



DBSQ/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: The file STN 125858/0

From: Salil K Ghosh, Ph.D., LAC/DBSQ/OCBQ/CBER

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

Tao Pan, Ph.D, Acting Lab Chief,
LAC/DBSQ/OCBQ/CBER

Sponsor: Ultragenyx Pharmaceuticals, Inc.

Subject: Review of Analytical Methods used for pariglasgene breCAPARVOC
(GENGLYCOS)

Recommendation: Approval

Executive Summary:

The following analytical methods used for lot release of GENGLYCOS drug substance (DS) and drug product (DP) and the associated analytical method validations or qualifications, were reviewed.

1. pH (b) (4) DP)
2. (b) (4) of DP
3. Appearance of DP
4. Poloxamer 188 by (b) (4) of DP
5. (b) (4) DP)
6. (b) (4) of DP
7. (b) (4) DP)
8. Capsid protein purity by (b) (4) DP)

Conclusion: The analytical methods and their validations and/or qualifications reviewed for the GENGLYCOS DS and DP were found to be adequate for their intended use.

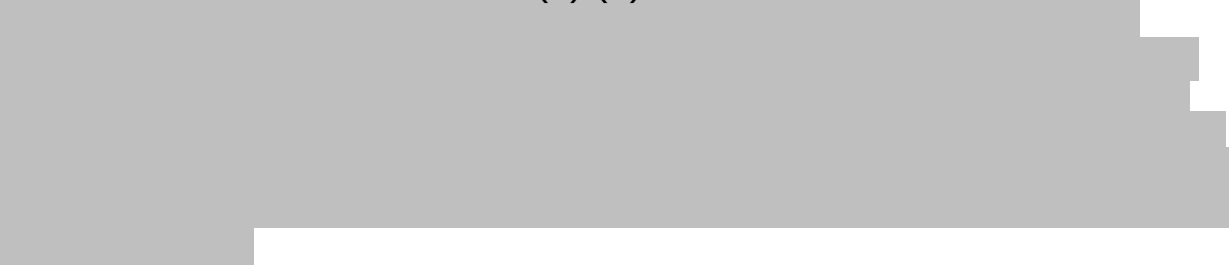
Documents reviewed:

Information in sections of the original submission that describe control of DS 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.

Background

On August 8, 2025, Ultragenyx (UGT) Pharmaceuticals, Inc. submitted a Biologics License Application (BLA; STN 125858) for pariglasgene brecaparvovec (GENGLYCOS), an intravenous (IV) gene therapy consisting of an adeno-associated virus serotype 8 (AAV8) vector carrying a functional copy of the human glucose-6-phosphatase (G6Pase) gene. The product is intended for the treatment of adult and pediatric patients with glycogen storage disease type 1a (GSD1a), a rare inherited disorder of carbohydrate metabolism caused by pathogenic biallelic variants in the G6PC gene. GSD1a is an ultra-rare, progressive, and potentially life-threatening disease with a well-established pathophysiology characterized by impaired glucose homeostasis and glycogen accumulation in multiple tissues.

Pariglasgene brecaparvovec DS is a (b) (4)



The drug product (DP) is formulated in a buffer containing 20 mM Tris, (b) (4) MgCl_2 , 200 mM NaCl, and 0.001% (w/v) poloxamer 188 (PF68), with a target concentration of (b) (4) and a target pH of (b) (4). The DP is filled into (b) (4) (8 mL) glass vials at a fill volume of 2 mL per vial and stored at $\leq -60^\circ\text{C}$. PF68 is used as a virus stabilizing agent (b) (4) manufacturing of DP.

DP DTX401 is supplied as a clear, colorless suspension for intravenous administration at a concentration of 3.0×10^{13} gene copies (GC)/mL. The recommended dose is 1.0×10^{13} GC/kg of body weight, delivered as a single intravenous infusion. Prior to administration, the DP is thawed at room temperature and aseptically diluted with sterile saline for infusion. Depending on the patient's body weight and the product concentration, multiple vials may be required to prepare an individual dose. The diluted DP DTX401 solution is administered through intravenous infusion over approximately three hours.

Review Narrative

1. pH (b) (4) DP)

Introduction

The pH specification of (b) (4) DP is 7.5 – 8.5. The lot release test for pH is performed at the UGT pharmaceutical facility in Woburn, MA.

Method

The pH of (b) (4) DP are tested following (b) (4)

Method Verification

The suitability of the (b) (4) pH method was verified and documented in Verification Report VV-11168 through testing of DTX401 (b) (4) DP lots in accordance with Verification Protocol VV-11431.

(b) (4)

Conclusion:

The pH test performed on (b) (4) DP at the UGT pharmaceutical facility in Woburn, MA is suitable for routine lot release testing.

2. (b) (4)

(b) (4)

(b) (4)

3. Appearance of DP

Introduction

The lot release test for appearance is performed at the UGT pharmaceutical facility in Woburn, PA. The DP release specifications are “liquid, colorless, clear to translucent, may contain proteinaceous particulates but free from foreign matter”.

Method:

The appearance test is a visual inspection of the DP vial performed in accordance with SOP VV-11926. The container is examined to verify integrity and confirm the absence of leaks, cracks, breakage, or other visible defects. This (b) (4) visual assessment is conducted in accordance with (b) (4) to evaluate the product’s appearance with respect to color, clarity, opalescence, and the presence of visible particulate matter.

Prior to testing, (b) (4). Each vial is then visually inspected (b) (4)

the visual examination.

Method Verification

Verification of the DP appearance test was conducted at the Woburn, MA facility and documented in Verification Report VV-19574. The study was performed in accordance with Verification Protocol VV-20269 using (b) (4) DP lots: (b) (4)

(b) (4) The lots were evaluated for color, clarity, visible particulate matter, and method specificity. Each sample was assessed on (b) (4) separate occasions by multiple analysts to demonstrate the reproducibility of the visual inspection procedure.

All (b) (4) lots were consistently observed to be colorless and either clear or translucent. The observed color of each sample was consistent with the corresponding (b) (4) reference standard. In addition, all samples were found to be visibly free of particulate matter. The results demonstrated that all tested lots met the predefined acceptance criteria for appearance, including color, clarity, and absence of visible particles, thereby confirming the suitability of the method for routine DP appearance testing.

(b) (4) analysts were able to unambiguously evaluate the analyte between the

(b) (4)

(b) (4) These results demonstrate that the method can reliably distinguish the analyte from other sample constituents and is therefore considered to be highly specific.

Conclusion:

The information provided shows that the appearance test performed at Woburn, MA is suitable for routine lot release testing.

4. (b) (4)

(b) (4)

(b) (4)

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

(b) (4)



5. Poloxamer 188 determination by (b) (4) of DP

Introduction

Poloxamer 188 (PF68) is a (b) (4) in the recombinant adeno associated virus (rAAV) vector product. The specification for PF68 in the DP is (b) (4). The release test is performed at the Woburn MA facility of UGT.

Method:

(b) (4)



1 page has been determined to be not releasable: (b)(4)

(b) (4)

A large rectangular area of the document is redacted with a solid gray fill.A rectangular area of the document is redacted with a solid gray fill.A rectangular area of the document is redacted with a solid gray fill.A rectangular area of the document is redacted with a solid gray fill.A rectangular area of the document is redacted with a solid gray fill.A rectangular area of the document is redacted with a solid gray fill.

Conclusion

The (b) (4) method for the quantitation of PF68 in DP was appropriately validated for its intended purpose at Woburn, MA and is suitable for lot release testing.

6. (b) (4)

A rectangular area of the document is redacted with a solid gray fill.

(b) (4)

A rectangular area of the document is redacted with a solid gray fill.A rectangular area of the document is redacted with a solid gray fill.

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

(b) (4)

8. Capsid protein purity by (b) (4) DP)

Introduction

The (b) (4) purity (b) (4) of capsid viral proteins in (b) (4) DP were quantified using (b) (4). The acceptance criterion for (b) (4) purity is (b) (4).

Method:

The proposed method (VV-08774) for the determination of capsid protein purity and related impurities in the (b) (4) DP utilizes (b) (4).

(b) (4)

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

(b) (4)



A large rectangular area of the document is redacted with a solid grey fill.



A rectangular area of the document is redacted with a solid grey fill.



A rectangular area of the document is redacted with a solid grey fill.



A large rectangular area of the document is redacted with a solid grey fill.

Conclusion

The (b) (4) method for quantifying capsid purity (b) (4) DP was successfully validated for its intended purpose at the Woburn, MA site and is suitable for lot release testing.