

DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: The file STN 125717/0

From:

Reviewer	Role	Date finalized	Stamp	Supervisor	Stamp
Claire H. Wernly	Reviewer	7/10/2022		James L. Kenney	
Esmeralda Alvarado Facundo	Reviewer	7/26/2022		Muhammad Shahabuddin	
M. Nahid Parvin	Reviewer	6/7/2022			
Tao Pan	Lead Reviewer	6/10/2022		Tao Pan	

Through Maryna Eichelberger, Ph.D.
Division Director, DBSQC/OCBQ

Applicant: bluebird bio

Subject: Review of Analytical Methods used for Lot release of Zynteglo (betibeglogene autotemcel) Drug Substance (DS) and Drug Product (DP)

Recommendation: Approval

Executive Summary:

The following analytical methods used for lot release of Zynteglo (betibeglogene autotemcel) and the associated analytic method validations or qualifications, were reviewed:

1. Sterility test of (b) (4) DP (Claire H. Wernly)
2. Endotoxin test of (b) (4) DP (Claire H. Wernly)
3. Mycoplasma test of (b) (4) DP (Claire H. Wernly)
4. (b) (4) (M. Nahid Parvin)
5. (b) (4) (Tao Pan)
6. (b) (4) (Tao Pan)

7. Appearance of (b) (4) DP (Tao Pan)
8. Quantitative β A-T87Q-globin protein expression assay of DP (Tao Pan)
9. (b) (4) (Esmeralda Alvarado Facundo)
10. (b) (4) (Esmeralda Alvarado Facundo)

Conclusion: The analytical methods and their validations and/or qualifications reviewed for Zynteglo (betibeglogene autotemcel) drug substance (DS) and drug product (DP) were found to be adequate for their intended use.

Documents Reviewed

Information in sections of the original BLA 125717 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. Additional information in amendments specified by each reviewer were also reviewed.

Background

bluebird bio submitted a rolling BLA, STN 125717 on September 20, 2021 for Zynteglo (betibeglogene autotemcel, beti-cel) for the treatment of patients with β -thalassemia who require regular red blood cell (RBC) transfusions. Zynteglo DS, the BB305 Lentiviral Vector (BB305 LVV), is used to transduce autologous CD34+ hematopoietic stem cells to manufacture the DP. BB305 LVV contains a positive-strand RNA that carries key viral elements necessary for LVV function, as well as sequences encoding the human β A-globin (β A-T87Q) gene, enclosed within a lipid envelope with essential structural proteins. BB305 LVV is produced by transient transfection of human embryonic kidney (HEK) cells, then harvested from the cell culture supernatant, purified and filled into a (b) (4) vial before storage at -65oC. Zynteglo DP (beti-cel) consists of an autologous CD34+ cell-enriched population that contains hematopoietic stem cells transduced with BB305 LVV, suspended in (b) (4) cryopreservation solution.

DBSQC reviews BLAs and their supplements to ensure analytical methods are appropriately described, validated and suitable for intended purposes. The following analytical methods used for DS and DP release by the manufacturer were reviewed:

1. Sterility test of (b) (4) DP (Claire H. Wernly)


Introduction:

This test is performed on the (b) (4) at the (b) (4)

Method:

(b) (4)

(b) (4)



Conclusion:

Due to the unique nature of cellular and tissue products, there are challenges associated with accruing enough material for subsequent testing. DBSQC is aware strict adherence to testing

standards for such products may not always apply due to limited production lot size. The main concern regarding smaller sample test volume for sterility testing is an increased potential for inadvertent infection associated with injection of contaminated product that may be detectable using larger sterility test sample volumes. Therefore, to support the request for the reduction in the amount of product tested, the sponsor was requested to submit a post marketing response showing an increased sterility assurance of the DP, by testing more sample size associated with the (b) (4). CBER discussed this with the sponsor and agrees with their proposed path forward, ensuring that the sterility test will be strengthened to provide greater assurance of detecting low level contaminants in the DP.

2. Endotoxin test of (b) (4) DP (Claire H. Wernly)

Introduction

This test is performed on the (b) (4) on the final cell suspension (i.e., DP) (b) (4)

Method:

(b) (4)

(b) (4)

Conclusion:

(b) (4) submitted bacterial endotoxin concentration results from (b) (4) DP lots, and all were within their proposed release specification (i.e., (b) (4) for DP). After review of the (b) (4) test, this reviewer concludes the test methods were performed and compliant with (b) (4)

3. Mycoplasma test of DS and DP (Claire H. Wernly)


Introduction

This test is performed on the (b) (4) final cell suspension (i.e., DP) at (b) (4)

Method:

(b) (4)


(b) (4)

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Conclusion:

(b) (4) were performed on (b) (4) DP, and the results were compliant with (b) (4), thus demonstrating these methods are suitable under the actual conditions of use.

(b) (4)


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(b) (4)




7. Appearance of (b) (4) DP (Tao Pan)

The appearance of (b) (4) Zynteglo (b) (4) DP (beti-cel) were determined by visual inspection to assess their color, clarity, and particulate matter; the methods are based on (b) (4)



(b) (4)



(b) (4)

Appearance of DP

Method:

The DP, beti-cel, is a cell suspension for infusion; for release, its appearance is defined as colorless to white to red, including shades of white or pink, light yellow, and orange. The appearance of beti-cel is assessed by visual inspection post filling but pre-cryopreservation (SOP-Visual Appearance (b) (4)). In brief, DP sample in a (b) (4)

was defined for the method. A detailed description of the method has been provided in the application.

Method Verification:

(b) (4)

(b) (4)

Conclusion:

The appearance method for DP is a simple method; based on information provided, it has been validated for its intended use of lot release testing of the beti-cel DP.

8. Quantitative β A-T87Q-globin protein expression assay of DP (Tao Pan)





Zynteglo DP (beti-cel) is manufactured by transducing an autologous CD34+ enriched cell population that contains hematopoietic stem cells with BB305 LVV DS; the expression of β A-T87Q-globin protein in the DP is determined by a (b) (4) method, the release specifications are: β A-T87Q-globin (b) (4) is positively identifiable with (b) (4) of that of (b) (4).

Method:

The β A-T87Q-globin protein expressed in the DP is identified and quantitated using a (b) (4)

(b) (4)

(b) (4)



Conclusion:

Based on information provided, β A-T87Q-globin protein expression by (b) (4) method is adequately described and validated for the identity and content determination of Zynteglo DP (beti-cel) release.

