch record was reviewed during the inspection process.

For the OTL-200 DP, a blank commercial MBR was provided, as well as two executed MBRs: a healthy donor PPQ batch ((b) (4), (b) (6)) and a compassionate use IND ((b) (4), (b) (6)). The differences in the commercial and previous MBR were reviewed during inspection; changes in the MBR were acceptable and part of process improvements for operators and manufacturing method changes.

***Reviewer Comment:** The batch records for the LVV and DP were reviewed in detail during the inspection by FDA inspectors. Inspectors observed operators using the MBR documents during manufacturing of both LVV and DP. Inspectors reviewed select completed MBRs with SMEs and discussed changes in the MBR made over time, as part of improvements and changes. For additional information, see the EIR. No concerns were noted.*

❑ Method Validation Package

❑ Combination Products

Reviewed by TML

The OTL-200 DP is not regulated as a combination product.

Overall Reviewer's Assessment of Executed Batch Records and Combination Products Sections:

- *The provided batch records are adequate to support review of the LVV and DP and the use of the proposed commercial batch record.*
- *OTL-200 is not a combination product; no additional assessment is necessary.*

❑ Comparability Protocols

No Comparability protocols or plans for future changes are provided in the BLA submission.

Prior to BLA submission, Orchard made several manufacturing changes which required comparability analysis for the OTL-200 DP, and were reviewed in detail in Section [3.2.S.2.6.2. Manufacturing Changes and Comparability Studies](#):

- Change in manufacturing method
- Change in starting material source (CD34+ cell sourced from bone marrow or mPB)
- Change in final formulation (fresh vs cryopreserved)

- Change in manufacturing site ((b) (4))
- Change in licensed (b) (4) used in final formulation

No Comparability protocols or plans for future changes are provided in the BLA submission.

Reviewer Comment: No comparability protocols or changes were discussed in the BLA. AGC Biologics informed FDA CMC inspectors that (b) (4)

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

Reviewed by TML

Orchard is claiming a categorical exclusion under 21 CFR 25.31(c) from the need to prepare an environmental assessment. Orchard is unaware of any extraordinary circumstances that would require the preparation of an environmental assessment.

Atidarsagene autotemcel is made from human cells transduced with an LVV. The LVV is derived from a (b) (4), replication-incompetent, self-inactivating HIV-1 vector. The LVV is generated from a (b) (4). No evidence of RCL was observed in any (b) (4), in any DP lot, or in any patient during clinical follow-up.

FDA generally considers products that consist of genetically modified human cells to be eligible for the naturally occurring categorical exclusion (21 CFR 25.31(c)) because these cells have stringent nutritional requirements for survival and therefore are not viable in the environment.

Reviewer Comment: We agree with the request for categorical exclusion under 21 CFR 25.31(c).

B. Labeling Review

Full Prescribing Information (PI):

Reviewed by TML

The following sections of the PI were reviewed: HIGHLIGHTS OF PRESCRIBING INFORMATION, Section 2 (Dose and Administration), Section 3 (Dosage Forms and Strengths), Section 11 (Description), Section 12 (Clinical Pharmacology – Mechanism of Action) and Section 16 (How supplied / storage and handling). The PI provides a detailed and correct description of atidarsagene autotemcel and its mechanism of action. The PI also accurately and correctly describes the receipt and preparation procedures for atidarsagene autotemcel.

Reviewer Comment: The PI review team had interactions with the applicant during review of the PI. The applicant was asked to clarify multiple details on the receipt, LENMELDY packaging, and administration preparation procedures of atidarsagene autotemcel. The applicant agreed to make the requested changes and the changes were found to be adequate.

Carton and Container Label:

Reviewed by TML in conjunction with Monique Cortez (DRPM)

Orchard provided labels for the entire chain of identity ([COI Numbering](#)) which includes descriptions for primary and secondary container labels. The carton container label, lot information sheet, overwrap bag, and tertiary cassette label were provided and reviewed [Figure 19](#), [Figure 20](#), [Figure 21](#), and [Figure 22](#). Labels were updated in Amendment 56 (received 03/08/2024) to remove the graphic next to the name "lenmeldy".

Figure 19. Carton Container Label for LENMELDY

NDC 83222-0200-1

atidarsagene autotemcel

lenmeldy™

383222020019

Suspension for IV infusion

10 to 20 mL containing 1.8 to 11.8 x 10⁶ CD34+ cells/mL

Suspension for IV infusion

For autologous use only.

For intravenous use only. Rx only. Single-dose.

Confirm Patient Identifiers

First Name: _____

Last Name: _____

Date of Birth: _____ DIN: _____

COI ID: _____ Bag ID: _____

LOT: _____ EXP: _____

Orchard

therapeutics™

Manuf. by: AGC Biologics S.p.A
20091 Bresso (MI), Italy

Manuf. for: Orchard Therapeutics
Boston, MA 02210

U.S. Lic. 2263
Label P/N: GMP_OTL_331417

Figure 20. Lot Information Sheet for LENMELDY

atidarsagene autotemcel

lenmeldy™

NDC 83222-0200-1

383222020019

Suspension for IV infusion

10 to 20 mL containing 1.8 to 11.8 x 10⁶ CD34+ cells/mL

LOT INFORMATION SHEET

SAVE THIS DOCUMENT AND PREPARE TO HAVE IT AVAILABLE AT THE TIME OF LENMELDY INFUSION

PATIENT INFORMATION

First Name: _____

Last Name: _____

Date of Birth (DD-MMM-YYYY): _____

Weight at First Collection (kg): _____

DIN: _____

COI ID: _____

INFORMATION ON SUPPLIED LOT(S)

For autologous use only. For intravenous use only. Rx only. Single-dose.

Confirm patient identifiers. Read the prescribing information before use.

The following lot was manufactured and included in the shipment for this patient:

Lot number	Bag ID	Volume of suspension for infusion (mL)	CD34+ Cells (x10 ⁶)	Expiry date (DD-MMM-YYYY)

Total number of bags: []

Total Volume: [] [mL]

Total Dose: [] [N.N x 10⁶ CD34+/kg]

The minimum recommended dose of Lenmeldy to be administered is based on the disease subtype. Refer to Section 2.1 of the USPI.

INSTRUCTIONS FOR STORAGE AND DISPOSAL

Keep infusion bag(s) in the metal cassette(s) and store and transport frozen (< -130 °C) until ready for thaw and administration. Use immediately after thawing. Do not unseal the overwrap bag until after thaw. Once thawed do not re-freeze.

Shelf life after thawing: maximum of 2 hours at room temperature.

This medicine contains genetically modified cells.

Orchard

therapeutics™

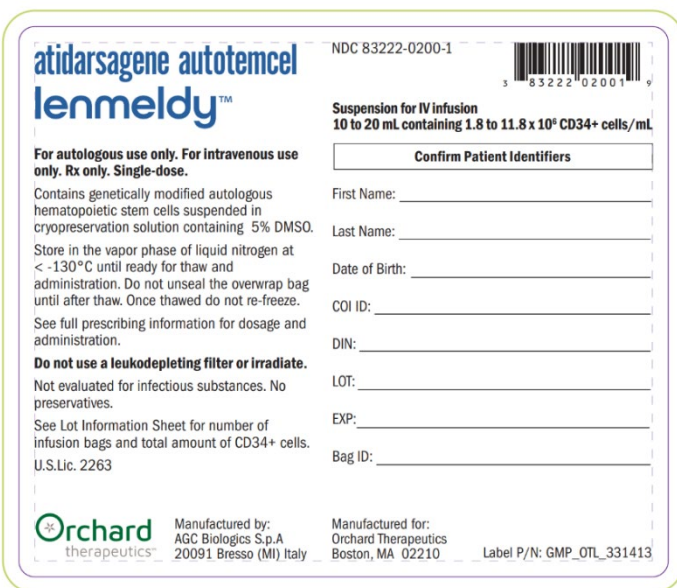
Manufactured by:
AGC Biologics SpA
20091 Bresso (MI)

Manufactured for:
Orchard Therapeutics
Boston, MA 02210

U.S.Lic. # 2263

205

Figure 21. LENMELDY Overwrap Bag



atidarsagene autotemcel
lenmeldy™

NDC 83222-0200-1

Suspension for IV infusion
10 to 20 mL containing 1.8 to 11.8 x 10⁶ CD34⁺ cells/mL

For autologous use only. For intravenous use only. Rx only. Single-dose.

Contains genetically modified autologous hematopoietic stem cells suspended in cryopreservation solution containing 5% DMSO.

Store in the vapor phase of liquid nitrogen at < -130°C until ready for thaw and administration. Do not unseal the overwrap bag until after thaw. Once thawed do not re-freeze.

See full prescribing information for dosage and administration.

Do not use a leukodepleting filter or irradiate.

Not evaluated for infectious substances. No preservatives.

See Lot Information Sheet for number of infusion bags and total amount of CD34⁺ cells.

U.S.Lic. 2263

Confirm Patient Identifiers

First Name: _____

Last Name: _____

Date of Birth: _____

COI ID: _____

DIN: _____

LOT: _____

EXP: _____

Bag ID: _____

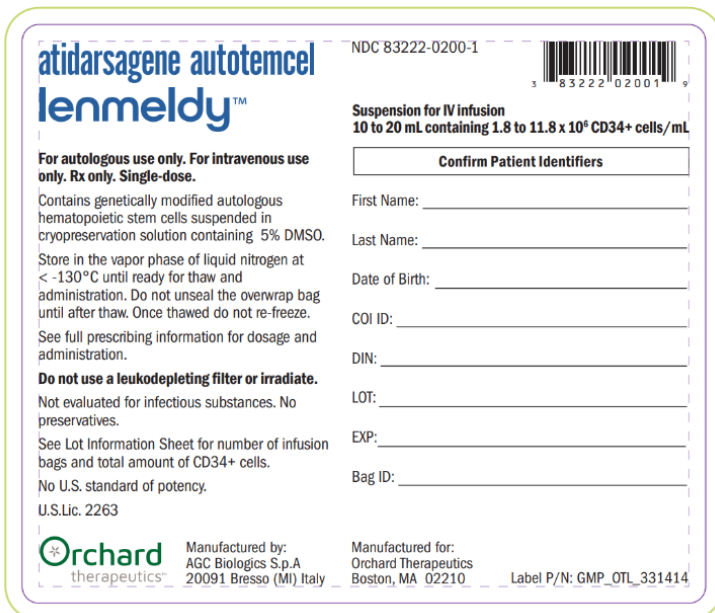
Orchard therapeutics

Manufactured by:
AGC Biologics S.p.A
20091 Bresso (MI) Italy

Manufactured for:
Orchard Therapeutics
Boston, MA 02210

Label P/N: GMP_OTL_331413

Figure 22. LENMELDY Tertiary Cassette Label. Includes additional instructions to maintain the bag within the cassette.



atidarsagene autotemcel
lenmeldy™

NDC 83222-0200-1

Suspension for IV infusion
10 to 20 mL containing 1.8 to 11.8 x 10⁶ CD34⁺ cells/mL

For autologous use only. For intravenous use only. Rx only. Single-dose.

Contains genetically modified autologous hematopoietic stem cells suspended in cryopreservation solution containing 5% DMSO.

Store in the vapor phase of liquid nitrogen at < -130°C until ready for thaw and administration. Do not unseal the overwrap bag until after thaw. Once thawed do not re-freeze.

See full prescribing information for dosage and administration.

Do not use a leukodepleting filter or irradiate.

Not evaluated for infectious substances. No preservatives.

See Lot Information Sheet for number of infusion bags and total amount of CD34⁺ cells.

No U.S. standard of potency.

U.S.Lic. 2263

Confirm Patient Identifiers

First Name: _____

Last Name: _____

Date of Birth: _____

COI ID: _____

DIN: _____

LOT: _____

EXP: _____

Bag ID: _____

Orchard therapeutics

Manufactured by:
AGC Biologics S.p.A
20091 Bresso (MI) Italy

Manufactured for:
Orchard Therapeutics
Boston, MA 02210

Label P/N: GMP_OTL_331414

Reviewer Comment: The final labels provided comply with 21 CFR 610.60-62. The initial labels required revision based on information requests from RPM Monique Cortez, APLB, and CMC; the final labels were provided in Amendment 60 (received 03/15/2024). The labels are acceptable.

Modules 4 and 5

5.3.1 Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

Reviewed by JLB

ARSA Activity in PBMCs

ARSA activity in PBMCs from patient samples was determined by a colorimetric assay performed and qualified by the San Raffaele Telethon Institute for Gene Therapy (SR-TIGET) Clinical Laboratory. This assay detects the activity of the ARSA enzyme in cells by hydrolysis of an artificial substrate, para-nitrocatechol (PNC), resulting in a product that can be measured through optical density (OD) at 515 nm. PBMCs are (b) (4) in 0.05M sodium acetate. (b) (4) assay.

For the enzyme assay, the (b) (4) with PNC and incubated at 37 °C for (b) (4). The reaction is stopped by addition of 1M NaOH, and the resulting samples are measured using a spectrophotometer. The enzyme activity is calculated based on the measured OD, the extinction coefficient of the product at 515 nm, and the known protein concentration and incubation time. Results are expressed as nmolPNC/mg/hour. Each run of the assay includes a QC sample, sourced from normal healthy donor PBMCs that have been qualified with a reference range. During qualification, the laboratory also used an (b) (4)

The assay was qualified for the following parameters: LOD, Linearity, LLOQ, intra-assay precision, inter-assay precision, and stability. For LOD, (b) (4)

Linearity was assessed using (b) (4)

The LLOQ was set based on the linearity assessment to be the lowest value in the linearity range ((b) (4)). Results between the LOD and LLOQ are reported as the LLOQ value. Intra-assay precision was assessed by (b) (4)

Inter-assay precision was assessed by (b) (4)

The %CV for these measurements met the acceptance criteria of (b) (4). Stability was assessed by (b) (4)

Reviewer Comment: The original submission did not contain the method SOP for measurement of ARSA activity in PBMCs. In CMC IR#2, we requested a copy of the method SOP. Orchard provided a copy of the SOP and an updated validation report in Amendment 10 (received 10/26/2023). This assay is suitably qualified for efficacy analysis of study/subject samples.

ARSA Activity in Cerebrospinal Fluid (CSF)

ARSA activity in CSF from patient samples was determined by a (b) (4) assay performed and qualified at the (b) (4). The assay consists of (b) (4)

(b) (4)
The assay was validated using (b) (4) ARSA enzyme as a reference standard for ARSA activity, as well as using CSF samples. The validation parameters and results are summarized in [Table 89](#).

(b) (4)

***Reviewer Comment:** This assay is suitably validated for the efficacy analysis of study/subject samples.*

Engraftment % LVV and Vector Copy Number (b) (4)

The engraftment of transduced cells was determined by (b) (4)

Originally, the engraftment was measured by (b) (4) following a published procedure. In 2018, the method was transferred and validated by SR-TIGET. Later in 2018, the (b) (4) method was validated and implemented. The (b) (4) method was only applied to Studies 201222 and 205029 starting in 2018, and all data up to 3 years after treatment for each subject was generated using (b) (4) to maintain consistency and data comparability.

Both methods quantified LVV ARSA sequence in human genomic DNA using (b) (4)

The (b) (4) method was validated using (b) (4)

The validation showed acceptable performance for accuracy, linearity, specificity, and precision.

The (b) (4) method was validated using (b) (4)

The method showed acceptable performance for threshold of negativity, range, linearity, accuracy, precision, and specificity.

***Reviewer Comment:** These assays are suitably validated for the clinical pharmacology analysis of study/subject samples.*

Integration Site Analysis in Peripheral Blood

Early in clinical development, integration site analysis was conducted at SR-TIGET using (b) (4)

In 2019, Orchard transferred integration site analysis to (b) (4). The new laboratory used (b) (4)

. The (b) (4) method was validated using (b) (4)

***Reviewer Comment:** This assay is suitably validated for the safety analysis of study/subject samples.*

Anti ARSA Antibodies

Two assays for anti-ARSA antibodies have been used at three locations through clinical development of OTL-200. Through 2016, an (b) (4) that was developed and validated at the (b) (4) was used. Beginning in 2016, an (b) (4)

(b) (4) was used in the laboratories of GlaxoSmithKline (GSK). This method was subsequently transferred and re-validated at (b) (4).

For the (b) (4) assay, (b) (4)

For the (b) (4) assay, (b) (4)

An additional validation for the (b) (4) assay was performed at (b) (4). The validation established (b) (4)

Reviewer Comment: In the original BLA submission, Orchard only included a protocol for the validation of the (b) (4) assay at (b) (4). In CMC IR #7 we requested a copy of the validation report. In Amendment 43 (received 02/20/2024), Orchard provided the validation report. The Anti-ARSA Antibody methods were suitably validated for the safety analysis of study/subject samples.

Overall Reviewer's Assessment of Relevant Sections of Module 4 and 5:

- The validations provided were adequately performed to assure the methods are suitable for their intended purposes, including clinical efficacy and safety assessments.
- In CMC IR#2, we requested a copy of the method SOP for the ARSA activity in PBMC method. Orchard provided a copy of the SOP and an updated validation report in Amendment 10 (received 10/26/2023).
- In CMC IR #7, we requested a copy of the report for the validation of the (b) (4) assay at (b) (4). In Amendment 43 (received 02/20/2024), Orchard provided the validation report.