BLA Clinical Review Memorandum

<table>
<tr><td>Application Type</td><td>351(a)</td></tr>
<tr><td>STN</td><td>125758</td></tr>
<tr><td>CBER Received Date</td><td>07/19/2023</td></tr>
<tr><td>PDUFA Goal Date</td><td>03/18/2024</td></tr>
<tr><td>Division / Office</td><td>DCEGM/OTP</td></tr>
<tr><td>Priority Review (Yes/No)</td><td>Yes</td></tr>
<tr><td>Reviewer Name(s)</td><td>Avanti Golikeri, MD</td></tr>
<tr><td>Review Completion Date / Stamped Date</td><td>3/28/2024</td></tr>
<tr><td>Supervisory Concurrence</td><td>Shelby Elenburg, MD
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Elizabeth Hart, MD
Branch Chief, General Medicine Branch 1</td></tr>
<tr><td>Applicant</td><td>Orchard Therapeutics (Europe) Limited</td></tr>
<tr><td>Established Name</td><td>atidarsagene autotemcel</td></tr>
<tr><td>(Proposed) Trade Name</td><td>LENMELDY</td></tr>
<tr><td>Pharmacologic Class</td><td>Gene therapy</td></tr>
<tr><td>Formulation(s), including Adjuvants, etc.</td><td>Autologous CD34+ hematopoietic stem cells transduced with lentiviral vector expressing human arylsulfatase A gene</td></tr>
<tr><td>Dosage Form(s) and Route(s) of Administration</td><td>Suspension for intravenous infusion</td></tr>
<tr><td>Dosing Regimen</td><td>
<table>
<tr><th>-</th><th>Minimum Recommended Dose ($CD34^+$ cells/kg)</th><th>Maximum Recommended Dose ($CD34^+$ cells/kg)</th></tr>
<tr><td>Pre-symptomatic late infantile</td><td>4.2×10^6</td><td>30×10^6</td></tr>
<tr><td>Pre-symptomatic early juvenile</td><td>9×10^6</td><td>30×10^6</td></tr>
<tr><td>Early symptomatic early juvenile</td><td>6.6×10^6</td><td>30×10^6</td></tr>
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<tr><td>Requested Indication(s) and Intended Population(s)</td><td>Treatment of pre-symptomatic late (PSLI), pre-symptomatic early juvenile (PSEJ), and early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD)</td></tr>
<tr><td>Orphan Designated (Yes/No)</td><td>Yes</td></tr>
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GLOSSARY

AE	adverse event
AESI	adverse event of special interest
aHUS	atypical hemolytic uremic syndrome
ALT	alanine aminotransferase
anti-CFH	anti-complement factor H
ARSA	arylsulfatase A
AST	aspartate transaminase
AUC	area under the curve
BLA	Biologics License Application
BM	bone marrow
CBER	Center for Biologics Evaluation and Research
CDC	Center for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CMC	Chemistry, Manufacturing, and Controls
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computed tomography
CVC	central venous catheter
DCOA	Division of Clinical Outcomes Assessment
EAP	Expanded Access Program
EEG	electroencephalogram
EJ	early juvenile
ESEJ	early symptomatic early juvenile
FDA	U.S. Food and Drug Administration
G-CSF	granulocyte colony stimulating factor
GMFC	Gross Motor Function Classification
GMFM	Gross Motor Function Measure
HSC	hematopoietic stem cells
HSCT	hematopoietic stem cell transplant
IR	information request
IRC	Independent Review Committee
IV	intravenous
LI	late infantile
LJ	late juvenile
LV	lentivirus
MedDRA	Medical Dictionary for Regulatory Activities
MLD	metachromatic leukodystrophy
MRI	magnetic resonance imaging
NCV	nerve conduction velocity
OTL-200	atidarsagene autotemcel / LENMELDY
OTP	Office of Therapeutic Products
PB	peripheral blood
PBMC	peripheral blood mononuclear cell
(b) (4)	
PSAP	prosaposin
PSEJ	pre-symptomatic early juvenile
PSLI	pre-symptomatic late infantile

RCL	replicant-competent lentivirus
SAE	serious adverse event
sMFS	severe motor impairment-free survival
SR-TIGET	San Raffaele Telethon Institute for Gene Therapy
STN	submission tracking number
TCR	T-cell receptor
U.S.	United States
USPI	United States Prescribing Information
VCN	vector copy number
VOD	veno-occlusive disease
WBC	white blood cell

1. EXECUTIVE SUMMARY

On July 19, 2023, Orchard Therapeutics (Europe) Limited submitted an original Biologics License Application (BLA), STN BL 125758, for licensure of atidarsagene autotemcel (also known as OTL-200; proprietary name LENMELDY). The Applicant proposed the indication "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)."

MLD is a rare autosomal recessive lysosomal storage disease that results from pathogenic biallelic mutations in the *ARSA* gene resulting in an absence or deficiency in the arylsulfatase A (ARSA) enzyme. ARSA is responsible for degradation of sulfatides, one of the most common sphingolipids in the myelin sheath of the central and peripheral nervous system. A deficiency or absence in ARSA results in accumulation of sulfatides in the myelin sheath and leads to neurologic impairment affecting motor function and cognition. MLD is divided into subtypes based on age of symptom onset. Late infantile (LI) MLD is defined by symptom onset prior to 30 months of age and early juvenile (EJ) MLD is defined by symptom onset after 30 months of age and prior to 7 years of age. Children with LI and EJ MLD experience psychomotor regression. The pace of progression in LI is generally homogenous and rapid with death occurring three to five years after symptom onset. In EJ MLD, the clinical course is slower and more heterogenous with some children experiencing rapid progression of symptoms, and others experiencing periods of stability and disease "plateau". In general, children with EJ MLD progress to severe neurologic impairment or death between 10 and 20 years of age.

There are no FDA-approved therapies for MLD, but hematopoietic stem cell transplant (HSCT) is a treatment option to slow motor and cognitive dysfunction for children with EJ MLD prior to symptom onset (Boucher et al. 2015). Patients with LI MLD and symptomatic EJ MLD appear to derive minimal benefit from HSCT and receive only supportive care. HSCT is associated with significant morbidity and mortality, particularly when a matched sibling donor cannot be found. There is substantial unmet medical need for patients with LI and EJ MLD.

OTL-200 is a gene therapy product comprised of autologous CD34+ hematopoietic stem and progenitor cells transduced ex vivo with a replicant-incompetent lentiviral vector (LV) encoding the human *ARSA* gene. In clinical trials of OTL-200, subjects underwent hematopoietic stem cell (HSC) mobilization and apheresis to produce the autologous CD34+ cells for transduction. After myeloablation with busulfan, the ex vivo transduced cells were administered via intravenous (IV) infusion to reconstitute the hematopoietic system with cells containing the integrated *ARSA* gene that can produce functional ARSA enzyme.

Consistent with 21 USC 355(d), substantial evidence of effectiveness of OTL-200 for this rare disease with unmet need is based on a single adequate and well-controlled investigation with confirmatory evidence. For the purpose of this approval decision, we considered pooled clinical data from two open-label, single arm studies (Study OTL-200-201222 and OTL-200-205756) and three studies in a European Union Expanded Access Program (EAP) (Studies OTL-200-205029, OTL-200-206258, and OTL-200-207394), compared to external control data from untreated MLD patients to constitute one adequate and well-controlled investigation. Confirmatory evidence includes mechanism of action, pre-clinical data, and clinical biomarkers, including ARSA enzyme levels and radiographic imagining from brain MRIs.

The clinical studies treating MLD patients with OTL-200 enrolled 39 children, of whom 37 had PSLI, PSEJ or ESEJ and were included in the efficacy analyses; there were 20 children with PSLI, 7 children with PSEJ and 10 children with ESEJ MLD. The natural history study included

28 children with LI MLD and 17 children with EJ MLD. Children were classified as having LI MLD based on expected disease onset of ≤30 months of age and an ARSA genotype consistent with LI phenotype. Children were classified as having EJ MLD based on expected disease onset >30 months and < 7 years with an ARSA genotype consistent with EJ phenotype. Children were considered pre-symptomatic if they were asymptomatic or had abnormal reflexes and abnormalities on MRI and nerve conduction tests without functional sequelae (e.g., tremor, peripheral ataxia). Early symptomatic was defined as walking independently and having IQ ≥ 85.

The primary efficacy endpoint was severe motor impairment-free survival (sMFS), defined as the interval birth to the earlier of the first occurrence of Gross Motor Function Classification-MLD (GMFC-MLD) ≥ Level 5 or death. GMFC-MLD is a standardized assessment of gross motor function in MLD, ranging from Level 0 to Level 6, where GMFC-MLD Level 0 is defined as "walking without support with quality of performance normal for age" and GMFC-MLD Level 6 is defined as "loss of any locomotion as well as loss of any head and trunk control" (Kehrer et al. 2011). GMFC-MLD MLD Level 5, utilized within the primary endpoint, is defined as "no locomotion nor sitting without support, but head control is possible." The efficacy data was analyzed separately by requested indication (PSLI, PSEJ, and ESEJ). Other study endpoints included assessment of cognitive function based on standard scores derived from age-appropriate neuropsychological tests administered according to the child's age and ability.

PSLI MLD Efficacy

Clear and robust evidence of efficacy was observed in analysis of the primary endpoint, sMFS, for the PSLI MLD population. Given the relatively homogenous clinical course of LI MLD, the untreated LI MLD subjects in the natural history study were considered suitable comparators for interpretation of efficacy. Among the 20 treated subjects, one (5%) had severe motor impairment or death compared with 28 (100%) of the natural history controls ($p<0.001$).

Efficacy on motor function was further demonstrated by retention of independent ambulation (GMFC-MLD ≤ 1) in 12 out of 17 subjects followed until 5 years of age. The oldest subject who retained independent ambulation was 13 years old. These are unexpected outcomes based on natural history of LI MLD where patients would be expected to lose all motor function by 5 years of age.

A treatment effect was also seen in the secondary endpoints of overall survival. Fourteen children treated with OTL-200 and 24 untreated children in the natural history had sufficient follow-up to determine survival at 6 years of age. All of the OTL-200 treated children with PSLI were alive compared to 14 (58%) of the untreated natural history children.

Additionally, efficacy in cognitive outcomes was observed based on both performance and language standard scores. In the LI natural history, severe cognitive impairment (standard score ≤55) for both performance and language scores occurred early in the disease course. However, for the OTL-200 treated children, throughout study follow-up, only 1 child (5%) developed severe cognitive impairment, and this occurred at age 6 years of age. Normal cognition (standard score ≥ 85) was seen for performance score in an 11-year-old and for language score in a 12-year-old. This represents a substantial deviation from the natural history.

PSEJ MLD Efficacy

The primary endpoint was not interpretable for this population based on the small sample size (n=7), heterogeneity of EJ MLD, insufficient follow-up in the treated subjects and missing data

from the natural history population. Given the small sample size, individual subject-level analyses of the motor and cognitive outcomes were performed and compared to data from the medical literature and, when available, matched sibling controls from the natural history study.

One child died at 2 years of age from a cerebral infarction assessed as potentially related to OTL-200. Three children were in the pre-symptomatic phase of the disease at last follow-up, and this was expected based on EJ natural history given their ages. Three treated children were observed to retain GMFC-MLD Level 0 (normal gait) or Level 1 (impaired gait but walking without support) at last follow-up at ages of 7.3, 11.0, and 13.6 years. Two of these subjects had improved motor function when compared to the matched sibling comparator. Untreated EJ MLD patients are expected to lose independent ambulation by the second decade of life, which further supports the motor treatment benefit (Fumagalli et al. 2021; Kehrer et al. 2021).

Two children treated with OTL-200 were followed to an age where cognitive function would be anticipated to decline based on published natural history data (Kehrer et al. 2014). Both children retained cognitive function in the "broadly average range" (performance and language standard score ≥85) at 11 years. A treatment effect for both motor and cognitive domains was observed for children with PSEJ MLD treated with OTL-200.

ESEJ MLD Efficacy

The pre-specified primary endpoint was not evaluable for this population based on the small sample size (n=10), limited duration of follow-up and lack of comparability between the OTL-200 treated children and the natural history controls. The natural history controls had more severe phenotypes than the OTL-200 treated children based on baseline age of symptom onset. Also, none of the controls had intermediate phenotypes, but two of the OTL-200 treated children had a baseline phenotype more consistent with late juvenile (LJ) MLD, which has a slower progression than EJ MLD.

Two subjects progressed to death by 6.6 and 7.0 years of age due to disease progression, approximately 1 year after treatment and 2 years after symptom onset for both subjects. This was considered faster disease progression than expected when compared to the published natural history, where events of death in untreated patients with EJ MLD were not observed until at least 5 years after symptom onset (Fumagalli et al. 2021).

The remaining six treated ESEJ subjects evaluable for efficacy all experienced motor disease progression. At last follow-up, three subjects were assessed as GMFC-MLD Level 5, two subjects as GMFC-MLD Level 3, and one subject as GMFC-MLD Level 2. Subject-level comparisons of motor outcomes between treated subjects and subjects in the natural history study were challenging given milder phenotype at baseline in the treated ESEJ subjects observed prior to OTL-200 administration. Based on individual subject-level analyses comparing motor function of OTL-200 treated children with the subset of natural history subjects who appear most comparable at baseline, there was no clearly discernable treatment benefit of OTL-200 in the slowing of motor progression. Exploratory statistical analyses were inconclusive on the impact of OTL-200 on motor function. Depending upon assumptions and imputation methods for missing natural history data, certain statistical analyses demonstrated a more rapid motor progression in OTL-200 treated ESEJ children compared to untreated children with EJ MLD. There is mechanistic rationale, as patients with EJ MLD have baseline residual ARSA activity, but there is a period where this residual activity is eliminated after myeloablation and prior to engraftment of the transduced cells. While there is uncertainty, the clinical team believes the potential for accelerated motor progression following OTL-200 treatment is an important risk of OTL-200 in ESEJ.

Neurocognitive performance over time demonstrates a positive treatment effect in four of the ten subjects in the ESEJ study population. Three of these subjects had typical onset and progression of disease, and one subject had an intermediate EJ and LJ phenotype. Maintaining average or near average cognitive function compared to typically developing same age peers despite continued motor progression is unexpected based on the published natural history literature indicating that motor and cognitive function decline in parallel in untreated EJ MLD (Kehrer et al. 2021). Therefore, OTL-200 meaningfully preserves cognitive function for some, but not all, ESEJ subjects.

Safety

The most significant observed risks from OTL-200 in the safety population include thrombosis, encephalitis, serious infections (including device-related infections, gastroenteritis, and viral infections). During the clinical trial, one child died from an extensive cerebral infarction one year after treatment with OTL-200. This event may be related to treatment with OTL-200; thus OTL-200 may elevate the risk of thrombosis and thromboembolic events. This risk will be further monitored in the applicant's post-marketing study. A child treated in the European Union (EU) commercial setting developed encephalitis 1 month after OTL-200 treatment. After the onset of encephalitis, this child had disease progression with a relapsing-remitting course of MLD. It is possible that treatment with OTL-200 could trigger an inflammatory response that results in this relapsing-remitting course of disease progression.

Theoretical risks of neutrophil engraftment and insertional oncogenesis were identified, but no events occurred in the safety population. However, given the small size of the safety population, continued monitoring for secondary malignancies is warranted in the post-marketing setting given the known risk of insertional oncogenesis with lentiviral vector gene therapy products.

The most common adverse events (AEs; >10%) in the first year after treatment with OTL-200 included febrile neutropenia, stomatitis, respiratory tract infections, rash, device-related infections, other viral infections, pyrexia, gastroenteritis, and hepatomegaly.

The only subtype specific safety signal was potential for more rapid progression of motor decline, which is limited to ESEJ population.

Conclusions

MLD is a rare, rapidly progressive neurologic disease with high unmet medical need. Given the phenotypic differences between the requested indications, the benefit-risk of PSLI, PSEJ, and ESEJ subpopulations are considered separately.

The efficacy data for the PSLI subpopulation demonstrated benefit on motor function, cognitive function, and survival. Pharmacodynamic evidence of a treatment response was also demonstrated in the post-treatment peripheral blood ARSA levels, which rapidly rose to supranormal levels after treatment and these levels were sustained. For this rapidly progressive and fatal disease, the dramatic treatment benefits clearly outweigh the potential known and unknown risks of OTL-200 for the PSLI subpopulation. As there was an observed correlation between weight, total CD34+ dose, and post-treatment ARSA levels, an inability to extrapolate to smaller infants based on modeling, lack of clinical data in infants <7 kg, and potential for increased risks from conditioning in infants with immature immune systems, the clinical review team recommends approval of OTL-200 for the modified indication of the treatment of children with PSLI MLD who are (b) (5) .

While there is uncertainty regarding the magnitude of treatment effect in PSEJ MLD based on the small sample size and heterogeneity of the disease, the clinical data demonstrates OTL-200 provides motor and cognitive benefits as the clinical outcomes are unexpected based on natural history. ARSA enzyme levels provide supportive evidence for the treated children who are still in the pre-symptomatic window. Given the seriousness and rarity of disease, despite the uncertainties, there is a favorable benefit-risk profile. Adequate dosage is necessary for treatment effect. Given the uncertainty of doses for infants <10kg and the lack of known benefit from treating earlier in the asymptomatic window, the clinical review team recommends traditional approval of OTL-200 for children with PSEJ MLD who weigh (b) (5). PSEJ is defined as children with EJ MLD between 30 months and 7 years of age who are asymptomatic or have physical exam findings limited to clonus and/or abnormal reflexes (to reflect the definition used in the efficacy analysis).

Some patients with ESEJ had preserved cognitive function, demonstrating that OTL-200 slows cognitive decline in some patients with ESEJ MLD. The clinical review team noted that in the ESEJ subpopulation, efficacy was only observed in children who did not have baseline brainstem involvement on brain MRI. This is consistent with the mechanism of action of OTL-200, such that it does not reverse neuronal damage that has already occurred. Preservation of cognition and language is very important to patients and families. This benefit needs to be considered in the context of the risks of OTL-200, including the potential for faster motor decline. Given the clinical meaningfulness of the observed cognitive benefit, the clinical team believes that OTL-200 should be approved for a modified indication: slowing progression of cognitive impairment in symptomatic patients with EJ MLD (defined as patients with GMFC-MLD Level 0 with ataxia or GMFC-MLD Level 1 with or without ataxia), and who do not have brainstem involvement on brain MRI at the time of treatment.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Thirty-nine subjects were treated with OTL-200 in 2 single-arm clinical trials and 3 expanded access clinical trials: 18 subjects were classified as having PSLI MLD, 8 subjects were classified as having PSEJ MLD, and 11 subjects were classified as having ESEJ MLD. The Applicant utilized an IRC comprised of three MLD physician-experts to adjudicate the symptomatic status and disease subtype of all subjects enrolled in the clinical program. As discussed in Sections 7.1.1 and 7.2.1, the clinical review team reclassified two subjects adjudicated by the Applicant as PSEJ and one subject adjudicated by the Applicant as ESEJ.

Two subjects (classified as symptomatic LI and progressively symptomatic EJ) are included in the safety analysis but are excluded from the efficacy analysis. Table 1 below provides the baseline demographic characteristics of the treated PSLI, PSEJ, and ESEJ subjects, as per the Applicant's classification.

Table 1: Demographic and Baseline Characteristics of PSLI, PSEJ, and ESEJ Subjects Treated With OTL-200

Parameter	PSLI (N=18)	PSEJ (N=8)	ESEJ (N=11)
Sex, n (%)	-	-	-
Female	5 (28)	2 (25)	5 (45)
Male	13 (72)	6 (75)	6 (55)
Country of residence, n (%)	-	-	-
U.S.	2 (11)	3 (38)	4 (36)
Non-U.S.	16 (89)	5 (63)	7 (64)
Race, n (%)	-	-	-
White/Caucasian European	16 (89)	7 (88)	11 (100)
Asian	2 (11)	0	0
Black or African American	0 (0)	1 (12)	0
Ethnicity, n (%)	-	-	-
Hispanic or Latino	1 (6)	0	0
Not Hispanic or Latino	17 (94)	8 (100)	11 (100)
Age at OTL-200 treatment (months)	-	-	-
Median	10	16	69
Min – max	8-18	11-49	30-140
Age at last contact or death (years)	-	-	-
Median	7.6	6.1	12.7
Min – max	3.2-13.4	2.1-12.0	5.1-19.0

Source: Adapted from BLA125758/0 – Module 2.5, Clinical Overview
Abbreviations: ESEJ, early symptomatic early juvenile; Max, maximum; Min, minimum; N, number of subjects; PSEJ, pre-symptomatic early juvenile; PSLI, pre-symptomatic late infantile; U.S, United States.

The Applicant also conducted a natural history study enrolling 26 LI MLD subjects and 17 EJ MLD subjects. Table 2 below provides the baseline demographic characteristics of the LI and EJ natural history subjects.

Table 2: Demographic and Baseline Characteristics of LI and EJ Natural History Subjects

Parameter	LI (N=26)	EJ (N=17)
Sex, n (%)	-	-
Female	14	9
Male	12	8
Country of residence, n (%)	-	-
U.S.	1 (4)	2 (12)
Non-U.S.	25 (96)	15 (88)
Race, n (%)	-	-
White/Caucasian European	26 (100)	17 (100)
Ethnicity, n (%)	-	-
Hispanic or Latino	2 (8)	0
Not Hispanic or Latino	24 (92)	17 (100)
Age at diagnosis (months)	-	--
Median	31	53
Min – max	19-44	31-91
Age at enrollment (months)	-	-
Median	61	101
Min – max	31-168	33-215
Age at last contact or death (years)	-	-
Median	6.2	10.3
Min – max	2.7-20.3	2.8-25.3

Source: Adapted from BLA125758/0 – Module 2.5, Clinical Overview
Abbreviations: EJ, early juvenile; LI, late infantile Max, maximum; Min, minimum; N, number of subjects; U.S., United States

Given the small study population, subgroup analyses by demographic parameters were not conducted.

Reviewer Comment: *The subjects treated with OTL-200 in the clinical trials are considered generally representative of children with LI and EJ MLD. The study enrolled primarily subjects who were White/Caucasian, not Hispanic or Latino, and from countries outside the United States. This is not unexpected given that the highest prevalence of MLD has been observed in North American and European populations. Additionally, the OTL-200 clinical trials were conducted at a single site in Italy enrolling primarily European patients. While the study predominantly enrolled males, MLD impacts male and females equally. Based on the pathophysiology of MLD, there are no known differences in clinical course based on race, ethnicity, sex, and country of origin. Therefore, the data in this study can be applied to all children with LI and EJ MLD.*

Discussion of the comparability of the natural history subjects and the treated subjects is discussed further in Section 6.4.10, 7.2.4, and 7.3.4.

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☒	Clinician-reported outcome	Section 7

☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☒	Natural history studies	Section 6.4
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☒	Patient-focused drug development meeting: MLD Externally-Led Patient-Focused Drug Development Meeting (10/21/2022)	1.2
☐	FDA Patient Listening Session	
☒	Other stakeholder meeting summary report – MLD Scientific Workshop (11/18/2022) and follow-up White Paper	1.2
☐	Observational survey studies	
☐	Other: (please specify)	

The patient perspective was considered and incorporated throughout this review based on information from the following sources:

- MLD Externally-Led Patient Focused Drug Development meeting held on October 21, 2022, which presented perspectives from patients, families and caregivers in the MLD community
- MLD Scientific Workshop held on November 18, 2022, where clinical experts in MLD presented issues faced by patients with MLD and their families.
- A white paper that followed the MLD Scientific Workshop entitled, “Integration of the Patient Perspective into Therapy Development for Metachromatic Leukodystrophy (MLD)”
- Perspectives heard from patient representatives at formal meetings with the Applicant during review of both the IND and the BLA, which have highlighted the impact of MLD on individual patients and their families.

Reviewer Comment: *The clinical review team acknowledges the following are the most significant aspects of MLD identified by patients, families, and caregivers in the MLD community: the rapid progression of disease, loss of communication skills, loss of ambulation and cognitive impairment. These are taken into consideration throughout evaluation of the clinical data submitted in this BLA.*

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

MLD is a rare, autosomal recessive lysosomal storage disease. It is caused by impaired degradation of sulfatides, one of the most common sphingolipids in the myelin sheath of the central and peripheral nervous systems. Accumulation of sulfatides in the myelin sheath leads to neuronal degeneration, astrocyte dysfunction, and an inflammatory response that causes progressive widespread demyelination (Shaimardanova et al. 2020). Sulfatides may also accumulate in other organs. Increased risk for gallbladder disease (including hyperplastic polyps and carcinoma) have been seen in patients with MLD. Less commonly, case reports of polypoid masses in the stomach and the duodenum have also been identified (Gomez-Ospina 2006).

MLD has an estimated global prevalence rate of 1 in 40,000 to 160,000. While MLD has been diagnosed in patients globally, there are higher prevalence rates in patients of Habbanite Jewish, Israeli Arab, Eskimo, and Navajo descent (Gomez-Ospina 2006). MLD is divided into three clinical subtypes that are distinguished based on the age of symptom onset: LI MLD, juvenile MLD (separated into EJ and LJ MLD), and adult MLD. LI and EJ MLD are the most severe forms of the disease. LI MLD is the most common form found in 50 to 60% of all patients (Shaimardanova et al. 2020).

MLD is caused by mutations in the *ARSA* and prosaposin (*PSAP)* genes. Mutations in the *ARSA* gene lead to a deficiency in the ARSA enzyme, which is responsible for the degradation of sulfatides. Mutations in the *PSAP* gene leads to a deficiency in prosaposin, which is a precursor to four types of saposin protein, including SapB. SapB is required for ARSA enzyme activity and a deficiency in SapB leads to the development of MLD. Approximately 200 ARSA mutations and 26 PSAP mutations have been described in patients with MLD (Cesani et al. 2016). It is estimated that 10 to 15% of the normal ARSA enzyme activity is sufficient to maintain sulfatide metabolism. ARSA pseudodeficiency occurs when there is a decrease in ARSA enzymatic activity (approximately 5 to 20% from normal) that is benign and does not result in the disease phenotype (Gomez-Ospina 2006).

Two types of alleles in MLD have been identified. Null alleles, which encode an inactive enzyme, and R alleles, which encode an enzyme with some residual activity. It is generally thought that two null alleles cause LI MLD, while two R-alleles or a combination of null and R alleles correlates to the juvenile and adult phenotypes. However, MLD has poor genotype-phenotype correlation, and many patients have novel mutations that are poorly characterized.

Late Infantile MLD

LI MLD is the most severe form of the disease. LI MLD is defined by the onset of disease symptoms prior to 30 months of age. Presenting symptoms include gait abnormalities, frequent falls, hypotonia, and decreased deep tendon reflexes. Within a few years of symptom onset, patients experience rapid psychomotor regression to a severely impaired state and death. As the disease progresses, patients experience ataxia, progressive loss of gross and fine motor function, neuropathy, seizures, and cognitive impairment. At the end stage of the disease, patients usually require gastrostomy tube placement and ventilatory support to address dysphagia, feeding difficulties, and respiratory compromise. There is minimal phenotypic heterogeneity in LI MLD, with children rapidly progressing to severe neurologic impairment within a few years of symptom onset. Most children die within five years of symptom onset, although survival can be extended into the second decade of life in a severely impaired state with maximal ventilatory and nutritional support (Elgun et al. 2019).

Early Juvenile MLD

For the purposes of review of this BLA submission, EJ MLD is defined as symptom onset between 30 months and 7 years of age. Amongst MLD experts, based on publications and clinician reports, there is variability in the definition of EJ MLD on whether the threshold for symptom onset is 6 years of age or 7 years of age. Irrespective of the cut-off age that distinguishes EJ MLD from LJ MLD, experts consider EJ and LJ MLD to be clinically distinct with EJ being a more severe sub-type(Fumagalli et al. 2021; Kehrer et al. 2021). Patients with EJ MLD may be asymptomatic with normal development until 7 years of age. Presenting symptoms can be motor (gait abnormalities or delay in early milestones) or cognitive (behavioral problems, psychiatric symptoms, or impaired attention) (Shaimardanova et al. 2020). In comparison to LI MLD which has a rapid and relatively uniform clinical course, patients with EJ MLD have a slower and more heterogenous clinical course. While some patients with EJ MLD may progress rapidly to severe motor impairment after symptom onset, some patients may experience slow disease progression and reach the end stages of the disease in adulthood (Fumagalli et al. 2021).

Late Juvenile & Adult MLD

LJ MLD (symptom onset after 7 years of age) and adult MLD (where symptom onset begins after 16 years of age) are the least severe forms of the disease. Slow disease progression with periods of relative stability can be observed in both LJ and adult MLD. However, patients still progress to severe motor impairment within 10 to 30 years of symptom onset (Shaimardanova et al. 2020; Fumagalli et al. 2021). Discussion of LJ and adult MLD are included in this discussion for completeness, but are not indications requested by the Applicant.

Gross Motor Function Classification in MLD (GMFC-MLD)

To assess for motor progression in LI and EJ MLD, the GMFC System designed to classify motor function in children with cerebral palsy was adapted for MLD to provide a reliable method for assessing gross motor function. As published in Kehrer et al (2011), Table 3 defines the levels used in the GMFC-MLD (Kehrer et al. 2011):

Table 3: Gross Motor Function Classification in MLD (GMFC-MLD)

Level	Gross Motor Function
0	Walking without support with quality of performance normal for age
1	Walking without support but with reduced quality of performance – i.e., instability when standing or walking
2	Walking with support. Walking without support not possible (fewer than five steps)
3	Sitting without support and locomotion such as crawling or rolling. Walking with or without support not possible
4	Sitting without support but no locomotion, OR Sitting without support not possible, but locomotion such as crawling or rolling
5	No locomotion nor sitting without support, but head control is possible
6	Loss of any locomotion as well as loss of any head and trunk control

Source: Adapted from (Kehrer et al. 2011)
Abbreviations: MLD, metachromatic leukodystrophy

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

There are no FDA-approved therapies for MLD. There are limited data published on outcomes in patients with LI and EJ MLD who have received treatment with hematopoietic stem cell transplant (HSCT). Minimal effect in slowing disease progression has been observed in patients with LI MLD, regardless of whether patients are symptomatic at the time of transplant. Patients with EJ MLD who are symptomatic at the time of transplantation have also been observed to derive minimal benefit from HSCT. Poor HSCT outcomes in these patients is thought to be related to inability of the transplanted monocytic bone marrow cells to pass the blood-brain barrier and differentiate into microglia cells in a sufficient time prior to the development of irreversible disease. There is evidence to suggest that patients with EJ MLD transplanted prior to symptom onset may experience benefit through slowing of both cognitive and motor dysfunction. However, these patients are still observed to progress to severe motor and cognitive impairment. The long-term outcomes after HSCT may also be dependent on the allograft source (with more success in those who received HLA-matched sibling grafts). Additionally, there are substantial risks of HSCT including graft failure, serious infections, graft versus host disease. As such, HSCT is considered a potential treatment option for children prior to symptom onset in EJ MLD, but is not considered standard of care (Boucher et al. 2015).

2.3 Safety and Efficacy of Pharmacologically Related Products

OTL-200 is a lentiviral gene therapy product. Lentiviral gene therapy products have been associated with insertional oncogenesis and subsequent clonal expansion. Additional known safety risks of lentiviral gene therapy products include humoral immunogenic responses to the expressed protein and adverse events consistent with the known safety profile of the required myeloablation (i.e., febrile neutropenia, delayed platelet engraftment).

2.4 Previous Human Experience With the Product (Including Foreign Experience)

OTL-200 received marketing authorization for the treatment of patients with PSLI, PSEJ, and ESEJ MLD by the European Medicines Agency on December 17, 2020, and by the United Kingdom Medicines and Healthcare Product Regulatory Agency on January 01, 2021. At the time of BLA submission, (b) (4) subjects had received OTL-200 in the international post-market setting.

2.5 Summary of Pre- and Post-Submission Regulatory Activity Related to the Submission

Investigational New Drug Application #26917 for the use of OTL-200 in the treatment of PSLI, PSEJ, and ESEJ MLD was filed to the FDA on October 15, 2020.

OTL-200 (previously referred to GSK2696274 when under development by the previous Sponsor, GlaxoSmithKline) was granted an orphan drug designation on March 8, 2018, (#DRU-2018-6315) and rare pediatric disease designation on April 16, 2018, for the treatment of MLD (#RPD2018-163). Regenerative Medicine Advanced Therapy (RMAT) designation was granted on January 13, 2021.

Throughout development, the Applicant met with the Agency to agree on the overall design of the development program, including the primary clinical efficacy endpoint of sMFS, the assignment of disease subtype and symptomatic status to both study subjects and natural history subjects, comparability of the natural history subjects, and duration of follow-up required to observe a treatment effect. Although the Agency agreed with the primary endpoint of sMFS

and the use of an IRC comprised of physicians with expertise in MLD to adjudicate disease subtype and symptomatic status, it was noted that comparability of the natural history subjects to the treated subjects and the adequacy of the duration of follow-up (particularly in the PSEJ and ESEJ subpopulations) would be assessed during the BLA review, as discussed further in Section 7.

Final guidance for the BLA content was provided in a pre-BLA meeting held on April 24, 2023.

Additional regulatory history:

- May 18, 2021 – Type B Meeting – Chemistry, Manufacturing, and Controls (CMC) and Clinical – CRMTS #13201
- June 04, 2021 – Type C Meeting – Facilities – CRMTS#13238
- November 23, 2021 – Type B (RMAT) Meeting – CMC – CRMTS #13698
- November 15, 2022 – Type B Meeting – CMC – CRMTS #14411
- January 31, 2023 – Type B Meeting – Clinical – CRMTS #14547

BLA review dates:
- Rolling Review Granted

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The two interventional studies (Studies #201222 and #205756), as well as the expanded access studies (Studies #205029, 206258, and 207394) and natural history study (Study #204949) were performed in compliance with good clinical practice.

The Bioresearch Monitoring Branch inspected Ospedale San Raffaele -Telethon Institute for Gene Therapy (SR-TIGET), the single clinical site where all clinical studies were performed. The Establishment Inspection Report did not reveal any problems that impacted the data submitted in the BLA.

3.3 Financial Disclosures

Covered clinical study (name and/or number):
Was a list of clinical investigators provided? X Yes ☐ No (Request list from applicant)
Total number of investigators identified: 39
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in sponsor of covered study: N/A Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☐ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? ☐ Yes ☐ No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 8 Is an attachment provided with the reason? X Yes ☐ No (Request explanation from applicant) 7 out of 8 investigators were assigned to the study prior to 2016 and are no longer active on the study. 1 investigator was only assigned to the study for less than 1 year, and the financial disclosure information was not collected in error and was unable to be retrieved. This does not raise questions about the integrity of the data.

The Applicant does not have any financial arrangements with any of the clinical investigators. Eight out of 39 investigators did not have financial disclosure forms collected, but this is not thought to have impacted the integrity of the data.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

There were significant changes in the product manufacturing process over the course of the clinical development program. Early in the clinical development program, the product was manufactured from bone marrow (BM) and administered fresh (without cryopreservation). To facilitate commercial use, the Applicant changed the manufacturing process to use CD34+ cells from the mobilized peripheral blood (mPB) and cryopreservation to increase the commercial shelf-life. These differences in product manufacturing were not deemed to impact clinical safety or efficacy.

Per CMC review, there was limited clinical data provided in the BLA submission on the intended commercial product to include for determination of the drug product acceptance criteria. Therefore, narratives for patients treated in the U.S. expanded access setting and E.U. commercial setting were requested to support finalization of the acceptance criteria. Five PSLI patients treated in the U.S expanded access and E.U commercial setting had adequate clinical data to demonstrate a treatment effect that was similar to that observed in the clinical trial subjects. No PSEJ or ESEJ patients had adequate follow-up to observe a treatment effect.

Please see CMC review memos for additional details.

Reviewer Comment: *While considered for the purposes of the acceptance criteria determination, the clinical data from the PSLI patients treated in the E.U. commercial and U.S. expanded access settings were not considered in the clinical efficacy analysis given the strength of the PSLI clinical data submitted in the BLA. The clinical review team analyzed patient narratives for the treated PSEJ and ESEJ patients to determine whether these patients could supplement the PSEJ and ESEJ efficacy analyses. However, the clinical data on these additional PSEJ and ESEJ patients was not informative given the limited duration of follow-up.*

4.2 Assay Validation

The assays analyzed for interpreting the clinical safety and efficacy data include peripheral blood ARSA enzyme assays, cerebrospinal fluid (CSF) ARSA enzyme assays, and anti-ARSA antibody assays. Please see CMC review memo for review of these assays.

4.3 Nonclinical Pharmacology/Toxicology

No significant efficacy or safety issues were identified in the nonclinical data package that informed the analysis of the clinical safety and efficacy data.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

OTL-200 is a biological product containing genetically modified $CD34^+$ hematopoietic stem and progenitor cells transduced ex vivo with a lentiviral vector encoding human ARSA. Following infusion, transduced CD34+ HSCs engraft in bone marrow, repopulate the hematopoietic compartment and the gene-corrected cells can synthesize functional ARSA. Appropriate levels of functional ARSA can breakdown or prevent the harmful accumulation of sulfatides. It is hypothesized that through this mechanism of action, OTL-200, can slow central and peripheral nervous system demyelination, inflammation, and atrophy which cause the clinical manifestations of MLD.

4.4.2 Human Pharmacodynamics

In conjunction with the clinical pharmacology reviewer, analyses of post-treatment ARSA enzyme levels were used in the efficacy analyses. These are discussed in detail in Section 7. Please see clinical pharmacology review memo for additional details.

4.4.3 Human Pharmacokinetics

The OTL-200 product is an autologous gene therapy derived from HSCs that have been genetically modified. As such, typical evaluations of pharmacokinetics, absorption, distribution, metabolism, and elimination are not applicable.

4.5 Statistical

The Statistical Analysis Plan (SAP) relied on an integrated efficacy analysis comparing OTL-200 treated subjects to natural history subjects with a primary endpoint of severe motor-impairment free survival. Each subpopulation of MLD was analyzed separately. Statistical analyses for efficacy were only informative for the PSLI subpopulation. The submitted data for PSLI demonstrated a clear and large treatment effect in all efficacy endpoints; this was robust against potential biases.

Statistical evidence of treatment effect on the pre-specified comparative analyses of the pre-specified efficacy endpoints was not informative for the PSEJ and ESEJ subpopulations due to the small sample size, heterogeneity of disease, and lack of baseline comparability between the treated subjects and natural history subjects. Given the lack of feasibility of formal statistical hypothesis testing for the PSLI and PSEJ subpopulations, they were analyzed descriptively, relying on subject-level analyses.

Based on the subject-level analyses of motor function on the GMFC-MLD scale, the clinical review team was concerned about accelerated motor progression relative to the natural history in the ESEJ population. To further investigate this observation of accelerated motor decline, FDA statistical team conducted exploratory post-hoc analyses for motor decline that included a subset of reasonably comparable EJ children from the natural history population and the OTL-200 studies. Given the multiple imputation methods and assumptions, there is no statistical evidence that the motor decline is either slower or faster in the ESEJ subjects treated with OTL-200 compared to the natural history. Statistical analysis using conservative imputation methods and assuming linearity in progression demonstrated a faster rate of decline from GMFC-MLD Level 1 to Level 2 in the treated ESEJ subjects compared to the comparable children in the natural history. This indicates there is a risk for accelerated motor progression in children with ESEJ MLD who receive treatment with OTL-200. See Section 7.3.10 for additional discussion.

4.6 Pharmacovigilance

We do not believe that Risk Evaluation and Mitigation Strategies (REMS) are necessary or recommended based on the identified risks during the clinical trials, potential risks based on the product, and the limited target population. We believe that these risks can be adequately conveyed through labeling, including instructions for patient counseling.

The clinical review team agrees with the Division of Pharmacovigilance's recommendation for a post-marketing requirement (PMR) study under Food and Drug Administration Amendments Act of 2007 Title IX. The PMR will require the Applicant to conduct a post-marketing, prospective observational study to assess and characterize the risk of secondary malignancies and long-term safety. During clinical development, there were a limited number of patients treated with OTL-200, and based on the size of the safety database, additional information is needed on long-term safety. Specifically, while there were no reported malignancies in this study, this class of products has been associated with insertional oncogenesis. During the clinical trial, there was a fatal cerebrovascular accident. This PMR study will provide a more comprehensive assessment of long-term risks and a better understanding of monitoring and potential risk mitigation. For additional discussion of the safety findings and analysis, please refer to Section 8. Please refer to the Pharmacovigilance review for additional details.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

Each subject treated in the clinical studies and expanded access program was evaluated individually to determine whether the symptomatic status (pre-symptomatic versus early symptomatic) and MLD subtype (LI versus EJ) were assigned appropriately by both the Applicant and the IRC. This was assessed using each subject's genotype, baseline physical exam prior to treatment, and clinical course after treatment. The clinical course of the treated subject's sibling was also used when available. Sibling data was available for each PSLI and PSEJ subject; it was not available for all ESEJ subjects. Given the minimal phenotypic variability in LI MLD, the Applicant's natural history study was used as a comparator. The clinical review

team observed that the patients with EJ MLD enrolled in the natural history study had a more severe phenotype than the PSEJ and ESEJ subjects treated in the clinical trials. Therefore, efficacy analyses of the PSEJ and ESEJ subjects were performed in comparison to natural history data published in the medical literature. The publications are cited for reference throughout the analysis of efficacy presented in Section 7.

Safety was analyzed by both pooling all subjects treated with OTL-200 in the clinical program (including two subjects with advanced disease who were not included in the efficacy analysis) and by separating subjects by indication (PSLI, PSEJ, and ESEJ). AEs were also analyzed at various timepoints after treatment.

Pooled statistical analyses were only feasible in the PSLI subpopulation, given the larger sample size (n=20) and the minimal phenotypic heterogeneity in LI MLD. Given the very small sample size of both the PSEJ (n=7) and the ESEJ (n=10) subpopulations and the substantial phenotypic heterogeneity in EJ MLD, pooled analyses were not considered informative and subject-level analyses were conducted in comparison to untreated patients with EJ MLD.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

Source documents for this review include documents filed under the original application for BLA 125758 and documents under IND#26917, which includes meeting minutes and correspondences between FDA and the Applicant. Eight clinical information requests (IRs) were sent to the Applicant during BLA review.

5.3 Table of Studies/Clinical Trials

Table 4 below provides an overview of the clinical studies. Additional information on the clinical studies will be presented in Section 6, including the number of treated OTL-200 subjects per indication and the study subjects who had their disease subtype and symptomatic status re-classified by the clinical review team.

Table 4: Summary of Clinical Data and Number of Subjects in Marketing Application, By Study

Study	Study Design	Study Objectives	Treatment Details	Number of Subjects	Study Status
201222	Open-label, single-center, single-dose, pivotal trial	Safety and efficacy of OTL-200	OTL-200 (fresh formulation b) 2-20x106 CD34+ cells/kg, single dose, IV	22	Ongoing (Closed for enrollment)
205756	Open-label, single-center, single-dose, uncontrolled pivotal trial	Safety and efficacy of OTL-200	OTL-200 (cryopreserved formulation b) 3-30x106 CD34+ cells/kg, single dose, IV	10	Ongoing (Closed for enrollment)
205029	Compassionate use study	Safety and efficacy of OTL-200	OTL-200 (fresh formulation) 2-20x106 CD34+ cells/kg, single dose, IV	3	Ongoing (Closed for enrollment)
206258	Compassionate use study	Safety and efficacy of OTL-200	OTL-200 (fresh formulation) 2-20x106 CD34+ cells/kg, single dose, IV	5	Ongoing (Closed for enrollment)
207394	Compassionate use study	Safety and efficacy of OTL-200	OTL-200 (fresh formulation) 2-20x106 CD34+ cells/kg, single dose, IV	1	Ongoing (Closed for enrollment)
204949	Mixed retrospective & prospective observational natural history study	Describe the disease course and clinical outcomes of untreated subjects with LI and EJ MLD	None – observational	43 (26 LI, 17 EJ)	Completed
OTL-200-10	Observational, multicenter, long-term follow-up study	Long-term safety of OTL-200	None – observational	Still enrolling	Ongoing

Source: BLA125758/0 5.2 Tabular Listing of All Clinical Studies
Abbreviations: EJ, early juvenile; IV, intravenous; LI, late infantile; MLD, metachromatic leukodystrophy

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

During BLA review, the clinical review team recommended that an Advisory Committee meeting be held to receive public comment and external expert advice on the EJ subpopulations. However, Office of Therapeutic Products (OTP) leadership determined that an Advisory Committee Meeting was not necessary.

5.4.2 External Consults/Collaborations

Clinical Outcomes Assessment Consultation

The clinical review team consulted two members from the Division of Clinical Outcomes Assessment (DCOA) in the Center for Drug Evaluation and Research (CDER), Dr. Laura Swett and Dr. Naomi Knoble.

The data obtained in the natural history study was assembled using retrospective chart review and prospective in-person assessments. Prior to submission of the BLA, FDA communicated to the Applicant that retrospective collection of data (specifically, of GMFC-MLD assessments) may be subject to bias, given the rater's knowledge of treatment and disease subtype assignment. To demonstrate comparability of retrospective and prospective GMFC-MLD assessments, the Applicant prepared a "Clinician Report Outcomes Evidence Dossier for GMFC-MLD", which presented the results of a GMFC-MLD reliability study aimed to investigate the inter-rater agreement between GMFC-MLD scores obtained retrospectively and GMFC-MLD scores obtained at in-person assessments. In this study, the Applicant randomly selected 35 in-person GMFC-MLD assessments and removed all identifying information about the patient. Three raters familiar with GMFC-MLD scoring (two pediatric neurologists and one physical therapist) were asked to provide a GMFC-MLD rating, which was compared to the rating obtained at the in-person visit. However, the results from the reliability study were confounded by utilization of the same pediatric neurologist involved in the clinical development program. Given that this rater is likely to be familiar with the individual subjects in the small study population and be able to identify the subjects from whom the charts originated, the interpretability of this study is limited. In the pre-BLA meeting held on April 24, 2023, FDA recommended that Applicant re-run the GMFC-MLD reliability study using qualified raters not involved in the natural history study or clinical trials. However, the Applicant elected not to re-run the study.

In this BLA submission, the Applicant provided results from neurocognitive testing aimed to assess for cognitive functioning of the treated subjects. Dr. Naomi Knoble provided review on the neurocognitive data, which is presented in detail in Section 7.

5.5 Literature Reviewed (if applicable)

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Kaufman, M, 2006, Juvenile Metachromatic Leukodystrophy Mimicking Relapsing-Remitting Multiple Sclerosis, Int J MS Care, 8(4):141-143.

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LOVD, 2023, The ARSA gene homepage.

Meier, K, J Gartner, and P Huppke, 2021, Tumefactive inflammatory lesions in juvenile metachromatic leukodystrophy, Neurology Neuroimmunol Neuroinflamm, 8(1):922.

Olive-Cirera, G, MJ Martinez-Gonazalez, and T Armangue, 2022, Pearls & Oy-sters: Tumefactive Demyelination Lesions with MOG Antibodies Preceding Late-Infantile Metachromatic Leukodystrophy, Neurology, 99(19):858-861.

Shaimardanova, AA, DS Chulpanova, VV Solovyeva, AI Mullagulova, KV Kitaeva, C Allegrucci, and AA Rizvanov, 2020, Metachromatic Leukodystrophy: Diagnosis, Modeling, and Treatment Approaches, 7:1-17.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: A phase I/II clinical trial of hematopoietic stem cell gene therapy for the treatment of Metachromatic Leukodystrophy (OTL-200-201222)

6.1.1 Objectives (Primary, Secondary, etc)

Primary Objectives

- Evaluation of the safety of gene therapy in MLD subjects, considering both the conditioning regimen safety and the safety of lentivirus (LV)-transduced cell infusion, short and long-term after the treatment.
- Evaluation of the efficacy of gene therapy, assessed as reduction in the progression of clinical motor impairment, in treated subjects as compared to the progression measured in untreated MLD subjects in the natural history study and accompanied by a significant increase of residual ARSA activity as compared to the subject's pre-treatment values.

Secondary Objectives

- Evaluation of the efficacy of the procedure in reducing the progression of demyelination (and atrophy) in the central and peripheral nervous system in comparison with that documented in the natural history study, as assessed by total brain MRI score and nerve conduction velocity (NCV) index.
- Evaluation of the efficacy of the procedure in reducing the progression of clinical motor impairment, as assessed by GMFC-MLD, in treated subjects compared to natural history subjects.
- Evaluation of the efficacy of the procedure in reducing the progression of the cognitive impairment, as assessed by the administration of neuropsychological tests.
- Evaluation the biological efficacy of the procedure in treated subjects, which consists of the sustained engraftment of the transduced cells, an essential pre-requisite for achieving clinical benefit. Long-term transduced cell engraftment will prove that: i) ARSA LV transduced HSPC with long-term repopulation potential and ii) the conditioning regimen was adequate for allowing transduced cell engraftment.
- Evaluation of correlations occurring between transduced cell engraftment levels and busulfan exposure.

6.1.2 Design Overview

OTL-200-201222 is a non-randomized phase I/II, open-label, prospective, single center study utilizing a non-current, natural history study as an external control.

Reviewer Comment: *The natural history study that serves as the external control for the integrated efficacy analysis is discussed in Section 6.4.*

6.1.3 Population

The key eligibility criteria were as follows, separated by indication:

Pre-symptomatic Late Infantile

Inclusion Criteria

- Age at symptom onset of older sibling(s) ≤30 months
- Two null mutations in the *ARSA* gene
- Absence of disease-related symptoms or neurological exam findings

Pre-symptomatic Early Juvenile

Inclusion Criteria

- Age at symptom onset in older sibling after 30 months of age and prior to the 7th birthday
- One null and one R mutation in the *ARSA* gene
- Absence of disease-related symptoms or neurological exam findings

Early-symptomatic Early Juvenile

Inclusion Criteria

- Age at symptom onset of the subject after 30 months of age and prior to the 7th birthday
- One null and one R mutation in the *ARSA* gene
- Intelligence Quotient (IQ) ≥70
- Ability to walk independently for ≥10 steps

Exclusion Criteria (Regardless of Disease Subtype)

- Patients who underwent an allogeneic HSCT in the previous 6 months or who had evidence of residual cells of donor origin.
- Patients with end-organ functions or any other severe disease, which in the judgement of the investigator, would make the patient inappropriate for entry into this study.
- Patients with neoplastic diseases or cytogenetic alterations typical of myelodysplastic syndrome or acute myeloid leukemia.

Reviewer Comment: *It is important to note that the terms of PSLI, PSEJ, and ESEJ are not used in clinical practice, and are defined for the purpose of this study.*

6.1.4 Study Treatments or Agents Mandated by the Protocol

Study treatments were mandated by the protocol for different phases including collection of back-up cells, BM harvest (for collection of cells to be transduced), busulfan conditioning, and infusion of the transduced CD34+ cells. Prior to initiation of study procedures, a central venous catheter (CVC) was placed while the subject was under general anesthesia.

Back-up Bone Marrow/PBSC Harvest

Four weeks before the collection of BM cells that would be transduced with the lentiviral gene therapy product, an unmanipulated backup of BM cells comprised of a minimum of ≥1 x 10^8 total nucleated cells per kg body weight and/or ≥2 x 10^6 CD34+ cells per kg body weight was collected from study subjects to be used in the event of engraftment failure.

The study protocol permitted collection of back up cells from the peripheral blood (PB) as an alternative to BM harvest. To facilitate mobilization, granulocyte colony stimulating factor (G-CSF) 10 to 12.5 µg/kg divided twice daily was administered. Daily complete blood counts were

performed until blood CD34+ cell count reached the target level. The target number of CD34+ cells is $5x10^6$ cells/kg, but a minimum of $\geq 2x10^6$ CD34+ cells/kg was considered the minimum required for collection.

The stem cells (either from the BM or PB) were suspended in dimethyl sulfoxide (DMSO) and stored in liquid nitrogen.

Bone Marrow Harvest

BM was collected in the operating room from the iliac crests under sterile conditions using general anesthesia on Day -4. The target for harvest was considered to be 20 to 25 mL/kg subject body weight of BM volume. The CD34+ cells collected from this BM harvest were then transduced ex vivo with the lentiviral gene therapy product.

Busulfan Conditioning

Fourteen doses of busulfan were administered to study subjects, given every 6 hours from Day -4 to Day -1. Up until December 2013, subjects received five doses of IV busulfan according to the subject's weight, shown below in Table 5. After the fifth dose, the busulfan dose was adjusted based on plasma busulfan levels with an ideal area under the curve (AUC) of 4200 to 5600 µg/L*h (target: 4800) or 900 to 1350 µmol/L/min (median: 1125 µmol/L/min). A further dose adjustment could be made after the ninth or tenth dose.

Table 5: Busulfan Dose According to Subject's Weight Administered to Subjects Treated Before December 2013

Weight	Dose
<9 kg	1 mg/kg/dose
9 - <16 kg	1.2 mg/kg/dose
16-23 kg	1.1 mg/kg/dose
>23-34 kg	0.95 mg/kg/dose
>34 kg	0.8 mg/kg/dose

Source: BLA125758/0, Module 5.3.5.1, Clinical Protocol, Study #201222

For subjects treated after January 2014, the conditioning regimen was modified to administer a total of four doses to subjects. Doses were based on the subjects' and body surface area, as shown in Table 6. After the first dose, doses were adjusted to target a plasma busulfan AUC level of 85 mg*h/L.

Table 6: Busulfan Dose According to Subject's age and Body Surface Area Administered to Subjects Treated after January 2014

Age	Dose
≤1 year	80 mg/m^2/dose
>1 year	120 mg/m^2/dose

Source: BLA125758/0, Module 5.3.5.1, Clinical Protocol, Study #201222

6.1.5 Directions for Use

Subjects were admitted to a pediatric transplant center in an isolation unit. Infusion of the transduced CD34+ cells (the OTL-200 drug product) occurred 24 hours after the end of the last busulfan dose. A slow infusion of OTL-200 over 10 to 20 minutes was administered through the CVC. Each subject received a dose of transduced CD34+ cells between 2 and 20 x 10^6 CD34+

cells/kg (using subject's weight at the time of infusion), depending on the yield of cells available after transduction. Subjects were hospitalized until hematopoietic recovery, between 60 and 90 days.

6.1.6 Sites and Centers

This is a single site study conducted at SR-TIGET in Milan, Italy. After the 42-month post-treatment visit, subjects were permitted to obtain follow-up locally after arrangements between SR-TIGET and the local health care provider were put into place. A full list of investigators was provided by the Applicant in the appendices of module 5 (16.1.4).

6.1.7 Surveillance/Monitoring

Subjects were actively monitored in this study until Year 3, on Days 7, 14, 21, 28, 35, 42, 49, and 60, and Months 3, 6, 9, 12, 18, 24, 30, and 36. Safety assessments included:

- Clinical evaluation including medical history, vital signs, and physical examination with assessment of performance status (Lansky)
- Diagnostic Imaging and instrumental tests: Chest X-ray, electrocardiogram (EKG) + echocardiogram, echo scan of abdomen and thyroid, and x-ray of hand bone to evaluate the bone age.
- Laboratory assessments: complete blood count with differential, C-reactive protein (CRP), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, blood glucose, blood urea nitrogen (BUN), creatinine, creatinine phosphokinase, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), electrolytes, protein content, urinalysis, protein electrophoresis, blood iron, transferrin, ferritin, reticulocyte, hemogas analyses, thyroid studies, coagulation (D-dimer, prothrombin time [PT], partial thromboplastin time [PTT], fibrinogen)
- BM evaluation: needle aspirate with immunophenotype: CD15+, CD13+, CD33+, CD33+/CD34+/CD13+, CD33+/CD61-, CD61+, Glycophorin A, CD3+, CD3+/CD4+, CD3+/CD8+, CD19+, CD20+, CD22+, CD20+/CD22+, CD2+, CD16+/CD56+, CD19+/IgM+, CD19+/kappa, CD19+/lambda, CD34+, (b) (4) of the BM.
- PB safety evaluation: immunophenotype with lymphocyte subpopulations: CD45+, CD3+, CD3+/CD4+, CD3+/CD8+, CD4+, CD8+ CD19+, CD2+, CD16+/CD56+, CD15, CD13+, CD14, CD14+/CD16+, CD14+/CD16-, CD56+, TCR1+ (alfa/beta), TCR2+ (gamma/delta), Ig-kappa+, and Ig-lambda+ (percentage and absolute count).
- Serum immunoglobulins (IgG, IgA, IgM, IgE).
- (b) (4) with monoclonal antibodies for T-cell receptor (TCR) Vbeta families.
- Cytogenetic analyses on leukocytes.
- Evaluation of the presence of genetically modified cells ((b) (4)) will be done after gene therapy on total peripheral blood mononuclear cell (PBMC; (b) (4) PB) and total BM MNCs cells ((b) (4) BM), and on PBMC cell populations (CD15+,CD14+, CD3+, CD19+, CD56+) and (b) (4) SubP PB and BM cell subpopulations (CD34+, CD13+ and, in case of exceeding sample, also on CD15+, CD19+, CD3+, CD56+,GLYA+) ((b) (4) SubP BM); %LV and vector copy number (VCN) will also be performed on clonogenic progenitors of BM mononuclear cells using (b) (4)
- Microbiological evaluation to test for bacteria, viruses and fungi
- Anti-ARSA antibody test
- Replicant-competent lentivirus (RCL) screening tests.

Table 7 below outlines the schedule for efficacy assessments.

Table 7: Efficacy Assessment Schedule for Study OTL-200-201222

Assessment	BL	S	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 60	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24	Month 30	Month 36
Neurological clinical evaluation	x	x	-	-		x	-	-	-	x	x	x	x	x	x	x	x	x
GMFM and GMFC- MLD	-	x	-	-	-	-	-	-	-	-	x	x	x	x	x	x	x	x
ENG	x	x	-	-	-	X	-	-	-	-	x	x	-	x	x	x	x	x
Brain MRI	-	x	-	-	-	x					x	x		x	x	x	x	x
ARSA gene sequencing	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
ARSA (peripheral blood)	-	x	-	x	-	x	-	x	-	x	x	x	x	x	x	x	x	x
ARSA bone marrow	-	x	-	-	-	x	-	-	-	-	x	x	-	x	x	x	x	x
ARSASubP (PB)[a]	-	x	-	-	-	x	-	-	-	x	x	x	x	x	x	x	x	x
ARSASubP (BM)[b]	-	x	-	-	-	x	-	-	-		x	x	-	x	x	x	x	x
(b) (4) PB[c]	-	x	-	x	-	x	-	x	-	x	x	x	x	x	x	x	x	x
(b) (4) BM[c]	-	x	-	-	-	x	-	-	-	-	x	x	-	x	x	x	x	x
(b) (4) subpopulations (PB)	-		-	x	-	x	-	x	-	x	x	x	x	x	x	x	x	x
(b) (4) Subpopulations (BM)	-	-	-	-	-	x	-	-	-	-	x	x	-	x	x	x	x	x
EEG	-	x	-		-	x	-	-	-		x	x	-	x	x	x	x	x
VEP / BAER / MEP	-	x	-	-	-	-	-	-	-		x	x	-	x	x	x	x	x
Neuropsychological tests	x	x	-	-	-	-	-	-	-			x	-	x	x	x	x	x
School attendance	-	x	-	-	-	-	-	-	-	-	-	x	-	x	x	x	x	x
ARSA CSF + standard chemistry	-	x	-	-	-	-	-	-	-		-	x	-	x	-	x	-	x
Skin biopsy	-	x	-	-	-	-			-	-	-	-	-	-	-	x	-	-
Urinary sulfatides	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	x	-	-

Source: Adapted from BLA125758; Study Protocol OTL-200-201222 v13.2 pp.85-86
a-ARSA measured in the peripheral blood subpopulations CD15+, CD14+, CD3+, CD19+, CD56+
b- ARSA measured in bone marrow cell subpopulations CD34+, CD13+, CD15+, CD19+, CD3+, CD56+,GLYA+
c-frequency of genetically modified cells measured using (b) (4) performed on the peripheral blood, bone marrow, peripheral blood subpopulations (CD15+, CD14+, CD3+, CD19+, CD56+) and bone marrow subpopulations (CD34+, CD13+, CD15+, CD19+, CD3+, CD56+,GLYA+
Abbreviations: ARSA, arylsulfatase A; BAER, brainstem auditory evoked response; BL, baseline; BM, bone marrow; CSF, cerebrospinal fluid; EEG, electroencephalogram; ENG, electroneurography recording; GMFM, Gross Motor Function Measure; GMFC-MLD, Gross Motor Function Classification -MLD**;** h-VEP, visual evoked potential; MEP, motor evoked potential; PB, peripheral blood; S, screening

6.1.8 Endpoints and Criteria for Study Success

The primary, secondary and exploratory endpoints for Study OTL-200-201222 are provided here for completeness. Discussion of the FDA's acceptability of the endpoints and analysis of the efficacy data are discussed in detail in Section 7.

Primary Endpoints

- Improvement in 10% of the total Gross Motor Function Measure (GMFM) in treated subjects when compared to the GMFM scores in the natural history population evaluated 24 months after treatment.
- Change from baseline in residual ARSA activity compared to pre-treatment values, measured in the total PBMCs at 2 years after treatment.

Secondary Endpoints

- GMFC-MLD: The GMFC-MLD levels at different ages in treated subjects compared with the historical control MLD population.
- NCV: NCV Index at Year 2 after treatment in comparison with the historical control MLD population. NCV was also evaluated in individual sensory and motor nerves.
- Brain MRI: Brain MRI total score at Year 2 after treatment in comparison with the historical control MLD population.
- Cognitive function (standard scores): The measurement of a performance standard score above 55 (threshold for severe disability) at neuropsychological testing performed at the Year 2, Year 2.5, and Year 3 follow-ups.
- Engraftment of transduced cells: Transduced cell engraftment above 4% in BM-derived clonogenic progenitor cells at Year 1 after transplant. VCN per cell in total PBMC, total BM, and PB and BM cell subpopulations was also evaluated.
- Correlations between transduced cell engraftment parameters and busulfan exposure: Evaluations of correlations occurring between transduced cell engraftment parameters (i.e., percentage of lentiviral vector-positive [%LVV+], VCN in total PBMC, and VCN in total BM) at Year 1 and busulfan exposure (i.e., total AUC) during the conditioning phase.
- Survival: Age at death in the treated subjects compared with the historical control MLD population.
- ARSA activity in hematopoietic cells and other cell types: Change from Baseline in residual ARSA activity as compared to pretreatment values, measured in total BM mononuclear cells (MNCs), and PB and BM subpopulations at 2 years after treatment. ARSA activity was also measured in CSF at multiple visits.

Exploratory Endpoints

6.1.9 Statistical Considerations & Statistical Analysis Plan

MLD is a rare disease. Enrollment in the study was primarily limited by feasibility. Initially, the study sought to enroll eight subjects (6 PSLI and 2 PSEJ or ESEJ). However, after 9 subjects had been treated, the myeloablative conditioning regimen was adjusted with the purpose of improving engraftment. An additional 11 subjects were treated and recruited with the purpose of fully investigating the risk-benefit profile of the modified conditioning regimen. See statistical reviewer's memo for discussion of the statistical analysis plan.

6.1.10 Study Population and Disposition

Given the small study population, this will be discussed in the integrated review of efficacy, Section 7.

6.2 Trial #2: A single-arm, open-label, clinical study of cryopreserved autologous CD34+ cells transduced with a lentiviral vector containing human ARSA cDNA OTL-200 for the treatment of early onset Metachromatic Leukodystrophy (MLD)

Reviewer Comment: *This study shares many similarities of Study OTL-200-201222. Study OTL-200-205756 was conducted to study the cryopreserved formulation of OTL-200, which is intended as the commercial product. This cryopreserved formulation* (b) (4) *of OTL-200. Only the differences between OTL-200-201222 and OTL-200-205756 will be highlighted in this section.*

6.2.1 Objectives (Primary, Secondary, Etc.)

Primary Objective

- Evaluate the clinical efficacy of the cryopreserved formulation of OTL-200.

Secondary Objectives

- Evaluate the clinical efficacy of the cryopreserved formulation of OTL-200.
- Evaluate the engraftment of the cryopreserved formulation of OTL-200.
- Evaluate the pharmacodynamic effect of the cryopreserved formulation of OTL-200.
- Evaluate the safety and tolerability of the cryopreserved formulation of OTL-200.

Exploratory Objectives

- Evaluate sulfatides and other exploratory analytes in urine, blood, and/or CSF.
- Evaluate peripheral neuropathy.
- Evaluate the effect of OTL-200 on activities of daily living.

6.2.2 Design Overview

OTL-200-205756 is a non-randomized, single-arm, open-label, prospective, single center study utilizing a non-current, natural history study as an external control.

Reviewer Comment: *The natural history study that serves as the external control for the integrated efficacy analysis is discussed in Section 6.4.*

6.2.3 Population

The PSLI and PSEJ study populations were similar between studies OTL-200-201222 and OTL-200-205756. Please see Section 6.1.3. However, the ESEJ population was defined as follows:

- Age at symptom onset of the subject after 30 months of age and prior to the 7th birthday
- GMFC-MLD ≤1
- IQ ≥85 on age-appropriate cognitive instruments

Reviewer Comment: *While Study OTL-200-201222 permitted enrollment of ESEJ population with more cognitive impairments (inclusion criteria of IQ >70), the ESEJ subjects treated in*

Study OTL-200-205756 did not contribute to the integrated efficacy analyses due to a limited duration of follow-up. No other differences in study population between these two pivotal studies were identified. Additionally, all subjects treated in OTL-200-201222 had baseline IQ ≥85.

Please refer to Section 7 for additional discussion.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Similar to study OTL-200-201222, study treatments were mandated by the protocol including collection of back-up cells, harvest of cells to be used as the source CD34+ cells, and busulfan conditioning and infusion of transduced CD34+ cells. A CVC was placed prior to initiation of study procedures. In this study, the decision to use BM or mobilized PB as the source material for the CD34+ cells and back-up cells was left to the discretion of the investigator.

Back-Up Cells

A minimum target collection of ≥100x10^6 total nucleated cells per kg of body weight and/or ≥2x10^6 CD34+ cells/kg of body weight was set. The unmanipulated BM or mobilized PB cells were stored and were available in the event of engraftment failure.

Cellular Harvest

In the event of BM harvest, the target was set as approximately 20 to 30 mL/kg subject body weight.

For CD34+ cells collected from the mobilized PB, G-CSF was administered twice daily. After 2 days of G-CSF administration, plerixafor was given as an additional mobilizing agent for some subjects, depending on measurements of white blood cell (WBC) count and CD34+ cell count. G-CSF and plerixafor were continued until sufficient CD34+ cells were harvested, occurring over a maximum of 3 leukapheresis cycles on 3 consecutive days or a maximum of 7 days of G-CSF administration. The target collection of CD34+ cells from either the BM or PB was 8x10^6 CD34+ cells/kg, to yield a minimum drug product dose of (b) (4) x10^6 CD34+ cells/kg.

Busulfan Conditioning

Busulfan was administered using the same regimen based on body surface area as Study OTL-200-201222 (See Section 6.1.4)

6.2.5 Directions for Use

The directions for use for OTL-200-205756 are similar to OTL-200-201222. Please see Section 6.1.5.

6.2.6 Sites and Centers

This study was conducted at the same site as OTL-200-201222 – Ospedale SR-TIGET.

6.2.2 Design Overview

OTL-200-205756 is a non-randomized phase II, open-label, prospective, single center study utilizing a non-current, natural history study (Section 6.4) as an external control.

6.2.7 Surveillance and Monitoring

The schedule of assessments did not differ significantly from Study OTL-201222. Please see Section 6.1.7.

6.2.8 Endpoints and Criteria for Study Success

Primary Endpoint

- GMFM score at 24 months post gene therapy

Secondary Endpoints

- GMFM score post gene therapy at multiple visits over time
- Clinical efficacy at 24 months post gene therapy at multiple visits over time, as measured by GMFC-MLD score, neurological examinations, assessment of NCV, evaluation of brain MR imaging assessments/parameters, and neurocognitive assessments
- Percent LV positive clonogenic progenitors in BM at Day 30 post-gene therapy and at multiple visits over time
- VCN in BM mononuclear cells at Day 30 post-gene therapy and at multiple visits over time
- VCN in PB mononuclear cells at Day 60 post-gene therapy and at multiple visits over time
- To evaluate the following at Day 60 post-gene therapy and at multiple visits over time:
  - ARSA activity in total PBMCs
  - ARSA activity in PB CD15+ cells
  - ARSA activity in PB CD14+ cells
- ARSA activity in CSF at Day 90 post-gene therapy and at multiple visits over time
- Safety and tolerability as measured by AE reporting including:
  - Conditioning regimen related toxicity and Aes
  - Non-conditioning related Aes
  - Hematological recovery (defined as reconstitution of absolute neutrophil count >500 neutrophils/µL associated with evidence of BM recovery) by Day 60
  - Incidence and titers of antibodies against ARSA
  - Absence of malignancy or abnormal clonal proliferation due to insertional oncogenesis
  - Absence of RCL

Exploratory Endpoints

- Analysis of sulfatides or other exploratory analytes in urine, blood, and/or CSF
- Analysis of skin biopsy
- Analysis of Vineland Adaptive Behavior Scale (VABS) and Pediatric Quality of Life Inventory (PedsQL).

6.2.9 Statistical Considerations & Statistical Analysis Plan

Similar to study OTL-201222, sample size is determined based on feasibility. See statistical reviewer memo for details on statistical considerations.

6.3 Expanded Access Program

There were three expanded access studies that comprised the expanded access program: #207394, #205029, and #206258. The study protocol of these studies was similar to OTL-200-201222.

6.4 External Control: Natural History Study in Subjects with Late Infantile and Early Juvenile Metachromatic Leukodystrophy (Study #OTL-200-204949).

6.4.1 Objectives

Describe the disease course in clinical outcomes of untreated subjects with LI and EJ MLD.

6.4.2 Design Overview

This is an observational, single-center, study of the natural history of MLD that was initiated in 2004. Data was obtained through a collection of prospective assessments and retrospective data collection.

Reviewer Comment: *This study, initiated in 2004, was not run concurrently with the clinical trials, which were initiated in 2010. Given that no new therapies or changes to standard of care for MLD occurred between 2004 and 2010, this was not considered a factor in the use as a comparator for the efficacy analysis. Limitations on the data obtained retrospectively are discussed below.*

6.4.3 Population

Inclusion of subjects was based on biochemical, molecular, genetic, and clinical criteria for the diagnosis of MLD. This includes low ARSA activity in the PB cells, increased urine sulfatides in a 24-hour sample, and the presence of pathogenic biallelic variants in the *ARSA* gene. All subjects were enrolled in the symptomatic stage of their disease.

6.4.4. Study Treatments or Agents Mandated by the Protocol

None – this is an observational study.

6.4.5. Directions for Use

Not applicable for this observational study.

6.4.6 Sites and Centers

This was a single-center study conducted at SR-TIGET.

6.4.7 Surveillance/Monitoring

Data was obtained through a collection of prospective assessments and retrospective data collection. Retrospective data collected included data on age and first nature of symptoms, achievement of early motor and language developmental milestones, GMFC-MLD classifications, and brain MRI results. Retrospective data was collected through a combination of medical chart review and parent interviews.

Prospective data included neurologic examinations, GMFM scores, neuropsychological assessments, laboratory measurements of ARSA activity, visual evoked potentials (VEPs), auditory evoked potentials (AEPs), electroneurography (ENG), and brain MRIs collected every 6 months for 72 months.

Reviewer Comment: *An important limitation of this natural history study is the use of retrospective data collection and enrollment of patients after symptom onset. Much of the data is collected through parental interviews, which are subject to recall bias. In the clinical review team's review of the subject level narratives for natural history subjects, we identify many subjects with incomplete data. This includes absent information on entry into each GMFC-MLD Level, lack of a specific age for symptom onset (i.e., symptom onset in EJ subject* (b) (6) *is recorded as occurring between 62 and 71 months), and large time periods of missing data in each individual subject. Additionally, retrospective data was collected at inconsistent timepoints for each subject.*

During discussions between FDA and the Applicant under IND #26917, FDA articulated concerns that differences in methodologies and bias introduced with retrospective data collection may limit interpretability of the natural history GMFC-MLD scores. To address this concern, the Applicant included in this BLA submission a "Clinician-Reported Outcome Evidence Dossier for the Gross Motor Function Classification for Metachromatic Leukodystrophy (GMFC-MLD)," which was reviewed by Dr. Laura Swett in CDER's DCOA. This dossier included results on study to assess inter-rater reliability between prospective and retrospective GMFC-MLD assessments, entitled "Study to Assess Agreement Among Raters in GMFC-MLD Scoring Done In-Person vs Retrospectively using Medical Records." In this study, three blinded raters (physicians or physical therapists experienced in GMFC-MLD scoring) provided GMFC-MLD scores on blinded study records (extracted from either the natural history study or the treatment studies), which were compared to scores obtained at in-person assessments. Complete agreement was reported by the Applicant as 86%, 89%, and 91% for the three raters.

Reviewer Comment: *In the analysis by Dr. Laura Swett, significant limitations in this dossier were identified. Specifically, one of the blinded raters used to conduct the retrospective scoring was a study investigator for the clinical trials, which may make may bias assessments due to knowledge of the small number of subjects enrolled in both the natural history study and the treatment study. During the pre-BLA meeting held with the Applicant on May 24, 2023 (CRMTS #14763), FDA advised the Applicant to re-run the study using qualified raters not involved in either the natural history or clinical trials. However, the Applicant did not elect to re-run the study. Given these limitations and the other limitations in methodology described in Dr. Swett's memo, the results of this dossier did not inform the clinical review team's approach to the integrated efficacy analysis.*

6.4.8 Endpoints and Criteria for Study Success

None – this is an observational study.

6.4.9 Statistical Considerations & Statistical Analyses

None.

6.4.10 Study Population and Disposition

Details about the study population are presented in Table 8.

Table 8: Characteristics of the LI and EJ Subjects in the Natural History Study

Parameter	LI (n=28)	EJ (n=17)
Sex, n (%)	-	-
Female	15 (54%)	9 (53%)
Male	13 (46%)	8 (47%)
Country of residence, n (%)	-	-
U.S.	1 (4%)	2 (12%)
Non-U.S.	27 (96%)	15 (88%)
Race, n (%)	-	-
White/Caucasian European	28 (100%)	17 (100%)
Asian	0	0
Black or African American	0	0
Age at symptom onset (months)[a]	-	-
Median	15	50
Minimum – maximum	9-28	24-75
Age at first assessment (months)	-	-
Median	19	60
Minimum – maximum	15-28	20-132
Age at enrollment (months)	-	-
Median	60	102
Minimum – maximum	31-168	55-215

Source: Reviewer analysis of Study #204949 ADSL Dataset
a In the event that a subject's exact age of onset is unknown, the earliest potential age is provided here.
Abbreviations: EJ, early juvenile; LI, late infantile ;U.S, United States

Reviewer Comment: *There are a few important features of the natural history population that should be highlighted. As discussed above, many assessments obtained from these natural history children were derived from retrospective chart review prior to enrollment. LI MLD has minimal phenotypic heterogeneity – symptom onset occurred between 9 and 28 months in the natural history subjects, which does capture the variability in age at onset. Therefore, the patients with LI MLD are considered an appropriate comparator to be used in the pooled PSLI efficacy analysis. However, the patients with EJ MLD are reported to have symptom onset between 24 and 75 months. By definition, EJ MLD may present as late as 7 years of age (84 months). Additionally, there is significantly more phenotypic heterogeneity in EJ MLD. Therefore, the clinical review team identified concerns about the suitability of the untreated patients with EJ MLD as comparators to the treated PSEJ and ESEJ subjects. This will be discussed further in Section 7.*

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1: Pre-symptomatic Late Infantile MLD (PSLI MLD)

7.1.1 Methods of Integration

All PSLI subjects from the two clinical trials (Study #201222 and #205756) and the three expanded access studies were integrated for efficacy analyses. Due to the known poor genotype-phenotype correlation and the presence of intermediate phenotypes in MLD, the Applicant utilized an IRC to adjudicate the disease subtype and symptomatic status of all subjects treated with OTL-200 and all subjects enrolled in the natural history study. The IRC was comprised of three independent U.S. physicians who have expertise in pediatric neurology and medical genetics with experience in the treatment of patients with MLD.

Two subjects originally classified as PSEJ by the Applicant and the IRC were reclassified as PSLI by the FDA during this review:

- (b) (6): This subject is homozygous for the c.925G > A mutation in the *ARSA* gene. This mutation encodes some residual enzyme activity (R allele) and has been identified in LI phenotypes (Cesani et al. 2016). This subject, treated at 18.8 months of age, was reported as having reduced/absent tendon reflexes in all four limbs at the Day 28 visit (19.7 months of age), irritability at the month 3 visit (21.8 months of age) and an inability to run at the month 6 visit (24.7 months of age).

Reviewer Comment: *Given the onset of disease symptoms prior to 30 months of age (despite treatment), this child met clinical criteria for the LI subtype. Given that this subject was asymptomatic at the time of treatment, the child is included in the PSLI efficacy analysis.*

- (b) (6) : This subject had the following genotype: c.346C > T and c.667C > T. c.667C > T is relatively uncharacterized in review of published literature and the Leiden Open Variation Database, which has documented all known mutations in the *ARSA* gene (LOVD 2023). This subject, treated at 13.4 months of age, developed mild ataxia at 22 months of age.

Reviewer Comment: *The onset of symptoms prior to 30 months of age is more consistent with the LI phenotype. Given that this child was also asymptomatic at the time of treatment, the child is included in the PSLI efficacy analysis.*

Reviewer Comment: *With the two additional re-classified PSLI subjects, there are a total of 20 subjects analyzed for efficacy for the PSLI indication.*

7.1.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics of the 20 PSLI subjects are shown in Table 9.

Table 9: Demographics and Baseline Characteristics of PSLI Subjects

Parameter	**PSLI (N=20)**
Sex, n (%)	-
Female	7 (35%)
Male	13 (65%)
Country of residence, n (%)	-
U.S.	3 (15%)
Non-U.S.	17 (85%)
Race, n (%)	-
White/Caucasian European	15 (75%)
Asian	2 (10%)
Black or African American	3 (15%)
Age at OTL-200 treatment (months)	-
Median	11.8
Minimum – maximum	7.6-18.8
Weight at the time of treatment (kg)	-
Median	9.2
Minimum – maximum	7.2-12.3

Source: Review analysis of Integrated Summary of Efficacy ADSL & ADVS Datasets
Abbreviations: PSLI, pre-symptomatic late infantile

7.1.3 Subject Disposition

All PSLI subjects were alive at last follow-up. No subjects have been lost to follow-up or have dropped out of the study. No subjects have completed the study. Subjects have been followed for 2.4 to 12.2 years since treatment (median 6.7 years).

7.1.4 Analysis of Primary Endpoint(s)

The primary endpoint is sMFS, 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. The natural history comparator groups for the analyses of the primary endpoint include data from natural history study #204949 and additional untreated siblings of subjects enrolled in Study #205756 (N=6).

Reviewer Comment:

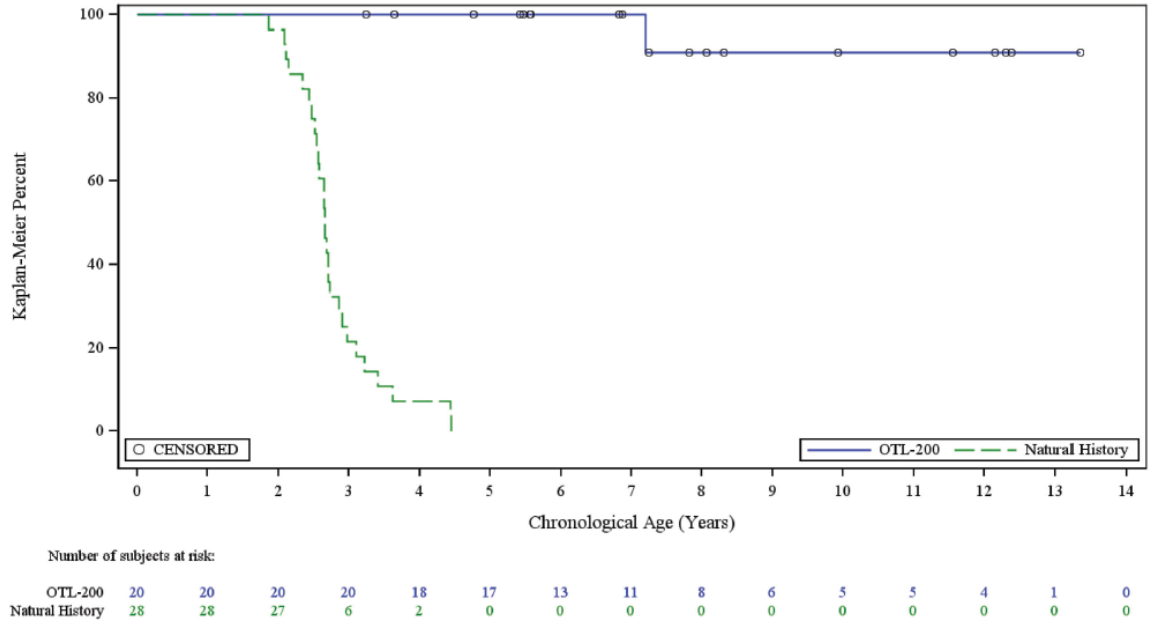
While this endpoint was not pre-specified in the clinical study protocols, it was agreed upon by the FDA and the Applicant as a suitable primary endpoint for efficacy analysis. Progression to GMFC-MLD ≥ Level 5 or death is recognized as clinically meaningful in patients with LI and EJ MLD.

FDA did not agree with the Applicant's pre-specified primary endpoint of change in GMFM given concern that some items on the GMFM scale were not clinically meaningful and there was uncertainty as to the magnitude of change in GMFM score that would be clinically meaningful in MLD.

Given the minimal phenotypic heterogeneity in LI MLD, both the natural history LI subjects and the untreated siblings were considered suitable comparators for the interpretation of the efficacy analysis.

Figure 1 shows a Kaplan-Meier plot of the primary endpoint comparing sMFS between PSLI subjects treated with OTL-200 and natural history LI subjects.

Figure 1: Severe Motor-Impairment Free Survival, PSLI Subjects



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

Reviewer Comment: *This plot demonstrates the robust treatment effect observed in the treated PSLI subjects. LI MLD has a homogenous clinical course with minimal phenotypic heterogeneity. Patients with LI MLD progress rapidly to severe motor impairment after the onset of symptoms early in life. This plot shows that by 5 years of age, all natural history subjects have progressed to severe motor impairment. In comparison, 0 out of 17 PSLI subjects treated with OTL-200 who have reached 5 years of age have progressed to severe motor impairment. This represents a robust and meaningful treatment effect on the primary endpoint in the treated PSLI subjects.*

7.1.5 Analysis of Secondary Endpoint(s)

The key secondary endpoints in the integrated efficacy analysis were as follows: the proportion of subjects who experienced severe motor impairment or death by Year 2 and Year 5 post-treatment and overall survival.

At Year 2, 0 PSLI subjects treated with OTL-200 had experienced severe motor impairment or death, while 15 out of the 26 age-matched natural history subjects (58%) had experienced severe motor impairment or death. At Year 5, only 1 PSLI subject (5%) treated with OTL-200 had experienced severe motor impairment, while all 26 natural history children had experienced severe motor impairment or death.

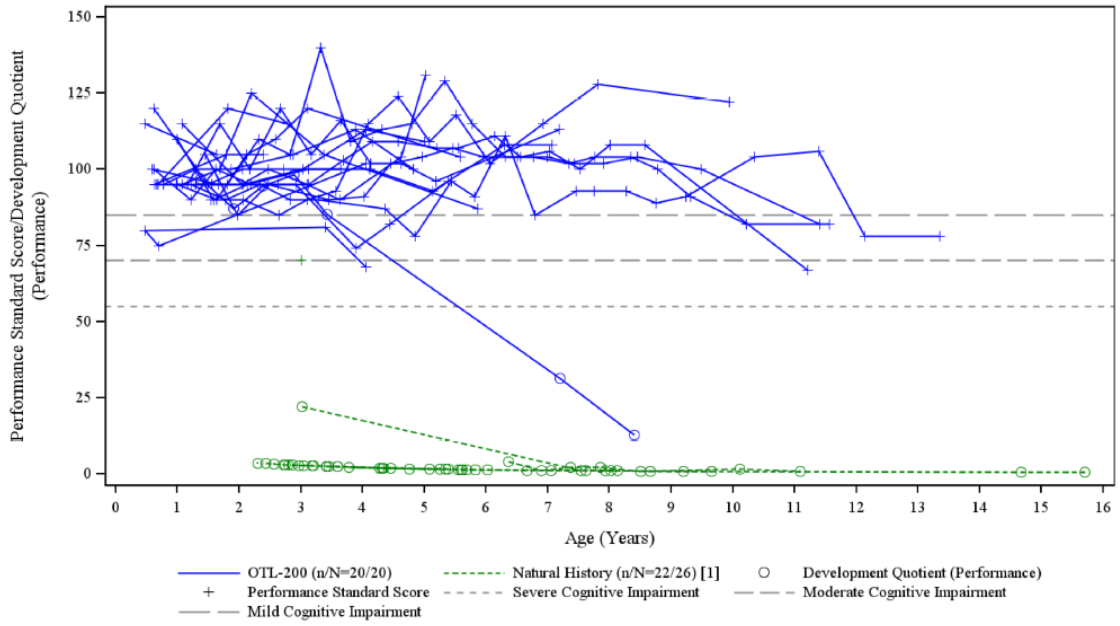
Overall survival was defined as the interval between birth and death from any cause. 100% of the 14 treated PSLI subjects followed until age 6 years were alive compared to only 58% of the 24 untreated LI natural history children.

Reviewer Comment: *The robust treatment effect in the PSLI subpopulation is also observed in analyses of the key secondary endpoints.*

7.1.6 Other Endpoints

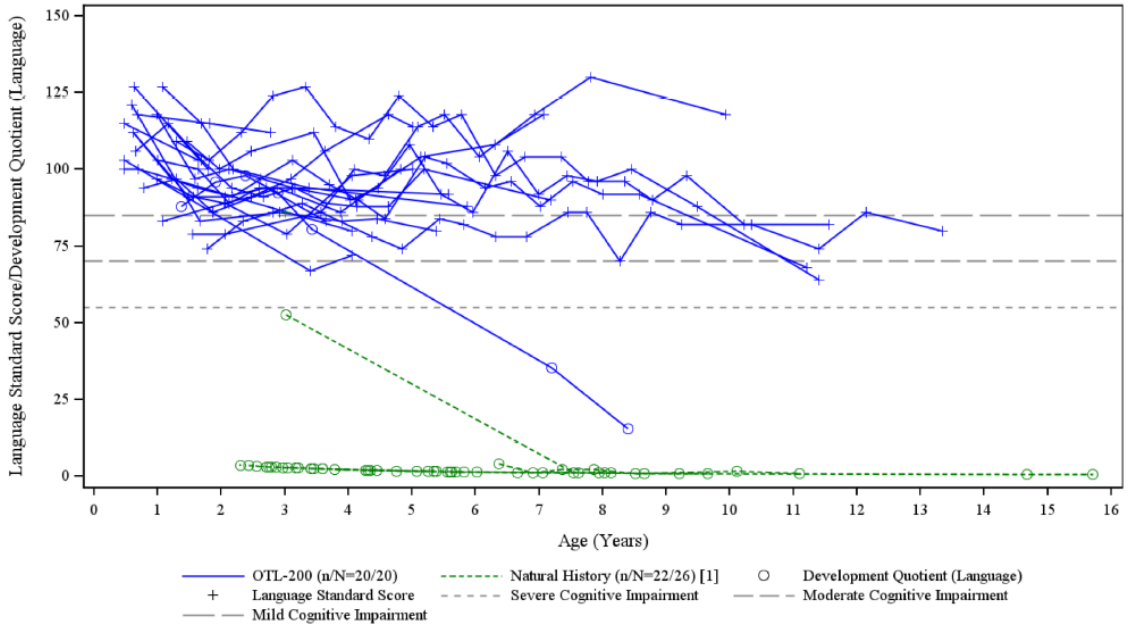
An additional endpoint of severe cognitive impairment-free survival was defined as the interval between birth and the first occurrence of severe cognitive impairment (defined as performance standard score ≤55 with no performance standard score >55 at later assessments). Figure 2 and Figure 3 show the performance and language standard scores of the PSLI treated subjects compared to the natural history subjects.

Figure 2: Performance Standard Score/Developmental Quotient (Performance) vs. Age for the PSLI Treated Subjects and LI Natural History Subjects



Source: Figure X42.1, Applicant Response to Clinical IR#8, BLA125758/0.47
Abbreviations: LI, late infantile; PSLI, pre-symptomatic late infantile

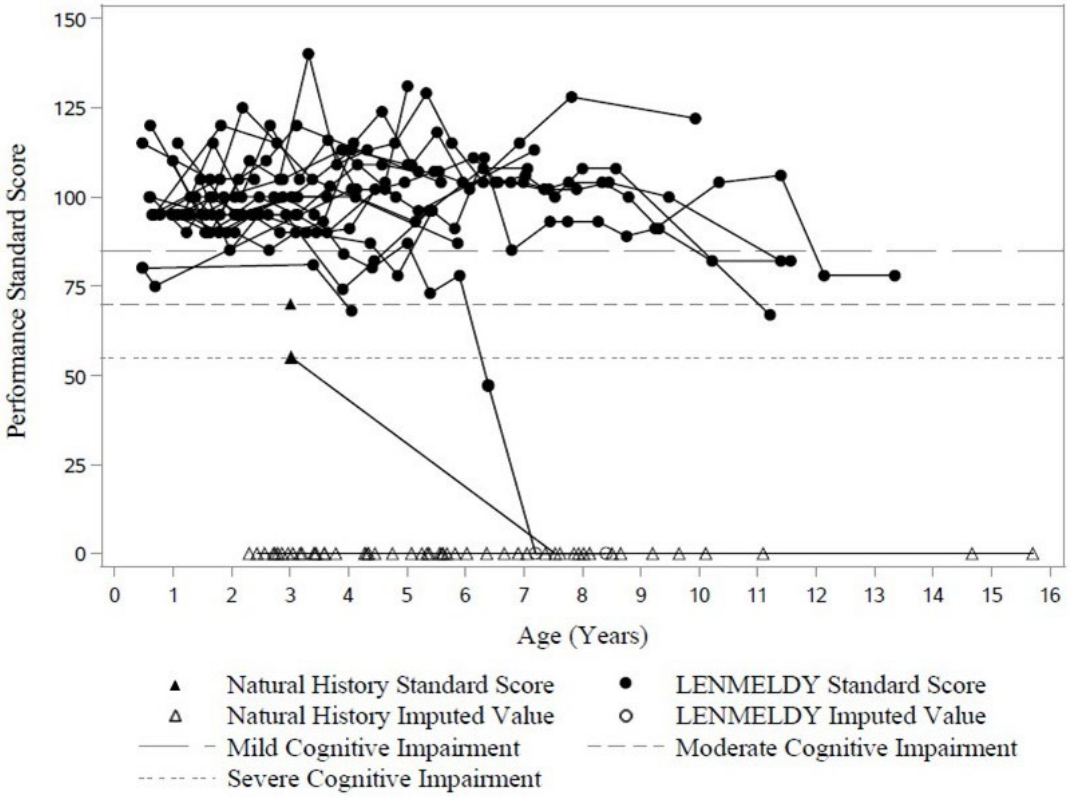
Figure 3: Language Standard Score/Developmental Quotient (Language) vs. Age for the PSLI Treated Subjects and LI Natural History Subjects



Source: Figure X42.1, Applicant Response to Clinical IR#8, BLA125758/0.47
Abbreviations: LI, late infantile; PSLI, pre-symptomatic late infantile

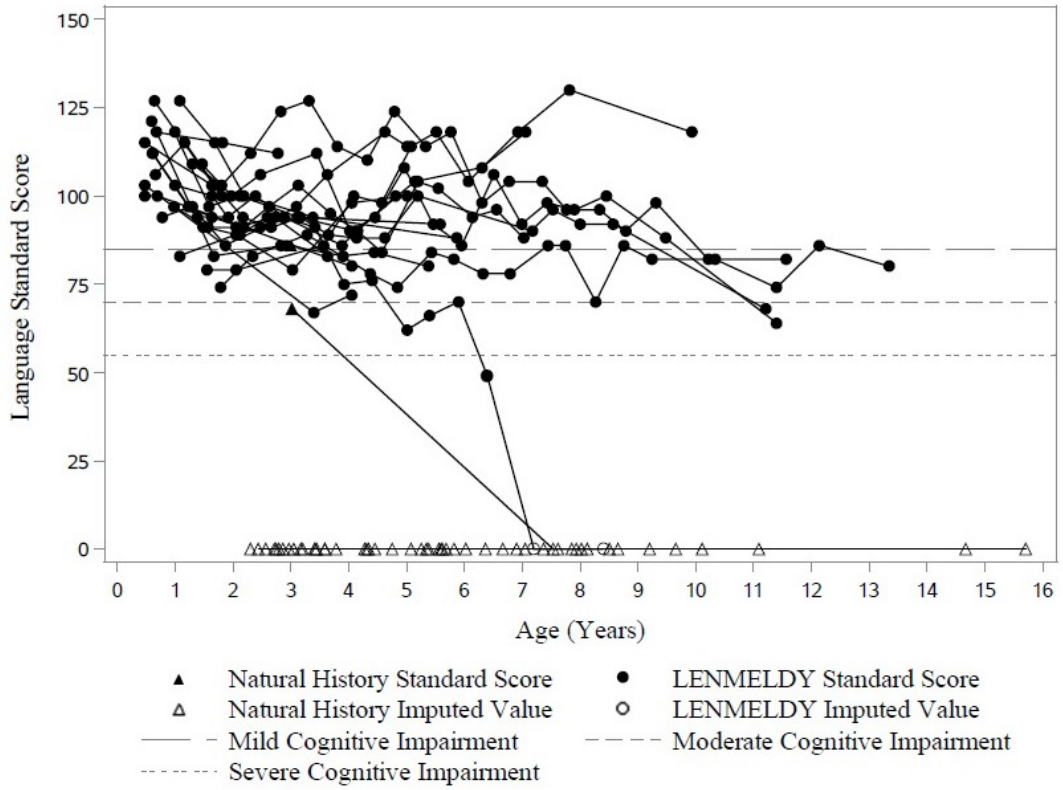
Reviewer Comment: *In these figures, the applicant has used developmental quotients in place of standard scores in the event that a subject could not complete the age-appropriate assessment due to cognitive impairment. However, developmental quotients are not equivalent to standard scores. Therefore, the applicant was asked to impute a standard score of "0" for any subjects who were unable to be tested on age-appropriate tests and had cognitive impairment (shown in the open circles on the graph). These are shown below in Figure 4 and Figure 5.*

Figure 4: USPI Plot of Performance Standard Score* vs Age in PSLI Treated Subjects and LI Natural History Subjects



Source: LENMELDY USPI
*Performance standard scores have been imputed as zero in cases where they could not be derived in the event of cognitive impairment and inability to administer the age-appropriate assessment.

Figure 5: USPI Plot of Language Standard Score* vs Age in PSLI Treated Subjects and LI Natural History Subjects



Source: LENMELDY USPI
*Language standard scores have been imputed as zero in cases where they could not be derived in the event of cognitive impairment and inability to administer the age-appropriate assessment.

Reviewer Comment: *Only 1 out of 20 treated PSLI subjects (5%) progressed to severe cognitive impairment at any point during follow-up while all natural history subjects experienced severe cognitive impairment. However, this subject still had significant slowing of cognitive disease progression with progression to severe cognitive impairment (on both performance and language standard scores) after 6 years of age. Most natural history children had progressed to severe cognitive impairment by 3 years of age.*

The remaining 19 of 20 subjects had standard scores above the threshold of severe impairment at last follow-up. Two subjects had progressed to moderate impairment (standard scores < 70). Seventeen subjects retained standard scores in the normal or mild impairment range.

Therefore, a clear and robust treatment effect was also observed on the cognitive disease manifestations.

Additional endpoints specified by the Applicant including motor-impairment-free survival (defined as interval from both to earlier loss of the ability to walk [GMFC-MLD ≥3] or death) and age at confirmed loss of ambulation did not contribute to characterization of efficacy in the PSLI subjects.

Reviewer Comment: *These endpoints were difficult to assess due to missing data in the natural history study, with uncertainty regarding precise timing of when these events occurred in the enrolled untreated children.*

7.1.7 Subpopulations

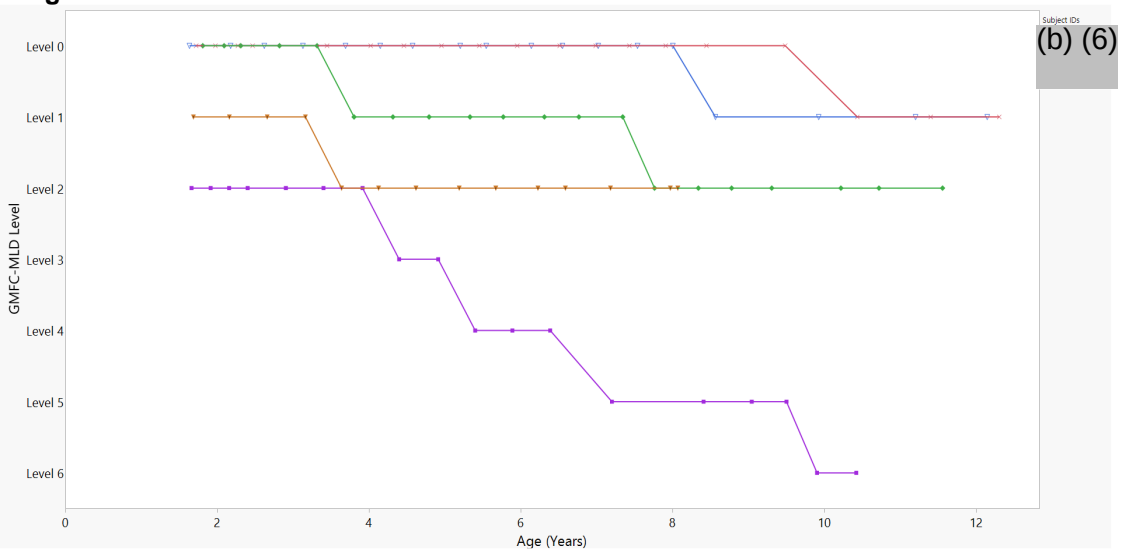
As discussed in Section 6.1.4, study subjects received two different dosing regimens of myeloablative conditioning. No differences in efficacy were observed between the two myeloablative regimens.

7.1.8 Persistence of Efficacy

Fifteen out of 20 treated PSLI subjects have been followed until at least 5 years of age:

- Four subjects maintained GMFC-MLD Level 0 at all timepoints after treatment and at last follow-up at ages 7.8, 8.3, 11.2, and 12.4 years.
- Two subjects were never able to achieve independent ambulation but were able to maintain supported ambulation (GMFC-MLD Level 2) at all timepoints after treatment and at last follow-up at ages 6.9 and 13.4 years.
- Six subjects experienced some disease progression after treatment, measuring Level 1, Level 2, or Level 6 at last follow-up, as shown in Figure 6.

Figure 6: GMFC-MLD Levels After Treatment in PSLI Subjects who Experienced Disease Progression



Source: Reviewer analysis of ISE ADFT Dataset
Abbreviations: GMFC, Gross Motor Function Classification; MLD, metachromatic leukodystrophy; PSLI, pre-symptomatic late infantile

Reviewer Comment: *While there are variable lengths of follow-up in the study subjects, there is evidence of persistence of efficacy beyond 5 years of age. While there are subjects that experienced disease progression (including one subject who progressed to severe motor impairment) and subjects that were unable to achieve independent ambulation, these clinical courses show either a stabilization of disease or a slowing of disease progression that represents a meaningful treatment effect.*

7.1.9 Product-Product Interactions

Although concomitant medications were documented for all subjects, no product-product interactions were expected or observed during the course of the clinical studies.

7.1.10 Additional Efficacy Issues/Analyses

ARSA Enzyme Levels

As discussed below in Section 7.2 and 7.3, there were challenges in interpreting the significance of the efficacy data for the PSEJ and ESEJ subpopulations. To facilitate interpretation of the PSEJ and ESEJ data, analyses of the ARSA enzyme levels in the PSLI subjects were conducted to understand whether there were trends in post-treatment ARSA levels and clinical benefit.

Reviewer Comment: *Brief review of ARSA enzyme activity in the CSF was conducted. However, there were less frequent assessments of CSF ARSA such that only the trends in PBMC ARSA were informative for efficacy analysis.*

After treatment, a rapid rise in PBMC ARSA to supranormal levels was observed in the PSLI subjects (normal range: 31 to 198 nmol/mg/h). The maximum post-treatment ARSA levels in PSLI subjects ranged from 402 to 7091 nmol/mg/h, with a median post-treatment maximum ARSA level of 3501 nmol/mg/h. The PBMC ARSA levels in PSLI subjects at various timepoints after treatment are shown in Table 10.

Table 10: Post-Treatment PBMC ARSA Levels in PSLI Subjects

Visit	N	N	Mean	Lower 95% CI	Upper 95% CI	Median	Minimum	Maximum
Baseline (Derived)	20	18	26	26	26	26	26	28
Day 60	20	17	386	195	764	420	26	2769
Month 3	20	18	492	269	900	682	61	3399
Month 6	20	16	583	264	1282	1095	37	2716
Month 9	20	9	203	85	484	310	26	721
Year 1	20	20	683	293	1590	1239	46	6467
Year 2	20	18	853	370	1966	935	26	5934
Year 3	20	18	1038	454	2372	1558	26	7091
Year 4	20	14	893	403	1979	1353	36	5222
Year 5	20	9	781	252	2414	755	28	3473
Year 6	20	7	617	233	1630	684	95	1938
Year 7	20	6	907	483	1700	963	402	2181
Year 8	20	5	912	413	2014	1034	331	1694

Source: Table X43.21, Applicant Response to Clinical IR#8, BLA125758/0.47
Abbreviations: ARSA, arylsulfatase A; CI, confidence interval; PBMC, peripheral blood mononuclear cell; PSLI, pre-symptomatic late infantile

Reviewer Comment: *PBMC ARSA levels in the PSLI subjects rapidly reached supranormal levels after treatment. Subjects developed PBMC ARSA enzyme levels up to 30 times the upper limit of normal. The clinical review team was unable establish a numerical threshold for PBMC ARSA enzyme levels that predicted clinical benefit. Some PSLI subjects were able to derive benefit at lower levels. Additionally, as shown in Table 10, there were subjects who experienced decreases in PBMC ARSA to below or near the lower limit of normal. However, these levels were observed to rebound to supranormal levels.*

There did appear to be a qualitative relationship between PBMC ARSA enzyme levels and clinical outcomes. For example, subject (b) (6) *(who had slowed progression to motor*

impairment after treatment, shown in Figure 6) experienced subtherapeutic PBMC ARSA enzyme levels that occurred in parallel with clinical decline.

Additionally, as discussed in the clinical pharmacology reviewer's memo, there was an association between higher PBMC ARSA levels and higher total administered CD34+ cells (determined by multiplying the administered dose per kg by the subject's weight at infusion). This suggests that a higher total CD34+ cell dose may result in more robust clinical efficacy.

In the PSLI subjects treated in the clinical trial, the minimum dose associated with clinical benefit was observed to be $4.2x10^6$ CD34+ cells/kg. The minimum weight of a treated subject associated with clinical benefit is 7.2 kg. Please see clinical pharmacology memo for additional dose-response analyses.

Reviewer Comment: *Given the association between higher CD34+ cells, higher ARSA enzyme levels and clinical efficacy, the clinical review team does not believe it is suitable to extrapolate efficacy to small total doses in younger infants who will weights less than those studied in the clinical trial.*

7.1.11 Efficacy Conclusions

In summary, the clinical review team concludes that there is substantial evidence of effectiveness of OTL-200 for the requested indication of PSLI MLD from analysis of the pooled data from two open-label, single-arm clinical trials and three expanded access studies utilizing a natural history study as an external control. Analyses of the primary endpoint of sMFS demonstrates that none of the PSLI subjects treated with OTL-200 followed until 5 years of age progressed to severe motor impairment, while all untreated LI natural history subjects had progressed to severe motor impairment. Efficacy was also demonstrated in the key secondary endpoints of overall survival, motor impairment at Year 2 and Year 5 after treatment, and cognition (measured on performance and language standard scores). Additional pharmacodynamic analyses of post-treatment PBMC ARSA levels also support evidence of efficacy, with subjects reaching supranormal levels rapidly after treatment. This data represents a dramatic treatment effect.

However, an important consideration is whether a minimum weight for treatment with OTL-200 should be specified. A relationship between total CD34+ cells (calculated from subject weight and dose administered) and PBMC ARSA levels was observed. Therefore, extrapolation of clinical benefit to lower weights than were studied in the clinical trial is not deemed to be feasible. Based on the weight of the smallest subject treated in the clinical trial, **the clinical review team recommends approval of OTL-200 for the treatment of PSLI MLD in patients who weigh** (b) (5) .

The clinical review team does recognize the importance to treat early in LI MLD, which is rapidly progressive and irreversible after symptom onset. Per the Center for Disease Control and Prevention (CDC) pediatric clinical growth charts, 7 kg represents approximately the 50^{th} percentile for 5 months of age in boys and 6 months of age in girls. Review of the literature suggests that most commonly, LI MLD presents after 12 months of age (Kehrer et al. 2021). Therefore, this minimum weight parameter for treatment would not prevent treatment prior the onset of symptoms.

7.2 Indication #2: Pre-symptomatic Early Juvenile MLD

7.2.1 Methods of Integration

All PSEJ subjects from the two clinical trials and three expanded access studies were integrated for efficacy analyses. The genotype, pre-treatment clinical course, baseline clinical exam, and post-treatment clinical course were assessed for each subject individually to determine whether the clinical review team agreed with the IRC adjudications of disease subtype and symptomatic status at the time of treatment.

One subject, (b) (6), was reclassified as PSEJ for the purposes of the efficacy analyses. This subject was originally adjudicated as ESEJ, though the IRC agreed that this subject was borderline between pre-symptomatic and early symptomatic. This subject was noted to have exam findings limited to brisk reflexes in the lower limb with clonus. No other findings were noted with a normal developmental assessment.

Reviewer Comment: *This subject, who had no symptoms and exam findings limited to clonus and brisk reflexes, appeared to be in a much earlier stage of disease progression when compared to the other ESEJ subjects. Therefore, this subject was considered to be more similar to the PSEJ subjects and was reclassified as such. Additionally, as discussed in* ***Section 7.1.1****, two subjects originally adjudicated as PSEJ were reclassified as PSLI. All analyses presented in this review account for these reclassifications. For the purposes of this clinical trial, PSEJ was defined as "children with EJ MLD who asymptomatic and those who have examination findings limited to clonus and/or abnormal reflexes." Per the definitions used by the Applicant in the clinical trial, pre-symptomatic subjects included subjects with abnormalities on brain MRIs and/or nerve conduction tests that were not associated with functional impairment.*

7.2.2 Demographics and Baseline Characteristics

Table 11: Demographics and Baseline Characteristics of PSEJ Subjects

Parameter	**PSEJ (N=7)**
Sex, n (%)	-
Female	1 (14%)
Male	6 (86%)
Country of residence, n (%)	-
U.S.	3 (43%)
Non-U.S.	4 (57%)
Race, n (%)	-
White	6 (85%)
Asian	0 (0)
Black or African American	1 (14%)
Age at OTL-200 treatment (months)	-
Median	31
Minimum – maximum	11-67
Weight at OTL-200 treatment (kg)	-
Median	14.5
Minimum – maximum	9.8-19.3

Source: Reviewer analysis of ISE ADSL and ADVS datasets
Abbreviations: PSEJ, pre-symptomatic early juvenile; US, United States

7.2.3 Subject Disposition

One subject died approximately 1 year after receiving the treatment due to a cerebral infarction unrelated to MLD disease progression. This is discussed further in Section 8.4.8. The remaining six subjects are still enrolled in the study. These six subjects have been followed for 2.4 to 8.5 years (median of 3.8 years) and are 3.9 to 13.6 years (median of 6.1 years at last follow-up).

Reviewer Comment: *There are three subjects who are between 3.9 and 5 years of age at last follow-up. Lack of treatment effect can be determined in these subjects if they showed progression of MLD symptoms. However, treatment effect of OTL-200 cannot be determined in these three subjects as untreated children with EJ MLD may not experience significant symptom onset until 7 years of age. Therefore, these three subjects are too young to detect a treatment effect from OTL-200. The endpoints will be presented individually for each subject given that summary statistics and statistical analyses have limited utility in this small PSEJ study population.*

7.2.4 Analysis of Primary Endpoints

The primary endpoint is sMFS, 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.

Reviewer Comment:

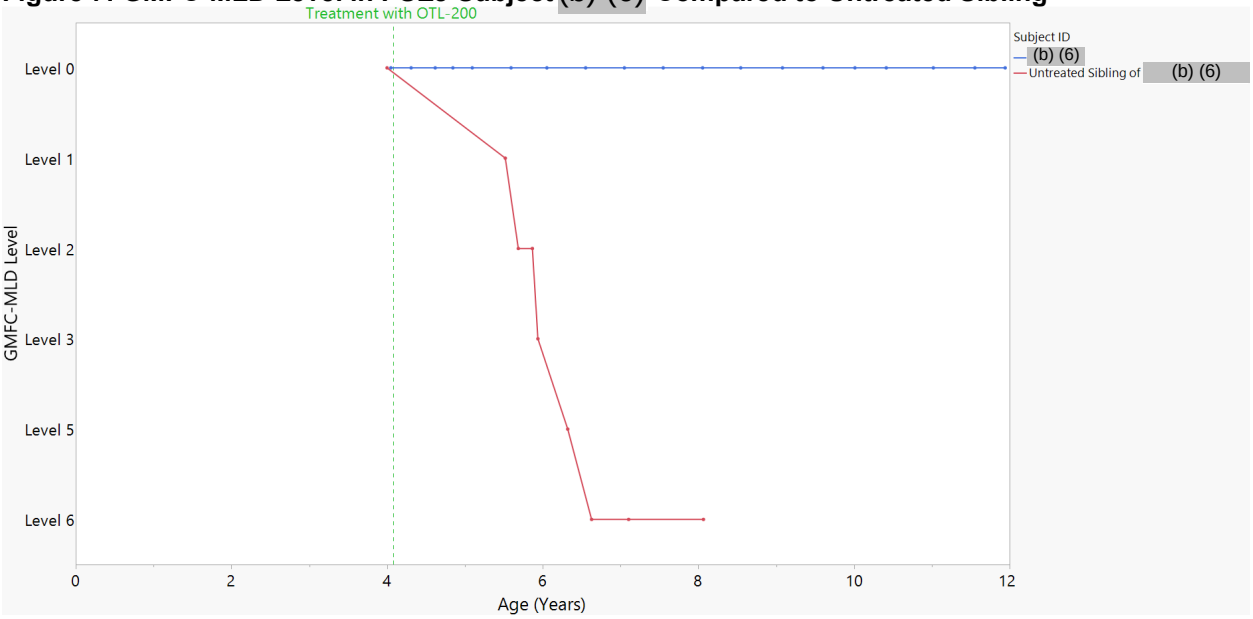
EJ MLD is heterogenous, where children may be asymptomatic until 7 years of age and experience variable disease progression after symptom onset. The clinical review team's assessment is that the EJ children enrolled in the natural history study represent patients on the more severe end of the disease spectrum; the natural history did not enroll children with a milder EJ phenotype. As presented in Section 6.4.10, the median age of symptom onset for the untreated children with EJ MLD was 50 months (range: 24 to 75). This includes one subject who presented <30 months of age with an intermediate phenotype between LI and EJ MLD. Given the relationship between age of symptom onset and disease severity, the clinical review team assesses these subjects to have a severe EJ phenotype. Patients with more mild disease (i.e., symptom onset closer to 7 years of age [84 months]) are not sufficiently captured in this natural history population. The rapid disease progression after symptom onset observed in the natural history EJ children was not considered representative of the well-documented phenotypic variability and slower disease progression observed in the published natural history of EJ MLD (Fumagalli et al. 2021).

Therefore, the natural history EJ children are not considered an appropriate comparator for the treated PSEJ subjects. The PSEJ subjects are analyzed and compared to the natural history of the disease characterized in published literature. Additionally, two subjects ((b) (6) *and* (b) (6) *) had data from an untreated sibling available. While variation in disease progression and even MLD subtype can exist between siblings, this is uncommon (Elgun et al. 2019). At the age when these two PSEJ subjects were asymptomatic and treated with OTL-200, their sibling controls were also asymptomatic. Therefore, both siblings are considered matched comparators for their treated sibling.*

Patients with EJ MLD may not progress to severe motor impairment until 10 years after symptom onset (Fumagalli et al. 2021). All PSEJ subjects were asymptomatic at baseline and no subject in the PSEJ cohort treated with OTL-200 was followed for 10 years. Thus, there is insufficient follow-up duration to assess treatment effect on the primary endpoint.

There were three subjects ((b) (6)) who were had sufficient follow-up to detect a treatment effect of OTL-200. Figure 7 shows the motor progression of subject (b) (6) in comparison to their untreated sibling who was enrolled in the natural history study ((b) (6)).

Figure 7: GMFC-MLD Level in PSEJ Subject (b) (6) Compared to Untreated Sibling



Source: Reviewer analysis of ISE ADFT Dataset
Abbreviations: GMFC, Gross Motor Function Classification; MLD, metachromatic leukodystrophy; PSEJ, pre-symptomatic early juvenile

Subject (b) (6) was treated at age 3.6 years. At last follow-up at age 7.3 years, this subject retained a normal gait (GMFC-MLD Level 0). The untreated sibling experienced symptom onset characterized by GMFC-MLD Level 1 at age 4.8 years.

Subject (b) (6) was treated at age 5.6 years. This subject maintained GMFC-MLD Level 0 until age 12.8 years, when they progressed to GMFC-MLD Level 1. At last follow-up at age 13.6 years, this subject remained at GMFC-MLD Level 1. This subject did not have an untreated sibling to use as a matched control.

Reviewer Comment: *There are three subjects who have sufficient follow-up to detect a treatment effect on motor outcomes. All three subjects retained independent ambulation at last follow-up:*

- (b) (6) *was followed until 11.9 years of age and retained a GMFC-MLD Level 0 at last follow-up.*
- (b) (6) *was followed until age 7.3 years and retained GMFC-MLD Level 0 at last follow-up.*
- (b) (6) *remained at GMFC-MLD Level 0 until age 12.8 years, when the subject declined to GMFC-MLD Level 1.* (b) (6) *maintained GMFC-MLD Level 1 at last follow-up at 13.6 years.*

Based on published literature of the natural history of EJ MLD (Fumagalli et al. 2021; Kehrer et al. 2021), maintenance of independent ambulation at these ages is unexpected in untreated EJ children. Independent ambulation at these ages has only been reported in LJ MLD or phenotypes that are intermediate between EJ and LJ MLD. Based on the genotype and the

clinical courses of the siblings for (b) (6) *and* (b) (6) *, it is highly unlikely that these subjects have an atypical presentation of EJ MLD.*

As siblings with EJ MLD typically have similar courses, there is additional evidence of efficacy of OTL-200 on motor outcomes when comparing (b) (6) *and* (b) (6) *to their matched sibling controls.* (b) (6) *retained GMFC-MLD Level 0 past the age when their sibling had already progressed to GMFC-MLD Level 6.* (b) (6) *was followed to age 7.3 years, retaining GMFC-MLD Level 0, more than 2 years after their untreated sibling had progressed to GMFC-MLD Level 1.*

Although there is very a small study population for which efficacy can be evaluated, there is evidence to demonstrate motor benefit in these three PSEJ subjects.

7.2.5 Analysis of Secondary Endpoints

The key secondary endpoints in the integrated efficacy analysis were proportion of subjects who experienced severe motor impairment or death at 2- and 5- years post-treatment and overall survival.

Reviewer Comment: *The clinical review team does not agree that the endpoints of severe motor impairment or death at 2-years and 5-years post-treatment are suitable or interpretable for the PSEJ population. In this population, children were treated when they were asymptomatic and the expected rate of progression to severe motor impairment in children with untreated EJ MLD may not occur until 10 years after symptom onset. Thus, two years or five years are insufficient to detect treatment effect.*

7.2.6 Other Endpoints

An additional endpoint of severe cognitive impairment-free survival was defined as the interval between birth and the first occurrence of severe cognitive impairment (defined as performance standard score ≤55 with no performance standard score >55 at later assessments). The performance standard scores and language standard scores at last neurocognitive assessment for the three PSEJ subjects are shown in :

Table 12: Performance and Language Standard Scores at Last Follow-Up for PSEJ Subjects
(b) (6)

Subject ID	Age at Neurocognitive Assessment	Performance Standard Score	Language Standard Score
(b) (6)	11.4 years	115	86
(b) (6)	12.0 years	130	122
(b) (6)	6.7 years	145	126

Source: ISE ADIQ Dataset
Abbreviations: PSEJ, pre-symptomatic early juvenile "Broadly average range" of cognitive functioning is defined as a standard score ≥85.

Please see memo from Dr. Naomi Knoble from the DCOA for additional discussion on the neurocognitive efficacy results.

Reviewer Comment*: Children with EJ MLD are expected to have some neurocognitive impairment after 7 years of age (Kehrer et al. 2014). Therefore, both* (b) (6) *and* (b) (6) *have performance and language standard scores that are unexpected in the natural history of EJ MLD.* (b) (6) *does not have neurocognitive assessments past 7 years of age; therefore, it*

is premature to assess whether this child has a neurocognitive treatment effect. Given the importance of cognitive functioning to patients with MLD, families and caregivers, the favorable neurocognitive outcomes in these two subjects provide clinically meaningful evidence of benefit of OTL-200 on cognition in PSEJ MLD.

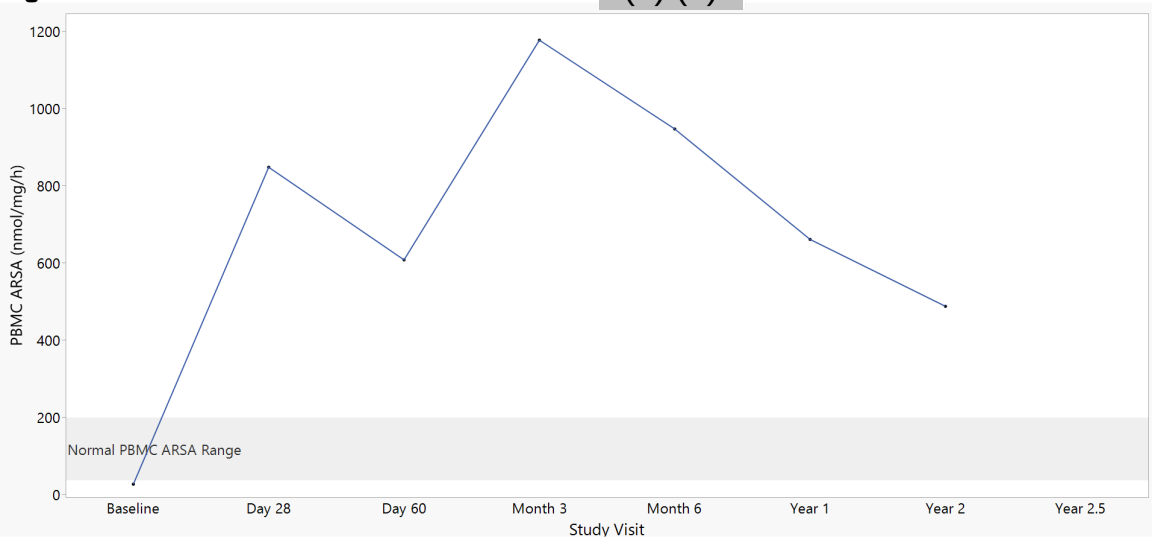
7.2.7 Subpopulations

As discussed in Section 6.1.4, study subjects received two different dosing regimens of myeloablative conditioning. No differences in efficacy were observed between the two myeloablative regimens.

7.2.8 Persistence of Efficacy

There is limited data on the persistence of efficacy. The range of the duration of follow-up in all treated subjects was 1.1 years to 8.1 years (median 3.9 years). At the time of BLA submission, there is no clinical data to suggest waning of product efficacy over time. Subject (b) (6), treated at age 30.9 months, is noted to have declining PBMC ARSA levels at last follow-up in the presence of anti-ARSA antibodies (see Section 8.5.8 for additional discussion). However, this subject remains in the pre-symptomatic phase of their disease and impact on efficacy of this declining ARSA level is unknown. The trend in ARSA enzyme levels over time in this subject is shown in Figure 8.

Figure 8: PBMC ARSA Level After Treatment in (b) (6)



Source: Reviewer analysis of ISE ADARSA Dataset
Abbreviations PBMC, peripheral blood mononuclear cells; ARSA, arylsulfatase A

7.2.9 Product-Product Interactions

Although concomitant medications were documented for all subjects, no product-product interactions were expected or observed during the course of the clinical studies.

7.2.10 Additional Efficacy Issues

Given the small number of PSEJ subjects who had adequate follow-up to detect efficacy in clinical outcomes, analyses of post-treatment ARSA levels in all PSEJ subjects were conducted and are shown in Table 13.

Table 13: Post-Treatment PBMC ARSA Levels in PSEJ Subjects

Visit	N	n	Mean	Lower 95% CI	Upper 95% CI	Median	Min	Max
Baseline	7	7	29	22	37	26	26	53
Day 60	7	7	712	244	2074	607	141	3700
Month 3	7	6	807	426	1530	1140	314	1300
Month 6	7	6	680	243	1907	983	150	1804
Year 1	7	7	855	462	1584	883	272	1977
Year 2	7	6	922	431	1970	1063	328	2205
Year 3	7	4	1101	420	2884	1157	539	2173

Source: Table X43.22, Applicant Response to Clinical IR#8, BLA125758/0.47
Abbreviations: ARSA, arylsulfatase A; CI, confidence interval; PBMC, peripheral blood mononuclear cell; PSEJ, pre-symptomatic early juvenile

Reviewer Comment: *Similar to the PSLI subpopulations, the PSEJ subjects were able to rapidly achieve supranormal PBMC ARSA levels (normal range 30.56 to 198.02 nmol/mg/h). In the three PSEJ subjects who did not have adequate follow-up to observe clinical outcomes that deviate from the natural history, two subjects had persistently high post-treatment ARSA enzyme levels (reaching a maximum of 1982 and 2205 nmol/mg/h). This is suggestive of a pharmacodynamic treatment effect that may indicate clinical benefit of OTL-200 in these subjects as well. It is unclear whether subject* (b) (6) *will have a treatment effect given the persistent anti-ARSA antibody levels and waning PBMC ARSA enzyme levels discussed above in Figure 8.*

The clinical review team also observes that the maximum post-treatment levels of PBMC ARSA in the PSEJ subjects, although supranormal, were considerably lower than PSLI subjects (who were able to achieve levels >5000 nmol/mg/h).

As discussed in the clinical pharmacology reviewer's memo and in discussion of the ARSA data for the PSLI subjects, a relationship between total CD34+ cells (based on weight and administered dose) was observed. The minimum dose used in the five subjects who demonstrated efficacy (either in clinical outcomes or post-treatment ARSA levels) was $9x10^6$ CD34+ cells/kg and the minimum weight at OTL-200 infusion was 10 kg. Please see clinical pharmacology memo for additional dose-responses analyses.

Reviewer Comment: *Given the association between higher CD34+ cells, higher ARSA enzyme levels, and clinical efficacy, the clinical review team does not believe it is suitable to extrapolate efficacy to smaller doses and younger weights (<10 kg) that have not been studied in the clinical trial. Of note,* (b) (6) *received a substantially higher dose (25 x 106 cells/kg) and was 16 kg at the time of infusion. Therefore, the clinical review team believes that their declining ARSA levels are more likely attributed to anti-ARSA antibodies, rather than the dose of CD34+ cells received.*

7.2.11 Efficacy Conclusions

Despite the limitations of a small study population, there is adequate evidence to support efficacy of OTL-200 for the requested PSEJ indication. In our analyses, we have defined PSEJ to include patients who are asymptomatic (including those with abnormalities on brain MRI and/or nerve conduction tests that are not associated with functional impairment) and those who have examination findings limited to clonus and/or abnormal reflexes. Three subjects had motor outcomes and two subjects had cognitive outcomes that were unexpected based on published literature of the natural history of the disease. Additionally, post-treatment ARSA enzyme levels

provided additional supportive evidence of efficacy, where subjects (even those with a limited duration of follow-up) demonstrated rapid rise to supranormal ARSA levels after treatment. 1 PSEJ subject died due to a cerebral infarction unrelated to MLD but potentially related to OTL-200. This subject is discussed in Section 8.

As was considered for the PSLI indication, a similar consideration for the PSEJ indication is whether a minimum weight for treatment with OTL-200 should be specified. In comparison to LI MLD, EJ MLD has a longer pre-symptomatic disease phase. As highlighted in Section 7.2.10 and the clinical pharmacology review memo, the observed relationship between dose, weight, and ARSA enzyme levels limits the ability to extrapolate the efficacy to a younger age and lower weight group. Additionally, patients have longer pre-symptomatic phases of their disease and there is limited evidence to demonstrate durability of treatment. The minimum weight at the time of infusion of the subjects who demonstrated efficacy (either through clinical outcomes or post-treatment ARSA enzyme levels) was 10 kg. Therefore, the clinical review team recommends that OTL-200 be approved for PSEJ MLD with a minimum weight for treatment of (b) (5) Therefore, this parameter would still allow patients to be treated early in their pre-symptomatic phase.

Additionally, as discussed in Section 2.1, there is discrepancy in both the literature and clinical practice on the upper age limit of EJ MLD (both 6 and 7 years of age are utilized). Given that the clinical data in this BLA submission was analyzed using a definition of less than 7 years of age, the primary clinical review team recommends the indication statement also utilize an upper age limit of 7 years to provide clarity to patients, families, and providers. Therefore, the clinical team recommends approval of OTL-200 for " (b) (5) .

7.3 Indication #3: Early Symptomatic Early Juvenile MLD

7.3.1 Methods of Integration

All ESEJ subjects from the two clinical trials and three expanded access studies were integrated for efficacy analyses. As discussed in Section 7.2.1, one subject originally classified as ESEJ by the Applicant was reclassified as PSEJ during the BLA review.

7.3.2 Demographics and Baseline Characteristics

Table 14: Demographics and Baseline Characteristics of ESEJ Subjects

Parameter	ESEJ (N=10)
Sex, n (%)	-
Female	4 (40%)
Male	6 (60%)
Country of residence, n (%)	-
U.S.	3 (30%)
Non-U.S.	7 (70%)
Race, n (%)	-
White	10 (100%)
Ethnicity, n (%)	-
Not Hispanic or Latino	10 (100%)
Age at OTL-200 treatment (months)	-
Median	70
Min – max	31-140
Age at Symptom Onset (months)	-
Median	62
Min – max	29-83

Source: Reviewer analysis, ADSL Dataset
Abbreviations: ESEJ, early symptomatic early juvenile; Max, maximum; Min, minimum

***Reviewer Comment**: As shown in Table 14, symptom onset in the OTL-200 subjects ranged from 29 to 83 months (median: 62 months). The symptom onset in the natural history population occurred between 24 and 75 months (median: 50). Given the earlier onset of symptoms in the natural history population, the clinical team assessed that the natural history population was not an appropriate comparator to the OTL-200 ESEJ subjects who had later symptom onset and more mild disease. This is discussed further in Section 7.3.4 in subject-level comparisons to the natural history.*

7.3.3 Subject Disposition

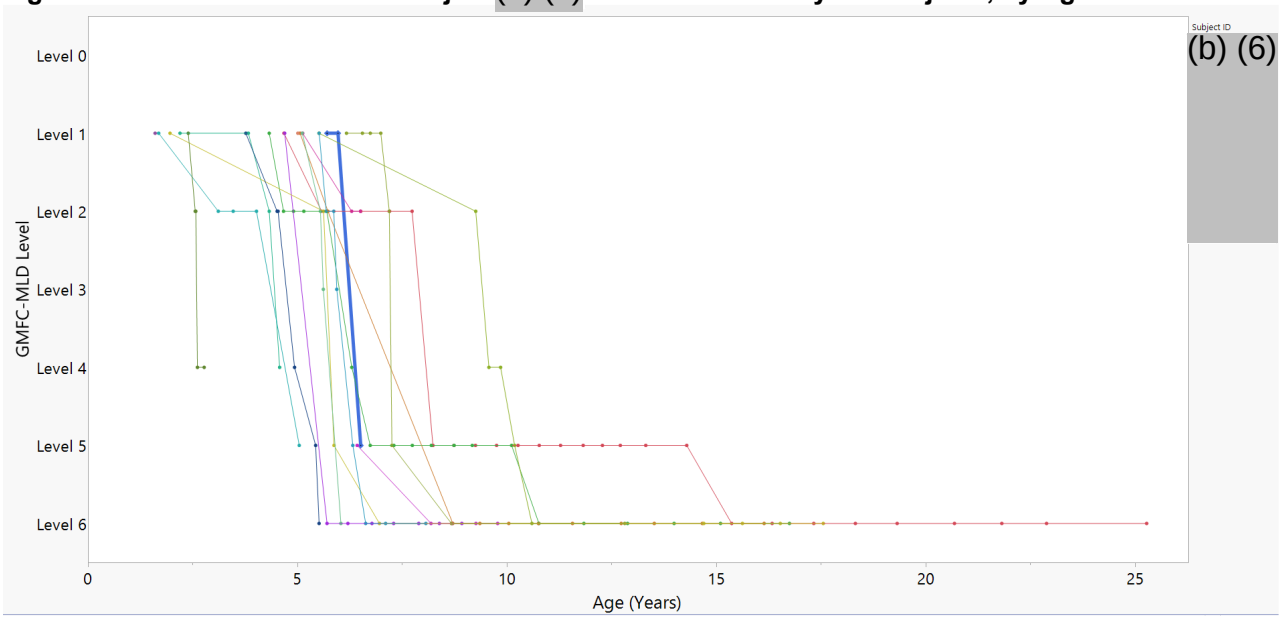
Two subjects (20%) died after treatment from MLD disease progression. The remaining eight subjects are still enrolled in the study, with age at last follow-up between 5.1 and 19.1 years of age (median: 13.8 years of age) and duration of follow-up between 2.6 and 9.4 years (median: 7.7 years).

7.3.4 Analysis of Primary Endpoints

The primary endpoint is sMFS, 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. Given the lack of comparability between the natural history subjects, substantial missing data in the natural history EJ subjects, and phenotypic heterogeneity in EJ MLD, pooled analysis of this primary endpoint was not considered suitable for the ESEJ subpopulation. Rather, motor progression of each individual ESEJ subject was analyzed separately in comparison to natural history children with EJ MLD. Two subjects had follow-up data for only 2 years ((b) (6) and (b) (6)), which is insufficient to detect clinical efficacy. Therefore, they are not considered in the efficacy analysis.

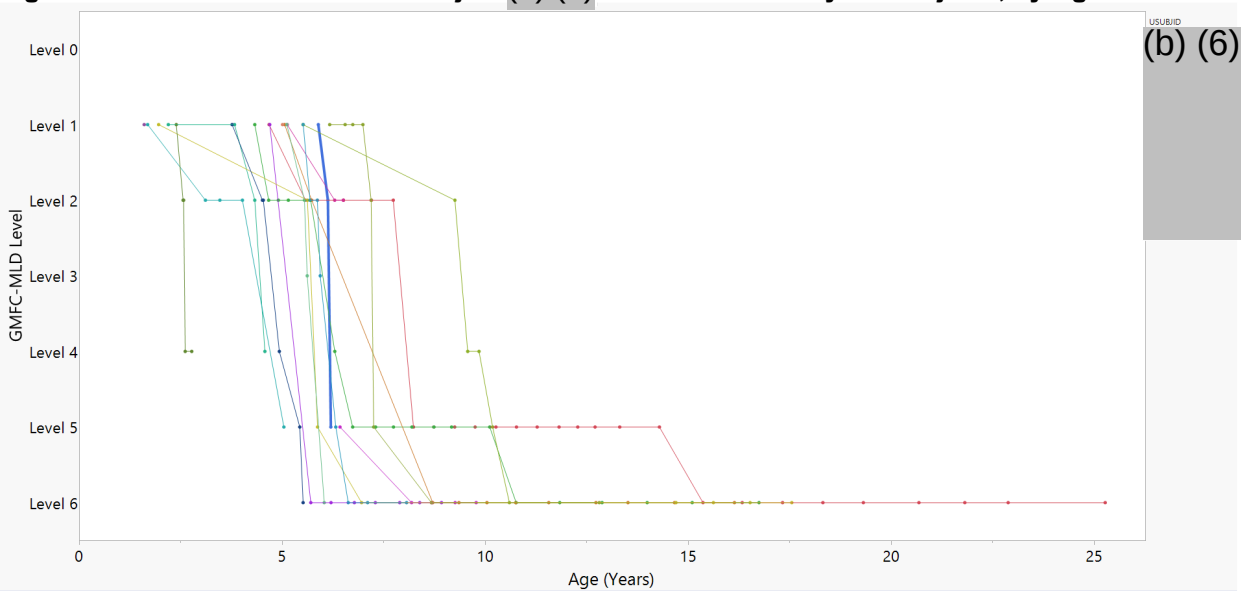
Two subjects, (b) (6) and (b) (6), developed rapid motor progression after treatment and progressed to death within 1.2 years and 0.6 years, respectively. Figure 9 and Figure 10 plot the GMFC-MLD level for these two subjects over age versus the natural history EJ subjects.

Figure 9: GMFC-MLD Level for Subject (b) (6) vs. Natural History EJ Subjects, by Age



Source: Reviewer analysis of ADFT Dataset
Abbreviations: EJ, early juvenile; GMFC, Gross Motor Function Classification; MLD, metachromatic leukodystrophy

Figure 10: GMFC-MLD Level for Subject (b) (6) vs. Natural History EJ Subjects, by Age



Source: Reviewer analysis of ISE ADFT Dataset
Abbreviations: EJ, early juvenile; GMFC, Gross Motor Function Classification; MLD, metachromatic leukodystrophy

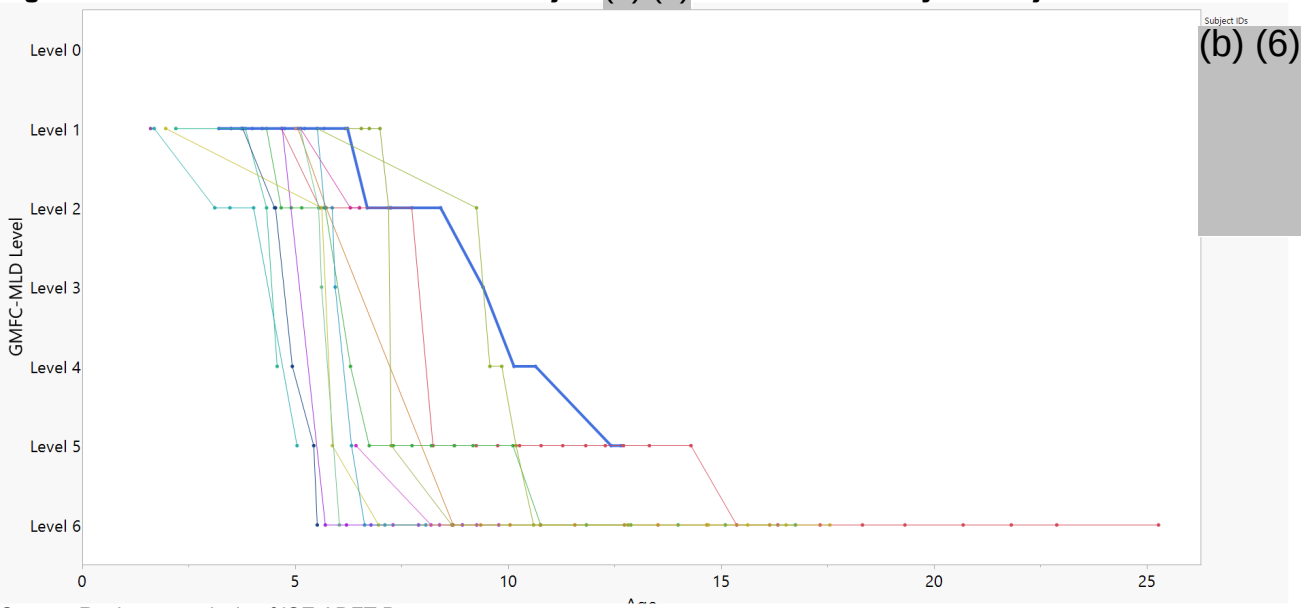
Reviewer Comment: *After treatment, both these subjects rapidly progressed to death due to MLD disease progression.* (b) (6) *had symptom onset at 5.0 years of age and died by 7.0 years of age.* (b) (6) *had symptom onset at 5.4 years of age and died at 6.6 years of age. This*

progression, as shown in both Figure 9 and Figure 10 above, appears faster than the progression in the natural history EJ subjects. The untreated natural history EJ subjects appear to have periods of plateau in motor function, while these two subjects progressed rapidly (without periods of plateau) to death. Additionally, natural history data published in Fumagalli et al (2021) demonstrates that 0 untreated EJ subjects had progressed to death within 5 years after symptom onset (publication Figure 1A), with events of death occurring more than 5 years after symptom onset. Therefore, the clinical review team is concerned that these subjects experienced progression from symptom onset to death at a rate that may be faster than what is expected in untreated EJ MLD.

An important consideration in this assessment is the potential pathophysiological explanation. Patients with EJ MLD are known to have genetic mutations that encode some residual ARSA enzyme activity. The clinical review team hypothesizes that the rapid post-treatment motor progression in these subjects may occur due to the interval of absent ARSA activity that occurs after myeloablative conditioning and prior to engraftment. Therefore, ESEJ subjects who have already begun to experience disease progression, are left with a period of decreased ARSA enzyme activity from baseline. This may lead to acceleration in progression of disease until engraftment and ARSA enzyme conferred by engraftment of OTL-200 can occur.

The data on GMFC-MLD in the remaining ESEJ subjects are presented individually below with the review team's assessments.

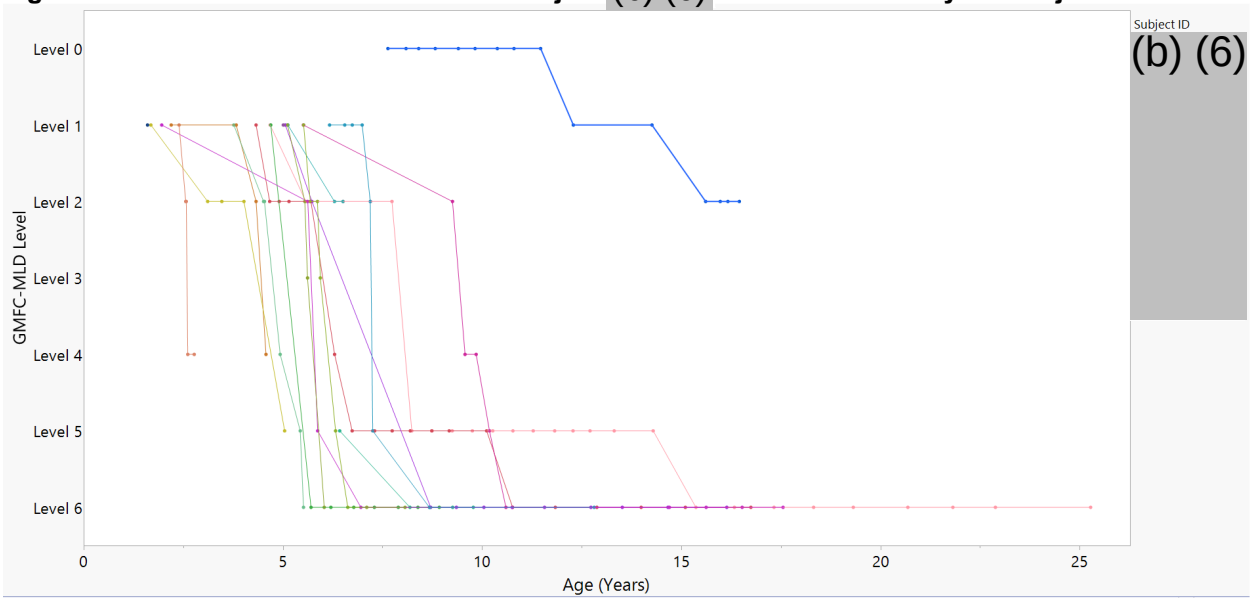
Figure 11: GMFC-MLD Scores for ESEJ Subject (b) (6) vs. Natural History EJ Subjects



Source: Reviewer analysis of ISE ADFT Dataset
Abbreviations: EJ, early juvenile; ESEJ, early symptomatic early juvenile; GMFC, Gross Motor Function Classification; MLD, metachromatic leukodystrophy

Reviewer Comment: *(b) (6) (Figure 11), treated at age 3.2 years, appears comparable to the natural history population at the time of treatment, progressing to GMFC-MLD Level 1 without treatment at a similar age to the natural history EJ subjects. This subject progressed to severe motor impairment (Level 5) by age 12.4 years. While it is possible that there is slowing of progression from Level 2 to Level 4, this is difficult to determine given the limitations of the natural history data (missing ages at entry to Level 4 in many subjects).*

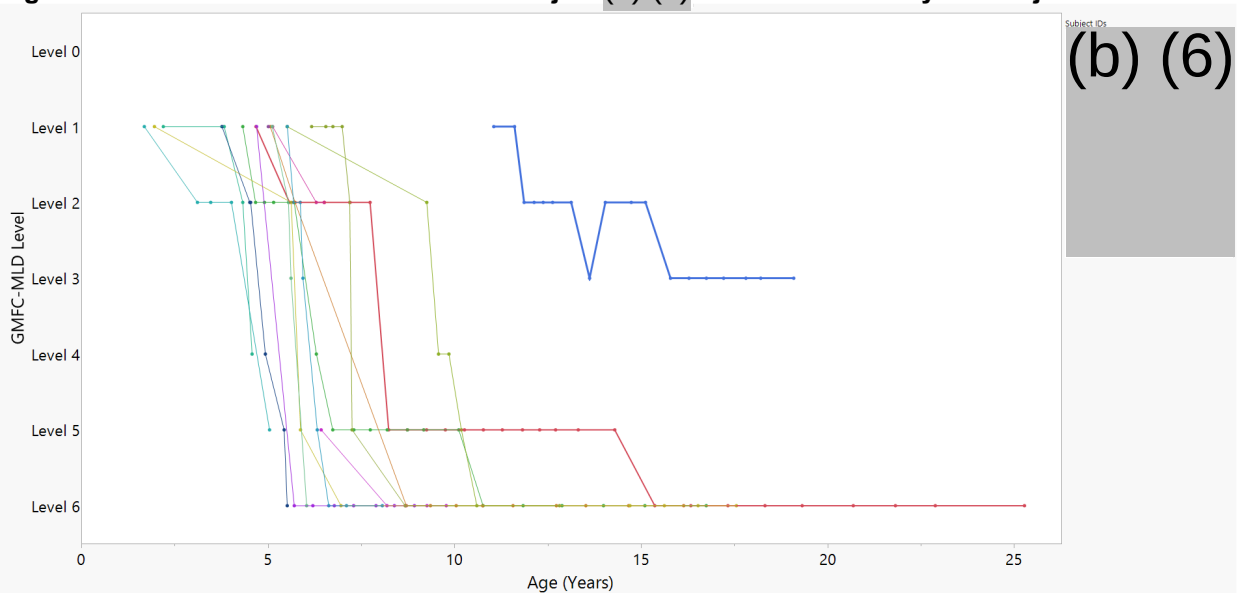
Figure 12: GMFC-MLD Scores for ESEJ Subject (b) (6) vs. Natural History EJ Subjects



Source: Reviewer analysis of ISE ADFT Dataset
Abbreviations: EJ, early juvenile; ESEJ, early symptomatic early juvenile; GMFC, Gross Motor Function Classification; MLD, metachromatic leukodystrophy

Reviewer Comment: (b) (6) *(Figure 12), even prior to treatment, had a more mild disease course than the natural history children, retaining GMFC-MLD Level 0 untreated at a much later age. Therefore, the natural history children with EJ MLD do not serve as an appropriate comparator for this study subject,* (b) (6) *. Subject* (b) (6) *developed symptom onset at 6.9 years of age and was treated at 7.8 years of age (retaining GMFC-MLD Level 0 untreated for 0.9 years). As published in Fumagalli et al (2021), most untreated children with EJ MLD would be expected to lose independent ambulation (progress to > GMFC-MLD 1) within the first year of symptom onset. Therefore, this subject represents a mild EJ phenotype in the spectrum of EJ MLD disease, or even a LJ phenotype given the symptom onset occurred at almost 7 years of age. Published natural history literature indicates that untreated children with LJ MLD may retain independent ambulation for more than 15 years after symptom onset (Fumagalli et al. 2021). Without appropriate natural history comparators, it is difficult to determine whether this subject's progression to GMFC-MLD Level 3 by 16.5 years of age represents a treatment effect or would be expected in their untreated natural course.*

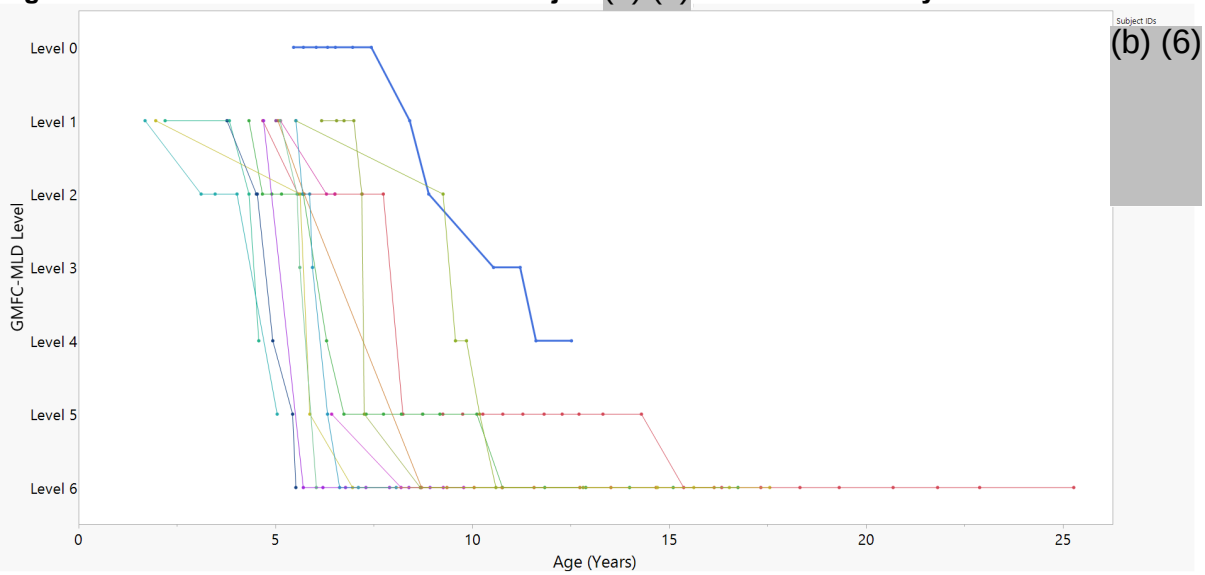
Figure 13: GMFC-MLD Scores for ESEJ Subject (b) (6) vs. Natural History EJ Subjects



Source: Reviewer analysis of ISE ADFT Dataset
Abbreviations: EJ, early juvenile; ESEJ, early symptomatic early juvenile; GMFC, Gross Motor Function Classification; MLD, metachromatic leukodystrophy

Reviewer Comment: (b) (6) *(Figure 13) was noted to have symptom onset defined as problems with balance and diminished deep tendon reflexes at 5 years and 4 months of age. Given that these symptoms are non-specific and may be influenced by both the compliance of a 5-year-old and the neurologic examination skills of the assessor, it is difficult to know whether these findings truly represented disease onset in this subject. At 9 years of age, the subject presented with more specific MLD disease symptoms including lower limb weakness and abnormal electroneurography results. Additionally, this subject retained independent ambulation at a much later age than would be expected, per the untreated EJ natural history children and published literature. Fumagalli et al indicates that all untreated patients with EJ progress to GMFC-MLD Level >1 within 5 years of symptom onset. As such, this subject appears to have a phenotype more consistent with LJ MLD (where symptom onset would be defined as occurring at 9 years of age). As discussed above, children with untreated LJ MLD may preserve independent ambulation for up to 15 years after symptom onset. Therefore, this subject's clinical course that is more similar to LJ MLD is not supportive of efficacy in ESEJ MLD.*

Figure 14: GMFC-MLD Scores for ESEJ Subject (b) (6) vs. Natural History



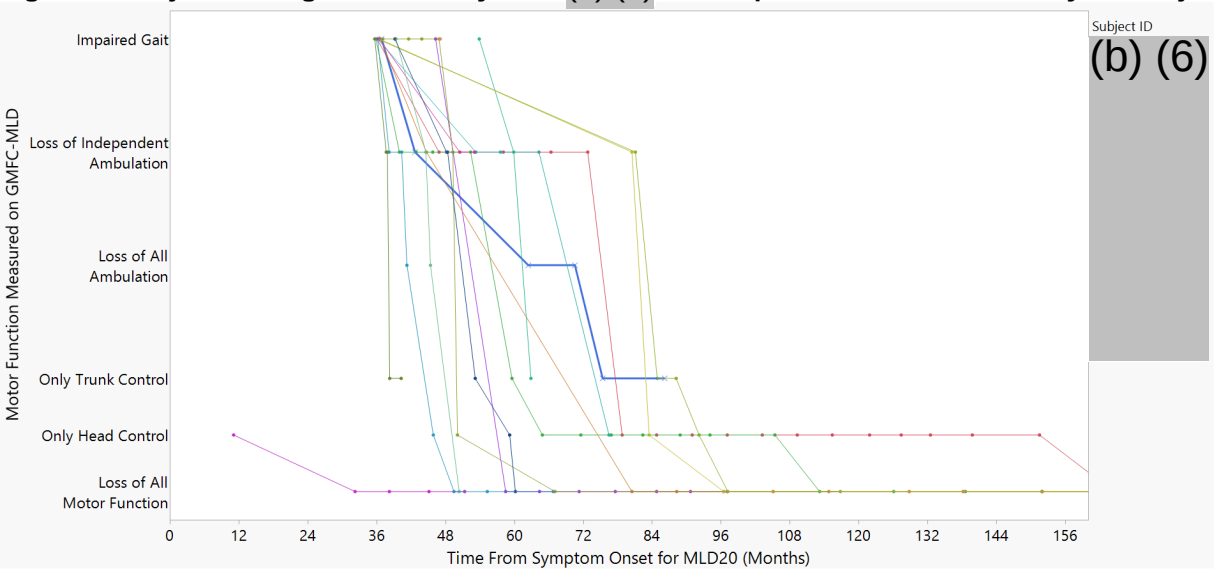
Source: Reviewer analysis of ISE ADFT Dataset
Abbreviations: ESEJ, early symptomatic early juvenile; GMFC, Gross Motor Function Classification; MLD, metachromatic leukodystrophy

Reviewer Comment: *Similar to other ESEJ subjects, (b) (6) (Figure 14 above) retained a normal gait (GMFC-MLD Level 0) at a later age than the natural history children. As such, the natural history study is not an appropriate comparator for this subject. This subject is observed to progress rapidly to GMFC-MLD Level 4 (retaining only trunk control) without periods of plateau, as observed in the natural history subjects. This is an unexpected outcome in this treated subject, given the more mild disease at baseline. Therefore, there is no evidence to suggest there is a treatment effect characterized by slowing of motor progression in this subject. Additionally, there is concern that there is faster progression of motor disease, with this treated subject (who has more mild disease) not experiencing times of motor function plateau, as seen in the natural history children (who have more severe disease).*

To provide a crude assessment of disease progression in this subject, an adjusted progression analysis was conducted whereby the natural history progression lines were adjusted to match the time (b) (6) reached GMFC-MLD Level 1 (Figure 15).

Reviewer Comment: *Figure 15 serves to assess the rate of motor progression of (b) (6) from GMFC-MLD Level 1 compared to natural history subjects, adjusting the natural history subjects such that Level 1 serves as "time 0". On the y-axis, the motor function correlates to each GMFC-MLD level as shown. When considering the GMFC-MLD levels, the difference between each level is not considered equivalent. There is significant variability in motor function that occurs between states of impaired gait, loss of independent ambulation, and loss of all ambulation and trunk control (Levels 1 to 3). Comparatively, there is less variability at the levels of motor function between loss of trunk control, head control, and all motor functions (Levels 4 to 6). Therefore, the y-axis has been adjusted to portray this difference.*

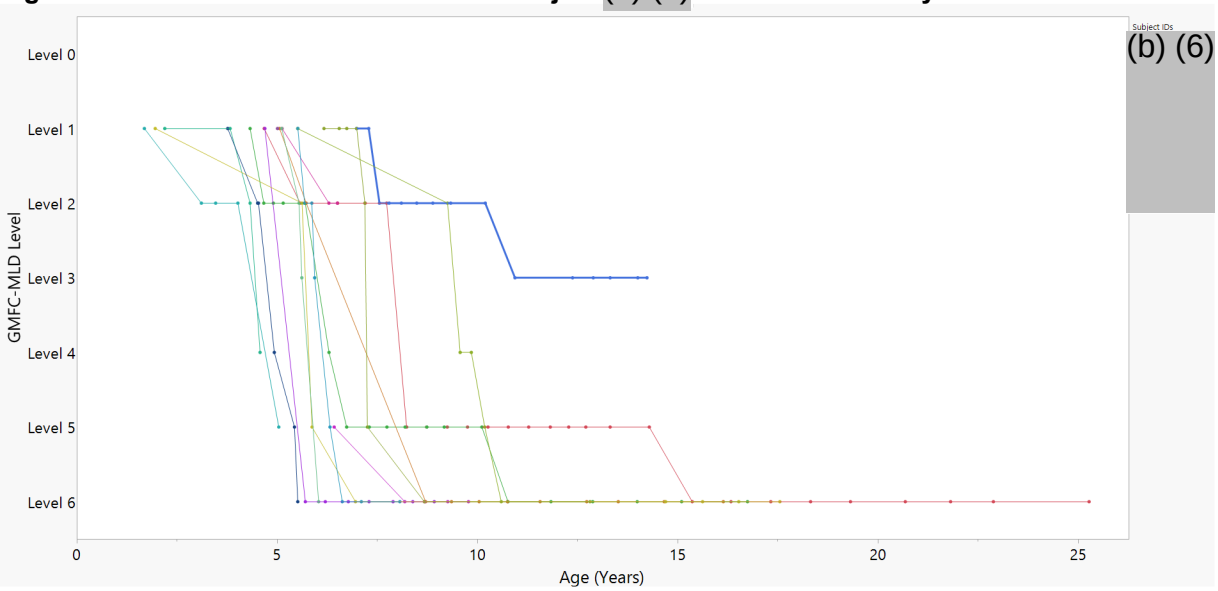
Figure 15: Adjusted Progression Analysis of (b) (6) in Comparison to Natural History EJ Subjects



Source: Reviewer analysis of ISE ADFT Dataset
Abbreviations: EJ, early juvenile; GMFC, Gross Motor Function Classification; MLD, metachromatic leukodystrophy

Reviewer Analysis: *In Figure 15, it appears that (b) (6) progressed from GMFC-MLD Level 1 (impaired gait) to retaining only trunk control faster than some natural history subjects.*

Figure 16: GMFC-MLD Scores for ESEJ Subject (b) (6) vs. Natural History



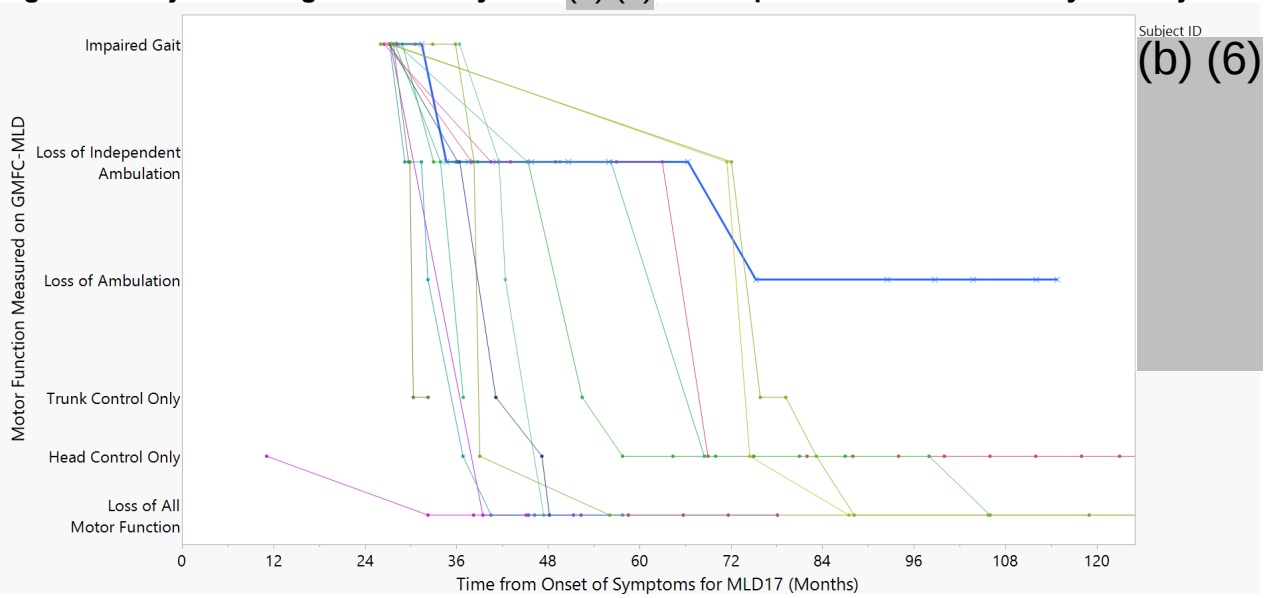
Source: Reviewer analysis of ISE ADFT Dataset
Abbreviations: ESEJ, early symptomatic early juvenile; GMFC, Gross Motor Function Classification; MLD, metachromatic leukodystrophy

Reviewer Comment: *Similar to the other ESEJ treated subjects, (b) (6) (Figure 16) appears to have a more mild course when compared to the natural history subjects. This subject developed symptom onset at 4.7 years of age and was treated at 7.0 years of age. Per natural history data in Fumagalli et al 2021, most children with EJ MLD lose independent ambulation (progress to GMFC-MLD Level >1) within 2 years of symptom onset (Fumagalli et al. 2021). Therefore, this*

subject represents a more mild EJ phenotype. Given the phenotypic heterogeneity in EJ MLD, it is difficult to determine whether this subject's progression to GMFC-MLD Level 3 at last follow-up (at 14.2 years of age) represents a slowed motor progression (and a treatment effect) or would be an expected outcome if the subject was not treated.

An adjusted progression analysis was conducted whereby the natural history progression lines were adjusted to match the time (b) (6) reached GMFC-MLD Level 1 to determine the progression of disease from onset of Level 1 onwards. This is shown in Figure 17 .

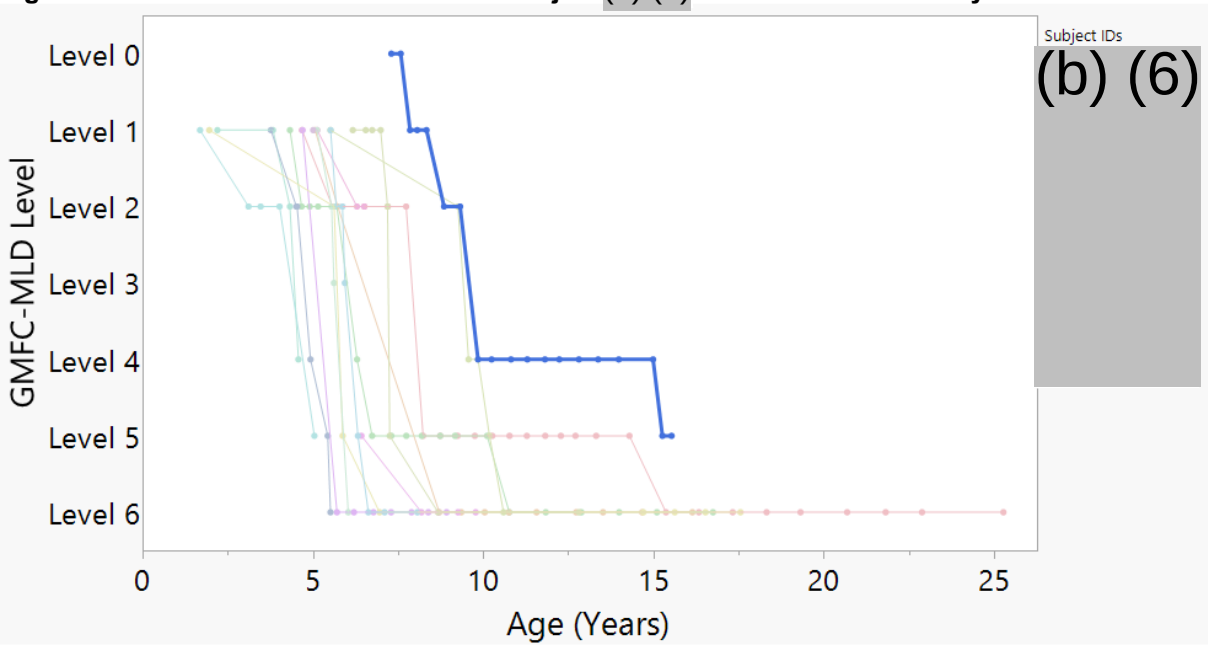
Figure 17: Adjusted Progression Analysis of (b) (6) in Comparison to Natural History EJ Subjects



Source: Reviewer analysis of ISE ADFT Dataset
Abbreviations: EJ, early juvenile; GMFC, Gross Motor Function Classification; MLD, metachromatic leukodystrophy

Reviewer Comment: *When adjusting for entry to Level 1, (b) (6) appears to progress to loss of independent ambulation faster than two natural history children, which is unexpected given the mild EJ phenotype observed at baseline (Figure 17).*

Figure 18: GMFC-MLD Scores for ESEJ Subject (b) (6) versus Natural History

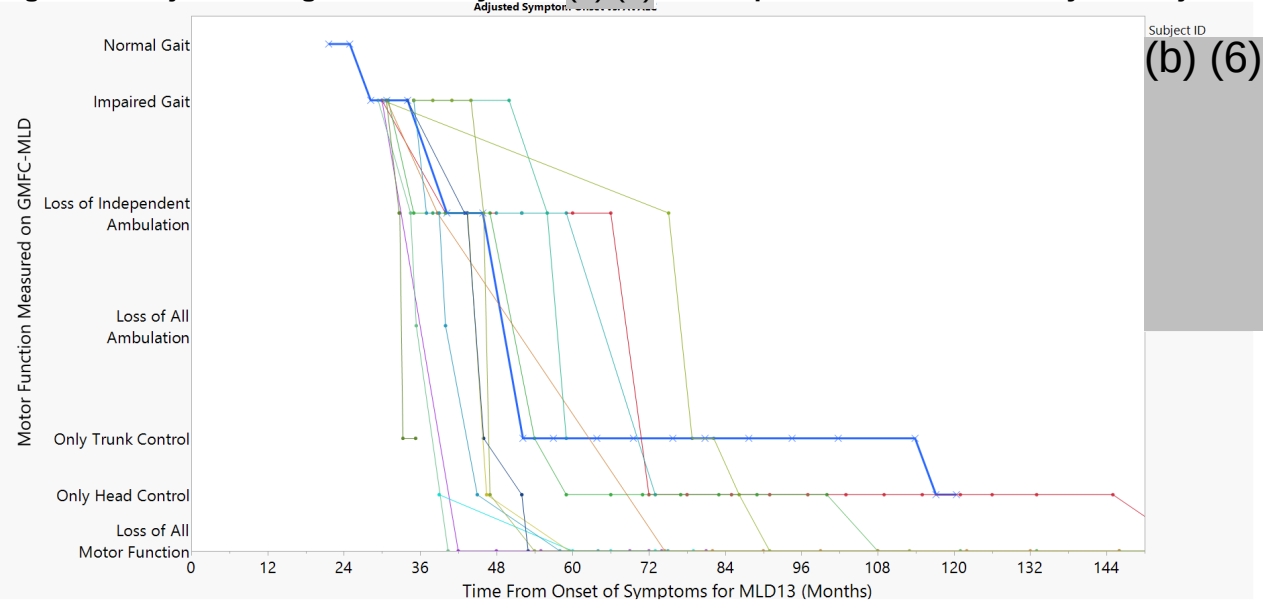


Source: Reviewer analysis of ISE ADFT Dataset
Abbreviations: ESEJ, early symptomatic early juvenile; GMFC, Gross Motor Function Classification; MLD, metachromatic leukodystrophy

Reviewer Comment: (b) (6) *(shown above in Figure 18), treated at 7.3 years of age, retained a normal gait (GMFC-MLD Level 0) at a much later age than the natural history children. Despite this more mild disease, this subject progressed to GMFC-MLD Level 4 (retained only trunk control) by 9.9 years of age, a similar age to natural history children. This is an unexpected outcome, given the subject's more mild disease at baseline. Therefore the clinical review team concludes that there is no treatment effect in this subject who experienced motor progression. Rather, the clinical review team is concerned that the motor progression to Level 4 is accelerated after treatment when considering this subject's pre-treatment mild disease. However, the review team does acknowledge that there is apparent stabilization at GMFC-MLD Level 4.*

Figure 19 presents the adjusted progression analyses to assess for progression from Level 1 onwards between the natural history children and (b) (6).

Figure 19: Adjusted Progression Analysis of (b) (6) in Comparison to Natural History EJ Subjects



Source: Reviewer analysis of ISE ADFT Dataset
Abbreviations: EJ, early juvenile; GMFC, Gross Motor Function Classification; MLD, metachromatic leukodystrophy

Reviewer Analysis: *Figure 19 shows that this subject progresses from Level 1 to Level 4 at a rate that seems faster than approximately half of the natural history subjects. This is unexpected given this subject's mild EJ phenotype.*

Based on these analyses, the clinical review team is concerned that motor progression in the treated ESEJ subjects appears faster than expected based on their pre-treatment clinical courses. However, it is challenging to do an analysis of the rate of progression of disease given that there is non-linearity in the decline and periods of plateau observed in the natural history of EJ MLD. Because there was substantial missing data on the progression past Level 3 in the natural history subjects, the statistical reviewer conducted an analysis comparing the time from GMFC-MLD Level 1 to 2 in the natural history EJ subjects and the treated ESEJ subjects who experienced motor progression. The analysis excluded natural history subjects who appeared to have more severe disease on the EJ phenotypic spectrum and, therefore, were deemed the least comparable to the treated OTL-200 ESEJ subjects who had more mild disease. The 10 natural history subjects included in the analysis were (b) (6) .

Because of the uncertainties on when Level 1 was first observed in many natural history subjects, the statistical reviewer used three separate scenarios to account for bias in observation time between the two groups. All scenarios used the first timepoint Level 2 was reported for all subjects.

- Scenario 1: Analysis was conducted using the first observation of Level 1 for both treated and natural history subjects.
- Scenario 2: Analysis was conducted using last level 1 for both treated and natural history subjects.
- Scenario 3: Analysis was conducted using last level 1 for treated subjects and first level 1 for natural history subjects. This is the most conservative ("worst scenario").

Results of the statistical reviewer's analysis are shown in Table 15:

Table 15: Time (in Years) from Level 1 to Level 2 in ESEJ Subjects Compared to Natural History EJ Subjects

S	Treatment	N	Mean	Std	Q1	Median	Q3	Min	Max
1	Natural history	8	1.1	1.14	0.4	0.8	1.1	0.2	3.7
1	Treated	6	1.5	1.48	0.5	0.8	3.3	0.3	3.5
2	Natural history	8	0.9	1.18	0.3	0.6	1.0	0.2	3.7
2	Treated	6	0.6	0.40	0.3	0.5	0.5	0.3	1.4
3	Natural history	8	1.1	1.14	0.4	0.8	1.1	0.2	3.7
3	Treated	6	0.6	0.40	0.3	0.5	0.5	0.3	1.4

Source: FDA Statistical Reviewer's Analysis
Abbreviations: S-scenario, Std-standard deviation, Q1-quartile 1, Q3-quartile 3, min-minimum, max-maximum

Reviewer Comment: *In scenario #3 of the statistical reviewer's analysis (the "worst scenario"), both the mean and median time from Level 1 to Level 2 in the treated subjects is faster than the natural history EJ subjects.*

Subject-level analyses and statistical analyses of motor progression indicate that there is clear evidence of slowing of motor progression in ESEJ MLD after treatment with OTL-200. There is evidence to suggest the potential for accelerated motor progression after treatment. A potential pathophysiologic explanation is that treatment with OTL-200 requires myeloablative conditioning eliminates the residual ARSA enzyme activity in ESEJ subjects, increasing the buildup of sulfatides and subsequent inflammation and demyelination. The clinical team acknowledges that statistical significance of these analyses cannot be reached given the small study population and the limitations of the natural history data. However, the review team believes that this is a potential risk of OTL-200 that patients, families, and providers should be aware of.

7.3.5 Analysis of Secondary Endpoints

There were two key secondary endpoints in the integrated efficacy analysis: motor function and overall survival.

Motor function was defined as proportion of subjects who experienced severe motor impairment (defined as GMFC-MLD Level ≥5) or death evaluated at 2 years and 5 years post-treatment with OTL-200 for treated subjects.

Reviewer Comment: *This analysis was not considered suitable for the ESEJ population given the lack of comparability between the ESEJ and EJ natural history children.*

At 7 years of age, 2 out of 10 subjects in the OTL-200 treated group (20%) had progressed to death due to MLD disease progression compared to 0 out of 16 age-matched natural history EJ subjects. Published natural history literature also indicates survival in untreated patients with EJ 10 years after symptom onset (Fumagalli et al. 2021).

Reviewer Comment: *There is no evidence of a treatment effect on overall survival in the ESEJ subjects. Rather, two subjects died from MLD progression at a much earlier age than expected, as discussed in Section 7.3.4.*

7.3.6 Other Endpoints

An additional endpoint of severe cognitive impairment-free survival was defined as the interval between birth and the first occurrence of severe cognitive impairment (defined as performance standard score ≤55 with no performance standard score >55 at later assessments). Given the

lack of comparability between the treated subjects and the natural history children, neurocognitive data was assessed individually for each subject looking at age, standard scores, and concurrent GMFC-MLD level. The Applicant has defined the following categories of cognitive function: “broadly average” (standard score ≥85), “mild impairment” (standard score <85 and ≥70), “moderate impairment” (standard score <70 and ≥55), and “severe impairment” (standard score <55). This endpoint was not assessed for the two subjects who progressed to death after treatment and the two subjects with limited follow-up. The results for the remaining six subjects are shown in Table 16.

Table 16: Performance and Language Standard Scores at Last Follow-Up for ESEJ Subjects

(b) (6)

Subject ID	Age at Neurocognitive Assessment (years)	Performance Standard Score	Language Standard Score	GMFC-MLD Score at Time of Neurocognitive Assessment
(b) (6)	12.5 years	N/A[a]	N/A[a]	Level 5
(b) (6)	15.5 years	87	82	Level 5
(b) (6)	20.0 years	104	90	Level 3
(b) (6)	15.1 years	71	74	Level 3
(b) (6)	7.4 years	N/A[b]	N/A[b]	Level 5
(b) (6)	17.7 years	77	69	Level 3

Source: DCOA and Reviewer Analysis from ADIQ and ADFT ISE Datasets; BLA125758/0.26 Response to Clinical IR#5
a-Standard scores are unable to be calculated for this subject. This subject experienced cognitive impairment such that they had to be transitioned to an out of age range test. They were administered the Bayley Scale for Infant and Toddler Development, which is to be administered to patients only as old as 42 months.
b-This subject had an adverse event of a Grade 3 cognitive disorder. There were significant gaps in the data due to this severe cognitive impairment.
Abbreviations: GMFC, Gross Motor Function Classification; MLD, metachromatic leukodystrophy

Reviewer Comment: *As per the DCOA reviewer’s analysis, three subjects demonstrated a neurocognitive treatment effect:* (b) (6) *. Based on the published literature of the natural history of EJ MLD, patients are expected to have motor and cognitive decline that occurs together (Kehrer et al. 2014). Therefore, retention of cognitive functioning without severe cognitive impairment despite progression of motor disease represents a favorable treatment effect.*

(b) (6) *has a particularly unexpected and striking cognitive outcome. Despite progression to severe motor impairment (retaining only head control), this subject retained cognitive functioning in the “broadly average range”. This represents a clear treatment effect. The clinical review team recognizes this to be a clinically meaningful outcome for patients and their families, whereby this subject can retain important independent thinking and communication skills in a severely impaired motor state.*

At last follow-up, both (b) (6) *and* (b) (6) *had lost all ambulation (with or without support, GMFC-MLD Level 3). Despite this significant progression in motor disease, their neurocognitive testing reveals only mild cognitive impairment. As discussed in Dr. Knoble’s memo, this indicates that these subjects were able to retain independent problem-solving abilities and verbally convey their perspective. This retention of cognitive skills is clinically meaningful and represents a treatment effect of OTL-200.*

(b) (6) *and* (b) (6) *both experienced severe cognitive decline that occurred in parallel to progression of motor disease. These subjects did not have a treatment effect.*

As discussed in Section 7.3.4, (b) (6) appears to be more consistent with a LJ phenotype rather than an EJ phenotype. Patients with LJ MLD may not experience cognitive decline until more than 10 years after symptom onset (Kehrer et al. 2021). However, this subject does retain cognitive functioning despite observed decline in motor function.

7.3.7 Subpopulations

As discussed in Section 6.1.4, study subjects received two different dosing regimens of myeloablative conditioning. No differences in efficacy were observed between the two myeloablative regimens.

7.3.8 Persistence of Efficacy

The subjects who have been assessed by this clinical reviewer as having a treatment effect in cognitive outcomes ((b) (6)) were 16.5, 14.2, 20.0 and 15.3 years of age at last follow-up. There is no data demonstrating persistence of efficacy at later ages.

7.3.9 Product-Product Interactions

Although concomitant medications were documented for all subjects, no product-product interactions were expected or observed during the course of the clinical studies.

7.3.10 Additional Efficacy Issues

As was analyzed in the PSLI and PSEJ subjects, post-treatment PBMC ARSA levels in the ESEJ subjects were analyzed and is shown in Table 17.

Table 17: Post-Treatment PBMC ARSA Levels for ESEJ Subjects

Visit	N	n	Mean	Lower 95% CI	Upper 95% CI	Median	Min	Max
Baseline (Derived)	10	10	26	26	26	26	26	28
Day 60	10	9	179	74	431	283	31	558
Month 3	10	10	181	108	303	210	50	426
Month 6	10	7	110	45	267	107	26	444
Month 9	10	7	100	33	308	62	32	659
Year 1	10	8	141	68	293	131	55	688
Year 2	10	7	101	67	153	82	70	219
Year 3	10	6	236	56	999	234	30	1271
Year 4	10	4	571	135	2410	704	205	1394

Source: Table X43.23, Applicant Response to Clinical IR#8, BLA125758/0.47
Abbreviations: ARSA, arylsulfatase A; CI, confidence interval; ESEJ, early symptomatic early juvenile; PBMC, peripheral blood mononuclear cell

Reviewer Comment: *The post-treatment PBMC ARSA levels in the ESEJ subjects are substantially lower than observed in the PSLI and PSEJ subjects. It is unclear whether or not this may be related to the dose, where the ESEJ subjects did not get high enough doses of OTL-200 to induce an ARSA response similar to the PSLI and PSEJ subjects. Additionally, supranormal ARSA levels >1000 nmol/mg/h were not observed to occur until much later (Year 3). A delayed and blunted ARSA response may be a potential explanation for the lack of motor benefit and the continued disease progression observed in the ESEJ subjects.*

An additional analysis was conducted to understand how to differentiate the subjects who had a treatment response (slowing of cognitive progression in subjects (b) (6)) and those who did not have a treatment response (continued progression of motor and cognitive disease in subjects (b) (6)). Of note, given the significantly different phenotype observed in (b) (6), this subject was not included in this analysis. We note that three out of the four subjects who did not have a treatment response were noted to have demyelinating lesions on the brainstem on brain MRI at baseline (as measured using an adapted Loes score) compared to none of the subjects who had a treatment response.

Reviewer Comment: *This is not an unexpected finding based on the published literature on brain MRIs in MLD. Involvement of the projection fibers into the brainstem has been identified as a feature of severe MLD disease (Eichler et al. 2009). Therefore, the four subjects considered to be treatment non-responders appeared to have more advanced MLD disease at baseline. It is well-known that advanced disease in patients with MLD is irreversible. Therefore, these subjects were not observed to derive benefit from treatment likely due to their irreversible, advanced MLD disease.*

While this analysis was performed on a very small number of subjects, there is literature to support this conclusion. Accordingly, the clinical review team believes that this is still an important consideration when determining the ESEJ subpopulation for whom OTL-200 is approved.

7.3.11 Efficacy Conclusions

As discussed in other sections of this memo, the clinical outcomes of the ESEJ subjects were challenging to interpret given the lack of comparability between the treated ESEJ subjects (where many subjects have a more mild EJ phenotype) and the untreated natural history children (who appear to have a more severe EJ phenotype).

As highlighted by the subject level analysis of the motor outcomes in Section 7.3.4, the clinical review team does not identify any clear evidence of efficacy on the motor outcomes in the treated ESEJ subjects, with many subjects still experiencing rapid motor progression after treatment with OTL-200. However, there is clear evidence to suggest a cognitive benefit (a slowing of cognitive disease progression) in some treated ESEJ subjects, that occurs despite concurrent motor progression. This is an unexpected outcome based on the natural history of the disease (where motor function and cognitive function would be expected to occur in parallel) and has been assessed as a meaningful treatment effect related to OTL-200. As shared at the externally-led Patient-Focused Drug Development Meeting for MLD, patients with MLD, their families, and their caregivers, emphasized the importance of preserving cognitive function to allow for communication of pain and other needs. It is important to note that the subjects who did not have a cognitive treatment response had radiographic evidence of more advanced disease with demyelinating lesions observed in the brainstem.

Therefore, based on the cumulative analysis of the clinical efficacy data, the clinical review team recommends approval of OTL-200 for: “the slowing of progression cognitive impairment in early symptomatic early juvenile MLD (defined as GMFC-MLD ≤1 with or without ataxia at the time of treatment) who do not have brainstem involvement on brain MRI.” It is important to note that “early symptomatic early juvenile MLD” is not a term used in clinical practice and has been designed for the purposes of the Applicant’s clinical development program. Therefore, the review team recommends that this definition be included within the indication to provide clarity to prescribers. Additionally, this specific indication would prevent treatment in children with

advanced disease (brainstem involvement on brain MRI) who the review team has deemed to have an unfavorable benefit-risk. Given the need to intervene as early as possible in patients who are already symptomatic for EJ MLD, no weight-based treatment parameters are recommended for this subpopulation.

Additionally, given the analyses revealing a potential for accelerated motor progression in the treated subjects, the clinical review team recommends that this be highlighted within the Limitations of Use section. It represents an important benefit-risk consideration for patients and their families.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

An assessment of safety was conducted by analyzing all subjects treated in the OTL-200 clinical development program. Analyses were conducted by study timepoint and by disease subtype.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety database includes 39 subjects treated with OTL-200 in studies #201222 and #205756, as well as the three expanded access studies (see Section 5.3) This includes two subjects who had advanced disease (one with symptomatic LI MLD and one with progressively symptomatic EJ MLD) who were not included in the efficacy analysis. An adverse event of special interest from commercial use of OTL-200 in Europe was identified; however, no additional safety data was available for this subject so they are not included within the safety database.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Table 18: Baseline Demographics and Duration of Exposure of Pooled Safety Populations

Parameter	Safety Population (N=39)
Sex, n (%)	-
Female	14 (36%)
Male	25 (64%)
Country of residence, n (%)	--
U.S.	9 (24%)
Non-U.S.	30 (76%)
Race, n (%)	-
White	36 (92%)
Asian	2 (5%)
Black or African American	1 (3%)
Age at OTL-200 treatment (months)	-
Median	15.8
Min - max	7.6-139.7
Duration of Follow-Up after OTL-200 treatment (years)	-
Median	6.8
Min - max	0.6-12.1

Source: BLA125758/0 ISE ADSL Dataset

8.2.3 Categorization of Adverse Events

The Applicant utilized MedDRA version 24.1 to code all AEs.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

At the time of BLA submission, no subject had completed the long-term follow-up study, OTL-200-10. The range of follow-up duration is shown above in Table 18.

8.4 Safety Results

8.4.1 Deaths

Three subjects died after treatment with OTL-200: one PSEJ subject and two ESEJ subjects:

- ESEJ Subject (b) (6) was treated with OTL-200 at 69 months of age. After treatment, the subject began to experience rapid motor and cognitive deterioration and died 15 months after treatment due to MLD disease progression.
- ESEJ Subject (b) (6) was treated with OTL-200 at 60 months of age. After treatment, the subject began to develop difficulties with walking and speech. The subject died due to MLD disease progression 8 months after treatment.
- Subject (b) (6) was treated with OTL-200 at 11.3 months of age, as a PSEJ study subject. At2.1 years of age (13.8 months after treatment), this subject presented with seizures and altered mental status, requiring intubation and intensive care unit admission. The subject was diagnosed with a Grade 5 ischemic cerebral infarction on brain computed tomography (CT) angiogram and died on study Day 415 due to severe brain infraction with subsequent cerebral edema and medullary and tonsillar herniation. The exact cause of this event was undetermined but was considered potentially related to OTL-200. This is discussed further in Section 8.4.8.

8.4.2 Nonfatal Serious Adverse Events

A total of 71 nonfatal SAEs were reported. SAEs for the entire safety population are shown in Table 19, broken down by study timepoint. There were no SAEs in study subjects reported between conditioning administered on Day -4 and administration of OTL-200.

Table 19: Serious Adverse Events in Safety Population by Study Timepoint (n=39)

System Organ Class / Adverse Reaction	Day 0-30	Day 31-90	Day 91-Year 1	Year 1-Year 2	Year 2-Year 5	After Year 5
Blood and lymphatic system	-	-	-	-	-	-
Anemia	1	-	-	-	-	-
Atypical hemolytic uremic syndrome	-	1	-	-	-	-
Thrombocytopenia	1	-	-	-	-	-
Gastrointestinal	-	-	-	-	-	-
Vomiting	-	2	-	-	2	-
Hepatobiliary	-	-	-	-	-	-
Gallbladder polyp	-	-	2	-	-	-
Veno-occlusive liver disease	1	-	-	-	-	-

System Organ Class / Adverse Reaction	Day 0-30	Day 31-90	Day 91-Year 1	Year 1-Year 2	Year 2-Year 5	After Year 5
Infections and infestations	-	-	-	-	-	-
Device-related infection	-	-	2	-	-	-
Escherichia infection	-	-	-	1	-	-
Gastroenteritis[1]	-	-	2	-	3	1
Pneumonia	-	-	-	2	-	-
Aspiration pneumonia	-	-	-	1	-	-
Postoperative wound infection	-	-	-	-	-	1
Upper respiratory tract infection[2]	-	-	-	1	1	1
Sepsis[3]	-	1	1	-	-	-
Viral infection	-	-	-	-	1	-
Injury, poisoning, and procedural complications	-	-	-	-	-	-
Joint dislocation	-	-	-	-	-	1
Metabolism and nutrition disorders	-	-	-	-	-	-
Dehydration	-	-	-	-	-	1
Metabolic acidosis	1	-	-	1	-	-
Musculoskeletal and connective tissue disorders	-	-	-	-	-	-
Foot deformity	-	-	-	1	1	4
Musculoskeletal deformity	-	-	-	-	1	1
Scoliosis	-	-	-	-	-	1
Nervous system disorder						
Febrile convulsion	-	-	-	-	1	-
Seizure	-	-	-	-	2	-
Status epilepticus	-	-	-	1	1	-
Vascular disorders	-	-	-	-	-	-
Kawasaki's disease	-	-	-	1	-	-

Source: BLA125758 Integrated Summary of Safety ADAE Dataset
1-Gastroenteritis includes gastroenteritis, enteritis, gastroenteritis rotavirus
2-Upper respiratory tract infection includes nasopharyngitis and respiratory tract infection
3-Sepsis includes sepsis and bacterial sepsis

Table 20, Table 21, and Table 22 show the SAEs separated by indication and study timepoint.

Table 20: SAEs in PSLI Study Subjects

System Organ Class Adverse Reaction	Day 0-30	Day 31-90	Day 91-Year 1	Year 1-Year 2	Year 2-Year 5	After Year 5
Gastrointestinal	-	-	-	-	-	-
Vomiting	-	-	-	-	1	-
Infections and infestations	-	-	-	-	-	-
Device-related infection	-	-	2	-	-	-
Escherichia infection	-	-	-	1	-	-
Gastroenteritis[1]	-	-	1	-	2	-
Pneumonia	-	-	-	1	-	-
Postoperative wound infection	-	-	-	-	-	1
Upper respiratory tract infection[2]	-	-	-	1	1	-
Sepsis[3]	-	1	1	-	-	-

System Organ Class Adverse Reaction	Day 0-30	Day 31-90	Day 91- Year 1	Year 1- Year 2	Year 2- Year 5	After Year 5
Injury, poisoning, and procedural complications	-	-	-	-	-	-
Joint dislocation	-	-	-	-	-	1
Metabolism and nutrition disorders	-	-	-	-	-	
Metabolic acidosis	-	-	-	1	-	-
Musculoskeletal and connective tissue disorders	-	-	-	-	-	-
Foot deformity	-	-	-	-	-	2

Source: BLA125758 Integrated Summary of Safety ADAE Dataset
1-Gastroenteritis includes gastroenteritis, enteritis, gastroenteritis rotavirus
2-Upper respiratory tract infection includes nasopharyngitis and respiratory tract infection
3-Sepsis includes sepsis and bacterial sepsis
Abbreviations: PSLI, pre-symptomatic late infantile; SAEs, serious adverse events

Table 21: SAEs in PSEJ Study Subjects

System Organ Class Adverse Reaction	Day 0-30	Day 31-90	Day 91-Year 1	Year 1- Year 2	Year 2- Year 5	After Year 5
Hepatobiliary	-	-	-	-	-	-
Gallbladder polyp	-	-	1	-	-	-
Infections and infestations	-	-	-	-	-	-
Gastroenteritis	-	-	-	1	-	-

Source: BLA125758 Integrated Summary of Safety ADAE Dataset
Abbreviations: PSEJ, pre-symptomatic early juvenile; SAEs, serious adverse events

Table 22: SAEs in the ESEJ Study Subjects

System Organ Class Adverse Reaction	Day 0-30	Day 31- 90	Day 91- Year 1	Year 1- Year 2	Year 2- Year 5	After Year 5
Hepatobiliary	-	-	-	-	-	-
Gallbladder polyp	-	-	1	-	-	-
Musculoskeletal and connective tissue disorders	-	-	-	-	-	-
Foot deformity	-	-	-	1	1	1
Musculoskeletal deformity	-	-	-	-	-	1
Scoliosis	-	-	-	-	-	1
Nervous system disorder						
Seizure	-	-	-	-	2	-
Vascular disorders	-	-	-	-	-	-
Kawasaki's disease	-	-	-	1	-	-

Source: BLA125758 Integrated Summary of Safety ADAE Dataset
Abbreviations: ESEJ, early symptomatic early juvenile; SAEs, serious adverse events

Table 23 and Table 24 show the SAEs for the two subjects who are not included in the efficacy analysis.

Table 23: SAEs for Subject (b) (6), With Progressively Symptomatic EJ MLD (not a Requested Indication)

System Organ Class Adverse Reaction	Day 0-30	Day 31-90	Day 91- Year 1	Year 1- Year 2	Year 2- Year 5	After Year 5
Metabolism and nutrition	-	-	-	-	-	-
Dehydration	-	-	-	-	-	x
Metabolic acidosis	x	-	-	-	-	-
Musculoskeletal and connective tissue disorders	-	-	-	-	-	-
Foot deformity	-	-	-	-	-	x

Source: BLA125758 Integrated Summary of Safety ADAE Dataset
Abbreviations: EJ, early juvenile; MLD, metachromatic leukodystrophy; SAEs, serious adverse events

Table 24: SAEs for Subject (b) (6), With Symptomatic Late Infantile MLD (not a Requested Indication)

System Organ Class Adverse Reaction	Day 0-30	Day 31- 90	Day 91- Year 1	Year 1- Year 2	Year 2- Year 5	After Year 5
Infections and infestations	-	-	-	-	-	-
Pneumonia	-	-	-	x	-	-
Aspiration pneumonia	-	-	-	x	-	-
Nervous system disorders	-	-	-	-	-	-
Seizure	-	-	-	-	x	-
Status epilepticus	-	-	-	x	x	-

Source: BLA125758 Integrated Summary of Safety ADAE Dataset
Abbreviations: MLD, metachromatic leukodystrophy; SAEs, serious adverse events

Reviewer Comment: *Given that PSLI subjects comprised >50% of the safety population, it is expected that more SAEs are reported in PSLI subjects. No relationship between SAEs and subtype were identified in this small safety population. Events under "nervous system disorders" and "musculoskeletal disorders" were assessed to be related to progression of MLD disease rather than related to treatment with OTL-200. Serious infections and VOD are important safety events that warrant consideration and monitoring in the commercial use of OTL-200. This is discussed further in Section 8.4.6.*

8.4.3 Study Dropouts/Discontinuations

There are no study dropouts or discontinuations.

8.4.4 Common Adverse Events

All AEs (regardless of whether considered to be related to OTL-200) for the entire safety population are shown in Table 25. This includes all AEs that occurred from the initiation of busulfan conditioning to last follow-up. Given the small safety population, all reported AEs are shown in Table 25.

Table 25: Adverse Events for the Safety Population

System Organ Class Adverse Reaction	Any Grade N (%)	Grade 3 or Higher N (%)
Blood and lymphatic system disorders	-	-
Anemia	6 (15%)	1 (3%)
Atypical hemolytic uremic syndrome	2 (5%)	2 (5%)
Febrile neutropenia	33 (85%)	32 (82%)
Leukopenia	1 (3%)	1 (3%)
Lymphadenopathy	1 (3%)	-
Neutropenia	10 (26%)	8 (21%)
Thrombocytopenia	1 (3%)	1 (3%)
Cardiac disorders	-	-
Aortic dilatation	1 (3%)	-
Bradycardia	1 (3%)	1 (3%)
Congenital, familial, and genetic disorders	-	-
Cryptorchism	4 (10%)	-
Phimosis	5 (13%)	-
Uterine hypoplasia	1 (3%)	-
Ear and labyrinth disorders	-	-
Deafness bilateral	1 (3%)	-
Hypoacusis	1 (3%)	1 (3%)
Middle ear disorder	1 (3%)	-
Mixed deafness	2 (5%)	-
Endocrine disorders	-	-
Hypothyroidism	2 (5%)	-
Precocious puberty	1 (3%)	-
Thyroid cyst	2 (5%)	-
Eye disorders	-	-
Amblyopia	1 (3%)	-
Astigmatism	3 (8%)	-
Conjunctivitis	1 (3%)	-
Myopia	2 (5%)	-
Ocular hyperemia	2 (5%)	-
Periorbital oedema	1 (3%)	-
Strabismus	1 (3%)	-
Visual impairment	1 (3%)	-
Gastrointestinal disorders	-	-
Abdominal pain[1]	3 (8%)	-
Ascites	1 (3%)	-
Constipation	7 (18%)	-
Diarrhea	3 (8%)	-
Dyspepsia	2 (5%)	-
Dysphagia	4 (10%)	4 (10%)
Gastritis erosive	1 (3%)	-
Gastrointestinal hemorrhage	1 (3%)	1 (3%)
Gastroesophageal reflux disease	3 (8%)	-
Nausea	2 (5%)	-
Salivary hypersecretion	1 (3%)	-
Stomatitis	30 (77%)	29 (74%)
Toothache	3 (8%)	-
Vomiting	8 (21%)	5 (13%)

System Organ Class **Adverse Reaction**	**Any Grade** **N (%)**	**Grade 3 or Higher** **N (%)**
General disorders and administration site conditions	-	-
Pyrexia	13 (33%)	1 (3%)
Hepatobiliary disorders	-	-
Cholecystitis acute	1 (3%)	-
Drug-induced liver injury	2 (5%)	-
Gallbladder disorder[2]	13 (33%)	-
Hepatic steatosis	1 (3%)	-
Hepatomegaly	7 (18%)	-
Hyperplastic cholecystopathy	1 (3%)	-
Increased hepatic enzymes[3]	10 (26%)	3 (8%)
Venoocclusive liver disease	3 (8%)	3 (8%)
Immune system disorders	-	-
Allergy to arthropod bite	1 (3%)	-
Hypogammaglobulinaemia	1 (3%)	-
Infections and infestations	-	-
Bacterial disease carrier	2 (5%)	-
Clostridium test positive	5 (13%)	2 (5%)
Conjunctivitis	6 (15%)	-
Device related infection[4]	11 (28%)	6 (15%)
Ear infection[5]	12 (31%)	-
Escherichia infection	1 (3%)	1 (3%)
Gastroenteritis[6]	21 (54%)	8 (21%)
Genital candidiasis	1 (3%)	-
Impetigo	2 (5%)	-
Lice infestation	1 (3%)	-
Lower respiratory tract infection[7]	7 (18%)	3 (8%)
Oral candidiasis	4 (10%)	-
Periodontitis	1 (3%)	-
Pneumonia aspiration	1 (3%)	1 (3%)
Positive bacterial culture[8]	7 (18%)	2 (5%)
Postoperative wound infection	2 (5%)	-
Upper respiratory tract infection[9]	37 (95%)	1 (3%)
Sepsis	2 (5%)	2 (5%)
Skin infection	3 (8%)	1 (3%)
Upper respiratory fungal infection	1 (3%)	1 (3%)
Urinary tract infection[10]	6 (15%)	-
Viral infection[11]	15 (38%)	2 (5%)
Viremia	1 (3%)	1 (3%)

System Organ Class **Adverse Reaction**	**Any Grade** **N (%)**	**Grade 3 or Higher** **N (%)**
Injury, poisoning and procedural complications	-	-
Arthropod bite	4 (10%)	-
Contusion	2 (5%)	-
Face injury	1 (3%)	-
Foot fracture	3 (8%)	-
Head injury	9 (23%)	-
Joint dislocation	4 (10%)	4 (10%)
Lower limb fracture	1 (3%)	-
Post procedural fever	1 (3%)	-
Post procedural inflammation	1 (3%)	-
Procedural pain	4 (10%)	-
Thermal burn	1 (3%)	-
Tibia fracture	1 (3%)	-
Transfusion reaction	2 (5%)	-
Investigations	-	-
Body mass index decreased	7 (18%)	1 (3%)
Oxygen saturation decreased	1 (3%)	1 (3%)
Urine output decreased	1 (3%)	1 (3%)
Metabolism and nutrition disorders	-	-
Dehydration	1 (3%)	1 (3%)
Fluid retention	1 (3%)	-
Folate deficiency	1 (3%)	-
Hypercholesterolemia	1 (3%)	-
Hypertriglyceridemia	1 (3%)	-
Hypervolemia	1 (3%)	-
Hypoalbuminemia	1 (3%)	-
Iron deficiency	11 (28%)	-
Metabolic acidosis	12 (31%)	10
Vitamin B6 deficiency	1 (3%)	-
Vitamin D decreased	2 (5%)	-
Musculoskeletal and connective tissue disorders	-	-
Arthralgia	1 (3%)	-
Back pain	2 (5%)	-
Bone pain	2 (5%)	-
Epiphyses premature fusion	1 (3%)	-
Foot deformity	6 (15%)	6 (15%)
Musculoskeletal deformity	2 (5%)	2 (5%)
Osteopenia	2 (5%)	-
Osteoporosis	5 (13%)	-
Scoliosis	2 (5%)	1 (3%)
Synovitis	1 (3%)	-
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	-	-
Dysplastic naevus	1 (3%)	-
Melanocytic naevus	1 (3%)	-
Osteochondroma	1 (3%)	-

System Organ Class **Adverse Reaction**	**Any Grade** **N (%)**	**Grade 3 or Higher** **N (%)**
Nervous system disorders	-	-
Aphasia	10 (26%)	10 (26%)
Cerebral microhemorrhage	1 (3%)	-
Cognitive disorder	12 (31%)	12 (31%)
Dysarthria	5 (13%)	5 (13%)
Epilepsy	2 (5%)	-
Febrile convulsion	1 (3%)	1 (3%)
Gait disturbance[12]	19 (49%)	19 (49%)
Headache	2 (5%)	-
Ischemic cerebral infarction	1 (3%)	1 (3%)
Loss of consciousness	2 (5%)	-
Motor dysfunction	12 (31%)	12 (31%)
Muscle spasticity	14 (36%)	14 (36%)
Seizure	2 (5%)	2 (5%)
Status epilepticus	1 (3%)	1 (3%)
Psychiatric disorders	-	-
Sleep disorder	2 (5%)	-
Tic	1 (3%)	-
Renal and urinary disorders	-	-
Bladder hypertrophy	1 (3%)	-
Hemoglobinuria	1 (3%)	-
Oliguria	1 (3%)	-
Pollakiuria	1 (3%)	-
Renal tubular acidosis	7	2 (5%)
Reproductive system and breast disorders	-	-
Genital erythema	1 (3%)	-
Ovarian failure	4 (10%)	3 (8%)
Vulval disorder	1 (3%)	-
Respiratory, thoracic, and mediastinal disorders	-	-
Adenoidal hypertrophy	2 (5%)	-
Bronchospasm	3 (8%)	-
Epistaxis	3 (8%)	2 (5%)
Oropharyngeal pain	1 (3%)	-
Respiratory distress	1 (3%)	-
Seasonal allergy	2 (5%)	-
Tonsillar hypertrophy	1 (3%)	-
Skin and subcutaneous tissue disorders	-	-
Ingrowing nail	1 (3%)	-
Rash[13]	23 (59%)	3 (8%)

System Organ Class Adverse Reaction	Any Grade N (%)	Grade 3 or Higher N (%)
Vascular disorders	-	-
Kawasaki's disease	1 (3%)	1 (3%)

Source: Reviewer Analysis, BLA125758 ISS ADAE Dataset
1-Abdominal pain includes abdominal pain and abdominal pain upper.
2-Gallbladder disorder includes gallbladder enlargement, gallbladder polyp, gallbladder disorder.
3-Increased hepatic enzymes includes hypertransaminasemia, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased, alkaline phosphatase increased, total bile acids increased, gamma-glutamyl transferase increased.
4-Device related infection includes device related infection, vascular device infections, catheter site infection and catheter site cellulitis.
5-Ear infection includes otitis media, otitis media acute, ear infection.
6-Gastroenteritis includes gastroenteritis, enteritis, gastroenteritis Aeromonas, rotavirus infection.
7-Lower respiratory tract infection includes bronchitis and pneumonia.
8-Positive bacterial culture includes haeomophilis infection, staphylococcal infection, stenotrophomonas test positive, 9-Acinetobacter infection, Klebsiella test positive.
9-Upper respiratory tract infection includes upper respiratory tract infection, pharyngitis, coronavirus infection, respiratory tract infection, pharyngitis, scarlet fever, sinusitis, cough, adenovirus, pharyngotonsillitis, influenza, influenza-like illness, rhinorrhea, rhinitis, tonsillitis
10-Urinary tract infection includes urinary tract infection and urinary tract infection bacterial.
11-Viral infection includes cytomegalovirus infection, coxsackie viral infection, varicella, roseola, hand-foot-mouth disease, asymptomatic COVID-19, Epstein-Barr virus infection, viral infection.
12-Gait disturbance includes ataxia and gait disturbance.
13-Rash includes dermatitis, dermatitis bullous, rash, rash erythematous, skin lesion, drug eruption, skin exfoliation, eczema, rash maculopapular, rash popular, dry skin.

AEs separated by disease subtype and study timepoint are shown in Table 26, Table 27, and Table 28.

Table 26: Adverse Events by Study Timepoint in PSLI Subjects (N=20)

System Organ Class Adverse Reaction	Day -4 to Day 0 # PSLI All Grades (# Grade 3 or higher)	Day 0-30 # PSLI All Grades (# Grade 3 or higher)	Day 31-90 # PSLI All Grades (# Grade 3 or higher)	Day 91-Year 1 # PSLI All Grades (# Grade 3 or higher)	Year 1-Year 2 # PSLI All Grades (# Grade 3 or higher)	Year 2-Year 5 # # PSLI All Grades (# Grade 3 or higher)	After Year 5 # PSLI All Grades (# Grade 3 or higher)
Blood and lymphatic system disorders	-	-	-	-	-	-	-
Anemia	0	1 (1)	0	0	0	2 (0)	1 (0)
Atypical hemolytic uremic syndrome	0	0	2 (2)	0	0	0	0
Febrile neutropenia	0	15 (15)	0	0	0	0	0
Neutropenia	0	0	6 (6)	0	0	1 (0)	0
Thrombocytopenia	0	1 (1)	0	0	0	0	0
Cardiac disorders	-	-	-	-	-	-	-
Aortic dilatation	0	0	0	0	0	1 (0)	1 (0)
Congenital, familial, and genetic disorders	-	-	-	-	-	-	-
Cryptorchism	0	0	0	0	1 (0)	2 (0)	1 (0)
Phimosis	0	0	0	0	1 (0)	2 (0)	0
Uterine hypoplasia	0	0	0	0	0	0	1 (0)
Ear and labyrinth disorders		-	-	-	-	-	-
Deafness bilateral	0	0	0	0	0	0	1 (0)
Hypoacusis	0	0	0	0	0	0	1 (1)
Middle ear disorder	0	0	0	0	0	0	1 (0)
Mixed deafness	0	0	0	0	0	0	1 (0)
Endocrine disorders	-	-	-	-	-	-	-
Hypothyroidism	0	0	0	0	0	2 (0)	0
Precocious puberty	0	0	0	0	0	0	1 (0)
Thyroid cyst	0	0	0	1 (0)	0	1	0
Eye disorders	-	-	-	-	-	-	-
Amblyopia	0	0	0	0	0	0	1
Astigmatism	0	0	0	0	1 (0)	2 (0)	0
Conjunctivitis	0	0	0	0	0	0	1 (0)
Myopia	0	0	0	0	0	1 (0)	0
Ocular hyperemia	0	0	1	0	0	0	0
Visual impairment	0	0	0	0	0	1 (0)	0

System Organ Class **Adverse Reaction**	**Day -4 to Day 0 # PSLI All Grades (# Grade 3 or higher)**	**Day 0-30 # PSLI All Grades (# Grade 3 or higher)**	**Day 31-90 # PSLI All Grades (# Grade 3 or higher)**	**Day 91-Year 1 # PSLI All Grades (# Grade 3 or higher)**	**Year 1-Year 2 # PSLI All Grades (# Grade 3 or higher)**	**Year 2-Year 5 # # PSLI All Grades (# Grade 3 or higher)**	**After Year 5 # PSLI All Grades (# Grade 3 or higher)**
Gastrointestinal disorders	-	-	-	-	-	-	-
Abdominal pain[1]	0	0	0	0	0	0	2 (0)
Ascites	0	1	0	0	0	0	0
Constipation	0	0	0	0	1	0	1 (0)
Diarrhea	0	0	1	0	0	1	0
Dyspepsia	0	0	1	0	0	0	1
Dysphagia	0	0	0	0	0	0	1 (1)
Gastrointestinal hemorrhage	0	0	1 (1)	0	0	0	0
Stomatitis	0	13 (12)	0	0	0	0	0
Toothache	0	0	1 (0)	0	0	1 (0)	1 (0)
Vomiting	0	0	2 (2)	0	1 (0)	3 (2)	1 (0)
General disorders and administration site conditions	-	-	-	-	-	-	-
Pyrexia	0	0	3 (1)	5 (0)	2 (0)	3 (0)	2 (0)
Hepatobiliary disorders	-	-	-	-	-	-	-
Gallbladder disorder[2]	0	0	0	1 (0)	1 (0)	4 (0)	0
Hepatic steatosis	0	0	0	0	0	0	1 (0)
Hepatomegaly	1 (0)	3 (0)	0	0	0	0	0
Increased hepatic enzymes[3]	0	0	2 (0)	1 (0)	2 (0)	0	0
Venoocclusive liver disease	0	3 (3)	0	0	0	0	0
Immune system disorders	-	-	-	-	-	-	-
Hypogammaglobulinaemia	0	0	0	0	0	1 (0)	0

System Organ Class Adverse Reaction	Day -4 to Day 0 # PSLI All Grades (# Grade 3 or higher)	Day 0-30 # PSLI All Grades (# Grade 3 or higher)	Day 31-90 # PSLI All Grades (# Grade 3 or higher)	Day 91-Year 1 # PSLI All Grades (# Grade 3 or higher)	Year 1-Year 2 # PSLI All Grades (# Grade 3 or higher)	Year 2-Year 5 # # PSLI All Grades (# Grade 3 or higher)	After Year 5 # PSLI All Grades (# Grade 3 or higher)
Infections and infestations	-	-	-	-	-	-	-
Bacterial disease carrier	1	0	1	0	0	0	0
Clostridium test positive	0	0	0	0	0	1	0
Conjunctivitis	0	0	0	3	0	1	1
Device related infection[4]	1 (1)	1 (0)	1 (1)	4 (2)	0	1 (1)	0
Ear infection[5]	0	0	2 (0)	6 (0)	2 (0)	4 (0)	0
Escherichia infection	0	1 (1)	0	0	1 (1)	0	0
Gastroenteritis[6]	0	1 (1)	0	5 (2)	3 (0)	5 (2)	4 (1)
Impetigo	0	0	0	0	1 (0)	1 (0)	0
Lice infestation	0	0	0	0	0	0	1 (0)
Lower respiratory tract infection[7]	0	0	1 (1)	1 (0)	3 (1)	0	0
Oral candidiasis	0	0	1 (0)	1 (0)	1 (0)	0	0
Periodontitis	0	0	0	0	0	0	1 (0)
Positive bacterial culture[8]	1 (0)	4 (2)	1 (1)	0	0	0	0
Postoperative wound infection	0	0	0	0	0	0	1 (0)
Upper respiratory tract infection[9]	1 (1)	1 (0)	1 (0)	9 (0)	10 (1)	15 (0)	12 (0)
Sepsis	0	0	1 (1)	1 (1)	0	0	0
Skin infection	0	0	0	0	1 (0)	0	2 (0)
Urinary tract infection[10]	0	0	1 (0)	1 (0)	0	1 (0)	2 (0)
Viral infection[11]	0	1 (0)	4 (0)	5 (1)	2 (0)	8 (1)	3 (0
Viremia	0	1 (1)	0	0	0	0	0
Injury, poisoning and procedural complications	-	-	-	-	-	-	-
Arthropod bite	0	0	1 (0)	0	2 (0)	0	0
Contusion	0	0	0	0	0	0	1 (0)
Foot fracture	0	0	0	0	0	0	1 (0)
Head injury	1 (0)	2 (0)	0	0	0	2 (0)	2 (0)
Joint dislocation	0	0	0	0	0	0	1 (1)
Post procedural fever	0	0	0	0	0	1 (0)	0
Post procedural inflammation	0	0	0	0	1 (0)	0	0
Procedural pain	1 (0)	0	0	0	0	1 (0)	1 (0)
Thermal burn	0	0	0	0	0	1 (0)	0
Tibia fracture	0	0	0	0	0	0	1 (0)
Transfusion reaction	0	2 (0)	0	0	0	0	0

System Organ Class Adverse Reaction	Day -4 to Day 0 # PSLI All Grades (# Grade 3 or higher)	Day 0-30 # PSLI All Grades (# Grade 3 or higher)	Day 31-90 # PSLI All Grades (# Grade 3 or higher)	Day 91-Year 1 # PSLI All Grades (# Grade 3 or higher)	Year 1-Year 2 # PSLI All Grades (# Grade 3 or higher)	Year 2-Year 5 # # PSLI All Grades (# Grade 3 or higher)	After Year 5 # PSLI All Grades (# Grade 3 or higher)
Investigations	-	-	-	-	-	-	-
Body mass index decreased	0	0	0	0	0	1 (0)	2 (0)
Oxygen saturation decreased	0	0	0	1 (1)	0	0	0
Urine output decreased	0	1 (1)	0	0	0	0	0
Metabolism and nutrition disorders	-	-	-	-	-	-	-
Hypercholesterolemia	0	0	0	0	0	0	1 (0)
Hypervolemia	0	1 (0)	0	0	0	0	0
Hypoalbuminemia	0	1 (0)	0	0	0	0	0
Iron deficiency	0	0	0	1 (0)	2 (0)	3 (0)	2 (0)
Metabolic acidosis	0	2 (1)	0	1 (1)	1 (1)	2 (1)	0
Vitamin B6 deficiency	0	0	0	0	0	0	1 (0)
Musculoskeletal and connective tissue disorders	-	-	-	-	-	-	-
Arthralgia	0	0	1 (0)	0	0	0	0
Bone pain	1 (0)	0	2 (0)	0	0	0	0
Epiphyses premature fusion	0	0	0	0	0	0	1 (0)
Foot deformity	0	0	0	0	0	0	3 (3)
Musculoskeletal deformity	0	0	0	0	0	1 (1)	0
Osteopenia	0	0	0	0	0	0	1 (0)
Osteoporosis	0	0	0	0	0	1 (0)	0
Scoliosis	0	0	0	0	0	1 (0)	0
Synovitis	0	0	0	0	1 (0)	0	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	-	-	-	-	-	-	-
Dysplastic naevus	0	0	0	0	0	1 (0)	0

System Organ Class Adverse Reaction	Day -4 to Day 0 # PSLI All Grades (# Grade 3 or higher)	Day 0-30 # PSLI All Grades (# Grade 3 or higher)	Day 31-90 # PSLI All Grades (# Grade 3 or higher)	Day 91-Year 1 # PSLI All Grades (# Grade 3 or higher)	Year 1-Year 2 # PSLI All Grades (# Grade 3 or higher)	Year 2-Year 5 # # PSLI All Grades (# Grade 3 or higher)	After Year 5 # PSLI All Grades (# Grade 3 or higher)
Nervous system disorders	-	-	-	-	-	-	-
Aphasia	0	0	0	0	0	0	3 (3)
Cerebral microhemorrhage	0	0	0	1 (0)	0	0	0
Cognitive disorder	0	0	0	0	0	1 (1)	5 (5)
Dysarthria	0	0	0	0	0	1 (1)	0
Febrile convulsion	0	0	0	0	0	1 (1)	0
Gait disturbance[12]	0	1 (1)	1 (1)	6 (6)	0	1 (1)	2 (2)
Loss of consciousness	0	0	0	1 (0)	0	0	0
Motor dysfunction	0	0	0	2 (2)	0	1 (1)	0
Muscle spasticity	0	0	0	1 (1)	0	2 (2)	2 (2)
Psychiatric disorders	-	-	-	-	-	-	-
Sleep disorder	0	0	1 (0)	0	0	0	0
Tic	0	0	0	0	0	1 (0)	0
Renal and urinary disorders	-	-	-	-	-	-	-
Bladder hypertrophy	0	0	0	0	0	0	1 (0)
Hemoglobinuria	0	0	0	0	0	0	1 (0)
Pollakiuria	0	0	0	0	0	0	1 (0)
Renal tubular acidosis	1 (0)	0	1 (0)	0	0	0	0
Reproductive system and breast disorders	-	-	-	-	-	-	-
Genital erythema	0	0	0	1 (0)	0	0	0
Ovarian failure	0	0	0	0	0	0	1 (0)
Vulval disorder	0	0	0	1 (0)	0	0	0
Respiratory, thoracic and mediastinal disorders	-	-	-	-	-	-	-
Adenoidal hypertrophy	0	0	0	0	0	0	1 (0)
Bronchospasm	0	0	0	0	1 (0)	1 (0)	1 (0)
Oropharyngeal pain	0	1 (0)	0	0	0	0	0
Respiratory distress	0	1 (0)	0	0	0	0	0

System Organ Class Adverse Reaction	Day -4 to Day 0 # PSLI All Grades (# Grade 3 or higher)	Day 0-30 # PSLI All Grades (# Grade 3 or higher)	Day 31-90 # PSLI All Grades (# Grade 3 or higher)	Day 91-Year 1 # PSLI All Grades (# Grade 3 or higher)	Year 1-Year 2 # PSLI All Grades (# Grade 3 or higher)	Year 2-Year 5 # # PSLI All Grades (# Grade 3 or higher)	After Year 5 # PSLI All Grades (# Grade 3 or higher)
Skin and subcutaneous tissue disorders	-	-	-	-	-	-	-
Rash[13]	1 (0)	9 (2)	1 (0)	2 (0)	4 (0)	2 (0)	2 (0)

Source: Reviewer analysis of BLA125758.0 ISS ADAE Dataset
1-Abdominal pain includes abdominal pain and abdominal pain upper.
2-Gallbladder disorder includes gallbladder enlargement, gallbladder polyp, gallbladder disorder.
3-Increased hepatic enzymes includes hypertransaminasemia, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased, alkaline phosphatase increased, total bile acids increased, gamma-glutamyl transferase increased.
4-Device related infection includes device related infection, vascular device infections, catheter site infection and catheter site cellulitis.
5-Ear infection includes otitis media, otitis media acute, ear infection.
6-Gastroenteritis includes gastroenteritis, enteritis, gastroenteritis Aeromonas, rotavirus infection.
7-Lower respiratory tract infection includes bronchitis and pneumonia.
8-Positive bacterial culture includes haeomophilis infection, staphylococcal infection, stenotrophomonas test positive, 9-Acinetobacter infection, Klebsiella test positive.
9-Upper respiratory tract infection includes upper respiratory tract infection, pharyngitis, coronavirus infection, respiratory tract infection, pharyngitis, scarlet fever, sinusitis, cough, adenovirus, pharyngotonsillitis, influenza, influenza-like illness, rhinorrhea, rhinitis, tonsillitis
10-Urinary tract infection includes urinary tract infection and urinary tract infection bacterial.
11-Viral infection includes cytomegalovirus infection, coxsackie viral infection, varicella, roseola, hand-foot-mouth disease, asymptomatic COVID-19, Epstein-Barr virus infection, viral infection.
12-Gait disturbance includes ataxia and gait disturbance.
13-Rash includes dermatitis, dermatitis bullous, rash, rash erythematous, skin lesion, drug eruption, skin exfoliation, eczema, rash maculopapular, rash popular, dry skin.
Abbreviations: AE, adverse event; PSLI, pre-symptomatic late infantile

Table 27: Adverse Events by Study Timepoint in PSEJ Subjects (n=7)

System Organ Class Adverse Reaction	Day -4-Day 0 # PSEJ All Grades / # Grade 3 or Higher)	Day 0-30 # PSEJ All Grades / # Grade 3 Or Higher)	Day 31-90 # PSLI All Grades / # Grade 3 or Higher)	Day 91-Year 1 # PSEJ All Grades / # Grade 3 or Higher)	Year 1-Year 2 # PSEJ All Grades / # Grade 3 or Higher)	Year 2-Year 5 # # PSEJ All Grades / # Grade 3 or Higher)	After Year 5 # PSEJ All Grades / # Grade 3 or Higher)
Blood and lymphatic system disorders	-	-	-	-	-	-	-
Anemia	0	0	0	1	0	0	0
Febrile neutropenia	0	7/6	0	0	0	0	0
Neutropenia	0	0	2/2	2	0	0	0
Congenital, familial, and genetic disorders	-	-	-	-	-	-	-
Phimosis	0	0	0	0	1	0	0
Eye disorders	-	-	-	-	-	-	-
Periorbital Edema	0	1	0	0	0	0	0

System Organ Class Adverse Reaction	Day -4-Day 0 # PSEJ All Grades / # Grade 3 or Higher)	Day 0-30 # PSEJ All Grades / # Grade 3 Or Higher)	Day 31-90 # PSLI All Grades / # Grade 3 or Higher)	Day 91-Year 1 # PSEJ All Grades / # Grade 3 or Higher)	Year 1-Year 2 # PSEJ All Grades / # Grade 3 or Higher)	Year 2-Year 5 # # PSEJ All Grades / # Grade 3 or Higher)	After Year 5 # PSEJ All Grades / # Grade 3 or Higher)
Gastrointestinal disorders							
Abdominal pain	0	0	0	0	0	1	0
Constipation	0	0	1	0	0	0	0
Stomatitis	0	7/7	0	0	0	0	0
General disorders and administration site conditions	-	-	-	-	-	-	-
Pyrexia	0	0	0	1	0	0	0
Hepatobiliary disorders	-	-	-	-	-	-	-
Gallbladder disorder[1]	0	2	0	1	1	0	0
Hepatomegaly	0	2	0	0	0	0	0
Increased hepatic enzymes[2]	0	1/1	2	0	0	0	0
Infections and infestations	-	-	-	-	-	-	-
Clostridium test positive	0	2/1	0	0	0	0	0
Conjunctivitis	0	1	0	0	0	0	0
Device related infection[3]	0	1	0	0	0	0	0
Gastroenteritis[4]	0	0	1	1	0	1/1	0
Lower respiratory tract infection[5]	0	0	0	1	0	0	0
Positive bacterial culture[6]	0	2	0	0	0	0	0
Upper respiratory tract infection[7]	0	1	2	4	3	5	1
Urinary tract infection[8]	0	0	1	0	0	0	0
Viral infection[9]	1	0	0	0	1	0	0
Injury, poisoning and procedural complications	-	-	-	-	-	-	-
Foot fracture	0	0	0	0	0	1	0
Head injury	0	0	0	1	0	1	0
Procedural pain	0	0	1	0	1	0	0
Metabolism and nutrition disorders	-	-	-	-	-	-	-
Fluid Retention	0	1	0	0	0	0	0
Hypertriglyceridemia	0	0	0	0	0	1	0
Iron Deficiency	0	0	1	1	0	1	0
Metabolic Acidosis	1/1	1/1	1/1	0	0	0	0

System Organ Class Adverse Reaction	Day -4-Day 0 # PSEJ All Grades / # Grade 3 or Higher)	Day 0-30 # PSEJ All Grades / # Grade 3 Or Higher)	Day 31-90 # PSLI All Grades / # Grade 3 or Higher)	Day 91-Year 1 # PSEJ All Grades / # Grade 3 or Higher)	Year 1-Year 2 # PSEJ All Grades / # Grade 3 or Higher)	Year 2-Year 5 # # PSEJ All Grades / # Grade 3 or Higher)	After Year 5 # PSEJ All Grades / # Grade 3 or Higher)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	-	-	-	-	-	-	-
Melanocytic Nevus	0	0	0	0	1	0	0
Nervous system disorders							
Headache	0	1	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	-	-	-	-	-	-	-
Adenoidal hypertrophy	0	0	0	0	0	1	0
Epistaxis	0	1/1	0	0	0	0	0
Seasonal allergy	0	0	1	0	0	0	0
Tonsillar hypertrophy	0	0	0	0	0	1	0
Skin and subcutaneous tissue disorders	-	-	-	-	-	-	-
Hyperkeratosis	0	0	1	0	0	0	0
Rash[10]	1	3	2	0	0	1	0

Source: Reviewer analysis of BLA125758.0 ISS ADAE Dataset
1-Gallbladder disorder includes gallbladder enlargement, gallbladder polyp, gallbladder disorder.
2-Increased hepatic enzymes includes hypertransaminasemia, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased, alkaline phosphatase increased, total bile acids increased, gamma-glutamyl transferase increased
3-Device related infection includes device related infection, vascular device infections, catheter site infection and catheter site cellulitis
4-Gastroenteritis includes gastroenteritis, enteritis, gastroenteritis Aeromonas, rotavirus infection.
5-Lower respiratory tract infection includes bronchitis and pneumonia.
6-Positive bacterial culture includes haeomophilis infection, staphylococcal infection, stenotrophomonas test positive, 9-Acinetobacter infection, Klebsiella test positive.
7-Upper respiratory tract infection includes upper respiratory tract infection, pharyngitis, coronavirus infection, respiratory tract infection, pharyngitis, scarlet fever, sinusitis, cough, adenovirus, pharyngotonsillitis, influenza, influenza-like illness, rhinorrhea, rhinitis, tonsillitis
8-Urinary tract infection includes urinary tract infection and urinary tract infection bacterial.
9-Viral infection includes cytomegalovirus infection, coxsackie viral infection, varicella, roseola, hand-foot-mouth disease, asymptomatic COVID-19, Epstein-Barr virus infection, viral infection.
10-Rash includes dermatitis, dermatitis bullous, rash, rash erythematous, skin lesion, drug eruption, skin exfoliation, eczema, rash maculopapular, rash popular, dry skin.
Abbreviations: AE, adverse event; PSEJ, pre-symptomatic early juvenile

Table 28: AEs by Study Timepoint in ESEJ Subjects (n=10)

System Organ Class Adverse Reaction	Day -4 to Day 0 # PSEJ All Grades / # Grade 3 or Higher)	Day 0-30 # PSEJ All Grades / # Grade 3 or Higher)	Day 31-90 # PSLI All Grades / # Grade 3 or Higher)	Day 91-Year 1 # PSEJ All Grades / # Grade 3 or Higher)	Year 1-Year 2 # PSEJ All Grades / # Grade 3 or Higher)	Year 2-Year 5 # # PSEJ All Grades / # Grade 3 or Higher)	After Year 5 # PSEJ All Grades / # Grade 3 or Higher)
Blood and lymphatic system	-	-	-	-	-	-	-
Anemia	0	0	0	1	0	0	0
Febrile neutropenia	0	9 (9)	0	0	0	0	0
Leukopenia	0	1 (1)	0	0	0	0	0
Lymphadenopathy	0	0	0	0	0	0	1
Cardiac	-	-	-	-	-	-	-
Bradycardia	1	0	0	0	1 (1)	0	0
Congenital, familiar, genetic	-	-	-	-	-	-	-
Phimosis	0	0	0	1	1	0	0
Ear and labyrinth	-	-	-	-	-	-	-
Mixed deafness	0	0	0	0	1	0	0
Eye	-	-	-	-	-	-	-
Myopia	0	0	0	1	0	0	0
Ocular hyperemia	0	1	0	0	0	0	0
Strabismus	0	0	0	0	0	1	0
Gastrointestinal	-	-	-	-	-	-	-
Constipation	0	0	0	0	0	1	3
Diarrhea	0	0	1	0	0	0	0
Dysphagia	0	0	0	2 (2)	0	0	0
Gastrooesophageal reflux disease	0	0	0	0	0	0	1
Nausea	1	0	0	0	0	0	1
Salivary hypersecretion	0	0	0	0	0	1	0
Stomatitis	0	9 (9)	0	0	0	0	0
Vomiting	0	1	1 (1)	0	1	0	1
Hepatobiliary	-	-	-	-	-	-	-
Drug-induced liver injury	0	1	0	0	0	0	0
Gallbladder disorder[1]	0	0	1	1	1	0	0
Hepatomegaly	1	0	0	0	0	0	0
Hyperplastic cholecystopathy	0	0	0	0	1	0	0
Increased hepatic enzymes[2]	2 (2)	1	1	0	0	1	0

System Organ Class Adverse Reaction	Day -4 to Day 0 # PSEJ All Grades / # Grade 3 or Higher)	Day 0-30 # PSEJ All Grades / # Grade 3 or Higher)	Day 31-90 # PSLI All Grades / # Grade 3 or Higher)	Day 91-Year 1 # PSEJ All Grades / # Grade 3 or Higher)	Year 1-Year 2 # PSEJ All Grades / # Grade 3 or Higher)	Year 2-Year 5 # # PSEJ All Grades / # Grade 3 or Higher)	After Year 5 # PSEJ All Grades / # Grade 3 or Higher)
Immune system	-	-	-	-	-	-	-
Allergy to arthropod bite	0	0	0	0	0	0	1
Infections and infestations	-	-	-	-	-	-	-
Clostridium test positive	0	2 (1)	0	0	0	0	0
Conjunctivitis	0	0	0	1	0	0	0
Device related infection[3]	0	1 (1)	1	0	0	0	0
Gastroenteritis[4]	0	0	0	1	2	2	0
Genital candidiasis	0	0	0	0	0	1	0
Lower respiratory tract infection[5]	0	0	0	0	0	1	0
Oral candidiasis	0	0	1	0	0	0	0
Postoperative wound infection	0	0	0	0	0	0	1
Upper respiratory tract infection[6]	0	0	2	4	3	4	4
Skin infection	0	1 (1)	0	0	0	0	0
Upper respiratory fungal infection	0	1 (1)	0	0	0	0	0
Urinary tract infection[7]	0	0	0	1	0	0	0
Injury, poisoning and procedural complications	-	-	-	-	-	-	-
Arthropod bite	0	0	1	0	0	0	0
Contusion	0	0	1	0	0	0	0
Face injury	0	0	0	1	0	0	0
Joint dislocation	0	0	0	0	0	0	2 (2)
Lower limb fracture	0	0	0	0	0	0	1
Investigations	-	-	-	-	-	-	-
Aspergillus test positive	0	1	0	0	0	0	0
Blood immunoglobulin e increased	0	0	0	3	1	0	0
Blood immunoglobulin m decreased	0	0	0	0	1	0	0
Body mass index decreased	0	0	0	0	1	2	0
Eosinophil count increased	0	0	0	0	0	1	0
Serum ferritin increased	0	3	1	0	0	0	0
Vitamin d decreased	0	0	0	0	1	2	0

System Organ Class Adverse Reaction	Day -4 to Day 0 # PSEJ All Grades / # Grade 3 or Higher)	Day 0-30 # PSEJ All Grades / # Grade 3 or Higher)	Day 31-90 # PSLI All Grades / # Grade 3 or Higher)	Day 91-Year 1 # PSEJ All Grades / # Grade 3 or Higher)	Year 1-Year 2 # PSEJ All Grades / # Grade 3 or Higher)	Year 2-Year 5 # # PSEJ All Grades / # Grade 3 or Higher)	After Year 5 # PSEJ All Grades / # Grade 3 or Higher)
Metabolism and nutrition disorders	-	-	-	-	-	-	-
Folate deficiency	0	0	0	0	1	1	0
Iron deficiency	0	0	0	0	2	0	0
Metabolic acidosis	3 (3)	0	0	0	0	1	0
Vitamin d decreased	0	0	0	0	0	2	0
Musculoskeletal and connective tissue	-	-	-	-	-	-	-
Back pain	0	1	0	0	0	1	0
Foot deformity	0	0	0	0	1 (1)	1 (1)	1 (1)
Musculoskeletal deformity	0	0	0	0	0	0	1 (1)
Osteopenia	0	0	0	0	0	0	1
Osteoporosis	0	0	0	0	1	1	0
Scoliosis	0	0	0	0	0	0	1 (1)
Neoplasms, benign, malignant, unspecified	-	-	-	-	-	-	-
Osteochondroma	0	0	0	0	0	1	0
Nervous system disorders	-	-	-	-	-	-	-
Aphasia	0	0	0	2 (2)	0	2 (2)	1
Cognitive disorder	0	0	0	0	0	2 (2)	2 (2)
Dysarthria	0	0	0	2 (2)	0	1	0
Epilepsy	0	0	0	0	0	1	0
Gait disturbance	0	1 (1)	2 (2)	2 (2)	1 (1)	2 (2)	0
Headache	0	0	1	0	0	0	0
Loss of consciousness	0	0	0	0	0	0	1
Motor dysfunction	0	0	0	2 (2)	1 (1)	3 (3)	2 (2)
Muscle spasticity	0	0	1 (1)	1 (1)	3 (3)	1 (1)	1 (1)
Seizure	0	0	0	0	0	1 (1)	0
Psychiatric disorders	-	-	-	-	-	-	-
Sleep disorder	0	0	0	0	0	1	0
Renal and urinary							
Renal tubular acidosis	2	0	1	0	0	0	0
Reproductive system and breast	-	-	-	-	-	-	-
Ovarian failure	0	0	0	0	0	2 (2)	0

System Organ Class Adverse Reaction	Day -4 to Day 0 # PSEJ All Grades / # Grade 3 or Higher)	Day 0-30 # PSEJ All Grades / # Grade 3 or Higher)	Day 31-90 # PSLI All Grades / # Grade 3 or Higher)	Day 91-Year 1 # PSEJ All Grades / # Grade 3 or Higher)	Year 1-Year 2 # PSEJ All Grades / # Grade 3 or Higher)	Year 2-Year 5 # # PSEJ All Grades / # Grade 3 or Higher)	After Year 5 # PSEJ All Grades / # Grade 3 or Higher)
Respiratory, thoracic and mediastinal	-	-	-	-	-	-	-
Epistaxis	0	0	0	0	1	0	0
Seasonal allergy	0	0	0	1	0	0	0
Skin and subcutaneous tissue	-	-	-	-	-	-	-
Ingrowing nail	0	0	0	0	0	1	0
Rash[8]	0	3 (1)	1	0	0	0	2
Vascular disorders	-	-	-	-	-	-	-
Kawasaki's disease	0	0	0	0	1 (1)	0	0

Source: Reviewer analysis of BLA125758.0 ISS ADAE Dataset
1-Gallbladder disorder includes gallbladder enlargement, gallbladder polyp, gallbladder disorder.
2-Increased hepatic enzymes includes hypertransaminasemia, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased, alkaline phosphatase increased, total bile acids increased, gamma-glutamyl transferase increased.
3-Device related infection includes device related infection, vascular device infections, catheter site infection and catheter site cellulitis.
4-Gastroenteritis includes gastroenteritis, enteritis, gastroenteritis Aeromonas, rotavirus infection.
5-Lower respiratory tract infection includes bronchitis and pneumonia.
6-Upper respiratory tract infection includes upper respiratory tract infection, pharyngitis, coronavirus infection, respiratory tract infection, pharyngitis, scarlet fever, sinusitis, cough, adenovirus, pharyngotonsillitis, influenza, influenza-like illness, rhinorrhea, rhinitis, tonsillitis
7-Urinary tract infection includes urinary tract infection and urinary tract infection bacterial.
8-Rash includes dermatitis, dermatitis bullous, rash, rash erythematous, skin lesion, drug eruption, skin exfoliation, eczema, rash maculopapular, rash popular, dry skin.
Abbreviations: AE, adverse event; PSEJ, pre-symptomatic early juvenile

Reviewer Comment: *No significant differences in adverse reactions were seen between the three different indications. AEs reported as "Nervous System Disorders" including aphasia, dysarthria, gait disturbance, seizure, cognitive disorder, motor function, and spasticity were attributed to the progression of MLD disease and, therefore, were not assessed as potential adverse reactions of OTL-200. Detailed discussion of the adverse events of special interest (AESIs) are included in Section 8.4.8.*

Additionally, there were no adverse reactions that were unexpected after Year 1. Therefore, given the variable duration of follow-up in the safety population, the Applicant was asked to present the adverse reactions in the final USPI for within Year 1 after treatment only. This excludes AEs associated with MLD disease progression.

Adverse reactions in >10% of the population within Year 1 after treatment for the entire safety population are shown in Table 29.

Table 29: Adverse Reactions in >10% of Subjects in Year 1 Safety Population

System Organ Class Adverse Reaction	Any Grade N (%)	Grade 3 or Higher N (%)
Blood and lymphatic	-	-
Febrile neutropenia	33 (85%)	32 (82%)
Neutropenia	11 (28%)	8 (21%)
Gastrointestinal disorders	-	-
Stomatitis	30 (77%)	29 (74%)
General disorders and administration site conditions	-	-
Pyrexia	8 (21%)	1 (3%)
Hepatobiliary disorders	-	-
Hepatomegaly	7 (18%)	0
Increased hepatic enzymes[2]	9 (23%)	3 (8%)
Infections and infestations	-	-
Device-related infection[3]	12 (31%)	7 (18%)
Gastroenteritis[4]	8 (21%)	3 (8%)
Respiratory tract infection[5]	21 (54%)	3 (8%)
Other viral infections[6]	11 (28%)	2 (5%)
Investigations	-	-
Arylsulfatase A antibody test positive	4 (10%)	0
Skin and subcutaneous tissue disorders	-	-
Rash[7]	13 (33%)	3 (8%)

Source: BLA125758 Integrated Summary of Safety ADAE Dataset
1-Gallbladder disorder includes gallbladder enlargement, gallbladder polyp, and gallbladder disorder
2-Increased hepatic enzymes includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hypertransaminasaemia, transaminases increased, blood alkaline phosphatase increased, gamma glutamyltransferase increased, total bile acids increased
3-Device-related infection includes device-related infection, vascular device infection, catheter site cellulitis
4-Gastroenteritis includes gastroenteritis Aeromonas, gastroenteritis, enteritis, gastroenteritis rotavirus, rotavirus infection
5-Respiratory tract infection includes bronchitis, nasopharyngitis, pharyngitis, pneumonia, respiratory tract infection, rhinitis, tonsillitis, upper respiratory fungal infection and upper respiratory tract infection.
6-Other viral infections includes adenovirus infection, cytomegalovirus infection, cytomegalovirus test positive, cytomegalovirus viremia, enterovirus infection, hand-foot-mouth-disease, herpes zosters, SARS-CoV-2 test positive, and viral infection
7-Rash includes dermatitis, dermatitis bullous, rash, rash erythematous, drug eruption, rash maculopapular.

8.4.5 Clinical Test Results

Vital Signs

Temperature

AEs of pyrexia are shown in the tables of Section 8.4.4. No instances of low temperature <35°C were reported.

Blood Pressure

No AEs of hypertension or hypotension were noted in treated subjects. Blood pressure readings were reviewed and no persistent elevations or trends in blood pressure after treatment were observed.

Heart Rate

Transient elevations in heart rate were reported, but there were no persistent events of tachycardia. One ESEJ subject, (b) (6), was noted to have bradyarrhythmia during conditioning that self-resolved. This subject also had a repeat Grade 3 self-resolving bradycardia event during sedation that resolved after administration of one dose of atropine.

Weight

Eight subjects were reported as having AEs of decreased body mass index. Subject (b) (6), with symptomatic LI MLD, was reported as having a Grade 3 event that is attributed to underlying disease progression. The remaining events were Grade 1 and were observed more than 1 year after treatment.

Complete Blood Count

Delayed neutrophil and platelet engraftment were considered AESIs and are reviewed in Section 8.4.8.

Chemistries

No significant or persistent derangements in electrolytes were observed in treated subjects. Serum ferritin was noted to be increased in six treated subjects (one PSLI, one PSEJ, and four ESEJ) within the first 90 days after treatment. All ferritin elevations were assessed as Grade 1 and did not require any intervention.

Liver Function Tests

Elevations in hepatic enzymes (ALT and AST) occurred within the first 90 days after treatment in 9 out of 39 subjects (2 PSLI, 3 PSEJ, and 4 ESEJ), with 3 subjects developing Grade 3 or higher elevations. Hepatoxicity is a known side effect of the busulfan conditioning agent. No subjects had elevations in hepatic enzymes that did not resolve. See Section 8.4.8 for discussion on the AEs of VOD.

8.4.6 Systemic Adverse Events

Refer to the discussion of AEs in Section 8.4.4.

8.4.7 Local Reactogenicity

There is no evidence of local reactogenicity in this submission.

8.4.8 Adverse Events of Special Interest

Thrombosis and Thrombotic Events

As discussed in Section 8.4.1, subject (b) (6) experienced an SAE of death on Day 414 after treatment. This PSEJ subject was treated at 11.3 months of age. At the routine Year 1 assessments (conducted on Days 366 and 373, 48 and 41 days prior to the SAE), the subject was noted to be doing clinically well with normal neurological examination, normal motor and language development, and normal abdominal and cardiac ultrasounds. Laboratory results drawn at the visit were significant for an elevated D-dimer at 81.98 nmol/L (normal: 1.48 to 4.22). Minor elevations in ALT (74 IU/L; normal: 13 to 45), AST (96 IU/L; normal: 20 to 60) and CK 250 IU/L (normal: 20 to 195) were observed. An electroencephalogram (EEG) showed normal background activity with no focal slow waves or epileptic abnormalities.

On Day 371 (approximately 41 to 48 days after the Year 1 assessments), the subject complained of a headache and the subject's mother noted sleepiness and reluctance to watch television. The mother also reported mild runny nose for a few days prior. The subject's mother was advised to take the subject to the Children's Hospital emergency room. However, the mother noted concerns for a seizure event (reported as "eye deviation") and took him to a closer local hospital. At the local hospital, the subject was discharged home with a diagnosis of viral illness. Later that afternoon, the subject had an episode of vomiting prior to going to sleep. During the evening, an ambulance was called when the family noticed heavy breathing and difficulty waking the subject. In the ambulance, the subject developed status epilepticus requiring intubation and administration of midazolam and levetiracetam. Initially, laboratory results demonstrated an elevated WBC count of 25.76×10^9/L (normal: 5 to 17) and neutrophil count of 21.1×10^9/L (normal: 1.5 to 8.5). Platelet count was normal. Given the elevation in WBC count, empiric treatment with IV ceftriaxone, vancomycin, and acyclovir was initiated. Repeat laboratory test demonstrated a normal WBC count of 14.51×10^9 (normal: 5 to 17) and decreasing neutrophil count of 11.5×10^9/L (normal: 1.5 to 8.5). Blood and urine culture showed no growth; EKG and chest x-ray were negative. Endotracheal aspirate showed no bacteria. Overnight, the subject became unresponsive and an urgent brain CT angiogram was performed, revealing an extensive left cerebral hemisphere infarction and edema with a 4 mm rightward midline shift and medullary and tonsillar herniation. Neuroradiologist evaluation of the CT images could not conclusively determine whether a carotid dissection had occurred. Reduced filling in the left internal carotid artery was assessed as secondary to swelling of the left brain hemisphere. The family of the subject did not permit an autopsy to be performed and no death certificate was available. The Applicant was unable to reach the treating healthcare provider to obtain additional laboratory or imaging results. The Applicant assessed this event as potentially related to an underlying infection and unrelated to the product.

Reviewer Comment: *This is a SAE of death that occurred in a treated subject in the pre-symptomatic stage of their disease. The etiology of this event is unclear. The clinical review team does not agree that an infectious etiology can be clearly attributed to this event. CSF cultures to evaluate for meningitis were not performed due to the instability of the subject. The subject is not reported to febrile throughout the course of the event and respiratory and blood cultures were negative. The rapid normalization of the WBC and the lack of clear infectious symptoms (the clinical team does not consider a few days of mild runny nose in this 2-year-old subject to be a clear sign of infection) is not consistent with infection. This appears to be a*

thrombotic event of unknown etiology. Additionally, it is concerning that this subject had a significantly elevated D-dimer level at the Year 1 visit, more than 1 month prior to the occurrence of this event. Given the limited information and the lack of post-mortem data, there is insufficient evidence to rule out attribution to the product.

Given the occurrence of this serious thrombotic event in (b) (6) and the elevated D-dimer level at the Year 1 visit, the safety data was analyzed to look for any other events of thrombosis or unexplained elevations in D-dimer. There were no other cases of CVA, and no pulmonary emboli, myocardial infarction or deep vein thrombosis. Out of 39 subjects treated with OTL-200, 26 (67%) had reported elevations in D-dimer levels ranging from 4.2 nmol/L to 109.5 nmol/L that occurred at various timepoints from Day 21 to Year 7 after treatment with OTL-200. The full list of D-dimer elevations are presented in Appendix I. Out of those 26 subjects, 3 subjects ((b) (6)) had D-dimer elevations in the presence of AEs of VOD. No significant associations between other AEs and elevations in D-dimer were seen. All subjects enrolled in study#205756 were given pre-treatment prophylaxis with either heparin or defibrotide (per investigator discretion).

***Reviewer Comment**: These elevations in D-dimer levels are seen at various timepoints after treatment, with some elevations occurring more than 1 year after treatment. For subjects enrolled in study #OTL-200-205756, these elevations occurred despite pre-treatment prophylaxis with anti-thrombotic agents. This clinical team is not aware of any similar elevations observed in other lentiviral gene therapy products. While a thrombotic event occurred in only one subject ((b) (6)), the size of the safety population is small and this risk should be investigated further. The Applicant agreed to include a safety outcome of "thromboembolic events" as a study objective and collect data on D-dimer levels and use of anti-thrombotic prophylaxis in their registry study, which will enroll all subjects treated in the post-market settings.*

Encephalitis

An 8-year-old patient with ESEJ MLD was treated with OTL-200 in the commercial setting in the European Union. This subject received 14.4 x 10^6 CD34+ cells/kg of OTL-200 and did not experience any unexpected AEs after treatment. One month and 10 days after treatment, the patient was admitted to the hospital with subacute neurological deterioration, characterized by asthenia, hypotonia (no longer able to walk or sit unsupported), cognitive deterioration, behavioral problems, vomiting, and difficulty swallowing. Patient was afebrile and blood cultures were negative. Work-up on admission was significant for negative CSF studies, EEG with slow waves consistent with encephalitis and brain MRI showing "new lesions with gadolinium enhancement, particularly in the left cerebellar peduncle and left temporally periventricular white matter, strongly suggesting a neuroinflammatory process." The treating physician reported that the event was consistent with non-infectious inflammatory encephalitis. After 5 days of plasmapheresis, the subject clinically improved with repeat brain MRI showing a significant decrease in inflammatory lesions and reduced gadolinium enhancement. Approximately 1 month later, the patient experienced similar subacute neurological deterioration with impairment in neurological status, hypotonia, and behavioral problems. Brain MRI showed the presence of unchanged MLD-related lesions and reduced inflammatory lesions. A recurrence of immune-mediated encephalitis was diagnosed by the treating physician and rituximab was administered. The patient experienced subsequent progression of MLD disease, assessed as a GMFC-MLD Level of 4 by 7 months after treatment. The patient had been diagnosed with chronic immune-mediated encephalitis, attributed by the treating physicians as potentially triggered by immunosuppression after busulfan conditioning and confounded by MLD. The Applicant

provided references to case reports that indicate that acute inflammatory demyelinating encephalitis can be a rare complication of MLD disease. Both the Applicant and treating physicians have assessed this event as not related to OTL-200.

Reviewer Comment: *It cannot be ruled out that this event of autoimmune encephalitis is related to OTL-200. There are only sparse case reports of acute encephalitis in LI and EJ MLD (Anlar et al. 2006; Kaufman 2006; Meier et al. 2021; Olive-Cirera et al. 2022). Given the onset of the event approximately 1 month after treatment, it is possible that OTL-200 may have triggered the event and the subsequent relapsing-remitting pattern of disease progression.*

Serious Infections

Given administration of the myeloablative conditioning regiment, serious infections were also AESIs. No Grade 4 or 5 infections were reported in treated subjects. Twenty-two events of serious, Grade 3 infections were reported in the safety population. Four subjects (10%) developed a CVC-related infection, including two serious events of Grade 3 sepsis and two serious events of Grade 3 localized CVC-related infection. All four events occurred within the first year of treatment (between Day 57 and Day 258). Identification of a bacterial pathogen occurred in three of the four subjects– one subject had a blood culture positive for *Enterobacter cloacae,* one subject had a swab taken from the tip of the catheter positive for *Staphylococcus aureus,* and one subject had a blood culture positive for *Pseudomonas aeruginosa.* All events resolved after CVC removal and antibiotic therapy.

Within the first year of treatment, two subjects (5%) developed serious gastrointestinal infections – one subject was reported as having a serious event of rotavirus gastroenteritis and one was reported as having a serious of event of enteritis. Both events resolved with support with IV fluids.

Veno-occlusive Disease

VOD is recognized as a known complication of busulfan conditioning. VOD occurred in three PSLI subjects – (b) (6) .

- (b) (6) : This subject developed VOD on study Day 1 with clinical examination that demonstrated hepatomegaly and an increase in body weight >2%. Ultrasound confirmed hepatomegaly and increased fluid accumulation in the abdominal cavity. Laboratory examinations demonstrated increased consumption of platelets, increase in coagulation time, and a reduction in antithrombin III. On Day 23, the event was assessed as a Grade 4 SAE. On Day 24, paracentesis was required to address worsening ascites with removal of 525 mL of fluid. Medications administered include IV acetylcysteine, ursodeoxycholic acid, albumin, furosemide, defibrotide, and antithrombin III. By Day 30, repeat abdominal ultrasound showed no ascites and normal blood flow in the portal district, and liver function tests were measured near normal range. On Day 61, the subject was diagnosed with Grade 4 atypical hemolytic uremic syndrome (aHUS), requiring therapy with eculizumab which delayed complete resolution of the event of VOD. The Grade 4 VOD event resolved on Day 70. This subject was determined to have a genetic mutation in the complement gene encoding membrane cofactor protein, a defect associated with inadequate control of complement activation, and aHUS. This subject was also noted to have anti-complement factor H (anti-CFH) antibodies. This is discussed further in Section 8.5.8.
- (b) (6) : This subject developed Grade 3 VOD on Day 21. This resolved by Day 42 after treatment with defibrotide.

- (b) (6) : This subject developed Grade 3 VOD on Day 22. This resolved by Day 53 after treatment with defibrotide.

Gallbladder Disease

Gallbladder disease is a known clinical manifestation of MLD. However, not all patients with MLD have gallbladder disease; the exact prevalence is unknown. Twenty-eight out of the 39 subjects treated in the safety population were reported to have pre-existing gallbladder disease prior to treatment with OTL-200. Fifteen out of 28 subjects (54%) with pre-existing gallbladder disease did not have resolution of their gallbladder disease at last follow-up after treatment with OTL-200. Additionally, 4 out of the 11 subjects who did not have pre-existing gallbladder disease prior to treatment developed gallbladder disease after treatment, with 2 subjects having ongoing gallbladder disease at last follow-up.

Reviewer Comment: *Regardless of MLD subtype, treatment with OTL-200 did not appear to consistently treat pre-existing MLD gallbladder disease or prevent new MLD gallbladder disease. This finding should be highlighted within the Limitations of Use section.*

Delayed Platelet Engraftment

Given the myeloablative conditioning used prior to treatment with OTL-200, delayed platelet engraftment was an AE of special interest. Platelet engraftment was defined as a platelet count >20 x 10^9/L for 3 consecutive days without transfusion support. Delayed platelet engraftment was defined as failure to achieve platelet engraftment by 60 days after treatment with OTL-200. Four subjects (10%) were reported as having delayed platelet engraftment occurring between 67 and 109 days. The minimum time to platelet engraftment in the safety population was 15 days, the maximum time was 109 days, and the median time was 39 days.

Neutrophil Engraftment Failure

Given the myeloablative conditioning used prior to treatment with OTL-200, neutrophil engraftment failure was an AE of special interest. Neutrophil engraftment failure was defined as failure to achieve three consecutive absolute neutrophil counts ≥500 cells/μL on different days by Day 60 after infusion with OTL-200. No subjects in the clinical development program were reported as having neutrophil engraftment failure.

Insertional Oncogenesis

Given that lentiviral gene therapy products integrate into the genome of the patients, insertional oncogenesis is a potential risk of OTL-200. Additionally, events of insertional oncogenesis have been seen in use of other lentiviral gene therapy products. There were no reported events of RCL, abnormal clonal proliferation, leukemia, or lymphoproliferation in the subjects treated in the clinical development program.

Hypersensitivity Reactions

Given the presence of DMSO in the drug product suspension, there is a risk of allergic reactions, including anaphylaxis. There were no reported events of serious hypersensitivity reactions in the clinical development program.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Determination of dose dependency for AEs is challenging in this small safety population. The dose administered to each individual subject was based on the number of cells harvested during apheresis. There are two ways to consider dose: the first is in the number of CD34+ cells administered per kilogram of body weight, while the second is the total number of CD34+ cells administered. No trends in dose and AEs (incidence or severity) were observed.

8.5.2 Time Dependency for Adverse Events

The most common AEs of febrile neutropenia, stomatitis, serious infections, and rash occurred within the first 90 days after treatment. AESIs tended to occur within the first year after treatment.

8.5.3 Product-Demographic Interactions

The ability of the data to determine product-demographic interactions is challenging due to the small size of the study population.

8.5.4 Product-Disease Interactions

This product is intended to restore ARSA enzyme activity, which is deficient in patients with MLD. Therefore, this is a direct product disease interaction. In Section 7.3.10, the potential for the treatment to accelerate disease progression is discussed.

8.5.5 Product-Product Interactions

No formal drug interaction studies were performed. OTL-200 is not expected to interact with the hepatic cytochrome P-450 family of enzymes or drug transporters.

8.5.6 Human Carcinogenicity

Given that OTL-200 uses a lentiviral vector, insertional oncogenesis is a potential risk of treatment. However, no cases of insertional oncogenesis or clonal expansion were observed in the study population.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.5.8 Immunogenicity (Safety)

At the time of data cut-off for the BLA submission, anti-ARSA antibodies were detected in 6 out of the 39 subjects who had received OTL-200 in the clinical development program. Each subject is discussed below:

(b) (6)

(b) (6) is a PSLI subject treated at 8 months of age with 18.2 x 10^6 cells/kg of the fresh formulation of the product. The subject developed severe hepatic VOD between study Day 18 and 30 and clinical signs of aHUS on Day 33. Laboratory assessments during this event

revealed positive anti-CFH antibodies and anti-ARSA antibodies at a level of 1:6400, the highest level detected in the clinical development program. Further testing of blood samples tested at baseline revealed pre-existing anti-CFH antibodies, anti-platelet antibodies, a positive direct Coombs test, and genetic abnormalities in the complement system genes. Eculizumab 300 mg IV once weekly was started on Day 41 to treat aHUS, and rituximab weekly for 4 weeks was initiated on Day 57 to treat the persistent multiple auto-antibodies. After initiation of immunomodulation, anti-ARSA antibodies were negative by Day 142. Given the thrombocytopenia and anemia related to the aHUS, the subject was administered their collection of back-up unmanipulated cells. ARSA levels in the PB decreased from a supranormal level of 1564 nmol/mg/hr on Day 89 (normal: 30.56 to 198.02 nmol/mg/h) to a normal level of 172 nmol/mg/hr on Day 405. Levels subsequently returned to supranormal levels on Day 769 (893 nmol/mg/hr) and remained supranormal until last follow-up. The subject was assessed as GMFC-MLD Level 4 at Day 295, Level 3 on Day 448, Level 2 at Day 626, and Level 1 at Day 791. At last follow-up, subject remained at GMFC-MLD Level 1 at 6.15 years of age.

Reviewer Comment: *This subject's decrease in ARSA enzyme levels at Day 405 may be partly explained by the reinfusion of back-up cells. This subject had a prolonged hospitalization due to the immune-mediated AEs that are likely due to the presence of underlying autoantibodies, rather than anti-ARSA antibodies. The anti-ARSA antibodies resolved after treatment with immunomodulation and do not appear to have adversely affected long-term clinical outcomes and PB ARSA levels.*

(b) (6)

(b) (6) is a PSLI subject treated at 9 months of age with $14.1x10^6$ cells/kg of the fresh formulation of the product. (b) (6) is the (b) (6) sibling of (b) (6) . Anti-ARSA antibodies were detected on Day 32 at a level of 1:320, reaching as high as 1:640 by Day 48. As was detected in (b) (6) sibling MLDHE01, this subject tested positive for anti-CFH and anti-platelet antibodies. Given the presence of multiple autoantibodies and the event of aHUS in the (b) (6) sibling, this subject received rituximab therapy for prophylaxis against immune-mediated AEs. Anti-ARSA antibodies resolved by Day 76. PB ARSA levels continued to rise in the presence of anti-ARSA antibodies, increasing from 109 nmol/hg/h at Day 29 to 662 nmol/mg/hr at Day 76 to 2612 nmol/mg/hr on Day 200. This subject has remained at GMFC-MLD Level 0 through last follow-up at 6.82 years of age.

(b) (6)

(b) (6) is a PSLI subject treated at 13 months of age with $14.2x10^6$ $CD34^+$ cells/kg of the fresh formulation of the product. Anti-ARSA antibodies were detected on Day 104 at 1:320 and resolved by Day 328 after administration of rituximab was initiated on Day 273. PB ARSA levels remained supranormal throughout the presence of anti-ARSA antiboides, measured at 1553 nmol/mg/hr on Day 103 and 2513 nmol/mg/hr on Day 270. This subject remains at GMFC-MLD Level 1 at last follow-up at 5.59 years of age.

(b) (6)

(b) (6) is a PSLI subjected treated at 10 months of age with $10.5x10^6$ CD34+ cells/kg of the fresh formulation of the product. Anti-ARSA antibodies were detected at Day 186 at titers of 1:640 and Day 265 at titers of 1:320. A course of rituximab (weekly for 4 weeks) was initiated on Day 277. Prior to commencement of rituximab, the antibody test drawn on Day 273 was negative. However, rituximab was still administered as a precautionary measure. Antibodies

remained negative from Day 273 to Day 358, with low titers again reported from Day 729 to Day 1041 (1:800 and 1:400, respectively). By Day 1096, antibodies were no longer detected. PB ARSA levels achieved supranormal levels at Day 91 (767 nmol/mg/hr) and subsequently continued to rise in the presence of anti-ARSA antibodies. This subject was assessed at GMFC-MLD Level 1 at last follow-up at 5.4 years of age.

(b) (6)

(b) (6) is a PSLI subject treated at 8.5 months of age with 26.29 x 10^6 CD34+ cells/kg of the cryopreserved formulation of the product. This subject tested positive for anti-ARSA antibodies at Day 32 (titer 1:400), which had resolved by Day 92. No treatment was required. PB ARSA levels were consistently supranormal, measured at 1464 nmol/mg/hr at Day 32 and 2274 nmol/mg/hr at Day 62. Subject had been assessed as GMFC-MLD Level 1 at last follow-up at 3.2 years of age.

(b) (6)

(b) (6) is a PSEJ subject treated at 27.3 months of age with 24.91 x 10^6 CD34+ cells/kg of the cryopreserved formulation of the product. This subject tested positive for anti-ARSA antibodies at Day 371 (titers 1:100) and Day 726 (titers:1:400). After treatment, PB ARSA levels reached a maximum of 1176 nmol/mg/hr by Day 84 but were slowly decreasing (remaining supranormal), with a last measurement of 487 nmol/mg/hr at Day 726. Anti-ARSA antibodies are still present at last follow-up. This subject remained in the pre-symptomatic stage of their disease at last follow-up at 4.56 years of age.

Reviewer Comment: *Out of the six subjects, there did not appear to be a long-term impact on PB ARSA levels or clinical outcomes in five of the subjects. It is premature to make conclusions about the impact of anti-ARSA antibodies in* (b) (6) *, as this subject continues to test positive and remains in the pre-symptomatic stage of their disease. Additionally, the impacts of the decreasing PB ARSA levels (although remaining still supranormal) are unknown at this time.*

8.5.9 Person-to-Person Transmission, Shedding

Person-to-person transmission and viral shedding do not appear to be risks with OTL-200.

8.6 Safety Conclusions

The most common AEs of febrile neutropenia, stomatitis, rash, and serious infections are not unexpected given the known safety profile of busulfan conditioning. The events of VOD were also not unexpected, as it is a known toxicity of busulfan conditioning. One subject ((b) (6)) had an atypical course of VOD that included aHUS. This event was likely complicated by underlying abnormalities in the complement genes and anti-complement antibodies.

The SAE of autoimmune encephalitis was unexpected. However, there are case reports to suggest that events of encephalitis may occur in patients with MLD, presenting in a relapsing-remitting pattern. An important consideration is the possibility that treatment with OTL-200 can precipitate or induce an inflammatory state, which may lead to events of encephalitis.

The SAE of cerebral infarction leading to death was also unexpected. There was limited information on the subject's clinical course and attribution to OTL-200 cannot be ruled out. Additionally, 28 out of 39 subjects had elevations in D-dimer levels at various timepoints after treatment without clear correlation to AEs, disease subtype, use of antithrombotic agents, or

timing after treatment. Therefore, it is important to monitor subjects treated with OTL-200 for D-dimer elevations and clinical signs or symptoms of thrombotic or thromboembolic events.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There is no available data with OTL-200 administration in pregnant women. Age at time of treatment for subjects treated with OTL-200 in the clinical studies ranged from 7.6 months to 11.6 years. Events of ovarian failure occurred in four female subjects.

Reviewer Comment: *Given the risks for ovarian failure, patients should be advised of the option to engage in fertility preservation treatments as applicable prior to treatment.*

9.1.2 Use During Lactation

There is no available data with OTL-200 administration during lactation, including no information regarding the presence of the product in human milk, effect on the breastfed infant, or effects on milk production.

9.1.3 Pediatric Use and PREA Considerations

LI and EJ MLD solely affect pediatric patients; as such, all clinical studies have been conducted in pediatric subjects.

9.1.4 Immunocompromised Patients

There are no available data from OTL-200 administration in immunocompromised patients.

9.1.5 Geriatric Use

There are no available data for OTL-200 administration in a geriatric population nor is it expected or intended to be used in this population.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

None.

10. Conclusions

In summary, the clinical review team concludes that there is substantial evidence of a favorable benefit-risk for use of OTL-200 in the subpopulations studied in the Applicant's clinical development program. However, each indication should be considered separately:

Pre-symptomatic Late Infantile MLD

There is a clear a robust treatment effect observed in the PSLI subjects treated in the clinical development program. While there are serious risks associated with busulfan conditioning (febrile neutropenia, serious infections, VOD) and significant unexpected AEs observed in treated subjects (encephalitis, D-dimer elevations with one event of fatal cerebral infarction), LI MLD is a devastating and rapidly progressive disease that leaves patients with complete

neurologic impairment by 5 years of age. The significant clinical efficacy data presented on survival, motor function, and cognitive function outweigh these identified risks. However, there are no clinical data on efficacy in subjects weighing less than 7 kg, with concern for a lower pharmacodynamic ARSA response when subjects are treated at younger ages (and at lower weights) that were not studied in the clinical trials. Additionally, there is a concern that younger infants (who have incompletely developed immune systems and smaller physiologic reserves) are at increased risks for the identified toxicities of OTL-200. Therefore, this clinical review team recommends approval for OTL-200 in children (b) (5) with pre-symptomatic LI MLD. The minimum effective dose in the treated PSLI subjects was identified as $4.2x10^6$ CD34+ cells/kg.

Pre-symptomatic Early Juvenile MLD

Despite a small study population, there was a clear treatment effect on both motor and cognitive outcomes in the PSEJ subjects with adequate follow-up data. This was supported by a clear and robust pharmacodynamic ARSA response, where treated subjects achieved and sustained supranormal levels of ARSA enzyme in the PB after treatment. Though characterized by a slower and more heterogenous disease progression in comparison to LI MLD, EJ MLD is similarly devastating and leaves patients with complete neurologic impairment in the second decade of life. While no conclusions were able to be made on the impact of OTL-200 on overall survival, benefits in preservation of independent ambulation and normal cognitive function were observed in the treated subjects. The smallest subject treated in the clinical trial weighed 10 kg. As discussed throughout this memo and the clinical pharmacology reviewer's memo, we are unable to extrapolate the efficacy data to younger subjects. In the analysis of the PSEJ data, subjects who have mild exam findings (clonus, abnormal reflexes) were observed to have comparable treatment responses to asymptomatic children. Therefore, the review team recommends approval for "(b) (5)
.

Early-symptomatic Early Juvenile MLD

Based on the review team's analysis, the treated ESEJ subjects did not demonstrate evidence of slowing of motor progression after treatment with OTL-200 compared to the natural history EJ subjects. Despite having a more mild EJ MLD phenotype prior to treatment, the review team observed that the treated EJ subjects experienced motor progression at a rate that appeared potentially faster than the natural history EJ subjects. This accelerated rate of motor progression was also observed in statistical analyses of the rate of progression from GMFC-MLD Level 1 to Level 2 (loss of independent ambulation). However, there was clear evidence of cognitive benefit, with subjects retaining meaningful cognitive function despite progression of motor disease. This cognitive benefit was only seen in the subjects who did not have advanced disease on brain MRI, characterized by the presence of demyelinating lesions of brainstem. Without treatment, these patients would be expected to progress to severe cognitive impairment. These effects on cognitive functioning are meaningful to patients, families, and caregivers, and outweigh the identified risks. Therefore, the clinical review team recommends approval for (b) (5)
"

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Risk benefit considerations are shown below in Table 30.

Table 30. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Metachromatic leukodystrophy (MLD) is a rare autosomal recessive, lysosomal storage disease that results in accumulation of sulfatides in the central and peripheral nervous system and progressive neurologic impairment. • LI MLD is the most rapidly progressive form of the disease, where patients experience symptom onset prior to 30 months of age with rapid progression to severe neurologic impairment by 5 years of age. There is minimal phenotypic heterogeneity in LI MLD. • EJ MLD presents with symptom onset after 30 months of age and before 7 years of age. There is considerable phenotypic heterogeneity in EJ MLD, where some patients experience rapid progression to severe neurologic impairment after symptom onset, and others have a slower clinical course with periods of neurologic plateau. Progression to severe neurologic impairment in EJ MLD usually occurs by adolescence.	• LI and EJ MLD are serious and devastating diseases. Children develop progressive severe neurologic impairment with premature mortality. • LI MLD has an early onset with rapid disease progression following symptom onset. • EJ MLD is phenotypically heterogeneous with regard to rate of neurodegenerative decline.
Unmet Medical Need	• There is no FDA-approved treatment for MLD. • There are no treatment options for LI MLD. • Hematopoietic stem cell transplant is sometimes used to treat children with EJ MLD. However, it is not considered standard of care, nor is it FDA-approved.	• For children with LI and EJ MLD, there is a substantial unmet medical need. • Slowing progression of disease for motor and neurocognitive disability are important treatment benefits for patients with LI and EJ MLD and their families.
Clinical Benefit	• OTL-200 demonstrated clear and robust benefit in all 20 treated PSLI subjects on the primary efficacy endpoint of severe motor-impairment free survival and on other endpoints of overall survival, motor function, and cognitive function compared to the external natural history subjects. There is also supportive pharmacodynamic evidence in the post-treatment ARSA enzyme levels in the peripheral blood. The smallest treated infant weighed 7 kg; there is uncertainty regarding efficacy for lower absolute doses in smaller infants, as extrapolation between dose, weight, total CD34+ cells administered and post-treatment ARSA levels is not feasible. • 7 children with PSEJ were treated, but given that 1 child died not from disease progression and 3 subjects were too young to assess at last follow-up, there is limited interpretable efficacy data for OTL-200 in PSEJ. Treatment effect in PSEJ is based on two children with neurocognitive outcomes that are unexpected compared to the natural history described in the literature, three children had independent ambulation at older ages than would be expected in the natural history based on literature and when available matched siblings, and supportive post-treatment ARSA enzyme levels in peripheral blood. For the PSEJ population, there is uncertainty on effect size, longitudinal duration of benefit (including whether there is a survival benefit) given the small sample size. The smallest treated infant was 10kg; there is also uncertainty regarding efficacy when smaller infants are treated given the inability to extrapolate dosing. • 10 children with ESEJ were treated with OTL-200. Four children were noted to have normal cognitive function (performance +/- language) in the setting of motor decline which is unexpected based on description of natural history in the literature. There is uncertainty on the impact of OTL-200 on motor function in ESEJ based on heterogeneity of disease progression and children treated with OTL-200 were less severe at baseline than the external controls. 2 children with	• Treatment with OTL-200 significantly extended severe motor impairment-free survival in children with PSLI MLD compared to untreated LI natural history children. There was a dramatic treatment effect of OTL-200 on overall survival, motor function and cognitive function in children with PSLI. • Treatment with OTL-200 offers motor and cognitive benefit in PSEJ. Although the evaluable study population is small, the outcomes are markedly different than expected natural history and supported by robust pharmacodynamic data. • There is no clinical data to demonstrate efficacy in PSLI subjects weighing less than 7 kg and PSEJ subjects weighing less than 10 kg. Given that OTL-200 is administered in cells/kg, there is a clear weight-based dose response in PSLI, infants are rapidly growing and there is insufficient data to support extrapolation, caution should be exercised in treating infants below those studied in clinical trials. • OTL-200 offers a cognitive benefit to 40% of the children with ESEJ in the clinical trial. While this is

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	ESEJ after treatment with OTL-200, had rapid progression of neurologic decline and death within 2 years, whereas the literature describes death typically occurring 5 years after symptom onset. The post-treatment ARSA enzyme levels were substantially lower than the treated PSLI and PSEJ subpopulations and took longer to achieve supranormal levels. • MLD gallbladder disease persisted in 14/28 (50%) of children with baseline disease prior to treatment with OTL-200, and five children developed new-onset gallbladder disease after OTL-200. There was no control group for comparison.	less robust efficacy than PSLI and PSEJ, it represents a very important clinical benefit to these children without alternative treatment. • OTL-200 did not provide a motor benefit and the treatment (including myeloablative conditioning) may have exacerbated motor progression. • Gallbladder disease persisted and new onset disease developed in children with MLD. OTL-200 does not adequately treat this manifestation of MLD.
Risk	• Serious risks identified during the clinical development include thrombosis and thrombotic events, encephalitis (with a relapsing-remitting pattern of disease progression), serious infections, veno-occlusive disease, and delayed platelet engraftment. • The most common adverse reactions were febrile neutropenia (85%), stomatitis (77%), respiratory tract infections (54%), rash (33%), device-related infections (31%), other viral infections (28%), pyrexia (21%), gastroenteritis (21%) and hepatomegaly 18%). • Insertional oncogenesis is a theoretical risk with LVV. Although no events were observed in the safety population this could occur after increased follow-up or when more children are treated. • In the ESEJ population, subject level analysis of motor progression and statistical analyses indicates that there is a potential for accelerated motor progression after treatment with OTL-200.	• There are serious risks associated with treatment of OTL-200. • Patients, providers, and families should be aware of the potential risk for accelerated motor progression in ESEJ MLD. • Baseline brainstem demyelination on MRI in the ESEJ population was associated with rapid disease progression and death.
Risk Management	• The safety database was small and included only 39 subjects. While no events of secondary malignancies were observed, this theoretic and serious risk that warrants continued surveillance. • One child died from cerebral thrombosis during the clinical trial that may be due to OTL-200. There is uncertainty regarding extent of risk, optimal monitoring, and mitigation.	• A post-marketing requirement to enroll a minimum of 17 subjects in an observational, long-term study has been issued. This will provide additional information on the long-term risks of OTL-200, including secondary malignancies and thrombosis. • Recommends labeling including a patient counseling section to describe risks and allow informed treatment decisions based on individual assessment of potential benefits and risks.

Abbreviations: EJ, early juvenile; ESEJ, early symptomatic early juvenile;LI, late infantile; MLD, metachromatic leukodystrophy; PSEJ, pre-symptomatic early juvenile; PSLI, pre-symptomatic late infantile

11.2 Risk-Benefit Summary and Assessment

LI and EJ MLD are serious conditions that result from deficiency of ARSA enzyme. This enzyme defect results in widespread demyelination of the central and peripheral nervous system and progressive severe neurologic impairment and death. There is a substantial unmet medical need; standard of care for MLD is limited to supportive care. OTL-200 is an autologous hematopoietic stem cell-based gene therapy that expresses the human *ARSA* gene. After infusion of OTL-200, transduced CD34+ HSCs engraft in bone marrow, repopulate the hematopoietic compartment and their progeny produce functional ARSA enzyme. Based on the mechanism of action, treatment early in the course of disease would be anticipated to offer maximal clinical benefit, as this treatment cannot reverse damage that has already occurred.

Clinical data from for 20 children with PSLI treated with OTL-200 shows a robust treatment effect based on the pre-specified primary endpoint compared to a natural history control group. A substantial treatment effect was also demonstrated for survival, independent ambulation, and performance and language cognitive function. As the PSEJ population treated with OTL-200 was only 7 children and EJ progresses more slowly than LI, the demonstrated OTL-200 treatment effect during the clinical trial in PSEJ was not statistically significant and was less dramatic than in PSLI. However, the treatment effect of OTL-200 on independent ambulation and cognition represented outcomes that are unexpected in the natural history and compared to available matched sibling controls.

The clinical efficacy data in ESEJ where children have already begun to demonstrate symptoms was limited to neurocognitive benefit. There were 4 children (40%) who maintained normal cognitive function despite motor decline. Retention of cognitive function has not been reported in this phase of EJ MLD in the natural history, as motor and cognitive function typically decline in parallel in untreated children with EJ. Maintaining cognitive function in advanced disease is important to families of children with EJ. It is important to note that there was no motor treatment benefit and there may be an accelerated motor progression in ESEJ.

The other observed risks are the same for PSLI, PSEJ and ESEJ. These include possible serious risks of thrombosis and thromboembolic events, encephalitis, serious infection, veno-occlusive disease, delayed platelet and neutrophil engraftment, hypersensitivity reactions and insertional oncogenesis.

Given the devastating nature of LI and EJ MLD, the observed benefits in all three subpopulations were considered to outweigh the uncertainties, identified and theoretical risks. To better understand risks associated with OTL-200, a post-marketing study will be required to assess insertional oncogenesis and other long-term safety risks, including thrombosis will be performed.

11.3 Discussion of Regulatory Options

The regulatory options were considered for each subtype separately. There was very clear and robust evidence of clinical efficacy based on the primary endpoint, overall survival, independent ambulation and preserved cognitive function, with supportive pharmacodynamic efficacy to support traditional approval in the PSLI subpopulation. Given the devastating nature of the disease including childhood mortality, the treatment effect overcomes the observed and theoretical risks. There is a favorable benefit-risk profile, and the clinical team supports traditional approval for this population.

Given the rarity of the disease, the observation that early treatment is beneficial in lysosomal storage diseases and the dramatic treatment effect in PSLI, the review team debated the ability to extrapolate to smaller and younger children. Modeling based on pharmacodynamics was not possible for infants below the weights treated in the clinical trial. Given the rapid growth in infants and the time needed to make the patient-specific product, there were concerns that dosing could be inadequate for young infants. The clinical review team was also concerned that very young, unvaccinated infants would be more susceptible to infections and complications from conditioning. Based on age of PSLI symptom onset, waiting until the children were at least 7kg, the smallest effectively treated infant in the clinical trial, would not place children at increased risk of becoming symptomatic. The primary clinical review team felt as though the risks of inadequately dosing young infants did not outweigh the potential benefits of earlier treatment.

For the PSEJ and ESEJ population, the sample size, heterogeneity of disease and comparability of the control group preclude formal statistical analysis on the pre-specified primary endpoint. However, given the rarity of this severe disease, we are exerting flexibility in analysis of the data. For the PSEJ subjects, after reviewing the original data and the adjudication committees reports, we believe that even though these children are asymptomatic at baseline (which precludes definitive differentiation between EJ and LJ subtypes), all of the PSEJ OTL-200 treated children have the EJ subtype. The totality of data demonstrated a clear treatment effect for those children who had been followed for an adequate duration to differentiate their clinical course from the natural history, and where available, matched sibling controls for independent ambulation and preservation of cognitive function. Irrespective of age, none of the OTL-200 treated PSEJ children had evidence of treatment failure related to disease progression. The ARSA level data is supportive, with all OTL-200 treated children showing a similar rapid rise to supranormal levels. One child in this sub-population died from a CVA, that may potentially be due to the therapy. There are serious observed and potential risks associated with OTL-200 therapy. However, the overall the benefit-risk profile is favorable and supports traditional approval for the PSEJ subpopulation.

For the ESEJ subpopulation, there was a great deal of internal debate regarding whether the clinical data was adequate to support approval, or if an indication for this sub-population should not be granted. The challenge arose from a large degree of uncertainty regarding the rapidity of decline for the ESEJ study subjects had they not received treatment with OTL-200. There were not appropriate matched controls in the submitted natural history study, and at baseline most of the treated children appeared less impaired than typically occurs in the untreated natural history. In particular, two children (20%) appeared to have a phenotype that was intermittent between the EJ and LJ.

The clinical data was not supportive of a clear treatment effect on the motor manifestations. The overall motor decline in the OTL-200 children appeared to be either consistent with the natural history or faster than would have been expected without treatment. Given the lack of data suggesting benefit, the primary clinical review team does not support approval of OTL-200 for the (b) (4) .

However, there was a treatment effect for slowing of neurocognitive decline. Slowing of cognitive disease progression was noted in 4/10 (40%) of ESEJ children treated with OTL-200. This preservation of cognitive function despite continued motor impairment is not reported in the literature; cognitive decline typically precedes or occurs in parallel with motor decline in EJ MLD. The observed slowing of cognitive impairment was attributed as a treatment effect of OTL-200.

The clinical review team appreciates feedback from patients and MLD patient advocates about the importance of preserved communication and cognition. Balancing the benefit (with a limited number of children demonstrating cognitive benefits) with the risks from the product (especially the potential that OTL-200 was hastening motor decline) was challenging.

The clinical review team believes that the benefit-risk of OTL-200 for the ESEJ population can be made more favorable by modifying the definition of "early symptomatic" to exclude children with brainstem involvement on brain MRI. Based on analysis of treatment successes and failures, baseline brainstem involvement on brain MRI was associated with poor prognosis. Based on the pathophysiology of MLD, neurobiology, and mechanism of action of OTL-200, there is a mechanistic rationale that patients with advanced radiographic findings will not benefit from OTL-200. Therefore, the clinical review team recommends traditional approval of OTL-200 for slowing of cognitive impairment in the sub-population of children with ESEJ who do not have clinically advanced disease (GMFC-MLD score<1) or evidence of advanced disease based on neuroimaging (brainstem involvement on brain MRI). However, given the concerns about motor progression, the primary clinical review team recommends that the product label highlight the risk for accelerated motor progression, such that patients, families, and caregivers can make an informed decision about pursuing treatment with OTL-200.

11.4 Recommendations on Regulatory Actions

The clinical review team recommends traditional approval for OTL-200 based on demonstration of safety and effectiveness.

While the Applicant requested approval for the indications of "treatment of pre-symptomatic late infantile, pre-symptomatic early juvenile, and early symptomatic early juvenile MLD", the primary clinical review team recommends approval for the following revised indications:

- Treatment of children (b) (5) with pre-symptomatic late infantile (PSLI) MLD.
- Treatment of children (b) (5) with pre-symptomatic early juvenile (PSEJ) MLD. (b) (5)
- Slowing of progression of cognitive impairment in children with early symptomatic early juvenile (ESEJ) MLD. ESEJ MLD includes children who develop symptoms between 30 months of age and 7 years of age, and at the time of treatment, have GMFC-MLD score of 0 with ataxia or GMFC score of 1, and do not have evidence of brainstem involvement on brain MRI.

The clinical review team's recommendations are based on the clinical data submitted in the BLA. Weight minimums for the PSLI and PSEJ indications are determined based on the weight of the smallest PSLI and PSEJ subjects treated in the clinical trial and are deemed an important aspect of the indication statement given the difficultly in extrapolating pharmacodynamic and clinical efficacy to children with smaller weights.

An upper age parameter of 7 years of age is recommended to be included for clarity in the indication statement for PSEJ and ESEJ MLD, given that there is known discrepancy in the definition of EJ MLD in the literature and in clinical practice (both 6- and 7- year age thresholds are used).

For the ESEJ indication, only clear evidence of slowing of cognitive progression was observed in the clinical team's analysis. "Early symptomatic" EJ MLD is not used in clinical practice, and therefore for clarity and consistency should be defined. Additionally, the clinical review team recommends the indication statement specify that OTL-200 is approved for those without brainstem involvement on brain MRI, as the clinical data demonstrated that this finding distinguished the treatment responders (cognitive benefit) from the non-responders (no cognitive benefit).

11.5 Labeling Review and Recommendations

The review team made substantial recommendations to each section of the Prescribing Information based on analyses of the safety and efficacy data.

The Applicant requested the following indications: "treatment of pre-symptomatic late infantile, pre-symptomatic early juvenile, and early symptomatic early juvenile MLD". No Limitations of Use were proposed in the initial draft label. Warnings and Precautions identified by the Applicant included delayed platelet engraftment, neutrophil engraftment failure, insertional oncogenesis, and neutrophil engraftment failure. The most significant revisions recommended by the clinical review team included:

Section 1 – Indications & Usage

Given the relationship between dose, weight and post-treatment ARSA enzyme response the review team recommended that section 1 specify minimum weights for treatment for the PSLI and PSEJ indications ((b) (5)). To ensure that the definition of PSEJ used for the BLA submission was clear in the label, the review team recommended that the indication statement define PSEJ as "children (b) (5) of age with PSEJ MLD. PSEJ includes children who are asymptomatic or have physical exam findings limited to clonus and/or abnormal reflexes".

Reviewer Comment: *This recommendation is made per the regulations outlined in 21 CFR §201.57 (c)(2)(i)(B), which states that section 1 must include the following information if applicable: "If evidence is available to support the safety and effectiveness of the drug or biological product only in selected subgroups of the larger population (e.g., patients with mild disease or patients in a special age group)". Given that there is no data to demonstrate efficacy at lower weights (where there may be a less robust post-treatment ARSA enzyme response given the response between dose, weight, and ARSA levels), the review team believes that inclusion of weight parameters in section 1 fulfills the requirements outlined in this regulation.*

The clinical review team did not observe substantial evidence of efficacy to support approval for the "treatment of early symptomatic early juvenile MLD" as requested by the Applicant, as efficacy was observed to be limited to the slowing of cognitive disease progression in patients without brainstem involvement of brain MRI. Therefore, the review team proposed the following modifications to the ESEJ indication within section 1: "Slowing of progression of cognitive impairment in children with early symptomatic early juvenile (ESEJ) MLD. ESEJ MLD includes children who develop symptoms between 30 months of age and 7 years of age, and at the time of treatment, have Gross Motor Function Classification-MLD (GMFC-MLD) ≤1 without or without ataxia, and do not have evidence of brainstem involvement on brain MRI."

Reviewer Comment: *These recommendations are made based on the following regulations:*

- *21 CFR §201.57(c)(2) states that section 1 should "state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with this recognized disease or condition". The clinical data only demonstrated efficacy in mitigating the cognitive manifestations in ESEJ MLD. Therefore, inclusion of this information in section 1 would satisfy this regulation.*
- *The FDA Guidance "Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" states that section 1 should "use terminology that is clinically relevant and scientifically valid and understandable to health care practitioners" (July 2018). Given that "early symptomatic early juvenile MLD" is not a clinically relevant term (and has been defined for the purposes of this clinical trial), ESEJ MLD should be defined in section 1 per guidance recommendations.*
- *21 CFR §201.57(c)(2)(i)(B) states that section 1 should list the following information as applicable: "if evidence is available to support safety and effectiveness of the drug or biological product only in selected subgroups of the larger population (e.g., patients with mild disease or patients in a special age group)…a succinct description of the limitations of usefulness and any uncertainty about the anticipated clinical benefits, with reference to the 'Clinical Studies' section for a discussion of the available evidence". Per this regulation, the primarily clinical review team recommends that section 1 describe that efficacy was only seen in a subpopulation of patients with EJ MLD (early symptomatic patients without brainstem involvement on MRI).*

Limitations of Use

Based on this review team's analysis, two Limitations of Use have been identified and proposed for inclusion in the Prescribing Information:

- The potential for accelerated motor progression in ESEJ subjects treated with OTL-200
- OTL-200 does not appear to treat gallbladder disease in PSLI, PSEJ, and ESEJ MLD.

Reviewer Comment: *These recommendations are based on FDA Guidance "Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format", which states that a limitations of use are appropriate for "drugs for which there is reasonable concern or uncertainty about effectiveness or safety in a certain clinical situation" (July 2018).*

Section 5 - Warnings and Precautions

Additional revisions to section 5 were proposed based on the review team's safety analysis. This includes thrombosis and thromboembolic events, encephalitis, serious infections, and VOD.

Section 14 – Clinical Studies

Revisions on section 14 were requested to reflect the reclassification of subjects discussed in Section 7 of this memo. Additionally, the Applicant was requested to remove statistical and pooled analyses in the presentation of the PSEJ and ESEJ clinical data, given the small study population. Based on the efficacy analyses, the review team made the following recommendations on the presentation of the efficacy data for the PSEJ and ESEJ subpopulations:

- Removal of comparisons to the natural history study population given lack of comparability issues.
- Present subject-level efficacy data on motor and cognitive outcomes in comparison to published natural history literature on the PSEJ subjects. Given heterogeneity and short duration of follow-up, efficacy conclusions on mortality and motor impairment at 2- and 5-years post treatment (secondary endpoints) cannot be made and should be removed.
- Discuss that there was no evidence to suggest slowing of motor disease in the treated ESEJ subjects.
- Present subject-level efficacy data on the cognitive outcomes in the ESEJ subjects, who demonstrate retention of cognitive function despite progression of motor impairment, which is unexpected in the published natural history literature.
- Present data on the persistence of pre-existing MLD gallbladder disease and the new events of MLD gallbladder disease that occurred in subjects treated with OTL-200, regardless of disease subtype.

Reviewer Comment: *This BLA submission will be approved by OTP leadership for the Applicant's originally requested indication of "treatment of pre-symptomatic late infantile, pre-symptomatic early juvenile and early symptomatic early juvenile MLD". OTP leadership did not agree with the primary clinical review team's proposed changes to section 1 or the addition of Limitations of Use statements. The lack of motor benefit in the ESEJ subjects will be detailed in section 14. The review team worked the Applicant to revise the Prescribing Information per clinical review team and OTP leadership's assessments.*

11.6 Recommendations on Postmarketing Actions

The review team notes two important considerations for post-marketing surveillance. The first is the small safety population and the continued monitoring for the incidence of secondary malignancies (a known risk of lentiviral gene therapy products). The second is the incompletely characterized risk of thrombosis, with 1 subject in the clinical trials progressing to death due to cerebral infarction, and 27 out of 39 subjects having elevated D-dimer levels of unknown significance at various timepoints after treatment. The clinical review team, the Division of Pharmacovigilance, and the Applicant mutually agreed upon the following clinical post-marketing requirements for this submission:

- 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). This study will enroll a minimum of 17 subjects. The enrolled patients will be followed for 15 years after product administration. Milestone dates include:
  - Final Protocol Submission: July 31, 2024
  - Study Completion Date: June 30, 2044
  - Final Study Report Submission: December 31, 2044

This post-marketing study will also include a safety outcome of "thromboembolic events" as a study objective, collection of data on D-dimer levels for all enrolled patients and collection of data on whether patients receive anti-thrombotic prophylaxis during condition or following treatment with OTL-200.

APPENDIX I: D-DIMER ELEVATIONS IN SAFETY POPULATION

Table 31: D-Dimer Elevations in Treated Subjects

Subject ID	Analysis Visit	D-Dimer (nmol/L FEU)	D-Dimer Flag (Normal, High, Low)	D-Dimer LLN[a]	D-Dimer ULN[b]
(b) (6)	Baseline	109.53	HIGH	1.20472	4.21652
	Day 28	50.05064	HIGH	1.20472	4.21652
	Month 3	8.04972	HIGH	1.20472	4.21652
	Month 6	4.43556	HIGH	1.20472	4.21652
	Month 9	4.05224	NORMAL	1.20472	4.21652
	Year 1	4.05224	NORMAL	1.20472	4.21652
	Year 1	4.27128	HIGH	1.20472	4.21652
	Year 1.5	2.02612	NORMAL	1.47852	4.21652
	Year 2	11.93768	HIGH	1.47852	4.21652
	Year 2.5	10.34964	HIGH	1.47852	4.21652
	Year 3	2.24516	NORMAL	1.47852	4.21652
	Year 4	1.47852	NORMAL	1.47852	4.21652
	Year 5	1.86184	NORMAL	1.47852	4.21652
	Year 6	1.58804	NORMAL	1.47852	4.21652
	Year 7	1.47852	NORMAL	1.47852	4.21652
	Year 8	1.47852	NORMAL	1.47852	4.21652
	Year 11	1.47852	NORMAL	1.47852	4.21652
	Year 12	3.12132	NORMAL	1.47852	4.21652
	Baseline	4.59984	HIGH	1.20472	4.21652
	Day 60	1.9166	NORMAL	1.20472	4.21652
	Month 3	1.69756	NORMAL	1.20472	4.21652
	Month 9	3.17608	NORMAL	1.47852	4.21652
	Year 1	3.34036	NORMAL	1.47852	4.21652
	Year 1.5	1.369	LOW	1.47852	4.21652
	Year 2	1.20472	LOW	1.47852	4.21652
	Year 2.5	2.08088	NORMAL	1.47852	4.21652
	Year 4	3.50464	NORMAL	1.47852	4.21652
	Baseline	4.81888	HIGH	1.20472	4.21652
	Day 28	5.09268	HIGH	1.20472	4.21652
	Day 60	1.9166	NORMAL	1.20472	4.21652
	Month 3	2.62848	NORMAL	1.20472	4.21652
	Month 6	8.7616	HIGH	1.20472	4.21652
	Month 9	7.17356	HIGH	1.47852	4.21652
	Year 1	5.42124	HIGH	1.47852	4.21652
	Year 1.5	5.2022	HIGH	1.47852	4.21652
	Year 2	2.51896	NORMAL	1.47852	4.21652
	Year 2.5	7.72116	HIGH	1.47852	4.21652
	Year 3	24.0944	HIGH	1.47852	4.21652
	Year 4	3.34036	NORMAL	1.47852	4.21652
	Year 5	2.84752	NORMAL	1.47852	4.21652

Subject ID	Analysis Visit	D-Dimer (nmol/L FEU)	D-Dimer Flag (Normal, High, Low)	D-Dimer LLN[a]	D-Dimer ULN[b]
(b) (6)	Year 6	1.75232	NORMAL	1.47852	4.21652
	Year 7	1.6428	NORMAL	1.47852	4.21652
	Year 8	2.4642	NORMAL	1.47852	4.21652
	Year 11	2.51896	NORMAL	1.47852	4.21652
	Baseline	1.42376	NORMAL	1.20472	4.21652
	Day 21	4.6546	HIGH	1.20472	4.21652
	Day 35	5.476	HIGH	1.20472	4.21652
	Day 60	5.7498	HIGH	1.20472	4.21652
	Month 3	3.0118	NORMAL	1.20472	4.21652
	Month 6	5.64028	HIGH	1.47852	4.21652
	Month 9	3.44988	NORMAL	1.47852	4.21652
	Year 1	2.79276	NORMAL	1.47852	4.21652
	Year 1.5	1.20472	LOW	1.47852	4.21652
	Year 2	1.47852	NORMAL	1.47852	4.21652
	Year 2.5	2.02612	NORMAL	1.47852	4.21652
	Year 3	1.80708	NORMAL	1.47852	4.21652
	Year 4	1.86184	NORMAL	1.47852	4.21652
	Year 5	2.29992	NORMAL	1.47852	4.21652
	Year 6	109.53	HIGH	1.47852	4.21652
	Year 7	2.13564	NORMAL	1.47852	4.21652
	Year 8	1.97136	NORMAL	1.47852	4.21652
	Baseline	1.20472	LOW	1.47852	4.21652
	Day 28	3.44988	NORMAL	1.47852	4.21652
	Day 60	1.369	LOW	1.47852	4.21652
	Month 3	1.9166	NORMAL	1.47852	4.21652
	Month 6	2.40944	NORMAL	1.47852	4.21652
	Month 9	3.2856	NORMAL	1.47852	4.21652
	Year 1	2.08088	NORMAL	1.47852	4.21652
	Year 1.5	1.47852	NORMAL	1.47852	4.21652
	Year 2	4.16176	NORMAL	1.47852	4.21652
	Year 2.5	3.39512	NORMAL	1.47852	4.21652
	Year 3	4.76412	HIGH	1.47852	4.21652
	Year 4	1.69756	NORMAL	1.47852	4.21652
	Year 5	1.6428	NORMAL	1.47852	4.21652
	Year 6	1.9166	NORMAL	1.47852	4.21652
	Year 7	1.6428	NORMAL	1.47852	4.21652
	Year 8	1.47852	NORMAL	1.47852	4.21652
	Year 9	2.4642	NORMAL	1.47852	4.21652
	Year 9	1.86184	NORMAL	1.47852	4.21652
	Year 10	2.13564	NORMAL	1.47852	4.21652
	Baseline	1.20472	LOW	1.47852	4.21652
	Day 28	1.47852	NORMAL	1.47852	4.21652
	Day 60	1.20472	LOW	1.47852	4.21652

Subject ID	Analysis Visit	D-Dimer (nmol/L FEU)	D-Dimer Flag (Normal, High, Low)	D-Dimer LLN[a]	D-Dimer ULN[b]
(b) (6)	Month 3	1.20472	LOW	1.47852	4.21652
	Month 6	1.75232	NORMAL	1.47852	4.21652
	Month 9	2.35468	NORMAL	1.47852	4.21652
	Year 1	2.51896	NORMAL	1.47852	4.21652
	Year 1.5	8.81636	HIGH	1.47852	4.21652
	Year 2	1.47852	NORMAL	1.47852	4.21652
	Year 2.5	1.47852	NORMAL	1.47852	4.21652
	Year 3	1.80708	NORMAL	1.47852	4.21652
	Year 4	1.47852	NORMAL	1.47852	4.21652
	Year 5	1.75232	NORMAL	1.47852	4.21652
	Year 7	7.1188	HIGH	1.47852	4.21652
	Baseline	1.369	LOW	1.47852	4.21652
	Day 28	2.4642	NORMAL	1.47852	4.21652
	Month 3	1.47852	NORMAL	1.47852	4.21652
	Month 6	1.6428	NORMAL	1.47852	4.21652
	Month 9	1.9166	NORMAL	1.47852	4.21652
	Year 1	1.47852	NORMAL	1.47852	4.21652
	Year 1.5	1.47852	NORMAL	1.47852	4.21652
	Year 2	47.58644	HIGH	1.47852	4.21652
	Year 2.5	2.02612	NORMAL	1.47852	4.21652
	Year 3	1.69756	NORMAL	1.47852	4.21652
	Year 4	1.47852	NORMAL	1.47852	4.21652
	Year 5	1.9166	NORMAL	1.47852	4.21652
	Year 6	1.80708	NORMAL	1.47852	4.21652
	Baseline	2.84752	NORMAL	1.47852	4.21652
	Day 28	2.68324	NORMAL	1.47852	4.21652
	Day 60	1.6428	NORMAL	1.47852	4.21652
	Month 3	1.9166	NORMAL	1.47852	4.21652
	Month 6	3.72368	NORMAL	1.47852	4.21652
	Month 9	2.62848	NORMAL	1.47852	4.21652
	Year 1.5	17.96128	HIGH	1.47852	4.21652
	Year 2	1.69756	NORMAL	1.47852	4.21652
	Year 2.5	1.47852	NORMAL	1.47852	4.21652
	Year 4	1.47852	NORMAL	1.47852	4.21652
	Year 5.5	3.0118	NORMAL	1.47852	4.21652
	Year 6	1.47852	NORMAL	1.47852	4.21652
	Year 8	1.47852	NORMAL	1.47852	4.21652
	Baseline	4.81888	HIGH	1.47852	4.21652
	Day 28	1.47852	NORMAL	1.47852	4.21652
	Day 60	1.47852	NORMAL	1.47852	4.21652
	Month 3	1.47852	NORMAL	1.47852	4.21652
	Month 6	1.86184	NORMAL	1.47852	4.21652
	Month 9	2.13564	NORMAL	1.47852	4.21652

Subject ID	Analysis Visit	D-Dimer (nmol/L FEU)	D-Dimer Flag (Normal, High, Low)	D-Dimer LLN[a]	D-Dimer ULN[b]
(b) (6)	Year 1	2.13564	NORMAL	1.47852	4.21652
	Year 1	3.34036	NORMAL	1.47852	4.21652
	Year 1	6.73548	HIGH	1.47852	4.21652
	Year 1.5	2.738	NORMAL	1.47852	4.21652
	Year 2	3.8332	NORMAL	1.47852	4.21652
	Year 3	1.47852	NORMAL	1.47852	4.21652
	Year 4	1.47852	NORMAL	1.47852	4.21652
	Baseline	8.59732	HIGH	1.47852	4.21652
	Day 28	2.51896	NORMAL	1.47852	4.21652
	Day 60	1.75232	NORMAL	1.47852	4.21652
	Month 3	1.47852	NORMAL	1.47852	4.21652
	Month 6	1.6428	NORMAL	1.47852	4.21652
	Month 9	1.47852	NORMAL	1.47852	4.21652
	Year 1	3.50464	NORMAL	1.47852	4.21652
	Year 1.5	1.47852	NORMAL	1.47852	4.21652
	Year 2	1.9166	NORMAL	1.47852	4.21652
	Year 2.5	1.47852	NORMAL	1.47852	4.21652
	Year 3	1.53328	NORMAL	1.47852	4.21652
	Year 5	2.02612	NORMAL	1.47852	4.21652
	Year 8	2.90228	NORMAL	1.47852	4.21652
	Baseline	2.02612	NORMAL	1.47852	4.21652
	Day 28	4.16176	NORMAL	1.47852	4.21652
	Day 60	2.29992	NORMAL	1.47852	4.21652
	Month 3	1.58804	NORMAL	1.47852	4.21652
	Month 6	1.47852	NORMAL	1.47852	4.21652
	Month 9	12.81384	HIGH	1.47852	4.21652
	Year 1	3.0118	NORMAL	1.47852	4.21652
	Year 1.5	2.79276	NORMAL	1.47852	4.21652
	Year 2	1.47852	NORMAL	1.47852	4.21652
	Year 2.5	2.13564	NORMAL	1.47852	4.21652
	Year 3	2.08088	NORMAL	1.47852	4.21652
	Year 4	2.08088	NORMAL	1.47852	4.21652
	Screening	492.84	NORMAL	0	1708.512
	Baseline	9.19968	HIGH	1.47852	4.21652
	Day 28	21	HIGH	1.47852	4.21652
	Day 28	39.53672	HIGH	1.47852	4.21652
	Day 28	17.46844	HIGH	1.47852	4.21652
	Day 28	31.43224	HIGH	1.47852	4.21652
	Day 28	37.34632	HIGH	1.47852	4.21652
	Day 60	13.47096	HIGH	1.47852	4.21652
	Day 60	8.15924	HIGH	1.47852	4.21652
	Year 3	1.47852	NORMAL	1.47852	4.21652
	Day 28	9.0354	HIGH	1.47852	4.21652

Subject ID	Analysis Visit	D-Dimer (nmol/L FEU)	D-Dimer Flag (Normal, High, Low)	D-Dimer LLN[a]	D-Dimer ULN[b]
(b) (6)	Year 2.5	2.08088	NORMAL	1.47852	4.21652
	Year 3.5	1.75232	NORMAL	1.47852	4.21652
	Baseline	9.3092	HIGH	1.47852	4.21652
	Day 28	7.77592	HIGH	1.47852	4.21652
	Day 60	1.47852	NORMAL	1.47852	4.21652
	Month 3	1.47852	NORMAL	1.47852	4.21652
	Month 6	1.47852	NORMAL	1.47852	4.21652
	Month 9	1.86184	NORMAL	1.47852	4.21652
	Year 1	1.9166	NORMAL	1.47852	4.21652
	Year 1.5	2.13564	NORMAL	1.47852	4.21652
	Year 2	1.47852	NORMAL	1.47852	4.21652
	Year 2.5	1.9166	NORMAL	1.47852	4.21652
	Year 3	2.40944	NORMAL	1.47852	4.21652
	Year 4	1.47852	NORMAL	1.47852	4.21652
	Year 5	2.51896	NORMAL	0	2.73794524
	Year 6	2.95704	NORMAL	1.47852	4.21652
	Screening	2.35468	NORMAL	1.47852	4.21652
	Baseline	2.08088	NORMAL	1.47852	4.21652
	Day 28	1.97136	NORMAL	1.47852	4.21652
	Day 60	1.58804	NORMAL	1.47852	4.21652
	Month 3	14.40188	HIGH	1.47852	4.21652
	Month 6	12.54004	HIGH	1.47852	4.21652
	Month 9	1.47852	NORMAL	1.47852	4.21652
	Year 1	3.39512	NORMAL	1.47852	4.21652
	Year 1.5	1.47852	NORMAL	1.47852	4.21652
	Year 2	1.47852	NORMAL	1.47852	4.21652
	Year 2.5	3.8332	NORMAL	0	5.47594524
	Year 3	1.47852	NORMAL	1.47852	4.21652
	Year 4	1.6428	NORMAL	1.47852	4.21652
	Screening	1.6428	NORMAL	1.47852	4.21652
	Baseline	1.53328	NORMAL	1.47852	4.21652
	Day 28	5.85932	HIGH	1.47852	4.21652
	Day 60	15.6066	HIGH	1.47852	4.21652
	Month 3	1.75232	NORMAL	1.47852	4.21652
	Year 1	3.17608	NORMAL	1.47852	4.21652
	Screening	1.80708	NORMAL	1.47852	4.21652
	Baseline	2.57372	NORMAL	1.47852	4.21652
	Day 28	14.89472	HIGH	1.47852	4.21652
	Day 60	5.31172	HIGH	1.47852	4.21652
	Month 3	3.88796	NORMAL	1.47852	4.21652
	Month 6	7.77592	HIGH	1.47852	4.21652
	Year 1	8.81636	HIGH	1.47852	4.21652
	Year 2	1.47852	NORMAL	1.47852	4.21652

Subject ID	Analysis Visit	D-Dimer (nmol/L FEU)	D-Dimer Flag (Normal, High, Low)	D-Dimer LLN[a]	D-Dimer ULN[b]
(b) (6)	Year 3	1.47852	NORMAL	1.47852	4.21652
	Year 4	3.50464	NORMAL	1.47852	4.21652
	Screening	1.53328	NORMAL	1.47852	4.21652
	Baseline	1.47852	NORMAL	1.47852	4.21652
	Day 28	5.42124	HIGH	1.47852	4.21652
	Day 60	4.21652	NORMAL	1.47852	4.21652
	Month 3	4.87364	HIGH	1.47852	4.21652
	Month 6	1.53328	NORMAL	1.47852	4.21652
	Month 9	1.47852	NORMAL	1.47852	4.21652
	Year 1	1.47852	NORMAL	1.47852	4.21652
	Year 2	1.47852	NORMAL	1.47852	4.21652
	Year 2.5	1.47851	-	0	2.68324
	Year 3	2.35468	NORMAL	1.47852	4.21652
	Screening	1.47852	NORMAL	1.47852	4.21652
	Baseline	1.47852	NORMAL	1.47852	4.21652
	Day 28	1.9166	NORMAL	1.47852	4.21652
	Month 3	1.9166	NORMAL	1.47852	4.21652
	Month 6	1.04043	-	0	2.738
	Month 9	1.0952	NORMAL	0	2.738
	Year 1	2.35468	NORMAL	1.47852	4.21652
	Year 1.5	1.80708	NORMAL	0	2.738
	Year 2	5.03792	HIGH	1.47852	4.21652
	Year 2.5	1.0952	NORMAL	0	2.738
	Year 3	1.47852	NORMAL	1.47852	4.21652
	Screening	3.8332	NORMAL	1.47852	4.21652
	Baseline	2.40944	NORMAL	1.47852	4.21652
	Day 28	3.77844	NORMAL	1.47852	4.21652
	Day 60	1.75232	NORMAL	1.47852	4.21652
	Month 6	10.886288	HIGH	0	1.25948
	Month 9	1.97136	NORMAL	1.47852	4.21652
	Year 1	2.1904	NORMAL	1.47852	4.21652
	Year 1.5	1.58804	NORMAL	1.47852	4.21652
	Year 2	2.1904	NORMAL	1.47852	4.21652
	Year 2.5	109.53	HIGH	1.47852	4.21652
	Screening	1.47852	NORMAL	1.47852	4.21652
	Baseline	1.53328	NORMAL	1.47852	4.21652
	Day 28	2.62848	NORMAL	1.47852	4.21652
	Day 60	2.68324	NORMAL	1.47852	4.21652
	Month 3	22.34208	HIGH	1.47852	4.21652
	Month 6	2.4642	NORMAL	1.47852	4.21652
	Year 1	1.9166	NORMAL	1.47852	4.21652
	Year 1.5	1.002108	NORMAL	0	1.20472
	Year 2	2.40944	NORMAL	1.47852	4.21652

Subject ID	Analysis Visit	D-Dimer (nmol/L FEU)	D-Dimer Flag (Normal, High, Low)	D-Dimer LLN[a]	D-Dimer ULN[b]
(b) (6)	Screening	1.47852	NORMAL	1.47852	4.21652
	Baseline	1.47852	NORMAL	1.47852	4.21652
	Day 28	1.86184	NORMAL	1.47852	4.21652
	Day 60	3.39512	HIGH	0	2.738
	Month 3	2.90228	NORMAL	1.47852	4.21652
	Month 6	1.47852	NORMAL	1.47852	4.21652
	Month 9	2.68324	NORMAL	0	2.73794524
	Year 1	1.0951	NORMAL	0	2.73794524
	Year 1.5	1.47852	NORMAL	1.47852	4.21652
	Year 2	2.29992	NORMAL	1.47852	4.21652
	Screening	109.53	HIGH	1.47852	4.21652
	Baseline	1.47852	NORMAL	1.47852	4.21652
	Day 28	8.4878	HIGH	1.47852	4.21652
	Day 60	1.75232	NORMAL	1.47852	4.21652
	Month 3	2.1904	NORMAL	1.47852	4.21652
	Month 6	1.47852	NORMAL	1.47852	4.21652
	Year 1	1.69756	NORMAL	1.47852	4.21652
	Year 2	1.47852	NORMAL	1.47852	4.21652
	Baseline	1.53328	NORMAL	1.47852	4.21652
	Day 28	7.99496	HIGH	1.47852	4.21652
	Day 60	1.47852	NORMAL	1.47852	4.21652
	Month 3	1.47852	NORMAL	1.47852	4.21652
	Month 6	1.47852	NORMAL	1.47852	4.21652
	Year 1	1.47852	NORMAL	1.47852	4.21652
	Year 1.5	1.9166	NORMAL	1.47852	4.21652
	Year 2	1.47852	NORMAL	1.47852	4.21652
	Year 2.5	1.80708	NORMAL	1.47852	4.21652
	Year 4.5	11.39008	HIGH	1.47852	4.21652
	Screening	1.86184	NORMAL	1.47852	4.21652
	Baseline	3.2856	NORMAL	1.47852	4.21652
	Day 28	15.27804	HIGH	1.47852	4.21652
	Day 60	6.5712	HIGH	1.47852	4.21652
	Month 3	19.00172	HIGH	1.47852	4.21652
	Month 6	3.0118	NORMAL	1.47852	4.21652
	Month 9	3.06656	NORMAL	1.47852	4.21652
	Year 1	3.06656	NORMAL	1.47852	4.21652
	Year 1.5	1.58804	NORMAL	1.47852	4.21652
	Year 2	3.88796	NORMAL	1.47852	4.21652
	Year 2.5	1.86184	NORMAL	1.47852	4.21652
	Year 3.5	1.20472	NORMAL	0	2.29992
	Year 4.5	1.47852	NORMAL	1.47852	4.21652
	Screening	1.47852	NORMAL	1.47852	4.21652
	Day 28	8.37828	HIGH	1.47852	4.21652

Subject ID	Analysis Visit	D-Dimer (nmol/L FEU)	D-Dimer Flag (Normal, High, Low)	D-Dimer LLN[a]	D-Dimer ULN[b]
(b) (6)	Day 60	35.15592	HIGH	1.47852	4.21652
	Month 3	1.6428	NORMAL	1.47852	4.21652
	Year 1	2.90228	NORMAL	1.47852	4.21652
	Year 1.5	83.67328	HIGH	1.47852	4.21652
	Year 2	1.6428	NORMAL	1.47852	4.21652
	Year 3	4.27128	HIGH	1.47852	4.21652
	Year 3.5	2.51896	NORMAL	1.47852	4.21652
	Year 4.5	2.1904	NORMAL	1.47852	4.21652
	Screening	1.47852	NORMAL	1.47852	4.21652
	Baseline	1.47852	NORMAL	1.47852	4.21652
	Day 28	2.62848	NORMAL	1.47852	4.21652
	Day 60	1.75232	NORMAL	1.47852	4.21652
	Month 6	1.75232	NORMAL	1.47852	4.21652
	Year 1	81.97572	HIGH	1.47852	4.21652
	Screening	3.61416	NORMAL	1.47852	4.21652
	Baseline	4.87364	HIGH	1.47852	4.21652
	Day 28	19.76836	HIGH	1.47852	4.21652
	Day 60	7.22832	HIGH	1.47852	4.21652
	Month 3	2.35468	NORMAL	1.47852	4.21652
	Month 6	2.57372	NORMAL	1.47852	4.21652
	Year 1	1.47852	NORMAL	1.47852	4.21652
	Year 1.5	21	HIGH	1.47852	4.21652
	Year 1.5	44.30084	HIGH	1.47852	4.21652
	Year 1.5	9.36396	HIGH	1.47852	4.21652
	Year 2	2.57372	NORMAL	1.47852	4.21652
	Year 3	1.69756	NORMAL	1.47852	4.21652
	Year 4	2.51896	NORMAL	1.47852	4.21652

Source: BLA125758/0.36 Applicant Response to Clinical IR#7
Abbreviations: a-LLN, Lower limit of normal; b-ULN, Upper limit of normal