Summary Basis for Regulatory Action

Date:	March 18, 2024
From:	Tiffany Lucas, PhD, Review Committee Chair, CBER/OTP/OGT
BLA STN:	125758
Applicant:	Orchard Therapeutics (Europe) Limited
Submission Receipt Date:	July 19, 2023
PDUFA* Action Due Date:	March 18, 2024
Proper Name:	atidarsagene autotemcel
Proprietary Name:	LENMELDY
Indication:	Treatment of children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD)

***** PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

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Director, Office of Clinical Evaluation

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Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Tiffany Lucas, PhD, CBER/OTP/OGT Jacob Bitterman, PhD, CBER/OTP/OGT Christelle Mbondji, PhD, CBER/OTP/OGT Timothy Kamaldinov, PhD, CBER/OTP/OGT Viviana Matta, CBER/OCBQ/DMPQ Ritu Agarwal, CBER/OCBQ/DBSQC/LAC Seth Schulte, CBER/OCBQ/DBSQC/LMIVTS George Kastanis, MS, CBER/OCBQ/DBSQC Wei Tu, CBER/OCBQ/DBSQC/LBVI
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	Avanti Golikeri, MD, CBER/OTP/OCE Jonathan Reich, CBER/OBPV/DPV/PB2 Jennifer Chan, PharmD, CBER/OCBQ/DIS Haecin Chun, MS, CBER/OCBQ/DIS
Statistical • Clinical data (OBPV/DB) • Non-clinical data	Shuya (Joshua) Lu, PhD, CBER/OBPV/DB Tianjiao Dai, PhD, CBER/OBPV/DB
Nonclinical/ Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Rukmini Bhardwaj, PhD, CBER/OTP/OPT
Clinical Pharmacology	Million Tegenge, PhD, CBER/OTP/OCE
Labeling • Promotional (OCBQ/APLB)	Benjamin Cyge, CBER/OCBQ/DCM/APLB Oluchi Elekwachi, PharmD, MPH, CBER/OCBQ/DCM/APLB
Other Review(s) not captured above categories, for example: • Consults • Devices • Software • Human Factors • FONSI	Laura Swett, PhD CDER/OND/ODES/DCOA Naomi Knoble, PhD CDER/OND/ODES/DCOA
Advisory Committee Summary	N/A

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1. Introduction

Orchard Therapeutics (Europe) Limited (herein Applicant or Orchard) submitted Biologics License Application (BLA) 125758 for atidarsagene autotemcel (OTL-200, or LENMELDY, proprietary name). LENMELDY is a cell-based gene therapy indicated for treatment of children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ), or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD).

MLD is a rare, autosomal recessive lysosomal storage disease, primarily due to a deficiency in the arylsulfatase A (ARSA) enzyme. ARSA deficiency leads to widespread demyelination in the central and peripheral nervous systems with to progressive severe neurologic impairment and ultimately death. MLD subtypes are defined by age at symptom onset. Late infantile (LI) MLD is the most severe subtype characterized by symptom onset prior to 30 months of age and progression to neurologic impairment or death by 5 years of age. Early juvenile (EJ) MLD is characterized by symptom onset between 30 months and 7 years of age, with progression to neurologic impairment or death during adolescence. There are no MLD-specific treatments available to patients and a substantial unmet medical need remains.

LENMELDY is an autologous hematopoietic stem cell-based gene therapy, which contains a CD34+ cell enriched population originating from hematopoietic stem and

progenitor cells (HSPCs), transduced with a lentiviral vector (LVV) expressing the human arylsulfatase (*ARSA*) gene (ARSA LVV). ARSA LVV integrates the *ARSA*-encoded gene into the patient's HSPC genomes. Expression of the integrated *ARSA* is driven by a ubiquitous promoter and is not cell-type specific. LENMELDY is supplied cryopreserved in 1-8 bags, with each bag containing between 10-20 mL. LENMELDY is administered as a one-time intravenous infusion.

The recommended LENMELDY dose is as follows:

Table 1: Minimum and Maximum Recommended Doses of LENMELDY for PSLI, PSEJ and ESEJ MLD

MLD Subtype	Minimum Recommended Dose ($CD34^+$ cells/kg)	Maximum Recommended Dose ($CD34^+$ cells/kg)
Pre-symptomatic late infantile	4.2×10^6	30×10^6
Pre-symptomatic early juvenile	9×10^6	30×10^6
Early symptomatic early juvenile	6.6×10^6	30×10^6

Source: LENMELDY USPI Table 1

This document summarizes the basis for approval of LENMELDY. Consistent with 21 USC 355, substantial evidence of effectiveness for LENMELDY for children with PSLI, PSEJ and ESEJ MLD is based on a single adequate and well controlled investigation with confirmatory evidence. Specifically, two single-arm, open-label clinical trials, a European Union (EU) Expanded Access Program (EAP), and an external control natural history study comprised the adequate and well controlled investigation. LENMELDY efficacy is based on analysis population consisting of 37 children enrolled in clinical trials (PSLI; n=13; PSEJ; n=6; ESEJ; n=9) and the EAP (PSLI; n=7; PSEJ; n=1; ESEJ; n=1), compared to an external control natural history study of 28 children with late infantile MLD and 17 children with early juvenile MLD. The safety of LENMELDY was assessed in 39 children treated with LENMELDY. The major efficacy outcomes were motor and cognitive function. Motor function was assessed using the Gross Motor Classification in MLD (GMFC-MLD), an established classification system for assessing gross motor function in MLD (Kehrer et al., 2011). Cognitive function was assessed using neuropsychological tests administered according to the child's age or ability, where performance and language standard scores were defined as: normal cognitive functioning refers to standard score > 85, mild cognitive impairment refers to standard score ≥ 70 and <85, moderate cognitive impairment refers to standard score >55 and <70, and severe cognitive impairment refers to standard score ≤ 55.

The review team recommends approval of LEMMELDY for the treatment of PSLI, PSEJ, and ESEJ MLD based on the demonstration of safety and effectiveness. In children with PSLI MLD, treatment with LENMELDY demonstrated improvement in severe motor impairment-free survival defined as the interval from birth to the first occurrence of loss of locomotion and loss of sitting without support (GMFC-MLD Level ≥ 5) or death, and in survival and cognitive function outcomes, when compared to natural history LI subjects. In children with PSEJ MLD, the effectiveness of LENMELDY was demonstrated by

slowing of the progression of motor and cognitive disease manifestations in LENMELDY-treated children, compared to untreated children and matched sibling comparators. In children with ESEJ MLD, LENMELDY effectiveness was demonstrated in a subject-level analysis which showed slowing of cognitive disease progression despite continued progression of motor disease in treated children, which is unexpected in untreated EJ MLD patients. The major risks of LENMELDY treatment include thrombosis and thromboembolic events, encephalitis, serious infection, veno-occlusive disease, and delayed platelet engraftment. The risks of LENMELDY are acceptable in the context of the severe, rapidly debilitating, and ultimately fatal disease that MLD is, with no effective standard of care treatments.

Overall, the benefit-risk assessment is favorable in the indicated population and approval will address a significant unmet need. Residual uncertainties remain pertaining to the risks of treatment including the risk of secondary malignancies. The review team recommends postmarketing requirement studies to assess and characterize the risk of secondary malignancies and long-term safety following treatment and perform additional leachables assessments for LENMELDY. In addition, the Applicant agreed to post-marketing commitments (PMC) related to product quality assessment.

2. Background

MLD is a rare autosomal recessive lysosomal storage disease caused primarily by mutations in the *ARSA* gene, leading to a deficiency in the ARSA enzyme. Deficiencies in ARSA enzyme led to impaired degradation of sulfatides, one of the most common sphingolipids in the myelin sheath. Accumulation of sulfatides in the myelin sheath of the central and peripheral nervous systems leads to neuronal degeneration, astrocyte dysfunction, and an inflammatory response that causes progressive widespread demyelination. Sulfatide accumulation can be observed in other organs, most commonly in the gallbladder where children may develop hyperplastic polyps and thickening of the gallbladder wall. MLD has an estimated global prevalence of between 1/40,000 to 1/160,000 births, occurring in approximately 1 in 40,000 births in the United States.

MLD subtypes are primarily defined based on age of symptom onset. The late infantile (LI) subtype is defined by symptom onset before 30 months of age, the early juvenile (EJ) subtype is defined by symptom onset between 30 months and 7 years of age, the late juvenile subtype is defined by symptom onset between 7 years and 16 years of age, and the adult subtype is defined by symptom onset after 16 years of age. LI MLD and EJ MLD are the most severe subtypes, where patients with LI MLD typically progress to severe neurologic impairment or death by 5 years of age and patients with EJ MLD typically progress to severe neurologic impairment or death by adolescence. Disease subtype and severity are based on the amount of residual ARSA enzyme activity.

Allogeneic hematopoietic stem cell transplant is considered a treatment option only for patients with EJ MLD but is not considered standard of care. LIBMELDY (atidarsagene autotemcel, produced by Orchard for EU and UK markets) was approved in the EU in 2020 and one month later in the UK in 2021. In the EU and UK, LIBMELDY is indicated for the treatment of metachromatic leukodystrophy (MLD) characterized by biallelic mutations in the *ARSA* gene leading to a reduction of the ARSA enzymatic activity in children with late infantile or early juvenile forms, without clinical manifestations of the

disease, or in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

The regulatory history of LENMELDY is outlined in Table 2.

Table 2. Regulatory History

Regulatory Events / Milestones	Date
1. Orphan Drug designation granted	March 8, 2018
2. Rare Pediatric Disease designation granted	April 16, 2018
3. Pre-IND meeting	April 10, 2020
4. IND 26917 submission	October 15, 2020
5. RMAT designation granted	January 13, 2021
6. Pre-BLA meeting	April 24, 2023
7. BLA 125758/0 submission	July 19, 2023
8. BLA filed	September 15, 2023
9. Mid-Cycle communication	November 15, 2023
10. Late-Cycle meeting	January 8, 2024
11. Action Due Date	March 18, 2024

3. Chemistry, Manufacturing, and Controls (CMC)

This BLA includes an adequate description of the manufacturing process and characterization LENMELDY. 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.

a. Product Quality

Manufacturing Summary

To manufacture LENMELDY 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) with or without plerixafor. The apheresis material is then shipped to the AGC Biologics drug substance (DS)/drug product (DP) manufacturing facility (Bresso, Milan, Italy). (b) (4) manufacturing, the apheresis material is enriched for cells expressing CD34+ by (b) (4) the cells are transduced (b) (4) with the ARSA LVV (b) (4). On the (b) (4) day of manufacturing, the cells are 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) for administration. The cells are resuspended at a target concentration of 1.8 x 10^6 to 11.8 x 10^6 viable CD34+ 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 per lot. The DP bags remain cryopreserved until immediately prior to infusion. The DP is shipped to the clinical site in a (b) (4) shipper at <-130°C; the receiving site is responsible for transfer of the DP to LN_2 storage at their facility.

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

Manufacturing Control Strategy

The LENMELDY manufacturing control strategy consists of (1) raw material, component, and reagent qualification programs; (2) in-process monitoring; (3) in-process control testing; (4) lot release and stability testing; (5) manufacturing process validation and continuous process verification; and (6) traceability through chain of identity and chain of custody (COI/COC). The raw material, component, and reagent qualification program consists of source material risk assessment, vendor qualification, confirmation of the certificate of analysis, and material testing. Raw materials derived from animals and humans are controlled to ensure the absence of microbial contaminants and adventitious agents. The manufacturing process has been adequately validated using a combination of healthy donor- and patient-derived starting material. Critical process parameters are established for unit operations based on process characterization and risk assessment studies. In-process monitoring, and controls are implemented throughout the process to support process consistency. The manufacturing process validation demonstrated removal of process-related impurities, including (b) (4) impurities. The LVV manufacturing processes were also validated. Additional validation studies, including aseptic process simulation and shipping validation studies, were also performed. Lot release test methods are suitably validated or verified. LENMELDY specifications are adequate to ensure product quality and consistency with DP used in the clinical study. Manufacturing and testing comply with Current Good Manufacturing Practice (GMP) requirements. COI/COC are established at the time of apheresis collection and maintained throughout the manufacturing process to administration to ensure that the patient receives the correct autologous lot.

Comparability Assessments

During the BLA review, comparability of products that were manufactured at different manufacturing facilities was assessed. Due to the long developmental nature of this clinical program, several comparability factors were assessed during review of the BLA: change in manufacturing facilities, change across (b) (4) different manufacturing processes, and use of two different starting source materials for patient CD34+ cells. (b) (4) AGC Biologics manufacturing facilities were used to manufacture LENMELDY. (b) (4) facilities were able to produce comparable products. Orchard transitioned from a fresh product to a cryopreserved product, in order to complete release testing and to allow for shipping of the product to patients. The cryopreserved and fresh product were considered comparable, except for the viability, which was expected due to the freezing process. The difference in viability does not impact the product, as the product is formulated based on viable CD34+ cells. Regarding the use of different source materials for CD34+ cells (bone marrow or peripheral blood), Orchard provided data generated with healthy donors and from the final two manufacturing methods ((b) (4)). Some differences were noted, although many parameters have similar attribute outcomes. Orchard did not perform a comparability study across all (b) (4) manufacturing methods (where different methods use different equipment and either bone marrow- or peripheral blood-source CD34+ cells) but did provide patient data. Each method appears to result in distinct outcomes in manufacturing, but the methods (b) (4) share an overlapping range with the final commercial (b) (4) outcome, suggesting a shared range of quality attributes between (b) (4) and the previous processes. Previous methods were considered appropriate to support clinical assessment of data and the data collected from the (b) (4) process were used to support the commercial release criteria.

Manufacturing Risks, Potential Safety Concerns, and Management

Product Mix-Up

LENMELDY is an autologous product manufactured in a multiproduct manufacturing facility; as such, product mix-ups, either of autologous lots or with other stem cell products manufactured at the same facility, would result in potential risks. The COI/COC ensures that the patient receives their autologous lot. COI/COC is established at the point of apheresis collection, checkpoints are implemented throughout the manufacturing process, and patient identifiers are confirmed prior to administration. The COI/COC is maintained through integrated computer-based programs with human-readable identifiers present on all labels as well. Additionally, only a single product lot is manufactured in a production suite at any given time. Prior to transduction, the LVV labels are confirmed to ensure the correct materials are used. A QR-code (quick-response graphics code) system is in place to prevent operator import of incorrect (b) (4) for LVV manufacture into the manufacturing suite. Lot release testing also confirms product identity and activity.

Insertional Oncogenesis

Results of clinical studies have shown no risk-associated integration profiles in drug product lots to date, and no patients have developed malignancies during the clinical studies. The risk of insertional oncogenesis is theoretically reduced through LENMELDY lot release testing acceptance criteria, with maximum upper limits for vector copy number

(VCN) integrations. The upper VCN limit is supported by effective lots manufactured with the commercial process.

CMC PMR/PMCs

The following issues were identified but could not be resolved during the review cycle. The issues will be resolved through postmarketing requirements (PMR) by August 31, 2025, and through postmarketing commitments (PMC) by December 31, 2024.

PMR
Orchard did not adequately perform a leachables safety assessment for LENMELDY based on the entire manufacturing process, storage, and in-use conditions. The PMR will include an assessment of elemental extractables, elemental and organic extractables and a full toxicological risk assessment for the identified leachables.

PMCs
Orchard committed to several PMCs during review. During inspection and BLA review, FDA CMC determined that sterility quality control samples were (b) (4) sterility testing. QC samples are typically (b) (4) sterility testing, as (b) (4) could potentially impact the ability to detect microbial organisms in the sample. The sterility test was validated with (b) (4) samples. Additional validation testing of the (b) (4) will be performed and container closure integrity will be expanded to include a positive control with a (b) (4). Orchard will test the impact of (b) (4) on a panel of microorganisms. Validation of the drug product (b) (4)-based mycoplasma test was insufficient as it did not include a comparability study with (b) (4) mycoplasma tests. Orchard has provided written commitment to complete a mycoplasma comparability study as required by 21 CFR 610.9.

The appearance testing is inadequate to support the proposed acceptance criterion and has not been adequately validated. Orchard did not collect product color data during the clinical study and based the commercial release criterion color on the (b) (4). Furthermore, the appearance testing protocol is lacking in specific instruction related to defining color ranges. Orchard will perform assay protocol revision, validation, and reassess the acceptance criterion.

Several assays were not adequately validated and PMCs were issued to address the shortcomings. The (b) (4) assay does not adequately validate the upper range of the assay; therefore, assay reassessment and re-validation is needed to support (b) (4) above (b) (4). The drug product (b) (4) assay did not test the full range that may be detected during performance of the assay. Therefore, additional range validation will be performed. Additional robustness studies will be performed for the following assays: (b) (4) test used to detect the (b) (4), the (b) (4) assay used for (b) (4), and the (b) (4) testing performed on the (b) (4). The (b) (4) assays will also receive additional robustness testing to ensure the impact of variable conditions on the two assays.

b. Testing Specifications

The final LENMELDY lot release specifications are shown in Table 3. LENMELDY lot release analytical methods, and their validations and/or verifications, were found to be adequate for their intended use.

Table 3. Final Commercial LENMELDY Release Specifications

Attribute	Test	Method	Acceptance Criteria
General	Cell Concentration (cells/mL)	(b) (4)	2.0 x 10^6 to 11.8 x 10^6 cells/mL
General	Total Volume (mL)	N/A	FIO
General	Appearance [1]	Visual inspection	A colorless to yellow or pink cell suspension
Identity	Transgene Function (ARSA activity)	(b) (4)	Detected
Potency	Viability (%)	(b) (4)	(b) (4)
Potency	Vector Copy Number (b) (4)	(b) (4)	(b) (4)
Potency	Vector Copy Number (b) (4)	Calculation	(b) (4)
Potency	Transduction Efficiency (%)	(b) (4)	(b) (4)
Potency	Transgene Function (ARSA Activity) (b) (4)	(b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)	(b) (4)
Identity/ Purity	(b) (4) $CD34^+$ (%)	(b) (4)	(b) (4)
Safety	(b) (4)	(b) (4)	(b) (4)
Safety	Sterility (Drug Product)	Detection of bacterial growth by (b) (4)	Negative
Safety	Endotoxin (EU/mL)	(b) (4)	(b) (4)
Safety	Mycoplasma	(b) (4)	Not detectable

[1] LENMELDY appearance in the (b) (4) bag is checked (b) (4) by GMP manufacturing operators (b) (4) .

(b) (4)

Impurity Profile
LENMELDY is a viable CD34+ cell enriched population, containing HSPCs, insertion of the human ARSA gene by the ARSA-encoding LVV. Impurities in LENMELDY can be divided into product-related impurities ((b) (4)) and process-related impurities (residuals derived from raw materials and manufacturing components, ARSA (b) (4), not intended to be in the final product). Impurities were evaluated in LENMELDY process characterization studies. The levels of all evaluated impurities in LENMELDY were acceptable, and the calculated possible impurity per dose was below the maximum permissible single exposure level outlined in literature, as applicable.

Stability
Long-term stability studies have been completed and support a LENMDELDY shelf life of 6 months when stored at ≤-130°C in vapor phase of liquid nitrogen. The stability studies utilized LENMELDY manufactured with the commercial process from normal healthy donor starting material. In-use stability testing supported the proposed post-thaw expiry of 2 hours.

A shelf life of (b) (4) was supported for ARSA LVV when stored at (b) (4).

c. CBER Lot Release

LENMELDY is not subject to CBER Lot Release testing, and product samples are not required to be submitted to CBER. The basis for this decision is that LENMELDY is an autologous product; as such, each lot will treat a single patient. Failure of a single lot will have minimal potential impact on public health.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of LENMELDY are listed in the table below. The activities performed and inspectional histories are noted in the table below.

Table 4. Manufacturing Facilities Table for LENMELDY

Name/Address	FEI Number	DUNS number	Inspection / Waiver	Justification /Results
(b) (4) **LVV manufacture,** in-process testing, release and stability testing OTL-200 Drug Substance characterization testing	(b) (4)	(b) (4)	Inspection	DMPQ (b) (4) VAI

OTL-200 Drug Product release/stability testing				
AGC Biologics S.p.A. Via Antonio Meucci 3, Openzone, Bresso, Milan, Italy 20091 **Drug Substance manufacture** and in-process testing **Drug Product manufacture**, in-process testing, release and stability testing, primary, secondary, tertiary packaging and storage	3020270660	428486752	Inspection	DMPQ Nov. 2023 VAI

Acronym key:
A*RSA – Human Arylsulfatase A gene*
FEI – Federal Establishment Identifier
LVV – Lentiviral Vector
MRA – Mutual Recognition Agreement
VAI – Voluntary Action Indicated

AGC Biologics S.p.A.

The Pre-License Inspection was conducted 11/08/2023 – 11/20/2023. At the end of the inspection a form FDA-483, Inspectional Observations, containing two observations, was issued. The observations are summarized as follows: failure to identify a root cause and implement corrective actions to address repeated incidents of alarms and failure to follow procedures. Management promised corrections and the inspection was classified as VAI.

e. Container/Closure System

The container closure system for the LENMELDY DP is listed in the table below.

Table 5. DP Container Closure Components

Component	Description	Manufacturer	Standards
(b) (4) Freezing Bags 50	(b) (4)	(b) (4)	510(k) cleared in the USA (510(k) No. (b) (4)) CE marked medical device, Class IIa in EU

Container closure integrity testing (b) (4) test) of all lots met the acceptance criteria. The LENMELDY DP container closure system integrity appears to be appropriately validated.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). This request and supporting information provided are acceptable to conclude that LENMELDY poses a negligible risk to the environment or to the general public. Data provided in the BLA indicates that the potential for recombination of the LVV into a replication competent form is low. The potential for LENMELDY to persist in the environment is negligible because these cells have stringent nutritional requirements for survival and therefore are not viable in the environment. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

In vitro studies with murine Lin- HSPCs (mHSPCs) from ARSA knockout ($As2^{-/-}$) mice transduced with ARSA LVV demonstrated reconstitution of sulfatide metabolism by the cerebroside 3-sulfate assay and increased ARSA activity compared to wild type cells as measured by p-nitrocatechol sulfate assay. *In vitro* studies with human bone marrow-derived CD34+ cells from healthy donors and a patient with MLD showed similar levels of transduction and reconstitution of ARSA activity. ARSA-LVV transduction did not affect clonogenic potential or differentiation capacity of the CD34+ cells.

In vivo pharmacology studies conducted in pre-symptomatic and symptomatic $As2^{-/-}$ mice demonstrated long-term engraftment of ARSA LVV-transduced mHSPCs in the bone marrow following intravenous (IV) administration of $1x10^6$ cells/mouse ($40\text{-}50x10^6$ cells/kg) in irradiated mice. Restoration of ARSA activity was observed in the peripheral blood monocytes and liver in these animals, and reached 10% of wild type levels in the brain. Improvement in motor conduction abnormalities, motor coordination by rotarod testing, and neuropathology were observed compared to mice receiving GFP LVV-transduced mHSPCs when evaluated between 4-12 months post-transplantation. Correction of the disease phenotype correlated with: 1) engraftment of mHSPCs and vector copy number in the bone marrow and 2) ARSA activity in blood and target tissues.

Biodistribution studies conducted in irradiated immunodeficient mice demonstrated long-term engraftment and multilineage differentiation of ARSA LVV-transduced hHSPCs. In addition to the bone marrow, spleen, thymus, and liver where the highest levels of the vector were detected, transduced human cells were also detected at lower levels in the brain, demonstrating migration of the transduced cells into target organs. Additionally, these studies showed that integrated LVV persists in the differentiated progeny of transduced HSPCs and remains stably integrated within human cells.

The *in vivo* safety of single IV administration of ARSA LVV-transduced mHSPCs at $1x10^6$ cells/mouse ($40\text{-}50x10^6$ cells/kg) in irradiated $As2^{-/-}$ mice was evaluated in a pivotal GLP study for up to 12 months post-transplant. No test article-related mortality, toxicity or hematologic malignancy was observed, with study findings primarily attributed

to the $As2^{-/-}$ phenotype, irradiation, and incidental age-related findings. No development of anti-ARSA antibodies or adverse neurobehavioral effects were observed in $As2^{-/-}$ mice transplanted with ARSA LVV-transduced mHSPCs. Integration site analysis showed polyclonal reconstitution of cells with no evidence of preferential expansion of integration sites near proto-oncogenes. A higher incidence of hepatocellular tumors was reported in a preceding non-GLP safety study in $As2^{-/-}$ mice receiving ARSA LVV-and mock-transduced mHSPCs. In that study, the increased tumor incidence was attributed to a possible effect of the genetic background since tumors were not observed in wild type mice receiving ARSA LVV-transduced mHSPCs, and/or the higher irradiation dose used for the myeloablative conditioning regimen compared to the pivotal study.

Genotoxicity risk was assessed *in vitro* using hHSPCs derived from healthy donors and MLD patients and showed no effects of LVV transduction or ARSA overexpression on the proliferation or differentiation of hHSPCs. No evidence of insertional mutagenesis of the LVV backbone in an *in vitro* immortalization (IVIM) assay and no increase in tumorigenesis *in vivo* in a tumor-prone mouse model were demonstrated using an LVV expressing GFP that shares the same LVV backbone as that of ARSA LVV.

Carcinogenicity and developmental and reproductive toxicity studies were not conducted with OTL-200. These studies are not warranted based on the product characteristics and safety profile.

5. Clinical Pharmacology

The data supporting clinical pharmacology of LENMELDY derive from two clinical studies (#201222 and #205756) and an Expanded Access Program (EAP). LENMELDY inserts one or more functional copies of the human Arylsulfatase A (ARSA) complementary DNA into patients' HSPCs, through transduction of autologous CD34+ cells with lentiviral vector. After LENMELDY infusion, transduced $CD34^{+}$ HSPCs engraft in bone marrow, repopulate the hematopoietic compartment and their progeny produce ARSA enzyme. Functional ARSA enzyme can breakdown or prevent the harmful accumulation of sulfatides.

The average number of integrated ARSA transgene vector copy number in peripheral blood mononuclear cells (VCN in PBMC), the proportion of lentiviral vector positive (% LVV+) in the bone marrow (BM) and ARSA in PBMC were evaluated as part of pharmacodynamic (PD) assessments. Following administration of LENMELDY, the VCN in PBMC was first detected at Month 1, continued to increase to relatively stable average levels at Month 12, and remained stable at the end the follow-up period for PSLI, PSEJ and ESEJ. The median % LVV+ exceeded the applicant defined 4% threshold at Month 1 and generally remained stable throughout the follow-up period for PSLI, PSEJ, and ESEJ.

Following administration of LENMELDY, median ARSA activity in PBMCs was at supranormal levels by Month 3 in the PSLI and PSEJ (normal range for ARSA activity is 30.6-198 nmol/mg/h) and supranormal median ARSA activity were sustained throughout the duration of follow-up. In ESEJ median ARSA activity was within normal range from Month 3 to Year 2 and supranormal level was achieved from Year 3 to Year 5. The time to reach supranormal ARSA activity is delayed in ESEJ and the actual peak ARSA

activity is substantially lower in ESEJ as compared to PSLI. The median [min, max] ARSA activity in PBMC (nmol/mg/h) was 1239 [46, 6467] for PSLI (n=20), 883 [272, 1976] for PSEJ (n=7) and 130 [55, 688] for ESEJ (n=8). The median [min, max) administered dose (x10^6 CD34+cells/kg] was 14.2 [4.2, 30] for PSLI, 17.6 [9, 30] for PSEJ and 9.5 [6,30] for ESEJ. Despite the supranormal ARSA activity, the available data are insufficient to establish a quantitative relationship between ARSA activity and clinical outcomes. Dose-response analysis showed a trend for increasing ARSA in PBMC with increasing dose for PSLI and ESEJ. Factors such as age at treatment appear to contribute to the observed variability in ARSA activity. Age is negatively correlated with ARSA activity for PSLI.

Anti-ARSA antibodies (AAA) were detected in 6 out 39 subjects (15%). There is no indication of decreased ARSA activity in five children with PSLI who developed AAA; here was a trend of decreasing ARSA activity in one child with PSEJ who had AAA. Overall, based on clinical pharmacology assessment of the dose-response relationship for ARSA activity and clinical outcome data, the recommended minimum and maximum dose is as follows:

Table 6. Recommended Minimum and Maximum Dose

	Minimum Recommended Dose ($CD34^+$ cells/kg)	**Maximum Recommended Dose ($CD34^+$ cells/kg)**
Pre-symptomatic late infantile (PSLI)	4.2 x 10^6	30 x 10^6
Pre-symptomatic early juvenile (PSEJ)	9 x 10^6	30 x 10^6
Early symptomatic early juvenile (ESEJ)	6.6 x 10^6	30 x 10^6

Source: Clinical Pharmacology assessment

6. Clinical/Statistical

a. Clinical Program

To support licensure of LENMELDY, Orchard Therapeutics (Europe) Limited submitted data from an adequate and well-controlled investigation comprised of two single arm, single-center, open-label studies, a European Union Expanded Access Program (EAP), and one ongoing long-term follow-up study and a natural history study. The clinical review team's recommendation for traditional approval of LENMELDY is based on pooled efficacy data from the clinical trials and EAP compared to natural history data, with confirmatory data. Confirmatory data included mechanism of action, pre-clinical data, clinical biomarkers, ARSA levels and radiographic imaging from brain MRIs.

The protocols for two clinical studies, Study OTL-200-201222 (n=18) and Study 205756 (n=10) and the EAP protocols did not differ substantially in their study design, eligibility criteria, and assessment schedule, thus supported a pooled analysis. Differences across protocols stemmed from differences in myeloablative conditioning regimens, source of the CD34+ cells for transduction (bone marrow versus mobilized peripheral

blood) and formulation of the drug product (fresh versus cryopreserved); these differences did not lead to differences in clinical outcomes.

The natural history comparator included a cohort of 28 children with LI MLD and 17 children with EJ. Natural history data was collected retrospectively through chart review and parental interviews and through prospective in-person assessments of the child. The Applicant supplemented the natural history study with narrative data describing the clinical course of 6 untreated siblings of children who received LENMELDY in the clinical studies. Children with EJ MLD in the natural history study appeared to have more severe MLD-related impairment at baseline compared to children in the efficacy analysis population; the comparative assessment of efficacy for EJ MLD therefore also included a review of the medical literature to further characterize the natural disease course.

Efficacy data was analyzed by subtype (PSLI, N=20; PSEJ, N=7; ESEJ, N=10). The safety database included the 37 subjects evaluated for efficacy of LENMELDY and an additional two subjects who were treated at advanced stages of MLD disease.

All subjects were classified as having MLD on the basis of two known pathologic mutations in ARSA, two null mutations for PSLI and at least one mutation encoding residual enzyme for PSEJ and ESEJ. Pre-symptomatic for LI was further defined as absence of disease-related symptoms or neurological examination findings. PSEJ was defined as children with EJ MLD who are asymptomatic or have physical exam findings limited to clonus and/or abnormal reflexes. ESEJ was defined as children with MLD who had symptom onset between 30 months and 7 years of age, and gross motor function classification in MLD (GMFC-MLD) score of 0 with ataxia or a score of 1 with or without ataxia, and intelligence quotient (IQ) ≥ 85 on age-appropriate neurodevelopmental testing.

Severe motor impairment-free survival (sMFS) was the primary efficacy endpoint specified in the integrated statistical analysis plan. sMFS was defined as the interval from birth to the first occurrence of death or GMFC-MLD ≥ Level 5 (no locomotion or sitting without support). Interpretation of the results of the analysis of this endpoint for the EJ population was limited due to the small sample size, heterogeneity of EJ, and limited comparability of clinical trial subjects to the natural history population. Analyses for the PSEJ and ESEJ population were based on descriptive analyses comparing available data and information that characterizes the natural course of disease to the data obtained in the clinical studies and EAP, rather than through formal statistical hypothesis testing.

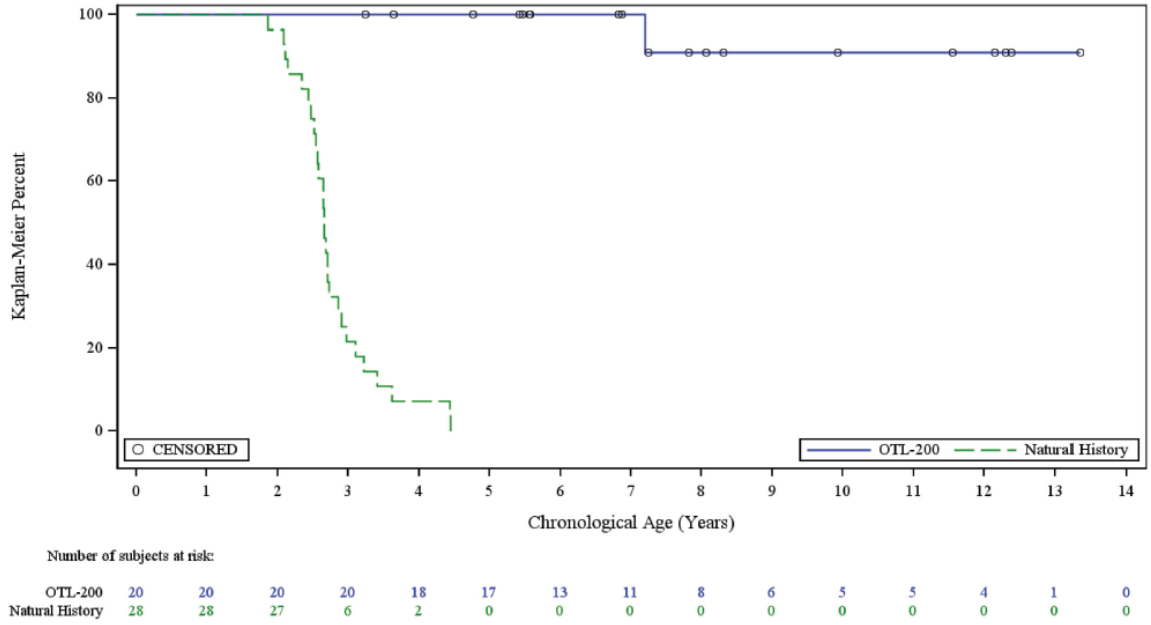
Efficacy

PSLI

Twenty subjects with PSLI MLD were treated in LENMELDY clinical studies. Sixty-five percent of LENMELDY-treated children were male and 35% were female. Study participant ages ranged between 8 and 19 months (median 12 months) of age at the time of LENMELDY treatment. Of the 20 treated children, 75% were White/Caucasian, 15% Black/African-American, and 10% Asian. Efficacy was observed in the analysis of the primary endpoint of sMFS (Figure 1). None of the 17 LENMELDY treated children

with PSLI who were followed until 5 years of age progressed to severe motor impairment, while 100% of the 28 children with LI in the natural history cohort did.

Figure 1: Kaplan-Meier Plot of Severe Motor Impairment-Free Survival in the PSLI Subjects

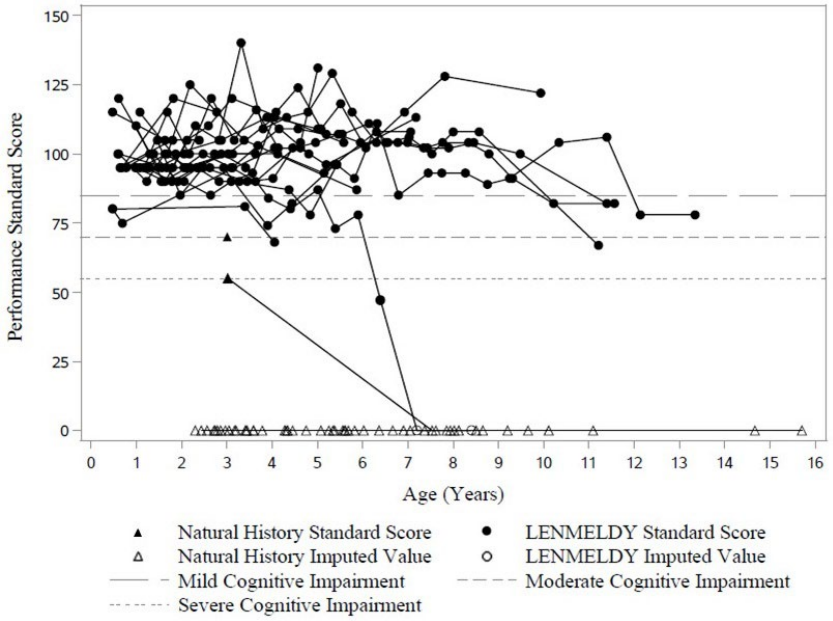


Source: Figure X44.4, Applicant Response to Clinical IR#8, BLA125758/0.47
Abbreviations: PSLI = pre-symptomatic late infantile

Independent ambulation (GMFC-MLD ≤ 1) was retained in 12 of 17 children who were followed until 5 years of age. The oldest child who retained independent ambulation was 13 years old. These are unexpected outcomes based on the natural history of LI MLD, where patients would be expected to lose all motor function by 5 years of age. Efficacy of LENMELDY was also seen on survival, where 100% of the 13 LENMELDY treated children with PSLI who were followed until 6 years of age were alive, compared to only 58% of the 24 untreated children with LI in the natural history cohort.

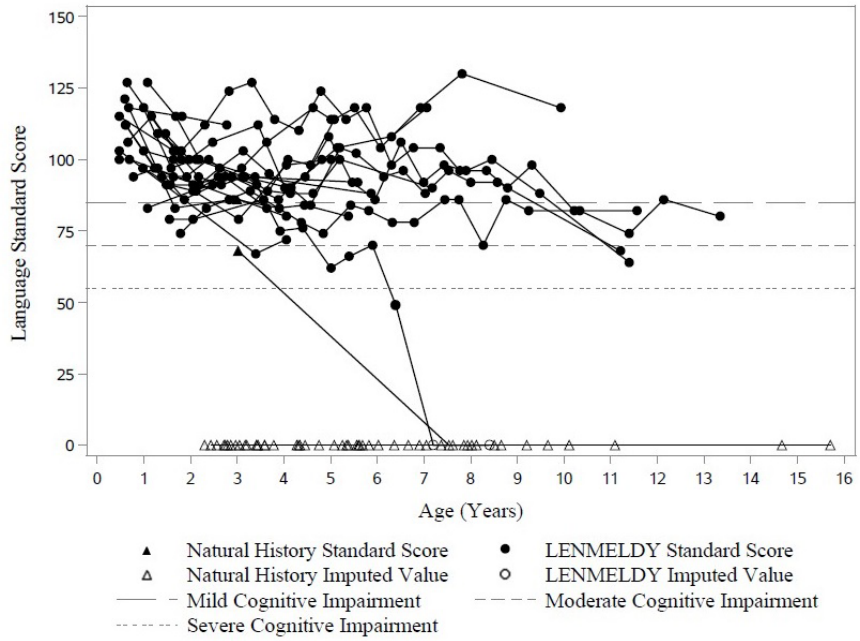
Efficacy was observed in the cognitive manifestations of LI MLD, as assessed by performance standard scores and language standard scores. Figure 2 and Figure 3 demonstrate the performance standard scores and language standard scores of the treated children with PSLI MLD compared to the children with LI MLD in the natural history study. Of note, performance and language standard scores are imputed as zero in the cases where they could not be derived due to severe cognitive impairment.

Figure 2: Plot of Performance Standard Scores vs Age (PSLI) in children with PSLI treated with LENMELDY and natural history children with LI MLD



Source: LENMELDY USPI, Figure 2

Figure 3: Plot of Language Standard Scores vs Age (PSLI) in children with PSLI treated with LENMELDY and natural history children with LI MLD



Source: LENMELDY USPI, Figure 3

Only 1 of the 17 children who were followed until 5 years of age progressed to severe cognitive impairment (standard score ≤ 55), an age when all untreated LI MLD would be expected to have severe cognitive impairment.

PSEJ
Seven children with PSEJ MLD were treated in the LENMELDY clinical trials. 14% of children were female and 86% of subjects were male. Subjects were between 11 and 67 months (median 31 months) of age at LENMELDY treatment. 85% of children were White/Caucasian and 14% were Black/African-American. One child died 14 months after treatment due to a cerebral infarction assessed as unrelated to MLD disease progression, but potentially related to LENMELDY.

Three children retained independent ambulation (GMFC-MLD ≤ Level 1) at last follow-up at ages 8.3, 11.0 and 13.6 years. Additionally, all three children retained cognitive functioning in the "broadly average" range (performance and language standard scores ≥ 85). Based on the published natural history of EJ MLD, untreated EJ MLD patients would be expected to lose independent ambulation (GMFC-MLD ≥ Level 2) and experience impairment in cognitive functioning at those ages (Fumagalli et al, 2011 & Kehrer et al, 2014). Three other children were still under 7 years of age at time of last follow-up, and as EJ MLD may be asymptomatic until 7 years of age, it is premature to detect clinical outcomes that deviate from the natural history in these children.

It is unknown whether LENMEDLY impacts survival in PSEJ MLD as the duration of follow-up was limited; untreated children with EJ MLD may not progress to death until adulthood.

ESEJ
Ten children with ESEJ MLD were treated in LENMELDY clinical trials. Forty percent were female and 60% were male. All children were White/Caucasian. Children developed symptom onset prior to treatment between 29 and 83 months of age (median 62 months) and were treated with LENMELDY between 31 and 140 months (median 70 months). Two children (20%) died from MLD disease progression 8 and 15 months after treatment with LENMELDY.

Despite having an atypical EJ phenotype at baseline when compared to the natural history, all treated ESEJ children experienced motor disease progression after treatment that did not appear slowed when compared to the natural history children. However, clinical benefit of LENMELDY was observed in the slowing of cognitive disease progression in the treated ESEJ children. Four children (40%) retained normal performance standard scores (≥85) and three of these children retained normal language standard scores (≥85) between the ages of 13 and 16 years. Preservation of cognitive functioning in these four children occurred despite progression of motor disease. This is unexpected in the natural history of EJ MLD where cognitive and motor functioning are expected to decline in parallel, with significant cognitive impairment expected by adolescence. (Kehrer et al, 2011) The cognitive benefit was attributed to a treatment effect of LENMELDY.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring inspection assignments were issued for one foreign sponsor and one foreign clinical investigator study site that participated in the conduct of Protocol OTL-200-201222. This clinical investigator site was the only study site participating in

this study. The inspections did not reveal significant issues impacting the data submitted in this original BLA.

c. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has an orphan drug designation, this application is exempt from this requirement.

As LI and EJ MLD are pediatric conditions, the clinical studies were conducted exclusively in children. Children between 7 months (7kg) and 11.6 years were treated with LENMELDY and studied. The clinical data support the safety and effectiveness of LENMELDY in children with PSLI, PSEJ and ESEJ MLD.

d. Other Special Populations

LENMEDLY has not been studied in other special populations relevant to this indication.

7. Safety and Pharmacovigilance

Safety
There were 39 children in the safety population, including the 37 children with PSLI, PSEJ and ESEJ MLD analyzed for efficacy and 2 additional children with advanced disease who received LENMEDLY treatment. Children underwent mobilization and apheresis (either from the bone marrow or peripheral blood) and myeloablative conditioning with busulfan prior to administration of LENMELDY. Children in the safety population were treated between 0.7 and 11.7 years of age (median 1.3 years). 36% were female and 64% were male. 92% were White/Caucasian, 5% Asian and 3% Black/African-American.

A risk of thrombosis and thromboembolic events with treatment with LENMELDY was observed. 1 PSEJ subject died due to a serious adverse event (SAE) of cerebral infarction approximately one year after treatment. While the exact etiology of the death in the PSEJ was unclear, attribution to LENMELDY could not be ruled out.

An SAE of encephalitis was also observed in an ESEJ subject treated in the European Union commercial setting. This subject was observed to develop encephalitis followed by a relapsing-remitting pattern of MLD disease progression, which may have been triggered by treatment with LENMELDY.

Additional risks of LENMELDY observed in the clinical trial include serious infections (occurred in 39% of all children, including 2 events of sepsis), veno-occlusive disease (occurred in 8% of children, with no events meeting Hy's law criteria), and delayed platelet engraftment (platelet engraftment after day 60 occurred in 10% of all children).

Theoretical risks of neutrophil engraftment, insertional oncogenesis and hypersensitivity reactions were not observed in the safety population. The most common adverse events (occurring in ≥10% of all patients) within one year of LENMELDY treatment were: febrile neutropenia (85%), stomatitis (77%), respiratory tract infections (54%), rash (33%), device-related infections (26%), other viral infections (23%), pyrexia (21%), gastroenteritis (21%), and hepatomegaly (18%). There were no observed differences in adverse events between the PSLI, PSEJ and ESEJ subpopulations.

Pharmacovigilance

Post licensure safety surveillance activities will include:

1. Routine pharmacovigilance: Adverse event reporting in accordance with 21 CFR 600.80.

2. Enhanced surveillance under 21 CFR 600.80 (c)(1)(i) for adverse events for 3 years following approval:

    - Submission of all serious post-marketing reports regardless of expectedness, as expedited (15-day) reports
    - Provision of aggregate assessment (based on interval and cumulative data) of all serious adverse events in periodic safety reports.

3. Post marketing requirement (PMR) under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA): A postmarketing, prospective, observational, study to assess and characterize the risk of secondary malignancies, and long-term safety following treatment with LENMELDY. This study will enroll a minimum of 17 children and the enrolled patients will be followed for 15 years after product administration. We will review applicant's plans for collection of tumor tissue and testing algorithms to assess for vector persistence and characterize occurrence of secondary malignancies when final protocol is received post-approval. The above study is in alignment with the FDA Guidance *Long Term Follow-up After Administration of Human Gene Therapy Products (January 2020)*, recommendations for 15-year long term follow up for products with integrating vectors.

The data available at this time do not suggest any safety signals that warrant a Risk Evaluation and Mitigation Strategy (REMS) for this product. There is no post-marketing commitment for a safety study for this product.

8. Labeling

The proposed proprietary name, LENMELDY, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on October 10, 2023, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on October 13, 2023.

The APLB reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), package and container labels on February 3, 2024, for comprehension and readability.

Based on the safety review, the following warnings and precautions for treatment with LENMELDY were identified: thrombosis and thromboembolic events, encephalitis, serious infections, veno-occlusive disease, delayed platelet engraftment, neutrophil engraftment failure, insertional oncogenesis, hypersensitivity reactions, anti-retroviral use, and interference with HIV serology testing

9. Advisory Committee Meeting

This BLA was not referred to the Cellular, Tissue, and Gene Therapies Advisory Committee because the information submitted, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

This application received Orphan Drug, RMAT, Priority Review designations, and a Rare Pediatric Disease Priority Review Voucher.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant provided substantial evidence of effectiveness and reasonable assurance of safety based on an adequate and well controlled clinical investigation. The review team recommends approval of LENMELDY for the treatment of PSLI, PSEJ, and ESEJ MLD.

b. Benefit/Risk Assessment

LENMELDY administration resulted in a clinically significant slowing of the progression of motor and cognitive disease manifestations in patients with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) and early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD). While significant risks such as thrombosis, encephalitis, veno-occlusive disease, and serious infections were identified, these did not outweigh the observed benefits given the known progression to severe neurologic impairment in untreated patients with LI and EJ MLD, and the lack of other available treatment options. Thus, the overall benefit-risk profile of LENMELDY is considered favorable.

The clinical trial data do not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS) Consistent with long term follow up requirements for gene therapy products with integrating vectors and the potential risk of insertional oncogenesis, a post-marketing safety study will be required to assess the serious risk of secondary malignancies following treatment with LENMELDY.

c. Recommendation for Post-marketing Activities

The Applicant will conduct routine and enhanced pharmacovigilance activities (with adverse event reporting as required under 21 CFR 600.80), and the following safety studies as PMRs under section 505(o) of the FDCA:

1. A post-marketing, prospective, observational, study to assess and characterize the risk of secondary malignancies, and long-term safety following treatment with atidarsagene autotemcel (OTL-200-12). This study will enroll a minimum of 17 subjects. The enrolled patients will be followed for 15 years after product administration.

   Study milestone dates:

   - Final Protocol Submission: July 31, 2024
   - Study Completion Date: June 30, 2044
   - Final Study Report Submission: December 31, 2044

2. 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.

   Study milestone dates:

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

<u>The Applicant agreed to the following PMCs:</u>

1. Orchard Therapeutics (Europe) Limited commits to perform a comparability study as part of the LENMELDY drug product (b) (4)-based mycoplasma assay as required by 21 CFR 610.9. (b) (4) mycoplasma testing will be performed by (b) (4) while the (b) (4) prepared

by (b) (4) will be tested by AGC Biologics S.p.A. Bresso site in Milan, Italy using the (b) (4)-based mycoplasma assay. The final validation study 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 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

3. 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

4. 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

5. 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

6. 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

7. 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

8. 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

9. 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

10. Orchard Therapeutics (Europe) Limited commits to perform validation of the (b) (4) used for the (b) (4) that are utilized in the aseptic manufacturing process of the OTL-200 DP drug product, in addition to performing (b) (4) testing. The final report will be submitted as a "Postmarketing Commitment - Final Study Report" by September 30, 2024.

    Final Report Submission: September 30, 2024

11. Orchard Therapeutics (Europe) Limited commits to submit a container closure integrity testing (CCIT) study to demonstrate the integrity of the (b) (4) with the inclusion of a positive control with (b) (4). The final report will be submitted as a "Postmarketing Commitment - Final Study Report" by December 31, 2024.

    Final Report Submission: December 31, 2024

12. **References**

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