

Office Director Memorandum

Office of Clinical Evaluation

Summary of Regulatory Decision on Biologics License Application

On July 19, 2023, Orchard Therapeutics Limited (Europe) submitted an original Biologics License Application (BLA 125758), for licensure of atidarsagene autotemcel (also known as OTL-200; proprietary name LENMELDY), seeking licensure for the following requested indication:

Proposed 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)

LENMELDY is an autologous hematopoietic stem cell-based gene therapy consisting of autologous CD34+ hematopoietic stem and progenitor cells (HSPCs), transduced ex vivo with a replicant incompetent lentiviral vector (LVV) that encodes the human arylsulfatase (ARSA) gene (ARSA LVV), which is deficient in individuals with metachromatic leukodystrophy (MLD), a rare, autosomal recessive lysosomal storage disease. The ARSA LVV integrates the ARSA-encoded gene into the patient's HSPC genomes. Expression of the integrated ARSA is driven by a ubiquitous promoter and is not cell-type specific.

ARSA deficiency which is also known as metachromatic leukodystrophy or MLD is typically suspected in individuals whose arylsulfatase A enzyme activity in leukocytes that is < 10% of normal controls. However, a finding in a proband of decreased arylsulfatase A enzyme activity is insufficient to diagnose MLD. Additional findings would include progressive neurologic dysfunction with characteristic findings of leukodystrophy in the white matter seen as hyperintense areas on T2-weighted brain MRI, are suggestive. Molecular testing will typically reveal biallelic ARSA pathogenic variants, and there may be increased urinary excretion of sulfatides.

Individuals affected by this neurodevelopmental disorder can have a range of presentations that depend on the subtype of the disease and the age at onset of symptoms with cognitive, motor, sensory dysfunction being hallmarks, the serious sequelae of which often result in death. Individuals with late infantile MLD typically have symptom onset before the age of 3 years, while those with juvenile MLD have symptoms that are evident between age 30 months and 16 years. Onset of adult MLD occurs in individuals after 16 years of age and sometimes, much later than this. As described in the clinical memo, children with late infantile (LI) and early juvenile (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. The distribution of affected individuals across these three main clinical subtypes is as follows: late-infantile MLD (50-60%), juvenile MLD (20-40%) and adult MLD (10-20%). Within a family, the age of onset is typically similar.

There are no FDA-approved therapies for MLD of any subtype. Hematopoietic stem cell transplant (HSCT) is an option that may slow the motor and cognitive dysfunction that occurs in children with EJ

MLD prior to symptom onset. Otherwise, treatments are supportive and if limited effectiveness to manage some symptoms of the disease and importantly, do not treat the underlying cause of the disease.

The primary evidence supporting the Applicant's claims of safety and effectiveness derives from two single-arm clinical studies (OTL-200-201222 and OTL-200-205756), and three Expanded Access Program studies (OTL-200-205029, OTL-200-206258, and OTL-200-207394). The clinical studies enrolled patients with presymptomatic late infantile (PSLI), presymptomatic early juvenile (PSEJ), and early symptomatic early juvenile (ESEJ) MLD. Patients in these studies were categorized as follows: LI MLD (expected disease onset of ≤ 30 months of age and an ARSA genotype consistent with LI phenotype); EJ MLD (expected disease onset > 30 months and < 7 years with an ARSA genotype consistent with EJ phenotype); pre-symptomatic (asymptomatic or have abnormal reflexes and abnormalities on MRI and nerve conduction tests without functional sequelae); Early symptomatic (walking independently and having IQ ≥ 85). Patients were excluded if met the following criteria: underwent an allogeneic HSCT in the previous 6 months or who had evidence of residual cells of donor origin, had 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, had neoplastic diseases or cytogenetic alterations typical of myelodysplastic syndrome or acute myeloid leukemia.

Enrolled patients underwent hematopoietic stem cell mobilization and apheresis to collect their CD34+ cells for the purposes of ex vivo transduction. After myeloablation with busulfan, these transduced cells were administered intravenously to reconstitute the hematopoietic system with cells containing the integrated ARSA gene to produce functional ARSA enzyme.

The data from these studies were pooled ($n=39$) and compared to a cohort of patients with MLD who were untreated (LI MLD; $n=28$ and EJ MLD; $n=17$). The primary efficacy endpoint was severe motor impairment-free survival (sMFS), defined as the interval from birth to the earlier of the first occurrence of Gross Motor Function Classification-MLD (GMFC-MLD) 2: 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 Level 5, utilized within the primary endpoint, is defined as "no locomotion nor sitting without support, but head control is possible." Additional endpoints and the analysis plan which consisted of descriptive analyses, are described in detail in the clinical review memo.

Among the 20 treated patients with PSLI MLD, one (5%) had severe motor impairment or death compared with 28 (100%) of the natural history controls. Motor function assessment demonstrated retention of independent ambulation (GMFC-MLD ≥ 1) in 12 out of 17 patients who were followed until 5 years of age, compared to the natural history where patients would typically lose all motor function by age 5 years. The effects in the EJ ($n=7$) and ESEJ ($n=10$) MLD cohorts were more challenging to discern due to small sample size, heterogeneity within and across the treated and comparator groups, rendering evaluation of the primary efficacy outcome measure infeasible. In the cohort of patients with EJ MLD, motor and cognitive function effects were observed as measured by retention of gait or ambulation and performance and language standard scores, where no such outcomes would be expected based on review of the literature. For the ESEJ MLD cohort, the effects of motor function were not observed however, the elimination of baseline residual ARSA activity after myeloablation and prior to engraftment of the transduced cells, may have contributed to challenges in discerning the treatment effects as measured by the primary efficacy outcome measure. Additionally, treatment early in the course of disease would likely result in the greatest gains based on the mechanism of action of the product. In this group, 4 of 10 patients maintained normal cognitive function despite motor decline, an outcome that is considered

clinically meaningful in this clinical setting, and that represents a deviation from the natural course of the disease.

Regulatory Recommendation

MLD is a rare, rapidly progressive neurologic disease with high unmet medical need. In consideration of the indication, we reviewed the clinical and clinical pharmacology's assessment of the data submitted in the BLA, the team's interpretation of the results, and the recommendations of the primary reviewers and branch chief, in addition to team meetings held during the review of the BLA.

I agree with the team's conclusions that MLD is a serious and life-threatening condition. I agree with the clinical review team that the pooled clinical studies compared to external data from untreated MLD patients constitute an adequate and well-controlled investigation and that the data submitted in the BLA demonstrate substantial evidence of effectiveness of LENMELDY. We acknowledge the heterogeneity in the study population across the subtypes of MLD and the challenges on the analyses of efficacy due to limitations of sample size. Notwithstanding these limitations, that data indicate reduced risk of death or motor impairment in patients in the PSLI MLD cohort compared to patients who are untreated.

Specifically, all patients who were treated with LENMELDY were alive at 6 years of age, compared to only 58% of children in the natural history group. At 5 years of age, 71% of treated patients were able to walk without assistance. Effects in language and performance IQ scores, although not the primary outcomes evaluated in studies of LENMELDY, also deviated from the natural course of the disease in patients who were already symptomatic at baseline. The applicant provided confirmatory evidence to support a favorable benefit – risk assessment, that includes mechanism of action, pre-clinical data, and clinical biomarkers, including ARSA enzyme levels and radiographic imaging from brain MRIs. Taken together, substantial evidence of effectiveness has been demonstrated to support approval of LENMELDY for the treatment of children with pre-symptomatic late infantile, pre-symptomatic early juvenile or early symptomatic early juvenile metachromatic leukodystrophy (MLD).

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