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## DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

**To:** The file STN 125874/0

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**Applicant:** Regeneron Pharmaceuticals, Inc.

**Product:** lunsotogene parvec-cwha (OTARMENI)

**Subject:** Review of suitability of lot-release analytical methods for drug substances and drug product.

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**Recommendation:** Approval

### 1. Summary

Regeneron Pharmaceuticals, Inc. submitted this rolling original Biologics License Application STN 125874/0 for lunsotogene parvec-cwha (DB-OTO). The release methods to determine the (1) (b) (4) Drug Product (DP), (2) (b) (4), (3) (b) (4), (4) (b) (4), (5) (b) (4), and (6) (b) (4) were reviewed. The assay to determine (b) (4) is performed by (b) (4) while the other assays are performed by (b) (4). The sponsor provided data that demonstrated these methods are validated and suitable for their intended use.

### 2. Conclusion

The analytical methods reviewed were described in sufficient detail and validated for their intended use. Data provided demonstrated the assays' precision, accuracy, specificity, linearity, and sensitivity and are suitable for lot release testing at the validated range.

### 3. Documents Reviewed

Information reviewed included Sections 3.2.S and 3.2.P. Additional information related to analytical methods for DS and DP release was also reviewed, this information was provided in Amendment 2 (Nov 17, 2025), Amendment 3 (Nov 19, 2025), Amendment 6 (Nov 25, 2025), Amendment 16 (Dec 15, 2025), and Amendment 26 (Jan 5, 2026). The two Standard Operation Procedures (SOP) for the (b) (4) method were cross referenced from (b) (4) Master File (b) (4).

### 4. Background

Regeneron Pharmaceuticals, Inc. submitted an original Biologics License Application (STN 125874/0) for lunsotogene parvec-cwha (DB-OTO), a dual adeno-associated virus serotype 1 (AAV1) gene therapy intended for the treatment of patients with biallelic human otoferlin protein (OTOF) variant-associated hearing loss. The product consists of two recombinant AAV1 vectors: DB-OTO-5, which encodes the 5' component of the OTOF transcript variant 5, and DB-OTO-3, which encodes the 3' component. When these two vectors co-transduce the same target cell, they recombine to form a functional OTOF transcript variant 5 expression cassette and produce functional human OTOF protein. The product is supplied in a single-dose 2 mL vial containing a nominal vector genome titer of  $3.0 \times 10^{13}$  total vector genomes (vg)/mL with an extractable volume of 0.63 mL. Patients receive a total nominal dose of  $7.2 \times 10^{12}$  vg/ear in a total infused volume of 0.24 mL per ear.

The manufacturing process for DB-OTO-5 and DB-OTO-3 drug substances is (b) (4)  
HEK 293 cells are (b) (4)

Drug product manufacturing begins with (b) (4) DB-OTO-3 and DB-OTO-5 drug substances, which are then (b) (4) is processed through filtration and filling steps. The commercial formulation is a frozen liquid suspension containing a total of  $3.0 \times 10^{13}$  vg/mL of DB-OTO-3 (b) (4) and DB-OTO-5 (b) (4) formulated in 10 mM sodium phosphate, 5% (w/v) sucrose, 180 mM sodium chloride, and 0.001% (w/v) poloxamer 188 at pH 7.3; long-term storage is -80°C.

The validation of analytical methods for lot release of drug substances and drug product is critical for ensuring product quality. The review of the methods to determine (b) (4) drug product and quantify impurities in (b) (4) is documented in this memo.

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