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Applicant	Orchard Therapeutics (Europe) Limited
Established Name	atidarsagene autotemcel
(Proposed) Trade Name	LENMELDY
Pharmacologic Class	Autologous hematopoietic stem cell-based gene therapy
Dosage Form(s) and Route(s) of Administration	A cell suspension for intravenous infusion at a single dose containing a minimum of $(b) (4) \times 10^6$ CD34+ cells/kg
Dosing Regimen	One-time treatment
Indication(s) and Intended Population(s)	Treatment of pediatric patients with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD)

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GLOSSARY

ARSA	arylsulfatase A
BSID	Bayley Scale of Infant Development
BLA	Biologics License Application
BM	Bone marrow
CNS	central nervous system
CMC	Chemistry Manufacturing and Controls
CUP	Compassionate Use Program
DP	Drug product
EJ	early juvenile
ESEJ	early symptomatic early juvenile
EU	European Union
EAP	Expanded Access Program
GMFC-MLD	Gross Motor Function Classification for Metachromatic Leukodystrophy
GMFM-88	Gross Motor Function Measure-88
HSCT	Hematopoietic stem cell transplant
HE	Hospital Exemption
IRC	Independent Review Committee
ISE	integrated summary of efficacy
IND	Investigational New Drug
KM	Kaplan-Meier
LI	late infantile
MLD	metachromatic leukodystrophy
NHx	natural history
OS	Overall Survival
PBMCs	peripheral blood mononuclear cells
PNS	peripheral nervous system
WISC	Wechsler Intelligence Scale for Children
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

1. Executive Summary

This original Biologics License Application (BLA) is for the approval of an autologous hematopoietic stem cell-based gene therapy, LENMELDY (also referred to as OTL-200), indicated for the treatment of pediatric patients with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD).

Efficacy

The primary evidence for efficacy to support the BLA was based on the integrated efficacy analyses of the comparisons between two groups of pooled data: The OTL-200 treated group and external untreated natural history (NHx) group. The treated group included 37 subjects from two single-arm, open-label clinical studies (Study 201222 [n=18] and Study 205756 [n=10]) and an European Union (EU) Expanded Access Program (EAP) (n=9). The untreated NHx group consisted of 43 subjects with late infantile (LI) and early juvenile (EJ) MLD in the NHx Study 204949, as well as another 6 untreated siblings of treated subjects in Study 205756 but not enrolled in Study 204949. Assessments were made separately for the PSLI, PSEJ, and ESEJ populations.

The primary efficacy endpoint was severe motor impairment-free survival (sMFS), defined as the time interval from birth to the first occurrence of loss of locomotion and loss of sitting without support (Gross Motor Function Classification for Metachromatic Leukodystrophy [GMFC-MLD] level ≥ 5) or death. There were two key secondary: the first key secondary endpoint was the proportion of subjects who had experienced severe motor impairment or death by Year 2 post-treatment evaluated in a subset of matched subjects. Similar analyses for Year 5 post-treatment were also performed in a descriptive manner. The second key secondary endpoint was overall survival (OS), defined as the time interval between birth and death from any cause. In addition, descriptive results on motor function progression to lower severity levels of GMFC-MLD and cognitive function, in terms of performance and language standard scores, were considered as other important measures for efficacy.

PSLI

For the PSLI population, there were 20 treated PSLI subjects and 28 untreated LI subjects from NHx. Among the 20 treated subjects, 1 (5%) subject had severe motor impairment or died compared with 28 (100%) of 28 NHx LI subjects. The p-value of unstratified log rank test was <0.001 . The Kaplan-Meier (KM) estimate for proportion of treated PSLI subjects event-free up to 5 years of age was 100% and the estimate for all NHx LI subjects was 0%. None of the 20 treated PSLI subjects had died versus 19/28 (68%) NHx LI subjects.

The proportion of treated subjects experienced severe motor impairment or death by Year 2 post-treatment was 0% (0/20) and NHx LI subjects was 60% (15/25). At Year 5 post-treatment, the proportion of treated subjects experienced severe motor impairment or death was 15% (2/13) and NHx subjects was 100% (26/26).

For both performance and language standard scores, 19 of 20 treated PSLI subjects had above the threshold of 55 through to the last follow-up. At the last assessment, 2 of these subjects were below the threshold for moderate impairment (< 70), with all others maintaining ≥ 70 and most maintaining normal scores (≥ 85). These results appeared to be substantial compared to that all of the LI NHx subjects having severe cognitive performance and language impairment (≤ 55).

PSEJ

For the PSEJ population, there were 7 treated PSEJ subjects and 21 untreated EJ subjects from NHx. Because of the small sample size and large heterogeneity in this population as well as questionable comparability with the NHx EJ subjects, the pre-specified comparative analyses of the efficacy endpoints would not provide meaningful information. Therefore, the efficacy was evaluated descriptively based on clinical knowledge and expectation of similar subjects in the literature, rather than being evaluated via confirmatory statistical hypothesis testing.

Among the 7 treated PSEJ subjects, 1 (14%) subject died. Among the 6 surviving PSEJ subjects, 3 subjects who had extended follow-up data retained the ability to walk without support (GMFC-MLD Level 1) at the last follow-up (ages 8-13.6 years). This finding surpassed the maximum age at which untreated EJ subjects would reach GMFC-MLD Level 5. The rest of the three PSEJ subjects with shorter follow-up time at the time of the analysis, all maintained the ability to walk independently. These observations suggested tendency of positively shifted distribution on survival for the treated subjects and were considered clinically meaningful.

All 6 surviving PSEJ subjects treated with OTL-200 maintained normal performance standard scores (performance standard scores ≥ 85) throughout available follow-up (range 3.9 to 11.9 years). The cognitive results in the treated subjects surpassed the expectation of similar subjects in the literature.

ESEJ

For the ESEJ population, there were 10 treated ESEJ subjects. The same 21 untreated EJ subjects from NHx used in the analyses for PSEJ was used in the analyses for ESEJ. Among the 10 treated ESEJ subjects, 4 (40%) subjects experienced severe motor impairment or died compared with 14 (67%) out of 21 NHx EJ subjects. The unstratified log rank test resulted in statistical significance with a p-value of 0.001. For overall survival, 2 (20%) of the 10 treated subjects died versus 3 (14%) of 21 NHx subjects died. This difference was not statistically significant.

For the ESEJ population, the proportion of treated subjects who had experienced severe motor impairment or death by Year 2 post-treatment was 20% (2/10) and

NHx subjects was 13% (2/15). The difference was not statistically significant. However, at Year 5 post-treatment, a positive difference in event rate was observed: 25% (2/8) vs 92% (11/12) in the treated and the NHx groups, respectively.

Because of similar concerns with the comparability of the EJ subjects between the ESEJ treated and untreated EJ NHx subjects in the above analyses, I performed further exploratory analyses of decline rate in motor function based on a more comparable subset of subjects per evaluations from the clinical team. These exploratory analyses, limited by small sample size, revealed inconclusive results, suggesting uncertainty in the efficacy on slowing motor function for OTL-200.

On the other hand, among the ESEJ subjects treated with OTL-200, 4 subjects retained normal performance standard scores (≥ 85) and three subjects retained normal language standard scores (≥ 85) between the ages of 13 and 16 years. Preservation of cognitive functioning in these four subjects occurred despite progression of motor disease, which is unexpected in the natural history of EJ MLD where cognitive and motor functioning are expected to decline in parallel and significant cognitive impairment is expected by adolescence (Kehrer et al, 2011). These cognitive outcomes were considered to be attributed to a treatment effect of OTL-200 by FDA review team.

Safety

For safety, among the 39 treated subjects including one subject classified as symptomatic LI and another as progressively symptomatic EJ, three deaths were reported during the studies. One death was in PSEJ population, and two deaths were in ESEJ population. These events were not considered to be related to OTL-200 by the investigators. The only treatment-related adverse event (AE) in the OTL-200 clinical development program was the report of anti-ARSA antibodies in six subjects: five PSLI subjects and one PSEJ subject. No evidence of malignancy, clonal expansion, or insertional oncogenesis have been observed that were associated with OTL-200 as of the data cut-off date for this BLA submission.

Conclusions and Recommendation

In summary, because of the ultra-rare disease nature of the studied population, the use of single arm studies and an external natural history cohort as comparator is reasonable. On the other hand, the study results are susceptible to biases due to the study design with uncertainties regarding classification of study subjects, comparability between treated subjects and untreated NHx subjects, reliability of limited data in NHx subjects. The definitions for the sMFS and overall survival endpoints also have statistical limitations because of the time origin.

The submitted data demonstrated clinical effectiveness of OTL-200 for the PSLI subjects with clear and large treatment effects in all efficacy endpoints that were robust against potential biases. However, the statistical evidence for treatment effects in the PSEJ and ESEJ subjects was limited due to small sample sizes and high heterogeneity of the disease trajectories in these populations as well as questionable comparability with the NHx EJ subjects. The clinical effectiveness cannot be confirmed with statistical confidence and guarded against potential biases noted above. Nevertheless, individual data evaluations suggested OTL-200 would be clinically beneficial for some subjects in terms of motor functions. Furthermore, although cognitive function endpoints were analyzed in a descriptive manner, the observed treatment effects on cognitive function appeared to be substantial for most subjects. There are no serious safety concerns based on the submitted data.

Therefore, based on the findings stated above and in consideration of the rarity of the disease and clear unmet need for the indicated MLD population, I recommend approval of LENMEDLY for treatment of MLD with the proposed indications.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

MLD is an ultra-rare autosomal recessive lysosomal storage disorder caused by biallelic pathogenic variants (mutations) in the arylsulfatase A (ARSA) gene that result in deficiency of the encoded lysosomal ARSA enzyme. Arylsulfatase A is essential for the metabolism of sulfatides, a major component of oligodendrocyte and Schwann cell myelin membranes in the central nervous system (CNS) and peripheral nervous system (PNS), respectively. Arylsulfatase A deficiency results in accumulation of the undegraded substrate in the lysosomes of oligodendrocytes, microglia, certain neurons of the CNS, Schwann cells, and macrophages of the PNS, leading to microglial damage, progressive demyelination, neurodegeneration, subsequent loss of motor and cognitive functions, and early death, especially in patients with early symptom onset (< 7 years of age).

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

No disease-modifying therapies are currently available in the United States (US) for the treatment of patients with MLD. The standard of care for these patients is supportive or palliative care, which does not alter the progressive and fatal course of MLD. Allogeneic hematopoietic stem cell transplantation (HSCT) has shown benefit in some patients with late-onset MLD who are pre-symptomatic or minimally symptomatic at the time of transplant, but it offers little or no benefit in patients with LI or EJ MLD.

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

OTL-200 was approved under the trademark of Libmeldy by the European Medicines Agency on 17 Dec 2020 and by the United Kingdom Medicines and Healthcare Product Regulatory Agency on 01 Jan 2021.

In November 2020, the Investigational New Drug (IND) was opened and in January 2021, regenerative medicine advanced therapy (RMAT) was granted by FDA. The applicant submitted a meeting request on February 9, 2023, to discuss and obtain FDA's feedback on several multidisciplinary topics to support the OTL-200 BLA filing. A pre-BLA meeting was held on April 24, 2023, to discuss the BLA submission contents and strategies. During the course of pre-submission interactions, concerns with comparability between the treated subjects and external natural history of untreated subjects and reliability of such comparisons were brought up by FDA multiple times and it was acknowledged that evaluation of reliability of the efficacy comparison results would be a review issue.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission is adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This BLA contains efficacy and safety information for:

- OTL-treated subjects in two single-arm, open-label clinical trials, Study 201222 and Study 205756,
- OTL-treated subjects an EU expanded access program (EAP),
- an external untreated natural history (Study 204949, NHx) population of subjects with LI and EJ MLD.
- additional untreated siblings not enrolled in NHx.

Because of the small sample sizes in studies, the efficacy evidence to support the license application is based on the integrated analyses, as agreed by FDA at pre-BLA meeting. In Section 6, I will briefly describe each study. In-depth review of the efficacy based on integrated data will be provided in Section 7 of this memo. Safety review will be provided in Section 8.

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

- BLA 125758/0.2, /0.47, /0.53

- Module 1.14 Labeling
- Module 2.5 Clinical Overview
- Module 2.7.3 Summary of Clinical Efficacy
- Module 2.7.4 Summary of Clinical Safety
- Module 5.3.5 Clinical Study Reports (CSRs), supporting documents, and data files and programs

5.3 Table of Studies/Clinical Trials

Table 1 summarizes the clinical studies in the OTL-200 development program.

Table 1. Summary of clinical studies in the BLA

Study Identifier (Identifier of Study Report)	Primary Objectives	Study Design	Healthy Subjects or Diagnosis of Subjects	Treatment Details (Test Product; Dosage Regimen, Route; Duration)	Number of Subjects	Study Status; Type of Report
201222 Uncontrolled Study	Safety and efficacy (0–8 years posttreatment)	SC, EC, OL, SD	Subjects with Early-Onset MLD: presymptomatic Late Infantile and presymptomatic or early symptomatic Early Juvenile	MLD OTL-200 (Fresh formulation) 2–20 x 10 ⁶ CD34 ⁺ cells/kg; single dose, IV	20	Ongoing, (Closed for enrolment) Interim CSR
205756 Uncontrolled Study	Safety and efficacy (0–8 years posttreatment)	SC, EC, OL, SD	Subjects with Presymptomatic Early-Onset MLD	OTL-200 (Cryopreserved formulation) 3–30 x 10 ⁶ CD34 ⁺ cells/kg; single dose, IV	10	Ongoing, (Closed for enrolment) Interim CSR
Other Studies						
205029 Hospital Exemption	Safety and efficacy	SC, EC, OL, SD	Subjects with Presymptomatic Early Onset MLD	MLD OTL-200 (Fresh formulation) 2–20 x 10 ⁶ CD34 ⁺ cells/kg; single dose, IV	3	Ongoing, (Closed for enrolment) Interim CSR
206258 CUP	Safety and efficacy	SC, EC, OL, SD	Subjects with Presymptomatic Early Onset MLD	MLD OTL-200 (Fresh formulation) 2–20 x 10 ⁶ CD34 ⁺ cells/kg; single dose, IV	5	Ongoing, (Closed for enrolment) Interim CSR
207394 Compassionate	Safety and efficacy	SC, EC, OL, SD	Subjects with Early-Symptomatic Early Juvenile MLD	MLD OTL-200 (Fresh formulation) 2–20 x 10 ⁶ CD34 ⁺ cells/kg; single dose, IV	1	Ongoing, (Closed for enrolment) Interim CSR
204949 NHx	Describe the disease course and clinical outcomes of untreated subjects with early-onset MLD	Observational, SC	Untreated subjects with early-onset MLD	Not Applicable	43	Final CSR
OTL-200-10 Long-term follow-up study	Safety and efficacy	Observational, multicenter, UC, OL, follow-up	Subjects with early onset MLD	Not applicable	Target approximately 72	Ongoing study protocol

CSR = Clinical Study Report; EC = Externally Controlled; EAP = Expanded Access Program; MLD=Metachromatic Leukodystrophy; NHx = Natural History; OL = Open label; SC = Single Centre; SD = Single Dose; UC = Uncontrolled.

Source: Adapted from BLA 125758/0.2; Module 5.2 Tabular Listing of all Clinical Studies.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

In clinical development program of OTL-200 and specifically intended for the proposed indication in the current application, patients with MLD were classified into three subtypes, PSLI, PSEJ, or ESEJ, based on the following criteria:

- PSLI MLD: Patients with expected disease onset ≤ 30 months of age and an ARSA genotype consistent with LI MLD. Pre-symptomatic status defined as 1) the absence of neurological signs and symptoms of MLD associated with cognitive, motor, or behavioral functional impairment or regression or 2) no delay in achievement of developmental milestones associated with abnormal signs at neurological evaluation.
- PSEJ MLD: Patients with expected disease onset > 30 months and < 7 years of age and an ARSA genotype consistent with EJ MLD. Pre-symptomatic status defined as the absence of neurological signs and symptoms of MLD associated with cognitive, motor, or behavioral functional impairment or regression.
- ESEJ MLD: Patients with disease onset > 30 months and < 7 years of age and an ARSA genotype consistent with EJ MLD. Early symptomatic status defined as walking independently (GMFC-MLD level 0 or 1), an IQ ≥ 85 , and no evidence of clinical deterioration indicative of disease progression past the early symptomatic stage of the disease.

In the following subsections, I will describe the brief study design for each of the studies included in the application.

6.1 Trial #1 201222

Study 201222 is an ongoing phase I/II, non-randomized, open-label, prospective, single-center study in children with LI MLD or EJ MLD treated with OTL-200 and followed for safety and efficacy endpoint measures post-treatment. Initially, Study 201222 was planned to enroll and treat 8 subjects (PSLI, PSEJ, ESEJ). The sample size and proportions of pre-symptomatic LI and pre-symptomatic or early symptomatic EJ subjects were revised multiple times during the course of the study in order to treat a total of 20 subjects.

Study 201222 comprises the following protocol phases:

1. Screening phase: The conditions required by the clinical protocol for subject enrollment were assessment and the study inclusion/exclusion criteria were evaluated.
2. Baseline phase (end of the Screening phase to the day before busulfan administration [i.e., Day ^{(b) (4)}]): Clinical and instrumental evaluations were conducted to establish a subject's disease status and general clinical condition at the latest possible timepoint prior to treatment.
3. Treatment phase (Day ^{(b) (4)} to Day 0): The Treatment phase started with the purification of a subject's stem cells from a Bone marrow (BM) harvest

- or from the mobilization of peripheral blood stem cell (PBSC) for the investigational Drug Product (DP) manufacture, as well as unmanipulated back-up to be infused in the event of engraftment failure, technical issues during DP manufacture, or for additional DP manufacture. The Treatment and Baseline phases overlap, as the Treatment phase is inclusive of purification and mobilization procedures for back-up, and baseline assessments should be performed as close to administration of the investigational DP as possible.
4. Follow-up phase: This comprises an initial follow-up period of 3 years after infusion of OTL-200 to evaluate study endpoints. During this phase, subjects are intended to reach the interim 2- and 3-year timepoints for assessment of efficacy and safety endpoints. Subjects continue to be followed under this protocol for 15 years post-treatment, with the option to roll-over into a long-term follow-up study under a separate protocol once available.

6.2 Trial #2 205756

Study 205756 is an ongoing open-label, single-arm study conducted in pre-symptomatic subjects with early-onset MLD (i.e., either LI, EJ, or an intermediate subtype between LI/EJ) and early symptomatic subjects with the EJ MLD subtype. This study used cryopreserved formulation of OTL-200 (vs. fresh formulation in Study 201222 and in the expanded access programs) and treated a total of 10 subjects based on feasibility.

Prior to the baseline and treatment phases, subjects were hospitalized for implantation of a central venous catheter (if not already implanted), according to local institutional practice and Standard Operating Procedures. During and following treatment, subjects remained hospitalized until hematological recovery or while deemed clinically necessary. Thereafter, subjects were generally followed on an outpatient basis unless invasive procedures were required or complications occurred.

The stem cell harvest for drug product manufacture occurred during the Baseline phase of the study on a date tailored to each subject's condition and clinical needs. Typically, the harvest occurred several (b) (4) prior to reinfusion into the subject to support the cryopreservation step and to enable the commencement of product-specific release testing.

All subjects in this study treated with OTL-200 will be followed up for a minimum period of 8 years post-treatment within the study. Beyond 8 years, subjects will continue to be followed for 15 years post-treatment in a long-term follow up study, in-line with prevailing regulatory guidelines.

6.3 Trial #3 EU Expanded Access Program (EAP)

The designs of the programs comprising the EAP were based on the design and preliminary results for Study 201222. These programs were conducted at the same clinical site, by the same study staff, using the same drug product and similar enrollment criteria and schedules of assessments as those from Study 201222.

6.3.1 Single Subject Compassionate Use Program (CUP 207394)

The design of CUP 207394 was based on the design of Study 201222. A single subject (Subject (b) (6)) with ESEJ MLD was treated in June 2013 under an individualized CUP, according to the Italian Ministerial Decree of 08 May 2003. No clinical studies with OTL-200 were open for recruitment of subjects with EJ MLD at that time; although Study 201222 was ongoing, it was closed at that time to further enrollment of EJ subjects. Additionally, this subject had exceeded the threshold for time since symptom onset stated in the Study 201222 inclusion criterion in effect at that time (i.e., ≤ 6 months from onset of symptoms). However, the subject was considered to have met all other eligibility criteria defined for Study 201222.

The overall objective of the program was to provide a mechanism to supply OTL-200 on a compassionate use basis for the treatment of a single subject. The individualized program was designed to allow collection of efficacy and safety data under a comparable schedule of assessments and clinical procedures that had been employed in Study 201222 and was conducted at the same clinical site.

6.3.2 Hospital Exemption (205029) and Compassionate Use Program (206258)

Three PSLI subjects were treated under a Hospital Exemption (HE) framework, according to the “Provisions on advanced therapy medicinal products which are prepared on a non-routine basis” (Italian Ministerial Decree, dated 16 Jan 2015), with an individual protocol for each subject.

The Compassionate Use Program (CUP) was subsequently initiated under the auspices of the Italian Ministerial Decree dated 07 Sep 2017 (superseding decree dated 08 May 2003), and 5 subjects (4 PSLI, 1 PSEJ) were treated.

The designs of the HE and CUP were closely aligned with each other and were based on the design of the prospective, single-center Study 201222. The objectives and endpoints of Study 201222 were applied to the meta-analysis of the HE and CUP data.

6.4 Natural History (NHx) Study 204949

Study 204949 was an observational, single-center, prospective study of the natural history of MLD. This study enrolled a subset of subjects participating in an NHx study set up by OSR in 2004 (Study LDM1). The NHx Study 204949 is also sponsored by OSR and conducted at SR-TIGET (Milan, Italy).

The objective of NHx Study 204949 is to describe the disease course and clinical outcomes of untreated subjects with early-onset MLD. The NHx Study 204949 included 43 untreated subjects who did not receive any treatments for MLD apart from supportive care.

6.5 Additional Untreated Siblings Study 205756

Data on age at entry to GMFC-MLD level and the age at death (if applicable) from untreated siblings who were not enrolled in the NHx Study 204949 were collected as part of the treated subject's family history in Study 205756. Data from five of these untreated siblings were adjudicated by the IRC and were included in the analyses of severe motor impairment-free survival and OS. One additional sibling was not adjudicated by the IRC but was assigned the same disease subtype as their treated sibling and included in the analyses of severe motor impairment-free survival and OS. Overall, there were two LI and four EJ subjects in this subset.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication: MLD

7.1.1 Methods of Integration and Statistical Analysis Plan

7.1.1.1 Data Pooling and External Comparator Group

To demonstrate the efficacy of OTL-200, the applicant conducted comparative analyses between the following two groups of pooled data:

- **OTL-200 treated group:** consisting of 39 treated subjects from 2 single-arm, open-label clinical trials [Study 201222 (n=20) and Study 205756 (n=10)] and an EU EAP (n=9). Of the 39 treated subjects, 37 were included in the key ISE analysis sets (PSLI, PSEJ, ESEJ); 2 subjects with advanced disease at the time of treatment were not included.
- **Untreated NHx group:** consisting of 43 untreated subjects with LI and EJ MLD from the NHx study [Study 204949], as well as another 6 untreated siblings not enrolled in NHx Study 204949 whose data contributed to the endpoints of severe motor impairment free survival and overall survival.

Pooling of data of the treated subjects across the individual studies is justified by comparable OTL-200 drug products (fresh vs cryopreserved formulations, please refer to the CMC review), subject eligibility criteria, study designs and objectives, and that studies were conducted at a single clinical site (SR-TIGET) located in Milan, Italy. To improve comparability, the applicant chose a subset of the subjects in the external NHx study (conducted in a single site) who were considered to have had early-onset MLD (LI or EJ). Due to the ultra-rare nature of the disease with a high mortality rate, pooling and utilizing an external NHx population is reasonable.

During the review, three treated subjects were reclassified by the clinical review team. Subject (b) (6) and (b) (6) were reclassified from PSEJ to PSLI. Subject (b) (6) was reclassified from ESEJ to PSEJ. As a result, the total treated subjects for PSLI are increased to 20, PSEJ are decreased to 7, and ESEJ are decreased to 10. The summaries of pooled subjects in the treated and untreated groups are provided in Table 2 and Table 3, respectively.

Table 2. Summary of Pooled Subjects in the OTL-200 Treated Group

OTL-200 Treated Group	PSLI	PSEJ	ESEJ
Study 201222	9	2	7
Study 205756	4	4	2
CUP 207394	0	0	1
HE 205029	3	0	0
CUP 206258	4	1	0
Total	20	7	10

Source: Adapted from Figure 2, Clinical Overview in BLA 125758/0. The table reflects the updated numbers per FDA's reclassifications.

Table 3. Summary of Pooled Subjects in the Untreated NHx Group

Untreated Group	LI	EJ
NHx Study 204949	26	17
Subset of Sibling data from Study 205756	2	4
Total	28	21

Source: Adapted from Figure 2, Clinical Overview in BLA 125758/0.

Reviewer's comments:

Despite the generally acceptable pooling and comparison strategies described above, the comparability of the treated and untreated groups remains uncertain due to the following limitations:

- *For the pre-symptomatic treated subjects, it's not possible to know the disease progression trajectory, had they not been treated with OTL-200, e.g., whether the expected onset of disease symptoms would be comparable with those among untreated NHx subjects. For example, it's difficult to determine whether the treated PSEJ subjects are comparable to the NHx EJ subjects.*

- *Although classification of disease subtypes was adjudicated by the Independent Review Committee (IRC), uncertainty exists due to high heterogeneity of the disease. This is particularly challenging for the EJ subjects due to the wider age range in the definition.*
- *Incomplete data and retrospectively collected data for the NHx subjects impact the assessment of the comparability and therefore reliability of the results.*

As a result of the above concerns, the efficacy analyses described in later sections may exclude certain subjects, per FDA clinical review team, to improve comparability. I will note the specific considerations/exclusions when applicable.

7.1.1.2 Objectives and Endpoints

The efficacy objectives and associated endpoints in the integrated analyses differed from those in the individual studies pursuant to FDA recommendation in consideration of clinical meaningfulness of the endpoints.

Objective:

The primary objective of this integrated summary of efficacy (ISE) is to assess the efficacy of OTL-200 in a population of subjects with MLD, compared with untreated NHx subjects (including siblings where available/applicable). This objective will be assessed in the PSLI, PSEJ, and ESEJ populations separately.

Endpoints:

Primary Endpoint:

The primary endpoint is severe motor impairment-free survival (sMFS), defined as the time interval from birth to the first occurrence of loss of locomotion and loss of sitting without support (GMFC-MLD level 5 or higher) or death. The definition of GMFC-MLD is listed in Table 4.

Table 4. Levels of Gross Motor Function Classification for MLD

Level	Description
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 5 steps)
3	Sitting without support and locomotion such as crawling or rolling. Walking with or without support not possible
4	(a) Sitting without support but no locomotion; or (b) Sitting without support not possible, but locomotion such as crawling or rolling possible
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: BLA 125758/0; Module 2.7.3 Summary of Clinical Efficacy, Table 2.

Key Secondary Endpoints:

- Proportion of subjects who experienced severe motor impairment (defined by a GMFC-MLD level ≥ 5) or death, evaluated at Year 2 post-treatment with OTL-200 for treated subjects, and based on assessments made at matching ages for NHx subjects.
- Overall survival, defined as the time interval between birth and death from any cause.
- Performance standard score over age.
- Language standard score over age.

Performance and Language standard scores are the tests to assess the cognitive impairment of MLD subjects. When assessed within the appropriate age ranges, a standard score with a mean of 100 and an SD of 15 can be derived, allowing comparison of a subject's performance with the normative population. Cognitive impairment was categorized as follows:

- Normal (performance standard score ≥ 85).
- Mild Impairment ($70 \leq$ performance standard score < 85).
- Moderate Impairment ($55 <$ performance standard score < 70).
- Severe Impairment (performance standard score ≤ 55).

7.1.1.3 Statistical Considerations & Statistical Analysis Plan

Analysis Populations

- The PSLI All Subjects analysis set was to consist of all treated subjects identified as PSLI and all NHx subjects identified as LI by the Independent Review Committee (IRC).
- The PSEJ All Subjects analysis set was to consist of all treated subjects identified as PSEJ and all NHx subjects identified as EJ by the IRC.
- The ESEJ All Subjects analysis set was to consist of all treated subjects identified as ESEJ and all NHx subjects identified as EJ by the IRC.

Primary Efficacy Endpoint Analysis

The Kaplan-Meier (KM) method was to be used to estimate the sMFS survival probabilities. The unstratified log-rank test was to be used to compare the treated and NHx groups.

Due to the rapid progression experienced by some subjects with MLD, an assessment recording age at occurrence of each GMFC-MLD level may not be available. To account for a missing GMFC-MLD level 5 assessment in the derivation of sMFS, the event of severe motor impairment was to be considered to have occurred at the time of the first GMFC-MLD assessment with level ≥ 5 .

Reviewer's Comments:

- *The primary endpoint is a time-to-event endpoint defined as the time interval from birth to the first occurrence of GMFC-MLD ≥ 5 . Analysis of such an endpoint would introduce bias in the estimation of treatment effect. This is*

*because for the treated subjects, the time **before** treatment (i.e., while untreated) contributed (but should not have) to the endpoint, not aligned with the purpose of the analysis being **post**-treatment effect. The impact may be small for the LI subjects since they were treated early during infancy (close to birth). However, for the EJ subjects, the impact could be larger and therefore the analysis results might be unreliable.*

- *Because of the above concerns, the applicant planned sensitivity analyses by varying time origins and censoring time and also performed post-hoc analyses using the time at treatment for the treated subjects as the time origin.*

Key Secondary Endpoints Analyses

(1) Proportion of Subjects who Experienced Severe Motor Impairment or Death at Year 2 Post-Treatment.

The proportion and exact 95% CI for the subjects who were event-free was to be calculated for each treatment group. The Fisher's exact test was to be used for the comparisons between the OTL-200 treated and NHx untreated groups.

To reduce bias in these comparisons made for endpoints assessed at fixed timepoints post-treatment, a cohort-level matching strategy was proposed based on the key factors influencing disease status. The factors considered for matching were MLD subtype, genotype, baseline functional status, age, and concomitant therapy; the final matching was based on age, within MLD subtype.

To handle intercurrent events and missing data, the applicant planned the following strategies:

The following subjects will be classified as having an event at a visit:

- Subjects who died or experienced the event at or prior to the visit.
- Subjects who were alive and had a missing assessment at the visit and had an assessment demonstrating they had experienced the event at their next visit or did not have a subsequent assessment.

The following subjects will be classified as not having an event at a visit:

- Subjects who were alive, did not experience the event at the visit and had not experienced the event prior to the visit.
- Subjects who were alive and had a missing assessment at the visit and had an assessment demonstrating they had not experienced the event at the next visit.

The following subjects would be excluded from the analyses:

- Subjects who had not experienced the event and withdrew from the study for a reason other than death prior to the analysis time point.
- Subjects who had not experienced the event and had not been followed up for the duration of the analysis time point.

Reviewer's comment:

As described in the data handling strategies above, the analyses of these secondary endpoints are vulnerable to potential biases with truth deviated from any of the scenarios above. The concern can only be alleviated by a substantial treatment effect and supportive sensitivity analyses.

(2) Overall Survival

The analyses of overall survival were to be performed in the same way as sMFS. The Kaplan-Meier (KM) method was to be used for estimating survival probabilities. Unstratified log-rank tests are used to compare treated and NHx groups.

(3) Performance standard score over age

No formal hypothesis testing was to be conducted. Descriptive statistics only.

(4) Language standard score over age

No formal hypothesis testing was to be conducted. Descriptive statistics only.

Multiplicity Control

In the pre-specified analysis plan for the integrated analyses, all statistical hypotheses were tested at the two-sided 5% significance level.

For each of the PSLI, PSEJ and ESEJ populations, a testing hierarchy across primary and key secondary endpoints was defined to control for type I error. The initial comparison in the hierarchy was to be tested at the two-sided 5% significance level, and if statistical significance is achieved, the next comparison in the hierarchy would be tested, also at the two-sided 5% significance level. If at any point in the hierarchy a test fails to reach statistical significance, no claims of statistical significance would be made for subsequent comparisons in the hierarchy. No account was to be taken of multiplicity across the subject populations.

Within each population, the testing hierarchy was planned as follows:

- sMFS.
- Proportion of subjects with severe motor impairment or death at Year 2 post-treatment
- Overall Survival

Reviewer's comment:

- *Note the multiplicity control and pooling strategies were agreed between the sponsor and FDA prior to the BLA submission in consideration of the rarity nature of the disease.*
- *Due to the disease rarity and therefore sample size limitations, statistical significance of the comparisons needs to be considered along with the magnitude of the effect and clinical evaluation of the observed effects.*

7.1.2 Demographics and Baseline Characteristics

The demographics and baseline characteristics of the pooled data are summarized in Table 5. There were slight differences on sex distributions with percent of males being 65% (13/20), 86% (6/7), 60% (6/10) in the treated PSLI, PSEJ, and ESEJ groups, respectively, compared to 46% (12/26) and 47% (8/17) in the NHx LI and EJ groups, respectively. Majority of the subjects were white/Caucasians. The median ages at OTL-200 treatment were 11.8, 30.9, and 70.0 months for PSLI, PSEJ, ESEJ subjects, respectively. In addition (data not shown in the table), the PSLI and PSEJ subjects in the treated group were diagnosed much earlier than the corresponding NHx LI and EJ subjects, due to the presence of an older affected sibling. The ages at diagnosis were comparable between the ESEJ and NHx EJ subjects. The actual mean age at disease onset for the ESEJ treated subjects was about 58 months, comparing to about 46 months in the NHx subjects.

Table 5. Summary of Demographic Characteristics

Parameter	Treated PSLI (N=20)	NHx (LI) ^a (N=26)	Treated PSEJ (N=7)	Treated ESEJ (N=10)	NHx (EJ) ^a (N=17)
Sex, n (%)					
Male	13 (65)	12 (46)	6 (86)	6 (60)	8 (47)
Female	7 (35)	14 (54)	1 (14)	4 (40)	9 (53)
Ethnicity, n (%)					
Hispanic or Latino	1 (5)	2 (8)	0	0	0
Not Hispanic or Latino	19 (95)	24 (92)	7 (100)	10 (100)	17 (100)
Race Detail, n (%)					
White/Caucasian	18 (90)	26 (100)	6 (86)	10 (100)	17 (100)
Asian	2 (10)	0	0	0	0
Black/African American	0	0	1 (14)	0	0
Age at OTL-200 treatment / first contact^b (months)					
Median	11.8	18.8	30.9	70.0	52.6
Min – max	7.6 – 18.8	14.5 – 27.9	11.3 – 66.7	30.5 – 139.7	19.2 – 74.1

a. Untreated subjects with the same MLD subtype in Study 204949.

b. Age at gene therapy for treated subjects; age at earliest assessment (including retrospective assessments) for the NHx subjects.

Source: Adapted from BLA 125758/0.2; Module 2.7.3 Summary of Clinical Efficacy, Tables 10 through 12. The numbers reflect the reclassifications by FDA clinical team.

Reviewer's comment:

Since the treated PSLI and PSEJ subjects did not exhibit symptoms at the time of treatment, the applicant provided "predicted" age of disease onset, being similar to the LI and EJ, at about 18 months and 46 months old on average, respectively. The reliability of these predictions is questionable.

7.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint sMFS was assessed for the PSLI, PSEJ, and ESEJ populations separately.

7.1.4.1. Primary Analysis for the PSLI Population

For the PSLI population, 1 treated subject (5%) had an event (GMFC-MLD Level 5) at 7.2 years of age while all 28 subjects (100%) had events in the NHx population (Table 6, Figure 1). The p-value from unstratified log rank test was <0.001. The finding of a significant treatment effect was supported by the sensitivity analyses and apparent lengthened survival time comparing the treated subjects with their untreated siblings (Figure 2).

Table 6. Summary of Severe Motor Impairment-Free Survival for PSLI Subjects

	OTL-200	NHx
PSLI		
N	20	26 ^a
Number of additional subjects	0	2 ^b
Number (%) of subjects with an event	1 (5%)	28 (100%)
Kaplan-Meier estimates for age at event (years) ^c		
Median	-	2.7
95% CI	(-, -)	(2.5, 2.7)
Unstratified log rank test vs. Natural History, p-value	<0.001	

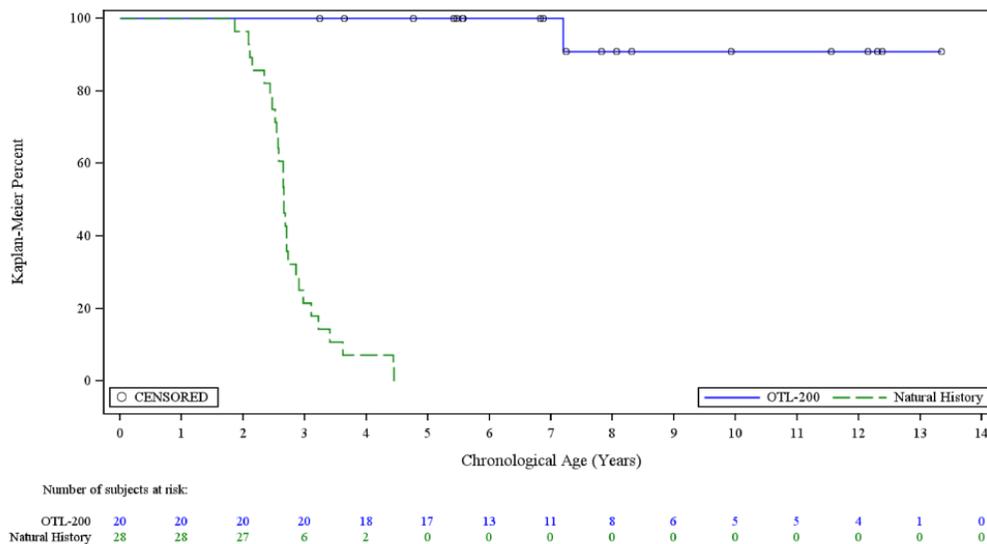
a. Untreated subjects with the same MLD subtype in Study 204949.

b. Information collected for siblings of treated subjects in Study 205756, who were not enrolled in Study 204949.

c. Age at event is defined as the interval from birth to the earlier of loss of locomotion and sitting without support (GMFC-MLD level 5 or higher) or death from any cause; otherwise subject is censored at the last GMFC-MLD assessment date.

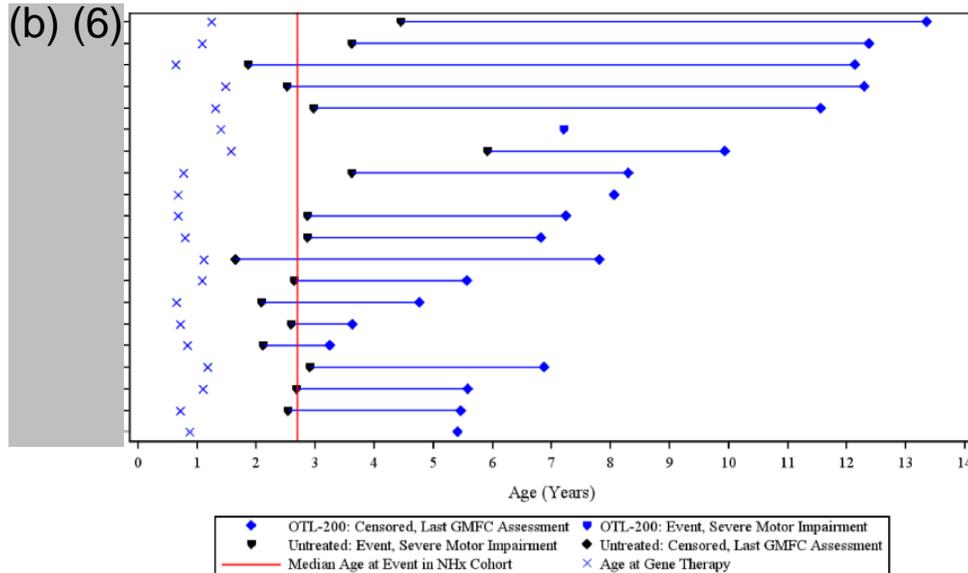
Source: Table X44.1, Revised Statistical Analysis in PSLI, PSEJ, and ESEJ with Reclassification of Subjects, BLA 125758/0.47.

Figure 1. Kaplan-Meier Plot of sMFS: PSLI



Source: Original BLA 125758/0.47; Module 1.11.3 Clinical Information Amendment, Figure X44.4.

Figure 2. Line Plot of sMFS Survival for Treated Subjects Compared with Their Untreated Sibling: PSLI



Source: Original BLA 125758/0.53; Module 1.11.3 Clinical Information Amendment, Figure 1.

7.1.4.2. Primary Analysis for the PSEJ Population

For the PSEJ population, 1 treated subject (14%) had event at 2 years of age (death) and 14 subjects (67%) had events in the NHx population (Table 7, Figure 3). The p-value from unstratified log rank test is 0.056. However, among the 6 surviving treated PSEJ subjects, 3 subjects who had extended follow-up data retained the ability to walk without support (GMFC-MLD Level 1) at the last follow-up (ages 8-13.6 years). This finding surpassed the maximum age at which untreated EJ subjects would reach GMFC-MLD Level 5. The rest of the three PSEJ subjects with shorter follow-up time at time of the analysis, all maintained the ability to walk independently. Furthermore, as shown in Figure 4, none of the treated PSEJ siblings have had an event, compared with two of the untreated siblings with events.

Reviewer's comments: For the survival analysis in the PSEJ population, statistical evidence was limited due to questionable comparability between the treated and the NHx untreated subjects as well as the small sample size (including short follow-up time for some subjects). The clinical effectiveness would be based on clinical evaluation of individual subjects, against clinical knowledge of the natural history of the similar population in the literature, rather than a hypothesis testing between two non-comparable groups.

Table 7. Summary of Severe Motor Impairment-Free Survival for PSEJ Subjects

	OTL-200	NHx
PSEJ		
N	7	17 ^a
Number of additional subjects	0	4 ^b
Number (%) of subjects with an event	1 (14%)	14 (67%)
Kaplan-Meier estimates for age at event (years) ^c		
Median	-	6.7
95% CI	(2.1, -)	(5.7, 8.2)
Unstratified log rank test vs. Natural History, p-value	0.056	

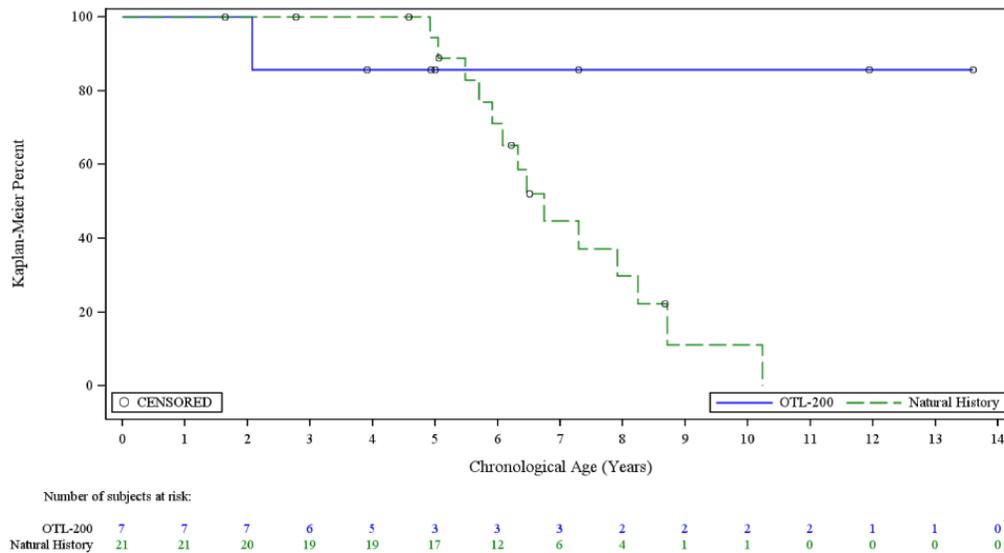
a. Untreated subjects with the same MLD subtype in Study 204949.

b. Information collected for siblings of treated subjects in Study 205756, who were not enrolled in Study 204949.

c. Age at event is defined as the interval from birth to the earlier of loss of locomotion and sitting without support (GMFC-MLD level 5 or higher) or death from any cause; otherwise subject is censored at the last GMFC-MLD assessment date.

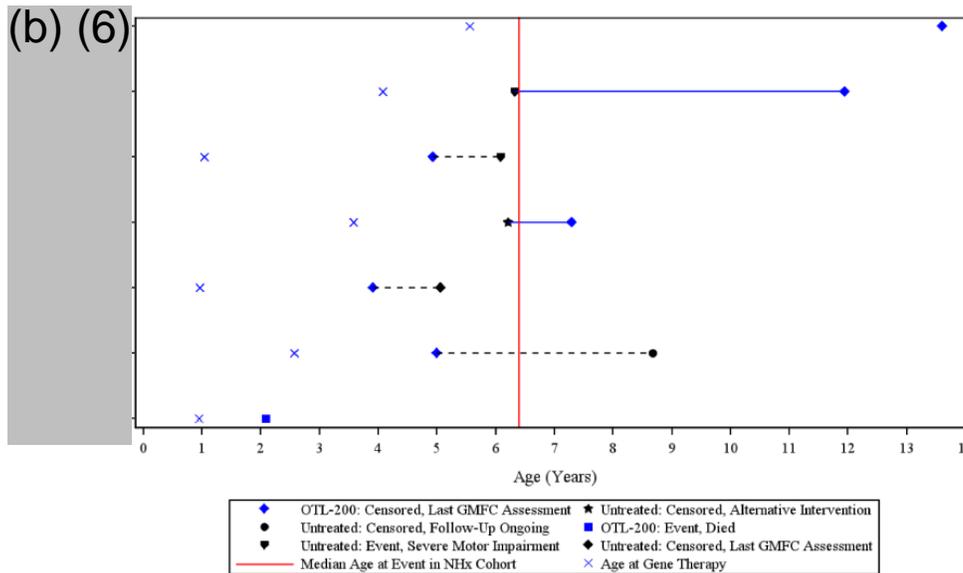
Source: Table X44.1, Revised Statistical Analysis in PSLI, PSEJ, and ESEJ with reclassification of subjects, BLA 125758/0.47.

Figure 3. Kaplan-Meier Plot of sMFS: PSEJ



Source: Original BLA 125758/0.47; Module 1.11.3 Clinical Information Amendment, Figure X44.5.

Figure 4. Line Plot of sMFS for Treated Subjects Compared with Their Untreated Sibling (PSEJ)



Source: Original BLA 125758/0.53; Module 1.11.3 Clinical Information Amendment, Figure 2.

7.1.4.3. Primary Analysis for the ESEJ Population

For the ESEJ population, 4 treated subjects (40%) had events (3 had GMFC-MLD ≥ 5 and one was death) and 14 subjects (67%) had events in the NHx population (Table 8, Figure 5). The p-value from unstratified log rank test is 0.001.

Of the six treated ESEJ subjects without events, two subjects had limited duration of follow-up for the assessment of treatment effect. Two subjects lost the ability to walk (with or without support) after treatment and one subject lost the ability to walk without support after treatment. The sibling pair comparison was limited to four pairs in which only two had sufficient follow-up (Figure 6).

Table 8. Summary of Severe Motor Impairment-Free Survival for ESEJ Subjects

	OTL-200	NHx
ESEJ		
N	10	17 ^a
Number of additional subjects	0	4 ^b
Number (%) of subjects with an event	4 (40%)	14 (67%)
Kaplan-Meier estimates for age at event (years) ^c		
Median	15.3	6.7
95% CI	(6.5, -)	(5.7, 8.2)
Unstratified log rank test vs. Natural History, p-value	0.001	

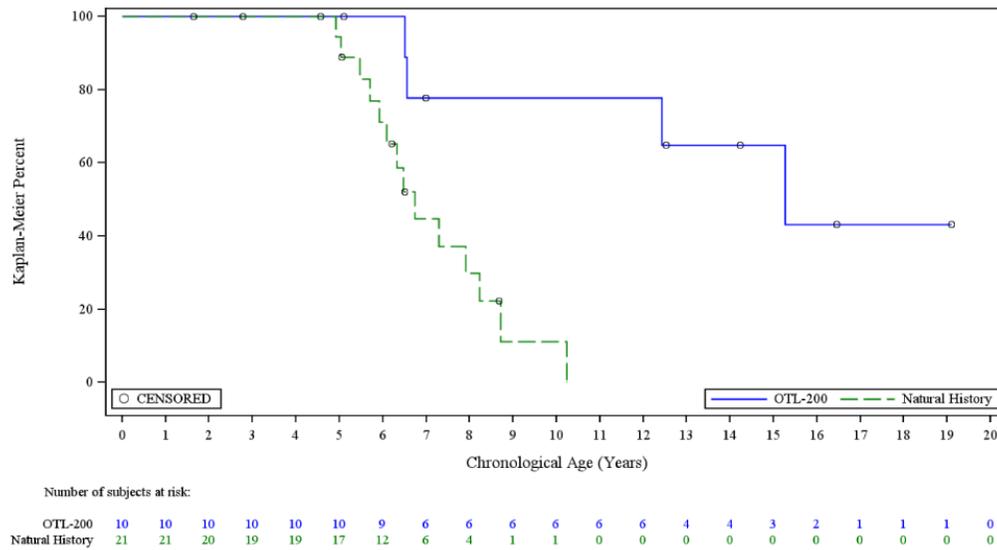
a. Untreated subjects with the same MLD subtype in Study 204949.

b. Information collected for siblings of treated subjects in Study 205756, who were not enrolled in Study 204949.

c. Age at event is defined as the interval from birth to the earlier of loss of locomotion and sitting without support (GMFC-MLD level 5 or higher) or death from any cause; otherwise subject is censored at the last GMFC-MLD assessment date.

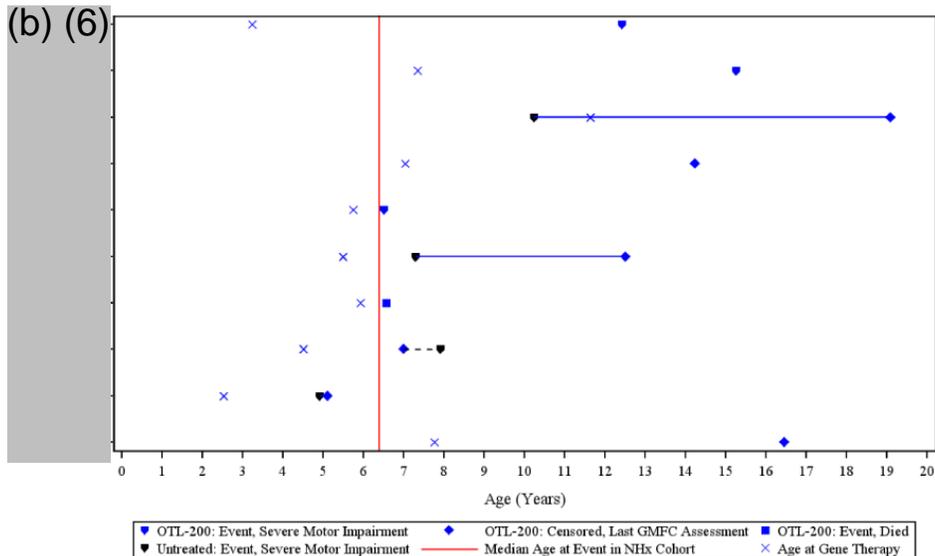
Source: Table X44.3, Revised Statistical Analysis in PSLI, PSEJ, and ESEJ with Reclassification of Subjects, BLA 125758/0.47.

Figure 5. Kaplan-Meier Plot of sMFS: ESEJ



Source: Original BLA 125758/0.47; Module 1.11.3 Clinical Information Amendment, Figure X44.6.

Figure 6. Line Plot of sMFS for Treated Subjects Compared with Their Untreated Sibling (ESEJ)



Source: Original BLA 125758/0.53; Module 1.11.3 Clinical Information Amendment, Figure 3.

Post-hoc analyses of decline in the motor functions in ESEJ Subjects

Having concern about the comparability between the treated ESEJ subjects and the NHx untreated EJ subjects, the FDA clinical team narrowed down two likely comparable groups, 6 treated subjects ((b) (6)) and 10 NHx subjects ((b) (6)). Because most of the treated ESEJ subject had not reached the severe level of GMFC-MLD, the clinical teams suggested evaluating the decline

over lower levels of the GMFC-MLD scores. I conducted the following two post-hoc exploratory analyses:

Post-hoc Analysis 1: Time from Level 1 declining to Level 2 in GMFC-MLD Score

Because data for Level 3 and beyond in GMFC-MLD score were not available for many subjects (due to missing data or limited follow up), I chose to initially analyze the decline from Level 1 to Level 2. Because there are uncertainties on when Level 1 was first observed in the NHx subjects, I used the following three scenarios to account for bias in observation time difference between the two groups:

- 1) The first level 1 was selected for both treated and NHx subjects.
- 2) The last level 1 was selected for both treated and NHx subjects.
- 3) For treated subjects, the last level 1 was selected. For NHx subjects, the first level 1 was selected. This is a conservative (“worst scenario”) approach under an assumption that the reported time of Level 1 for NHx subjects was towards the end time of the level.

In all scenarios, I used the first timepoint when Level 2 was reported for all subjects.

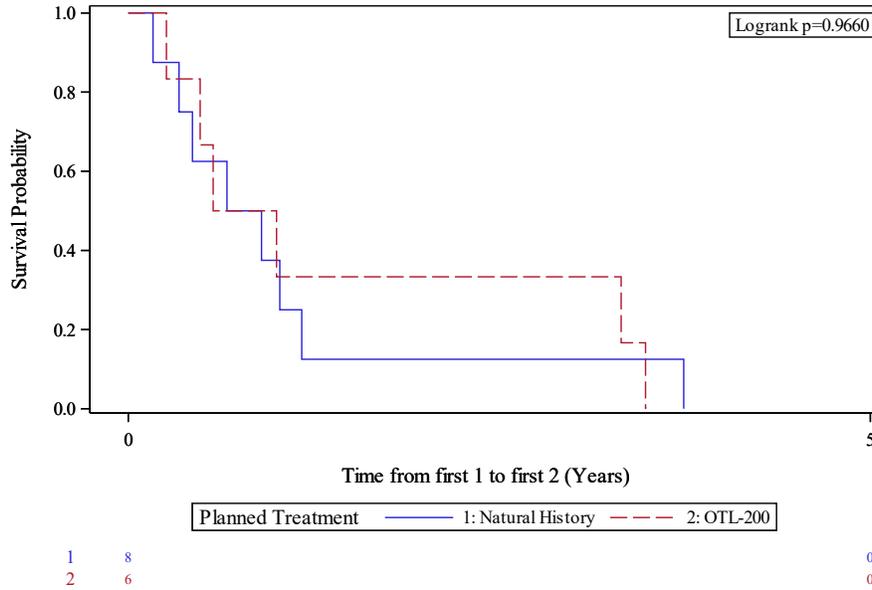
The summary of time intervals from Level 1 to Level 2 was presented in Table 9. One NHx subject ((b) (6)) did not have Level 1 and Level 2 records, and another NHx subject ((b) (6)) only had Level 1 record, so the total number of NHx subjects reduced to 8. The corresponding Kaplan-Meier survival analyses are presented in Figure 7 through Figure 9. The analysis results suggested similar declines between the treated and NHx subjects in Scenarios 1 and 2. In the worst Scenario (Scenario 3), the mean or median of the decline time for the treated subjects is almost half of the NHx subjects, indicating the trend of faster decline rated in treated ESEJ subjects compared to the NHx subjects. Due to the small sample size, none of the analyses reached statistical significance at the conventional 5% level. The directions/trends of the differences were volatile to assumptions as illustrated by different scenarios. Therefore, the treatment effect of OTL-200 in this regard for the ESEJ subjects is inconclusive. This conclusion is consistent with findings when evaluating individual subjects – some treated subjects appeared to have better results than the untreated subject while some others didn't.

Table 9. Time (in Years) from Level 1 to Level 2 in ESEJ Subjects

Scenario	Treatment	N	Mean	Std	Q1	Median	Q3	Minimum	Maximum
1	NHx	8	1.1	1.14	0.4	0.8	1.1	0.2	3.7
	Treated	6	1.5	1.48	0.5	0.8	3.3	0.3	3.5
2	NHx	8	0.9	1.18	0.3	0.6	1.0	0.2	3.7
	Treated	6	0.6	0.40	0.3	0.5	0.5	0.3	1.4
3	NHx	8	1.1	1.14	0.4	0.8	1.1	0.2	3.7
	Treated	6	0.6	0.40	0.3	0.5	0.5	0.3	1.4

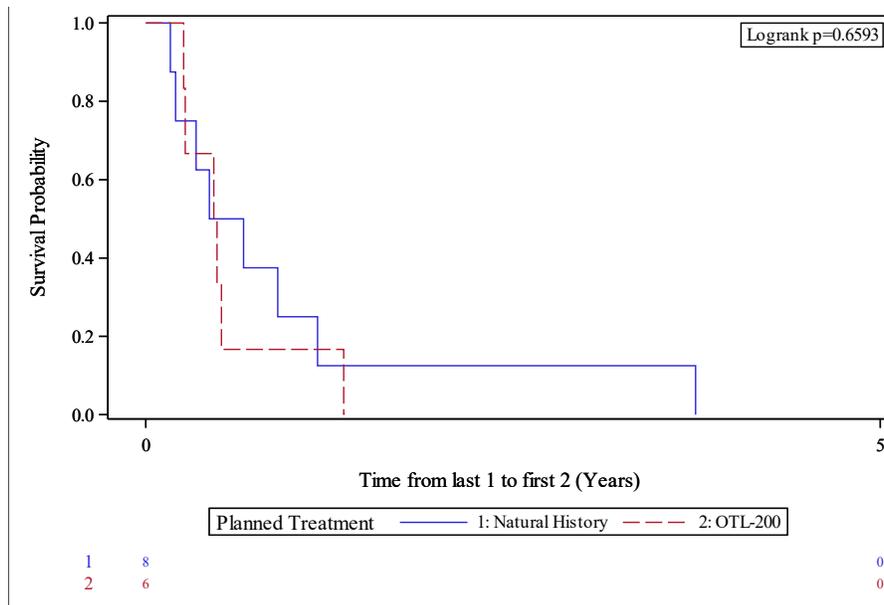
Source: FDA Statistical reviewer's analysis

Figure 7. Kaplan–Meier Plot for Time-to-Level 2 Since Level 1 in ESEJ Population (Scenario 1)



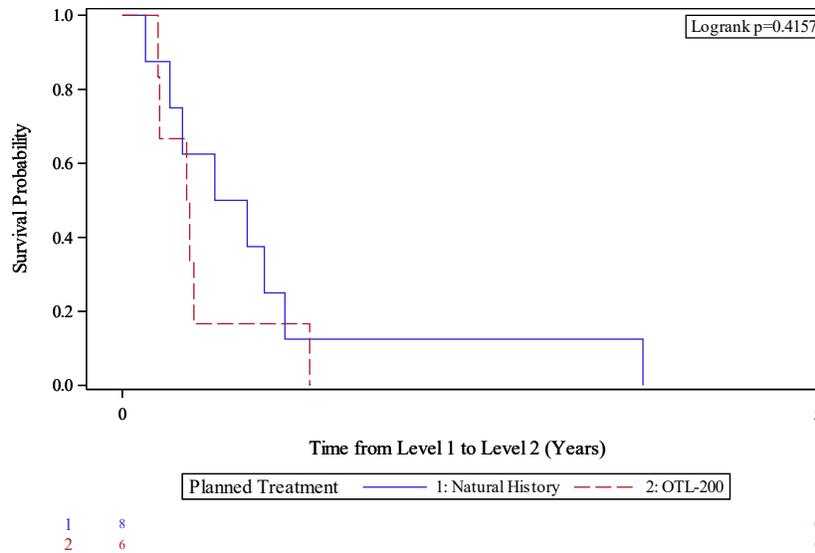
Source: FDA Statistical reviewer's analysis

Figure 8. Kaplan–Meier Plot for Time-to-Level 2 Since Level 1 in ESEJ Population (Scenario 2)



Source: FDA Statistical reviewer's analysis

Figure 9. Kaplan–Meier Plot for Time-to-Level 2 Since Level 1 in ESEJ Population (Scenario 3)



Source: FDA Statistical reviewer’s analysis

Post-hoc analysis 2: Regression Line from Level 1 to Level 4 in GMFC-MLD Score

In this analysis, I made several assumptions which are not necessarily valid therefore caution needs to be exercised when interpreting the results. I used all available data through the Level 4 and assumed a linear decline from Level 1 to Level 4. The decline rate (slope) was estimated for each individual by a regression analysis. Table 10 lists the decline rates for individual subjects under the “worst” scenario (Scenario 3 described earlier in Analysis 1). The mean (median) decline for NHx subjects is -0.136 (-0.105) and for treated subjects is -0.128 (-0.142). This exploratory analysis also resulted in an inconclusive finding. Therefore, there is no statistical evidence to indicate that the motor decline is slower or faster in the treated ESEJ subjects when compared to the NHx subjects.

Table 10. Regression Slopes Results

	Treatment	USUBJID	Slope
1	Natural History	(b) (6)	-0.105
2	Natural History		-0.293
3	Natural History		-0.098
4	Natural History		-0.095
5	Natural History		-0.182
6	Natural History		-0.179
7	Natural History		-0.080
8	Natural History		-0.189
9	Natural History		0
10	OTL-200		-0.203
11	OTL-200		-0.156
12	OTL-200		-0.085
13	OTL-200		-0.128
14	OTL-200		-0.164
15	OTL-200		-0.035

Source: FDA Statistical reviewer's analysis

7.1.5 Analysis of Secondary Endpoints

7.1.5.1 Proportion of Subjects who Experienced Severe Motor Impairment or Death at Year 2 and Year 5 Post-Treatment

Table 11 presents the analysis results of this key secondary endpoint. The Year 5 post-treatment results are provided in a descriptive manner.

For PSLI population, the proportions with event at Year 2 post-treatment were 0% (0/20, treated subjects) vs. 60% (15/25, NHx subjects) and the p-value from Fisher's exact test is <0.001. The proportions with event at Year 5 post-treatment were 13% (2/15, treated subjects) vs. 100% (26/26, NHx subjects).

For PSEJ population, the proportions with event at Year 2 post-treatment were 14% (1/7, treated subject) vs. 0% (0/15, NHx subject) and the p-value from Fisher's exact test is 0.318. The proportions with event at Year 5 post-treatment were 33% (1/3, treated subjects) vs. 69% (9/13, NHx subjects).

For ESEJ population, the proportions with event at Year 2 post-treatment were 20% (2/10, treated subject) vs. 13% (2/15, NHx subject) and the p-value from Fisher's exact test is >0.999. The proportion with event at Year 5 post-treatment were 25% (2/8, treated subjects) vs. 92% (11/12, NHx subjects).

Results of the proportion with event at Year 2 post-treatment are consistent with findings for the primary endpoint. Statistically speaking, a significant treatment effect can be concluded for the PSLI population, however, for the PSEJ and ESEJ populations, the treatment effects on this secondary endpoint are inconclusive.

Table 11. Summary of Proportion of Subjects with Severe Motor Impairment or Death at Year 2 and Year 5 Post-treatment

Endpoint Statistic	OTL-200 (N=20)	NHx^a (N=26)
PSLI		
Year 2 Post-treatment		
Number of matched subjects	20	25
Number (%) of subjects with event	0	15 (60%)
Absolute difference in proportions (OTL-200 vs. NHx) (95% CI)	-60% (-79%, -38%) (p< 0.001)	
Year 5 Post-treatment		
Number of matched subjects	15	26
Number (%) of subjects with event	2 (13%)	26 (100%)
Absolute difference in proportions (OTL-200 vs. NHx) (95% CI)	-87% (-98%, -60%)	
PSEJ		
Endpoint Statistic		
OTL-200 (N=7)		
NHx^a (N=17)		
Year 2 Post-treatment		
Number of matched subjects	7	15
Number (%) of subjects with event	1 (14%)	0
Absolute difference in proportions (OTL-200 vs. NHx) (95% CI)	14% (-11%, 58%) (p=0.318)	
Year 5 Post-treatment		
Number of matched subjects	3	13
Number (%) of subjects with event	1 (33%)	9 (69%)
Absolute difference in proportions (OTL-200 vs. NHx) (95% CI)	-36% (-79%, 27%)	
ESEJ		
Endpoint Statistic		
OTL-200 (N=10)		
NHx^a (N=17)		
Year 2 Post-treatment		
Number of matched subjects	10	15
Number (%) of subjects with event	2 (20%)	2 (13%)
Absolute difference in proportions (OTL-200 vs. NHx) (95% CI)	7% (-26%, 43%) (p>0.999)	
Year 5 Post-treatment		
Number of matched subjects	8	12
Number (%) of subjects with event	2 (25%)	11 (92%)
Absolute difference in proportions (OTL-200 vs. NHx) (95% CI)	-67% (-92%, -20%)	

a. Untreated subjects with the same MLD subtype in Study 204949.

Source: Original BLA 125758/0.47; Module 1.11.3 Clinical Information Amendment, Tables X44.7-X44.9.

7.1.5.2 Overall Survival

Table 12 presents the analysis results of overall survival for the three populations. For PSLI population, no treated PSLI subjects had died at the time of data cut-off. In comparison, 19 of 28 NHx LI subjects (68%) had died. The p-value from unstratified log rank test is < 0.001, demonstrated significantly improved survival for the treated PSLI subjects compared with NHx subjects. But for PSEJ and ESEJ populations, there was no significant difference between the treated and NHx subjects. Figures 10 through 12 present the Kaplan-Meier plots of overall survival analyses for PSLI, PSEJ, and ESEJ subjects, respectively. The overall survival analysis results are consistent with the primary endpoint analysis results, leading to the same conclusion of significant effect in the PSLI subjects while inconclusive for the PSEJ and ESEJ subjects.

Table 12. Summary and Analysis of Overall Survival, for PSLI, PSEJ, and ESEJ Subjects

	OTL-200	NHx
PSLI		
N	20	26 ^a
Number of additional subjects		2 ^b
Number (%) of subjects who died	0	19 (68%)
Kaplan-Meier estimates for age at event (years) ^c		
Median		6.4
95% CI		(5.7, 11.5)
Unstratified log rank test vs. Natural History, p-value	<0.001	
PSEJ		
N	7	17 ^a
Number of additional subjects		4 ^b
Number (%) of subjects who died	1 (14%)	2 (10%)
Kaplan-Meier estimates for age at event (years) ^c		
Median	-	-
95% CI	(2.1, -)	(9.4, -)
Unstratified log rank test vs. Natural History, p-value	0.583	
ESEJ		
N	10	17
Number of additional subjects		4
Number (%) of subjects who died	2 (20%)	3 (14%)
Kaplan-Meier estimates for age at event (years) ^c		
Median	-	-
95% CI	(6.6, -)	(9.4, -)
Unstratified log rank test vs. Natural History, p-value	0.772	

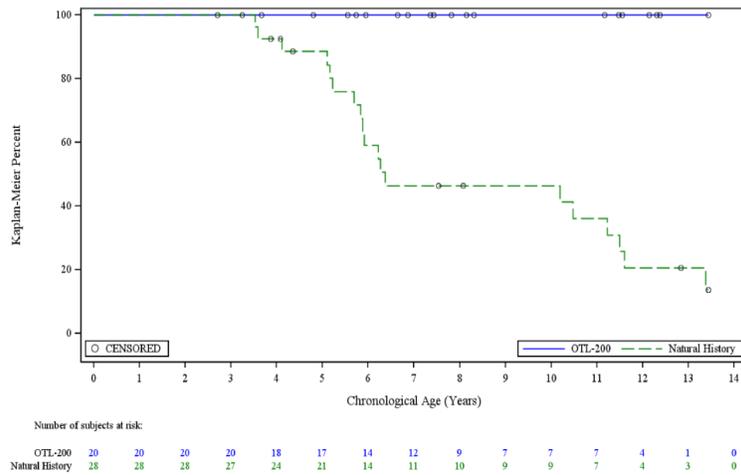
a. Untreated subjects with the same MLD subtype in Study 204949.

b. Information collected for siblings of treated subjects in Study 205756, who were not enrolled in Study 204949.

c. Age at death is defined as the interval from birth to death from any cause; otherwise subject is censored at the last contact date.

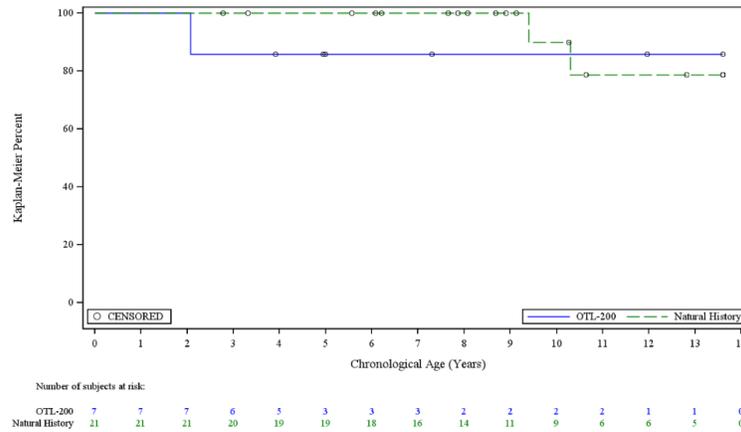
Source: Original BLA 125758/0.47; Module 1.11.3 Clinical Information Amendment, Tables X44.10-X44.12.

Figure 10 Kaplan-Meier Plot of Overall Survival (PSLI)



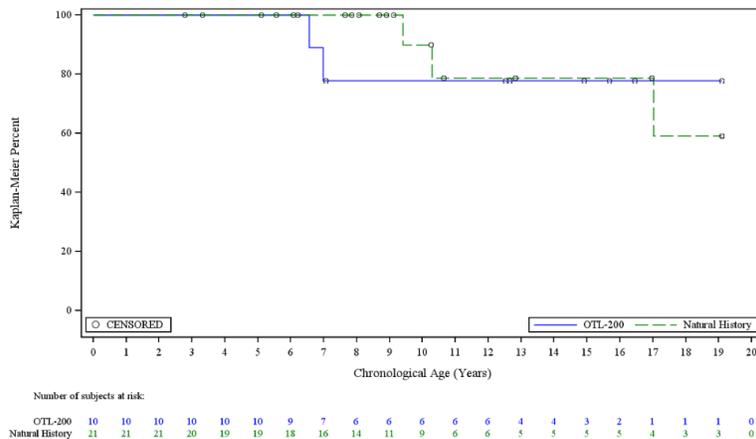
Source: Original BLA 125758/0.47; Module 1.11.3 Clinical Information Amendment, Figure X44.13.

Figure 11. Kaplan-Meier Plot of Overall Survival (PSEJ)



Source: Original BLA 125758/0.47; Module 1.11.3 Clinical Information Amendment, Figure X44.14.

Figure 12. Kaplan-Meier Plot of Overall Survival (ESEJ)



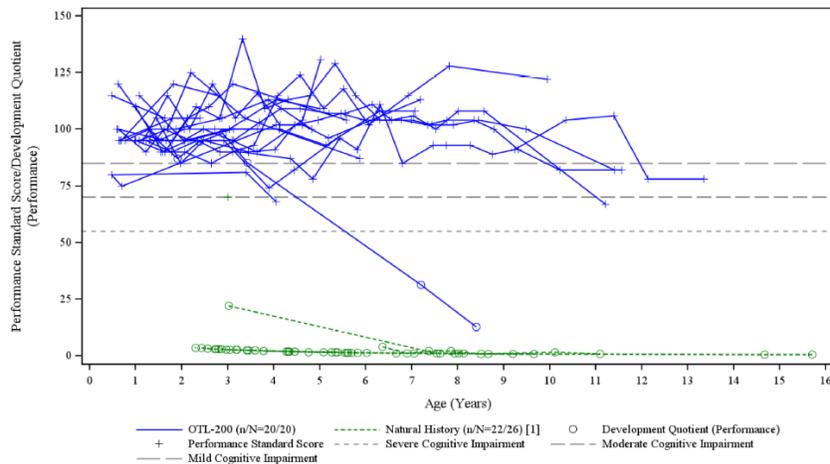
Source: Original BLA 125758/0.47; Module 1.11.3 Clinical Information Amendment, Figure X44.15.

7.1.5.3 Cognitive Function

Cognitive function was captured by neuropsychological tests (Bayley Scale of Infant Development [BSID], Wechsler Preschool and Primary Scale of Intelligence [WPPSI], Wechsler Intelligence Scale for Children [WISC] or Wechsler Adult Intelligence Scale [WAIS]), according to the subject's age. Where required due to the limitations of the available evidence, standard scores were derived from age equivalents.

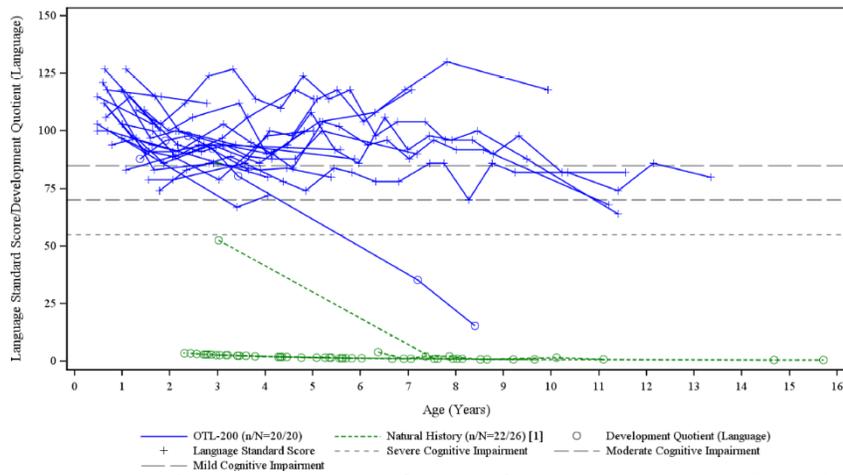
As shown in Figure 13 and Figure 14, respectively, for individual performance and language scores changes over time, 19 of 20 treated PSLI patients had standard scores above the threshold of severe cognitive impairment (standard score > 55) through to the last follow-up. At the last assessment, two of these patients were below the threshold for moderate cognitive impairment (< 70), with all others maintaining performance standard scores ≥ 70 and most maintaining normal scores (≥ 85). This contrasts markedly with results in untreated LI NHx patients with completed neuropsychological assessments who demonstrate severe cognitive impairment early in their disease course.

Figure 13. Performance Standard Score Over Age, PSLI



Source: Original BLA 125758/0.47; Module 1.11.3 Clinical Information Amendment, Figure X42.1.

Figure 14. Language Standard Score Over Age, PSLI



Source: Original BLA 125758/0.47; Module 1.11.3 Clinical Information Amendment, Figure X42.2.

All 6 surviving PSEJ subjects treated with OTL-200 maintained normal performance standard scores (performance standard scores ≥ 85) throughout available follow-up (range 3.9 to 11.9 years). This finding surpasses the expectation based on available literature that describes cognitive or behavioral abnormalities as one of the first symptoms in EJ NHx subjects with onset between 2.5 and 7 years of age, followed by rapid cognitive decline accompanied by progressive loss of speech. Among the surviving PSEJ subjects, 4 had normal cognitive function at an age which surpasses the oldest age (approximately 7 years) at which all EJ NHx subjects experienced cognitive deterioration.

Among the ESEJ subjects treated with OTL-200, 4 subjects retained normal performance standard scores (≥ 85) and three subjects retained normal language standard scores (≥ 85) between the ages of 13 and 16 years. Preservation of cognitive functioning in these four subjects occurred despite progression of motor disease, which is unexpected in the natural history of EJ MLD where cognitive and motor functioning are expected to decline in parallel and significant cognitive impairment is expected by adolescence (Kehrer et al, 2011). These cognitive outcomes were considered to be attributed to a treatment effect of OTL-200 by FDA review team. Please refer to Dr. Naomi Knoble’s review.

7.1.7 Subpopulations

There were also no consistent patterns of results observed across any of the subgroup analyses in the PSLI, PSEJ, or ESEJ populations. The subgroup analyses based on such small numbers of subject who may be highly heterogeneous would be unlikely to provide interpretable information. Therefore, subgroup analyses for each of the three populations are not presented in this review.

7.1.11 Efficacy Conclusions

In summary, the submitted data have provided sufficient evidence of clinical effectiveness of OTL-200 for the PSLI subjects. The statistical evidence of clinical effectiveness for the PSEJ and ESEJ subjects was not conclusive.

8. INTEGRATED OVERVIEW OF SAFETY

8.4 Safety Results

The safety data reflect experience from 39 subjects treated in clinical trials of OTL-200: PSLI (n=20), PSEJ (n=7), ESEJ (n=10), and 2 subjects with advanced disease at the time of treatment. The median (min, max) years of follow-up for the safety population was 6.8 (0.6, 12.2).

8.4.1 Deaths

Three deaths were reported in the clinical development program. Two deaths (Subject (b) (6), and Subject (b) (6)) in Study 201222 were attributed to rapid progression of underlying disease that eventually led to severe dysphagia; both subjects were in the ESEJ Safety Set. The subjects died at 8- (7 years old) and 15- (6.5 years old) months post-gene therapy. One death (Subject (b) (6)) in the EAP, a subject in the PSEJ Safety Set, occurred at approximately 14 months post-gene therapy due to left hemisphere cerebral ischemic stroke. These events were not considered to be related to OTL-200 by the investigators.

8.4.2 Nonfatal Serious Adverse Events

The only treatment-related AE in the OTL-200 clinical development program was the report of anti-ARSA antibodies in six subjects. Five subjects ((b) (6)) in the EAP, and (b) (6) in Study 205756) were in PSLI Safety Set and one subject ((b) (6)) was in PSEJ Safety Set. Five of six events resolved spontaneously or after a short course of rituximab, with one event ongoing as of the data cut-off date.

8.4.8 Adverse Events of Special Interest

No evidence of malignancy, clonal expansion, or insertional oncogenesis have been observed that were associated with OTL-200 as of the data cut-off date.

8.6 Safety Conclusions

No major safety concerns were identified as of the data cut-off date.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The primary evidence for efficacy to support the BLA was based on the integrated efficacy analyses of the comparisons between two groups of pooled data: The OTL-200 treated group and external untreated natural history (NHx) group. The treated group included 37 subjects from two single-arm, open-label clinical studies (Study 201222 [n=18] and Study 205756 [n=10]) and an European Union (EU) Expanded Access Program (EAP) (n=9). The untreated NHx group consisted of 43 subjects with late infantile (LI) and early juvenile (EJ) MLD in the NHx Study 204949, as well as another 6 untreated siblings of treated subjects in Study 205756 but not enrolled in Study 204949. Assessments were made separately for the PSLI, PSEJ, and ESEJ populations.

The primary efficacy endpoint was severe motor impairment-free survival (sMFS), defined as the time interval from birth to the first occurrence of loss of locomotion and loss of sitting without support (Gross Motor Function Classification for Metachromatic Leukodystrophy [GMFC-MLD] level ≥ 5) or death. There were two key secondary: the first key secondary endpoint was the proportion of subjects who had experienced severe motor impairment or death by Year 2 post-treatment evaluated in a subset of matched subjects. Similar analyses for Year 5 post-treatment were performed in a descriptive manner. The second key secondary endpoint was overall survival (OS), defined as the time interval between birth and death from any cause. In addition, descriptive results on motor function progression to lower severity levels of GMFC-MLD and cognitive function, in terms of performance and language standard scores, were considered as other important measures for efficacy.

PSLI

For the PSLI population, there were 20 treated PSLI subjects and 28 untreated LI subjects from NHx. Among the 20 treated subjects, 1 (5%) subject had severe motor impairment or died compared with 28 (100%) of 28 NHx LI subjects. The p-value of unstratified log rank test was <0.001 . The Kaplan-Meier (KM) estimate for proportion of PSLI subjects event-free up to 6 years of age was 100% and the estimate for all NHx LI subjects was 0%. None of the 20 treated PSLI subjects had died versus 19/28 (68%) NHx LI subjects.

The proportion of treated subjects experienced severe motor impairment or death by Year 2 post-treatment was 0% (0/20) and NHx LI subjects was 60% (15/25). At Year 5 post-treatment, the proportion of treated subjects experienced severe motor impairment or death was 15% (2/13) and NHx subjects was 100% (26/26).

For both performance and language standard scores, 19 of 20 PSLI treated subjects had above the threshold of 55 through to the last follow-up. At the last assessment, 2 of these subjects were below the threshold for moderate

impairment (< 70), with all others maintaining ≥ 70 and most maintaining normal scores (≥ 85). These results appeared to be substantial compared to that all of the LI NHx subjects having severe cognitive performance and language impairment (≤ 55).

PSEJ

For the PSEJ population, there were 7 treated PSEJ subjects and 21 untreated EJ subjects from NHx. Because of the small sample size and large heterogeneity in this population as well as questionable comparability with the NHx EJ subjects, the pre-specified comparative analyses of the efficacy endpoints would not provide meaningful information. Therefore, the efficacy was evaluated descriptively, rather than being evaluated via confirmatory statistical hypothesis testing.

Among the 7 treated PSEJ subjects, 1 (14%) subject died. Among the 6 surviving PSEJ subjects, 3 subjects who had extended follow-up data retained the ability to walk without support (GMFC-MLD Level 1) at the last follow-up (ages 8-13.6 years). This finding surpassed the maximum age at which untreated EJ subjects would reach GMFC-MLD Level 5. The remaining three PSEJ subjects with shorter follow-up time at the time of the analysis, all maintained the ability to walk independently. These observations suggested tendency of positively shifted distribution on survival for the treated subjects and were considered clinically meaningful.

All 6 surviving PSEJ subjects treated with OTL-200 maintained normal performance standard scores (performance standard scores ≥ 85) throughout available follow-up (range 3.9 to 11.9 years). The cognitive results in the treated subjects surpassed the expectation of similar subjects in the literature.

ESEJ

For the ESEJ population, there were 10 treated ESEJ subjects. The same 21 untreated EJ subjects from NHx used in the analyses for PSEJ was used in the analyses for ESEJ. Among the 10 treated ESEJ subjects, 4 (40%) subjects experienced severe motor impairment or died compared with 14 (67%) out of 21 NHx EJ subjects. The unstratified log rank test resulted in statistical significance with a p-value of 0.001. For overall survival, 2 (20%) of the 10 treated subjects died versus 3 (14%) of 21 NHx subjects died. This difference was not statistically significant.

For the ESEJ population, the proportion of treated subjects who had experienced severe motor impairment or death by Year 2 post-treatment was 20% (2/10) and NHx subjects was 13% (2/15). The difference was not statistically significant. However, at Year 5 post-treatment, a positive difference in event rate was observed: 25% (2/8) vs 92% (11/12) in the treated and the NHx groups, respectively.

Because of similar concerns with the comparability of the EJ subjects between the ESEJ treated and untreated EJ NHx subjects in the above analyses, I performed further exploratory analyses of decline rate in motor function based on a more comparable subset of subjects per evaluations from the FDA clinical team. These exploratory analyses, limited by small sample size, revealed inconclusive results, suggesting uncertainty in the efficacy on slowing motor function for OTL-200.

On the other hand, among the ESEJ subjects treated with OTL-200, 4 subjects retained normal performance standard scores (≥ 85) and three subjects retained normal language standard scores (≥ 85) between the ages of 13 and 16 years. Preservation of cognitive functioning in these four subjects occurred despite progression of motor disease, which is unexpected in the natural history of EJ MLD where cognitive and motor functioning are expected to decline in parallel and significant cognitive impairment is expected by adolescence (Kehrer et al, 2011). These cognitive outcomes were considered to be attributed to a treatment effect of OTL-200 by FDA review team.

For safety assessment of OTL-200, among the 39 treated subjects including one subject classified as symptomatic LI and another as progressively symptomatic EJ, three deaths were reported during the studies. One death was in PSEJ population and two deaths were in ESEJ population. These events were not considered to be related to OTL-200 by the investigators. The only treatment-related adverse event (AE) in the OTL-200 clinical development program was the report of anti-ARSA antibodies in six subjects: five PSLI subjects and one PSEJ subject. No evidence of malignancy, clonal expansion, or insertional oncogenesis have been observed that were associated with OTL-200 as of the data cut-off date for this BLA submission.

10.2 Conclusions and Recommendations

In summary, because of the ultra-rare disease nature of the studied population, the use of single arm studies and an external natural history cohort as comparator is reasonable. On the other hand, the study results are susceptible to biases due to the study design with uncertainties regarding classification of study subjects, comparability between treated subjects and untreated NHx subjects, reliability of limited data in NHx subjects. The definitions for the sMFS and overall survival endpoints also have statistical limitations because of the time origin.

The submitted data demonstrated clinical effectiveness of OTL-200 for the PSLI subjects with clear and large treatment effects in all efficacy endpoints that were robust against potential biases. However, the statistical evidence for treatment effects in the PSEJ and ESEJ subjects was limited due to small sample sizes and high heterogeneity of the disease trajectories in these populations as well as

questionable comparability with the NHx EJ subjects. The clinical effectiveness cannot be confirmed with statistical confidence and guarded against potential biases noted above. Nevertheless, individual data evaluations suggested OTL-200 would be clinically beneficial for some subjects in terms of motor functions. Furthermore, although cognitive function endpoints were analyzed in a descriptive manner, the observed treatment effects on cognitive function appeared to be substantial for most subjects. There are no serious safety concerns associated with OTL-200 based on the submitted data.

Therefore, based on the findings stated above and in consideration of the rarity of the disease and clear unmet need for the indicated MLD population, I recommend approval of LENMEDLY for treatment of MLD with the proposed indications.