

**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE PLAN REVIEW MEMORANDUM

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To: Monique Cortez, RPM, ORMRR/OTP

Through: Christopher Jason, MD
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Subject: Review of Pharmacovigilance Plan for Atidarsagene
autotemcel

Applicant: Orchard Therapeutics

Product: Atidarsagene autotemcel/**Lenmeldy** (trade name)
OTL-200 – research name of drug and active product

Application Type/Number: 125758/0. Original BLA

Indication: Atidarsagene autotemcel is indicated for the treatment
of pediatric patients with pre-symptomatic late infantile
(PSLI), pre-symptomatic early juvenile (PSEJ) or early
symptomatic early juvenile (ESEJ) metachromatic
leukodystrophy (MLD).

1 Objective

The purpose of this review is to assess the adequacy of the applicant's pharmacovigilance plan (PVP), submitted under 125758/0, based on the safety profile of Lenmeldy/atidarsagene autotemcel and determine the adequacy of the Applicant's plans for post-marketing safety monitoring.

2 Product Information

2.1 Clinical Background

Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal disorder that results in a buildup of sulfatides that leads to the destruction of the neuron's myelin sheath, leading to progressive demyelination of the central and peripheral nervous system.¹ Metachromatic leukodystrophy is a progressive disease beginning from minor symptoms at onset to total loss of all muscle and mental functions eventually. Lifespan often depends on the age at which a person is first diagnosed.

- **Late infantile form:** The prognosis is worse than later-onset forms of the diseases; progression to death typically occurs within five to six years.
- **Juvenile form:** Progression is slower in this form of the disease, and the patients may survive until early adulthood.
- **Adult form:** The course in this form of the disease may be static or of insidious progression.¹

The incidence is estimated to be 1:40,000 births in the U.S..¹ While metabolic tests exist to screen for MLD, in general newborns in the U.S. are not screened for MLD.²

2.2 Product Description

OTL-200 is a gene therapy containing autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) transduced *ex vivo* with a replication-incompetent lentiviral vector encoding the human arylsulfatase A (ARSA) gene.

OTL-200 is manufactured from cells collected from the patient's mobilized peripheral blood (mPB). During clinical development, the patient's bone marrow (BM) was also used as a source of HSPCs, but the proposed manufacturing process will not use them. OTL-200 drug product (DP) is a cryopreserved suspension for intravenous infusion, administered after thawing, without any further manipulation, as a one-time treatment and for autologous use only. OTL-200 is supplied in one or more 50 mL (nominal volume) (b) (4) infusion bag(s) at a concentration of 2×10^6 cells per mL, in a volume of 10 to 20 mL of cryopreservation medium [5% dimethylsulfoxide (DMSO), (b) (4)] per (b) (4) bag.

The minimum recommended dose of OTL-200 is $(b) (4) \times 10^6$ CD34+ cells/kg.

2.3 Proposed Indication

Atidarsagene autotemcel is indicated for the treatment of pediatric patients with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD). OBPV defers to product office on the final language for the indication statement in the USPI.

2.4 Pertinent Regulatory History

The sponsor, Orchard Therapeutics, has submitted a request for a priority review. This request is based on the applicant's contention that atidarsagene autotemcel meets the criteria for priority review as the condition it is treating, MLD, is a life-threatening and severely debilitating illness. Currently, there are no approved therapeutic options for MLD in the US and if Atidarsagene autotemcel is approved, it would provide a significant improvement in safety and effectiveness for this illness.

Orchard Therapeutics was granted rare pediatric disease designation for OTL-200 (RPD-2018-163) on 16 Apr 2018. Based on this designation, Orchard is also requesting a rare pediatric disease priority review voucher.

2.5 Known Safety Information for this Class of Product

This therapy is proposed as a first in its class product for MLD. The majority of the safety information for therapy for this disease is contained in the clinical trials submitted and post-market data on 8 patients that received the medication under a compassionate use protocol. However, there has been information on the adverse events in gene therapy and lentiviral vectors. Adverse events associated with the product class are highlighted below and adverse events associated with atidarsagene are reviewed in detail in the following sections.

The risk of oncogenesis exists for atidarsagene as it does in all therapeutics which employ gene therapy with integrating vectors.³ The risks of lentiviral vectors in gene therapy was reviewed in a study evaluating the long-term safety of lentiviral gene therapy with the following endpoints: mortality, engraftment (in particular platelet engraftment), replication-competent lentivirus, and clonal dominance.³ No long-term adverse events were noted in this study, and the patients had experienced remissions from the primary diagnosis and its therapeutic interventions.³ This study is particularly applicable because the patients were pretreated with Busulfan. This protocol is identical to the protocol used in the safety studies supporting this application.

3 Documents Reviewed

The following documents were reviewed in support of this application:

Table 1: Documents Reviewed

Source	STN Number	Description
Applicant	125758/1	Clinical Review
Applicant	125758/0	Non-clinical review

Applicant	125758/1, 5.3.5.3	Integrated Summary of Safety
Applicant	125758/2, 5.3.5.4	Protocol, U.S. Long-term Registry
Applicant	125758/3, 1.14.1.3	Draft Labeling
Applicant	125758/1, 1.16	Proposed PVP
FDA, January 2020		Guidance: Long-term Follow-up After Administration of Gene Therapy Products
Applicant	125758/0, 1.11.3	Response to IR dated January 12, 2024

4 Clinical Studies Submitted in Support of this Application

4.1 Clinical Trial Overview

OBPV defers to the product office on final review of the clinical safety database, which will inform the final language in the USPI. Below is our focused review of the Applicant data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125758/0 be approved. Please refer to the package insert for the final clinical safety data.

The applicant submitted an Integrated Safety Summary on July 6, 2023, which contains safety data from 39 subjects. These subjects’ enrollment status is listed in the table below:

Table 2: Clinical Information Overview

Trial	Number of subjects	Description
201222	20	Non-randomized, open-label, prospective, single center study. Phase I/II
205756	10	Non-randomized, open-label, prospective, single-center
<i>Hospital Exemption-205029</i>	3	Hospital exemption
<i>Single Use Protocol-207394</i>	1	Compassionate Use Protocol
<i>Multi-Use Protocol-206258</i>	5	Compassionate Use Protocol

4.2 Patient Demographics

The median age of the subjects was 15.7 months (range 7.6 to 139.7 months, SD \pm 32.8 months). Of the subjects, 14/39 (36%) were female, and 25/39 (64%) were male. 31/39 (79%) subjects were considered Caucasian of European Descent, 5/39 (13%) subjects we considered Caucasian of non-European descent, and 2/39 (5%) subject were considered of Asian descent. One subject/39 (3%) was a “Black American.”

4.3 Safety Analysis

The induction of therapy with Atidarsagene requires Busulfan, a chemotherapeutic agent with an extensive profile of adverse events.ⁱ The analysis of the adverse events reported after Atidarsagene includes a high percentage of adverse events presumably secondary to Busulfan. For example, nearly all patients reported febrile neutropenia, which is a common side effect of Busulfan.⁴

Of note, platelet engraftment refers to the length of time it takes for the platelet count in a patient receiving lentiviral gene therapy to return to normal and for the platelets to function normally, i.e. the patient avoids a hemorrhagic episode. In lentiviral gene therapy it is considered a safety endpoint rather than an efficacy endpoint.⁵

4.3.1 Deaths

There were 3 deaths reported after infusion of Atidarsagene. None of the deaths were adjudicated by the applicant to be secondary to the Atidarsagene therapy.

Case (b) (6) (study 201222): female patient diagnosed with MLD at 64 months of age and began treatment with OTL-200 at 69 months of age. She demonstrated rapid progression of her disease including dysphagia, muscle dysfunction, and muscle spasticity. Eventually she passed away due to inability to eat and worsening muscle weakness.

Case (b) (6) (study 201222): female patient diagnosed with MLD at 68 months of age and began treatment with OTL-200 at 71 months of age. She demonstrated rapid progression of her disease including dysphagia, muscle dysfunction, and muscle spasticity. The parents chose not to insert a feeding tube. She passed away due to inability to eat.

Case (b) (6) (expanded access protocol): Male patient diagnosed at 11 months of age. The patient was doing well until 2.1 years of age when he had a seizure. A brain CT angiogram was performed and revealed an extensive left cerebral hemisphere infarction and edema. The death was deemed due to a cerebral hemorrhage. The

ⁱ Busulfan is an alkylating agent with a boxed warning for severe and prolonged myelosuppression and warnings and precautions of seizures, hepatic veno-occlusive disease, and cardiac tamponade. Adverse events seen in >60% in studies are myelosuppression, nausea, stomatitis, vomiting, anorexia, diarrhea, insomnia, fever, hypomagnesemia, abdominal pain, anxiety, headache, hyperglycemia and hypokalemia. Busulfan USPI 1/2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020954s014lbl.pdf

parents refused an autopsy and the provider did not respond to requests for additional information. No predisposing factors were identified.

The 2 deaths in study 201222 were adjudicated by the investigator to be secondary to the progression of the primary diagnosis dying 8 and 15 months post-gene therapy (GT) respectively. The other subject who died was enrolled through the expanded access protocol. The subject experienced an ischemic stroke which was adjudicated to be unrelated to the therapy and was 14 months status-post the initiation of GT.

Reviewer Comment: The first two death reports appear to be due to the progression of the primary diagnosis. In the last case there is no definitive explanation. Part of this is due to the patient’s parents and care providers not cooperating. The diagnosis remains of unknown etiology, but the MO does not identify the therapy as the underlying cause. However, given the concern of the clinical team thromboembolic events were added to the postmarketing study (see section 7.2 below).

4.3.2 Serious Adverse Events

Table 3: Summary of Adverse Events (Total AEs/SAEs) in Treated Patients (extrapolated from ISS, pg. 27-36)

Data-lock date: November 1, 2022

Category	During GT Treatment Induction/SAEs	Acute (Days 2-3 s/p treatment)/ SAEs	Between 4 days-3 months s/p treatment	Short-term (3 months to 3 years)/SAE/ deaths	Long term (> 3 years)
PSLISS (n=18) LT n=16	6 events (33%)/0 SAEs	1 event (6%)/0 SAEs	17 events (94%)/4 SAEs (22%)	17 events (94%)/8 SAEs (44%)	16 events (100%)/5 SAEs (31%)
PSEJSS (n=8) LT n=5	4 events (50%)/0	1 event (13%)/0	8 events (100%)/0	8 events (100%)/1 SAE-death	5 events (100%)/0
ESEJSS (n=11) LT n=7	11 events (100%)/0	2 (18%)/0	11 (100%)/1 (9%)	11 (100%)/7 (64%)/2 (18%)	7 (100%)/0
Other** (n=2)***	2 (100%)/1 (50%)				

SAE: Significant Adverse Event, PSLISS: Pre-symptomatic Late Infantile Safety Set, PSEJSS: Pre-symptomatic Early Juvenile Safety Set, ESEJSS: Early Symptomatic Early Juvenile Safety Set, LT: Long term data set

** Other: This category consists of two patients who are not included in the two safety sets defined above. These patients are designated the “Symptomatic L1 Safety Set” (n=1) and the “Progressively Symptomatic EJ Safety Set” (n=1). The safety results of these two patients are not included in the ISS reference in the table’s title.

***The results for these two patients can be found in the ISS between pages 951-1051. The results are not broken down by time-periods.

The applicant performed an analysis of the adverse events subdivided by demographic and treatment groups. There were no significant differences demonstrated.

Reviewer Comment: The safety results demonstrate nearly all the subjects developed at least one adverse event during treatment. Taking into consideration the high-risk nature of the treatment regimen, for example pre-treatment with Busulfan has a high adverse event profile independent of the rest of the therapy, the safety profile is neither unexpected nor worthy of additional regulatory actions.

4.3.3 Patient Withdrawals

There were three withdrawals, all due to subject deaths.

4.4 Most Common Adverse Events/Analysis

Common AEs in the three sub-groups of subjects (n=37) at any interval in the 3 years s/p treatment are listed below. The following sub-groups are included: PSLISS: Pre-symptomatic Late Infantile Safety Set (n=18), PSEJSS: Pre-symptomatic Early Juvenile Safety Set, (n=8), and ESEJSS, and Early Symptomatic Early Juvenile Safety Set, (n=11). As noted above, the two additional compassionate use patients are presented as a narrative and their AE profiles are not defined in reference to time before or after treatment. The adverse events presumably related to Busulfan are included because it is a part of the therapy regimen.

- 1) Febrile neutropenia, n=31
- 2) Upper respiratory tract infections, n=18
- 3) Infection with Coronavirus, n=12
- 4) Gastrointestinal complaints, i.e. nausea/vomiting, n=11
- 5) Pyrexia, n=11
- 6) Gait Disturbance, n=10
- 7) Iron Deficiency, n=9
- 8) Ear Infection, n=7

Reviewer Comment: All of these AEs are listed under “Adverse Reactions” on the first page of the package insert, with these exceptions noted: “Ear Infection” is not listed but the related infection “pharyngitis” is listed and “Iron Deficiency” is labeled as “anemia”. No additional regulatory action is required.

4.5 Subgroup Analysis

The ISS contains a breakdown of the safety profile of Atidarsagene by sex, country of residence, cellular source of the drug product, busulfan conditioning regimen (MAC or SMAC-defined below), and formulation (cryopreserved or fresh).

4.5.1 Subgroup analysis – general comments

No notable differences were observed between males and females, country of residence/country of treatment, and safety by formulation (fresh vs. cryopreserved).

Safety by Formulation - In the safety by formulation analysis the fresh treatment product cohort consisted of 29 subjects and the cryopreserved treatment product cohort consisted of 10 subjects, there was a significant difference in the length of follow-up for those patients who had fresh formulation of the therapy (almost 8 years) as opposed to those who received a cryopreserved formulation (roughly 3 years). This is because the cryopreserved formulation wasn't introduced until 2018. (5.3.5.4, 205029, p. 25) This is notable because some of the commonly reported AEs, e.g. muscle spasticity, aphasia, and gait disturbance, are more likely to appear later in follow-up.

Safety by Cellular Source - Differences of note were detected in the subgroup analysis of the cellular source of the drug product. The cellular source is subdivided by mobilized peripheral blood product (mBP) (n=8), Bone Marrow Aspirate (BM) (n=29), or a combination of both (mBP+BM) (n=2). Once again, over the short-term (< 3 months), a period in which all groups had follow-up data, the AE profile was similar without any significant differences. The groups with the longer follow-up (BM and mBP+BM) had more cases of muscle spasticity and aphasia as would be expected and noted above.

Safety by Busulfan Regimen - The busulfan conditioning regimens are either sub-myeloablative conditioning (SMAC) (n=13) or myeloablative conditioning (MAC) (n=26). The number of adverse events in this analysis involved one or two patients in each group and therefore the numbers were too small to detect a significant difference between the two sub-groups. Serious AEs associated with Busulfan, and therefore noted by the applicant, are veno-occlusive disease (VOD) and atypical Hemolytic Uremic Syndrome (aHUS). Two subjects in the SMAC group developed VOD compared to one in the MAC group. There were two cases of aHUS, both in the MAC group.

4.5.2 Statistically significant differences not related to length of follow-up, Cellular source of therapy

A small difference between subgroups was observed in the number of days with absolute aplasia and the number of days to platelet engraftment. The number of days with absolute aplasia was shorter in the mPB collection subgroup (mPB) collection geometric mean 6.2 days, range 3 days, 15 days; BM aspiration geometric mean 10.2 days, range 2 days, 29 days; mPB collection + BM aspiration actual 4 days in both subjects). The number of days to platelet engraftment was also shorter in the mPB collection subgroup (mPB collection geometric mean 25.8 days, range 15 days, 35 days; BM aspiration geometric mean 44.1 days, range 24 days, 109 days; mPB collection + BM aspiration range 50 days, 52 days).

Reviewer Comment: This finding is consistent with the literature.⁶

4.5.3 Statistically significant differences, not related to length of follow-up, Formulation

The same safety endpoint, platelet engraftment, was statistically different in this comparison also. The number of days to platelet engraftment was shorter in the cryopreserved group than the fresh plasma group. The applicant's believe this is the same finding as noted in section 4.4.1.2 and attribute the difference to the cellular source rather than the formulation.

Reviewer Comment: The differences in platelet engraftment are worthy of consideration in regard to choosing between the various treatment variables, i.e. fresh plasma vs. cryoprecipitate. The applicant has included it in the PVP. This should provide the applicant with current information regarding recommendations for product preparation. Should post-market data demonstrate cellular source of therapy is a variable associated with improved platelet performance, the labeling should be amended to address this finding.

4.6 Safety Results in Vulnerable Populations

The applicant identified pregnant women as a vulnerable population. However, the upper age at time treatment in this study was 11.3 years (ISS, p. 25). Although it is unlikely this product will be used to treat many patients who are pregnant or lactating at the time of treatment, it can't be ruled out because the label does not provide an age range for which this treatment is indicated. It is also possible that during the follow-up period a subject will become pregnant.

In section 8.1, the label states there is no evidence for safety regarding pregnancy or lactation for this product.

Reviewer Comment: The inclusion of pregnant and/or lactating women as a vulnerable population is appropriate.

5 Post-market data

There is no domestic post-marketing experience with this product.

6 Foreign postmarket safety data

An IR was sent to the sponsor on January 12, 2024. The IR requested the sponsor specify the number of patients treated with Atidarsagene from their foreign post marketing experience (with the data lock point provided). The FDA also requested the sponsor's assessment of any reported AEs from foreign post marketing use.

The sponsor responded on January 14, 2024, with the following information compiled with a data lock point of December 16, 2023:

Atidarsagene is approved in three European countries under the trade name Lebmeldy. As of the data lock point, (b) (4) patients have been treated in Europe.

- 4 serious adverse events have been reported in 3 patients. These events include one case of encephalitis, one case of disease progression, and a case of vomiting (occurred twice in one patient).
- 2 non-serious adverse events were reported. Both cases consisted of a positive ARSA antibody test greater than 120 days after treatment.

Encephalitis: The case of encephalitis was adjudicated not to have been due to the treatment per the treating physician and the physician employed by the sponsor to adjudicate the case.

Disease Progression: The case of disease progression was seen in a patient with the early symptomatic early juvenile form of MLD. The patient began therapy at the age of 6 years and three months and the treating physician noted further clinical deterioration soon after treatment started. The diagnosis of disease progression was officially made after roughly 8 months of treatment. The patient is currently stable.

The adjudicating physician determined disease progression is a phenomenon of the underlying disease and was not related to treatment.

Vomiting: A 9-year-old patient had two episodes of vomiting. The first was treated with antibiotics and IV fluids and she recovered. The second was after a lumbar puncture. She recovered after a day of treatment. Neither episode was adjudicated to be secondary to the therapy.

Positive ARSA antibodies: Two patients developed weakly positive ARSA antibodies (i.e. 1:10 and 1:20).⁸ The treating physician documented that these weak ARSA antibody titers had no clinical effect and did not affect treatment.

Reviewer Comment: The safety profile based on foreign postmarketing experience to date is neither unexpected nor a source of additional new safety concerns. The reviewer agrees with the adjudicating physicians that the serious adverse events were not related to the treatment. Disease progression in older children starting therapy was also seen in the U.S. experience and is presumably due to starting therapy later.

ARSA antibodies degrade Arylsulfatase (ARSA) which is required for the lysosomal degradation of cerebroside-3-sulfatase. ARSA is a major contributor to the myelin sheath. Lack of ARSA is the biochemical etiology of MLD. Therefore, the presence of ARSA antibodies would be an expected side effect of treatment.⁸

7 Pharmacovigilance Plan and Routine Pharmacovigilance

7.1 Routine Pharmacovigilance

The pharmacovigilance plan provided with the application includes 3 adverse events for which the sponsor proposes risk minimization procedures and pharmacovigilance to provide surveillance.

Table 4: Pharmacovigilance plan for Atidarsagene

	Safety Specification	Proposed risk minimization
Important identified risks	Delayed platelet engraftment	Routine Pharmacovigilance
Important potential risks	Malignancy due to insertional oncogenesis Engraftment failure	Routine Pharmacovigilance Postmarket Clinical study OTL-200-10 Postmarket Study OTL 200-12
Missing information	Long-term safety and efficacy data	Routine Pharmacovigilance

For these adverse events, the sponsor proposes routine pharmacovigilance as in 21 CFR 600.80. This routine pharmacovigilance includes the submission of individual case safety reports (ICSRs) as received by the sponsor, the preparation and submission of aggregate periodic safety reports detailing adverse events (i.e. PBRERs or similar reports), and signal evaluation and detection.

Reviewer Comments: All three identified AEs are labeled prominently on the first page of the label, under the heading Warnings and Precautions. Therefore, identification of individual AE reports of these three AEs would not affect labeling. However, if there are sufficient reports of an adverse event large enough to affect the risk/benefit determination of this therapy, the long term follow up study detailed below is designed to detect it. This Medical Officer is not aware of any other AEs which should be included either in the PVP or mentioned as an AE of interest in this long-term follow-up study. The MO's opinion is the risk minimization strategy is adequate.

7.2 Additional Long-term Pharmacovigilance

In addition to the PVP and routine pharmacovigilance detailed above, the sponsor proposes three additional methods of long-term follow-up.

1) OTL-200-10 -- An observational long-term follow up (LTFU) study (LongTERM-MLD study, OTL-200-10), which will capture AEs/SAEs for clinical trial patients who have been exposed to OTL-200 in the clinical development program (CDP), in nominal compassionate use programs apart from the OTL-200 CDP, and in the commercial setting in the European Union (EU).

2) OTL-200-11 -- An interventional sub-study (Sample Collection Study to Monitor the Risk of Malignancy Due to Insertional Oncogenesis, OTL-200-11) of the LongTERM-MLD study for patients who have been exposed to OTL-200 in the CDP; the objective of

the sub-study is to monitor the long-term risk of malignancy due to insertional oncogenesis following treatment with OTL-200.

3) OTL-200-12 -- A prospective, observational, non-interventional, registry study. The study begins once the therapy is approved in the U.S. market and ends 5 years after enrollment begins.. Data from the treatment visit, early posttreatment period, and follow-up visits conducted as part of routine clinical care will be recorded up to 15 years post-treatment with OTL-200. The first interim report is to be submitted 5 years after the first patient is enrolled.

Data collected up to 15 years post-treatment will be extracted from the registry database and reported in the interim/final study reports, in line with regulatory recommendations for follow up post administration of a gene therapy. The registry study will collect data on: Baseline characteristics, Treatment information, Post-treatment data (visit frequency determined by routine clinical care), including: disease status, gene-therapy specific data, safety outcomes including malignancy and events of insertional oncogenesis detected using genetic characterization of the malignancy. We will review sponsor plans for collection of tumor tissue and their proposal for testing algorithms to assess for vector persistence and characterize occurrence of secondary malignancies when final protocol is received post-approval.

An IR was sent to the sponsor on December 13, 2023, requesting estimates of patient enrollment and milestone dates for the study. The sponsor responded with an estimate of 17 patients enrolled over 5 years based on the incidence of the disease and a 50% enrollment. Product office provided concurrence for the acceptability of this sample size.

The following milestone dates were proposed:

- Estimated final protocol submission – 07/31/2024
- Estimated study completion – 06/30/2044
- Estimated final study report submission to BLA - 12/31/2044

Because the risk of oncogenesis and other long-term safety issues associated with this class of products, as detailed in section 2.5, will require the study above to be classified as a Post-Marketing Requirement (PMR) under section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) to identify an unexpected serious risk . This PMR was presented to the Safety Working Group (SWG) on January 11, 2024. SWG had only minor comments relating to tumor specimen collection and a testing algorithm. An IR was sent to the sponsor to clarify SWG's concerns. A PMR notification letter was sent to the sponsor on February 5, 2025, relaying the criteria provided above as the basis of the PMR.

As noted in section 5, case (b) (6) was brought to the attention of the sponsor due to the elevation in d-dimer which preceded the ischemic stroke. As a result, another IR was sent to the sponsor on February 2, 2024. The IR requested the sponsor add the safety outcome of “thromboembolic events” as a study objective.

Additionally, the IR requested the sponsor include the following criteria in the study design:

- Collection of data on D-dimer levels for all enrolled patients
- Collection of data on whether patients receive anti-thrombotic prophylaxis during conditioning or following treatment with Atidarsagene Autotemcel.

The sponsor agreed to include these considerations in the PMR.

OTL-200-12 is designated a PMR. The details of the study and projections for enrollment are found in section 12.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA, known in CBER as the Biologics Effectiveness and Safety (BEST) Initiative, is not sufficient to assess this serious risk. An assessment of the sufficiency of the BEST Initiative indicated that its data sources are not sufficient to assess the long-term safety following treatment with Atidarsagene in lieu of a post-marketing requirement (PMR) under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA).

As per the 2019 draft guidance, Post-marketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry, this determination “takes into consideration multiple factors, some of which may be uncertain at the time of the sufficiency assessment (e.g., the future uptake of a newly approved drug, subsequent exposure of patients to a drug).” At this time, the available data sources in the CBER BEST Program are not sufficient to identify the safety outcomes. CBER BEST system includes claims based data sources. Long term study with 15-yr follow up and collection of clinical samples and tumor tissue analysis for vector persistence are not feasible in claims-based databases.

Reviewer Comment: The submitted studies as well as the literature cited (references 3-6) do not report that the long-term AEs to be surveilled in these three long-term studies have been noted in significantly higher percentages than would be expected. However, the concern for identification of signals regarding these AEs remains appropriate.

As is observed in many long-term post-market studies the sponsor can't predict the number of patients who will be enrolled because the sponsor can't predict the utilization of the therapy. This is a rare disease and thus the presumed number of patient-years is expected to be small. The sponsor describes a study which in theory will identify signals, in particular the signals proposed for additional surveillance in the PVP. However, due to the small number of anticipated subjects that will be enrolled it will be difficult to determine the validity of any observed signals.

The PVP is appropriate. The three additional long-term studies demonstrate adequate surveillance for the potential long-term adverse events detailed in section 2.5. Study 3

complies with the FDA Guidance document titled *Long Term Follow-up After Administration of Human Gene Therapy Products* (available at <https://www.fda.gov/media/113768/download>). Furthermore, the based on BEST insufficiency, we recommend this study by classified as a PMR.

8 Labeling

There is no Post-marketing Experience section in the proposed label with this product.

9 Assessment and Conclusion

OBPV has reviewed the data provided by the applicant and it is our conclusion that this Applicant has adequately described the safety concerns in the submitted pharmacovigilance plan and the proposed actions, including a postmarketing requirement (PMR) for a long term follow up observational safety study, are adequate for postmarketing safety monitoring for Lenmeldy.

- Delayed platelet engraftment: Of the 49 patients included in the ISS, 4 (8.2%) demonstrated delayed platelet engraftment. There were no reports of bleeding and all patients received platelet transfusions as described by the protocol. Routine pharmacovigilance is appropriate for this risk.
- Malignancy: with more than 12 years follow-up for the earliest treated subjects, 250 subject-years of follow-up in subjects enrolled in the MLD clinical development program, and almost 300 subject-years cumulatively from all Orchard's LVV (lentiviral vector) programs no cases of malignancy have been documented. However, given the limited number of enrollment in premarket safety studies a postmarketing study will be performed as a PMR for this important potential risk.
- Engraftment failure for neutrophils and platelets: No cases of engraftment failure were reported. The mean for demonstrating normal levels of these cells 46.5 days (range 29 - 109) for the PSLI Safety Set, 45.2 days (range 28 - 88) for the ESEJ Safety Set, and 37.4 days (range 25 - 48) for the PSEJ Safety Set.
- Long term safety data was limited to only 49 patients in the clinical trials and postmarket setting. Because of this, the FDA proposes additional pharmacovigilance including enhanced reporting of serious adverse events to the FDA and a post-market requirement as proposed in section 10 to further evaluate the risk of secondary malignancies and long term safety.

DPV recommendations below are consistent with FDA guidance on the Long-Term Safety of Gene Transfer products.⁷

10. DPV Recommendations

Should this submission be approved, the PVP is adequate, and OBPV/DPV recommends the following for post-marketing safety monitoring of atidarsagene autotemce (Lenmeldy):

- Routine pharmacovigilance: Adverse event reporting in accordance with 21 CFR 600.80 and quarterly periodic safety reports for 3 years and annual thereafter.
- Enhanced pharmacovigilance in accordance with 21 CFR 600.80, for 3 years following product licensure, as follows:
 - o The Applicant will submit all serious adverse events (SAEs), regardless of expectedness or seriousness, as expedited (15-day) reports to FAERS.
 - o In the narrative summary of periodic safety reports, the Applicant will include aggregate analysis and assessment for SAEs.
- Postmarketing requirement (PMR) under section 505(o)(3) of the FDCA: 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.

The following milestone dates were proposed:

- Estimated final protocol submission – 07/31/2024
- Estimated study completion – 06/30/2044
- Estimated final study report submission to BLA - 12/31/2044

The final protocol will be reviewed post-approval.

The available data do not indicate a safety concern which would require a Risk Evaluation and Mitigation Strategy (REMS). There is no agreed upon postmarketing commitment for safety study. Refer to the final version of the U.S. Prescribing Information (USPI) submitted by the applicant for the final agreed-upon language for the label.

11 References

- ¹Lamicchane, A, et. Al., Metachromatic Leukodystrophy, StatPearls, NIH, 2022, [Metachromatic Leukodystrophy - StatPearls - NCBI Bookshelf \(nih.gov\)](#)
- ²[MLD Newborn Screening](#)
- ³ Magin, E, et. Al., Nature Medicine, 2022, 28:81-8.
- ⁴Lancet Haematol. 2019 May;6(5):e239-e253.
- ⁵ Magnani, A, “Long term safety and efficacy of lentiviral gene therapy”, [Nature](#), 2022
- ⁶ Biol Blood Marrow Transplant. 2017 Aug;23(8):1241-1249.
- ⁷FDA guidance document for long-term follow-up After Administration of Human Gene Therapy Products, January 2020, pp. 23-5.
- ⁸ [Arylsulfatase - an overview | ScienceDirect Topics](#)