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DBSQ/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: STN125874/0

From: Hsiaoling Wang, Ph.D., CMC reviewer, CBER/OCBQ/DBSQ/LAC

Through: Kenneth S. Phillips, Ph.D., LAC Chief, CBER/OCBQ/DBSQ/LAC
Maryna Eichelberger Ph.D., Division Director, CBER/OCBQ/DBSQ

Product: OTARMENI (lunsotogene parvec)

Applicant: Regeneron Pharmaceuticals, Inc.

Subject: Analytical Methods for the Lot Release of (b) (4) Drug Product

Recommendation: Approval

Summary:

The following analytical methods used for lot release of OTARMENI (lunsotogene parvec) (b) (4) drug product (DP) and the associated validations and qualifications were reviewed:

1. (b) (4)
2. (b) (4)
3. Poloxamer 188 by (b) (4) DP)
4. (b) (4)
5. Appearance (b) (4) DP)
6. pH (b) (4) DP)
7. (b) (4)
8. Extractable Volume (DP)
9. Particulate Matter (DP)

Conclusion: The analytical methods and their validations and qualifications reviewed for OTARMENI (b) (4) drug product were found to be suitable for their intended use.

Documents Reviewed

Pre-submission, dated November 6, 2025:

- Cover letter
- Form 356h

- Sections describing control of (b) (4) (3.2.S.4) (b) (4) DP (3.2.P.5), including descriptions of (b) (4) DP specifications, analytical procedures of (b) (4) DP, qualifications of these analytical procedures, and (b) (4) DP batch analyses.

Amendment 2, dated November 17, 2025

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Amendment 3, dated November 19, 2025

- Response to FDA request dated 17Nov2025
- Updated S.2.1 Manufacturer(s)
- Updated P.3.1 Manufacturer(s)

Amendment 6, dated November 25, 2025

- Response to FDA request dated 17Nov2025
- Updated S.4.3 Validation of Analytical Procedures – (b) (4)
Validation package
- Updated S.4.3 Validation of Analytical Procedures – (b) (4)
Validation package

Amendment 26, dated January 5, 2026

- Response to FDA request dated 19Dec2025
- Updated S.4.2 Analytical Procedure
- Document AV-LE-1383-04.01: DB-OTO (b) (4) Testing Protocol
- Updated P.5.2 Analytical Procedure
- Updated SOP-CTP6588: Purity by (b) (4) for DB-OTO
- Updated (b) (4) STM-00090: Quantitation of Poloxamer 188 (b) (4)
- Updated P.5.3 Validation of Analytical Procedures

Amendment 35 dated January 21, 2026

- Response to FDA request dated 15Jan2026
- Updated (b) (4) STM-00090: Quantitation of Poloxamer 188 (b) (4)
- Document STY-LE-1383-01.01: DB-OTO (b) (4) Testing Protocol

Amendment 48 dated February 2, 2026: Commitments to FDA IRs #4 and #19

- VSR-LE-1383-05.01: DB-OTO (b) (4) Testing Summary Report
- SR-LE-1383-02.01: DB-OTO (b) (4) Testing Summary Report
- Updated S.4.2 Analytical Procedure

Amendment 57 dated February 10, 2026

- Response to FDA request dated 6Feb2026
- Updated S.4.2 Analytical Procedure
- Updated S.4.1 Specifications
- Updated P.5.1 Specifications

Background

OTARMENI (lunsotogene parvev, also referred as DB-OTO) is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with biallelic otoferlin (OTOF) variant-associated hearing loss. It is administered by a one-time intracochlear infusion.

OTARMENI (b) (4) consists of two independently produced adeno-associated viral serotype 1 (AAV1) vectors, DB-OTO-3 [encoding the 3' component of the human Otoferlin transcript variant 5 (*hOtof5*)], and DB-OTO-5 (encoding the 5' component of *hOtof5*). (b) (4) formulated in the buffer of 10 mM sodium phosphate, 180 mM sodium chloride, 5% sucrose (w/v), 0.001% poloxamer 188 (w/v) at pH 7.3 with the vector genome titer (b) (4) 3.0×10^{13} vector genomes (vg)/mL. The (b) (4) are stored at (b) (4) OTARMENI DP is a sterile frozen liquid suspension (b) (4) DB-OTO-3 and (b) (4) DB-OTO-5. DP is (b) (4) stored at -80 (b) (4) °C.

In this memo, lot release tests for the (b) (4) DP and their associated validations and qualifications were reviewed.

(b) (4)

(b) (4)

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(b) (4)

3. Poloxamer 188 by (b) (4) DP)

Poloxamer 188 (P188) is an excipient for the (b) (4)

(b) (4). The targeted P188 content in the (b) (4) is 0.001% (w/v) for (b) (4) DP manufacturing. The specification of P188 for (b) (4) DP is 0.001(b) (4) %.

Method

(b) (4)

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(b) (4)

(b) (4)

(b) (4)

5. Appearance (b) (4) DP)

The specifications of appearance (clarity and color) for (b) (4) . The specifications of appearance (clarity, color and physical form and condition) for DP are (b) (4) colorless, and essentially free from visible particles.

Method

The analytical procedure for appearance test used at (b) (4) was provided in CGT-03.0150, which is in accordance with (b) (4)

(b) (4)

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Conclusion

Based on information provided in the pre-submission and Amendment 57, this (b) (4) method has been verified for its intended use.

6. pH (b) (4) DP)

The pH specification for (b) (4) DP is (b) (4)

Method

The analytical procedure for pH determination according to (b) (4) is provided in CGT-03.0276. (b) (4)

Method Verification

Verification of the pH assay at (b) (4) was provided in document QCTD-0732-B-REP. (b) (4)

. The DP sample result was 7.3, which met the DP specification.

(b) (4)


All met the proposed specification.

Conclusion

Based on the information provided in the pre-submission, this simple (b) (4) method was verified for its intended purpose.

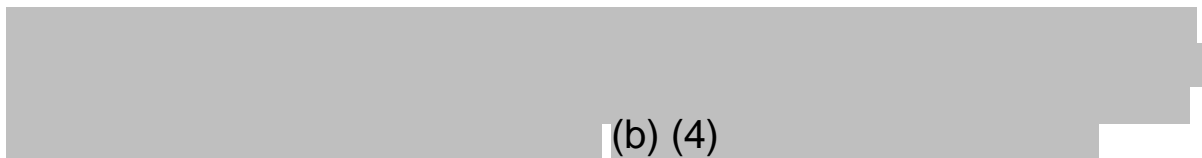

(b) (4)

(b) (4)




(b) (4)

(b) (4)



(b) (4)

(b) (4)




8. Extractable Volume (DP)


The specification of extractable volume for DP is ^{(b) (4)} 0.63 mL.

Method

The Analytical procedure for determination of extractable volume used at (b) (4) is provided in SOP-CTP6786, which is accordance with (b) (4)



(b) (4)



(b) (4)

(b) (4)

Conclusion

Based on the information provided in the pre-submission and Amendment 26, this simple (b) (4) method is verified for its intended use by the Regeneron lab.


9. Particulate Matter (DP)

The specifications of particulate matter for DP are (b) (4) particles/container for particles (b) (4) particles/container for particles (b) (4) .

Method

(b) (4)

(b) (4)

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Conclusion

Based on the information provided in the pre-submission, this (b) (4) method is verified for its intended use.