

DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: The file STN 125758/0

From:

Reviewer	Role	Date finalized	Stamp	Supervisor	Stamp
Wei Tu	Lead Reviewer	3/6/2024		Muhammad Shahabuddin	
	Reviewer				
	Reviewer				

Through: Maryna Eichelberger, Ph.D., Director, DBSQC/OCBQ/CBER

Applicant: Orchard Therapeutics (Europe) Limited

Subject: Review of Analytical Methods used for atidarsagene autotemcel (OTL-200) Drug Substance (DS) and Drug Product (DP)

Recommendation: Approval

Executive Summary:

The following analytical methods used for lot release of atidarsagene autotemcel and the associated analytical method validations or qualifications, were reviewed:

1. (b) (4) (Wei Tu)
2. (b) (4) (Wei Tu)
3. (b) (4) (Wei Tu)
4. (b) (4) (Wei Tu)
5. (b) (4) (Wei Tu)
6. (b) (4) (Wei Tu)
7. (b) (4) in DP by (b) (4) (Wei Tu)

Conclusion: The analytical methods and their validations reviewed for the atidarsagene autotemcel drug substance(s) and drug product were found to be adequate for their intended use.

Documents Reviewed

Information in sections of the original submission that describe control of DS (OTL-200 (b) (4)) and DP (3.2.S.4 and 3.2.P.5, respectively), including descriptions of DS and DP specifications, analytical procedures of DS and DP and validation of these analytical procedures were reviewed. Additional information in amendment 24, amendment 42, and amendment 52, were also reviewed.

Background:

On July 19, 2023, Orchard Therapeutics (Europe) Limited submitted Biological License Application (STN 125758) for atidarsagene autotemcel (OTL-200), a treatment of metachromatic leukodystrophy (MLD) for pediatric patients with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) MLD. MLD is a rare, fatal, autosomal recessive inherited lysosomal storage disorder caused by mutations in the arylsulfatase A (ARSA) gene, resulting in deficiency of its corresponding enzyme. OTL-200 contains autologous CD34+ hematopoietic stem and progenitor cells (HSPC) transduced with a non-replicating recombinant lentiviral vector (LVV) encoded with the human ARSA gene. OTL-200 is a treatment for autologous use only. The ARSA LVV is manufactured from (b) (4)

The autologous CD34+ cells are selected from (b) (4) products (b) (4) and enriched, then transduced with ARSA LVV. The cells are harvested, washed, and concentrated. The DP is formulated with cryopreservation formulation medium. The manufacturing process leaves potential impurities such as (b) (4), which may result in adverse toxic or immunologic reaction. For the product quality and efficacy as well as safety reasons, the residual impurities need to be reduced to the lowest level. Several analytical methods, including (b) (4) assay are used to monitor and quantify the impurity level in (b) (4) DP.

(b) (4), Wei Tu

(b) (4)

24 pages have been determined to be not releasable: (b)(4)