CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761228Orig1s000

PRODUCT QUALITY REVIEW(S)

First Approval for Indication/Expedited or Breakthrough Assessment: Yes

Recommendation: Approval

BLA Number: 761228
Assessment Number: 01
Assessment Date: 10/12/2021

Drug Name/Dosage Form	KIMMTRAK- tebentafusp-tebn, IMCgp100/Injection
Strength/Potency	0.1 mg/0.5 mL (0.2 mg/mL) solution in a single-dose 2 mL Type (b) (4) clear glass vial
Route of Administration	Intravenous (IV) administration
Rx/OTC dispensed	Rx
Indication	Unresectable or metastatic uveal melanoma (mUM)
Applicant/Sponsor	Immunocore Limited
US agent, if applicable	Immunocore LLC

Product Overview:

KIMMTRAK (tebentafusp-tebn) is a bispecific fusion protein composed of a soluble, affinity enhanced T cell receptor (TCR) fused to an anti-cluster of differentiation 3 (CD3) single-chain variable fragment (scFv). The TCR domain of tebentafusp-tebn targets a glycoprotein 100 (gp100) peptide fragment (YLEPGPVTA) when presented by human leukocyte antigen (HLA)-A*02:01 on the cell surface. The gp100 peptide fragment is a melanocyte-lineage antigen expressed exclusively in normal melanocytes and overexpressed on melanocytic tumors. An immune synapse is formed when the TCR targeting domain of tebentafusp binds to UM cells and the CD3 effector domain binds to polyclonal T cells. The immune synapse results in redirection, proliferation, and activation of polyclonal T cells. Tebentafusp-activated polyclonal T cells release inflammatory cytokines and cytolytic proteins, which result in direct lysis of UM tumor cells. In addition, tebentafusp-mediated lysis may prime an endogenous antitumor response via epitope spreading. Tebentafusp is a heterodimeric protein consisting of an alpha and a beta sub-unit. Tebentafusp drug substance is manufactured by (b) (4) which are produced in *E. coli* (b) (4). Kimmtrak injection is supplied as a sterile solution in a single-dose 2 mL Type (b) (4) clear glass vial. Kimmtrak drug product is formulated in citric acid monohydrate (0.95 mg), di-sodium hydrogen phosphate (2.91 mg), (b) (4) mannitol (5 mg), Trehalose (25 mg), polysorbate 20 (0.1 mg) and Water for injection, at approximate pH of 6.5.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance, Drug Product, Immunogenicity	Samuel Mindaye	OPQ/OBP/DBRR II
Labeling	Koung Lee	OPQ/OBP
DS Microbiology and Facility	Zhao (Joe) Wang	OPQ/OPMA/DBM2
DP Microbiology and Facility	Maria Gutierrez-Hoffmann	OPQ/OPMA/DBM2
Microbiology and Facility Team Lead	Candace Gomez-Broughton	OPQ/OPMA/DBM2
Regulatory Business Project Manager	Kelly Ballard	OPQ/OPRP/DRBPMI/RBPMB I
Application Team Lead	Yanming An (*served as Application Team Lead through Oct. 30, 2021*) Xianghong Jing	OPQ/OBP/DBRR II
OBP Review Chief	Xianghong Jing	OPQ/OBP/DBRR II

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Nataliya Fesenko	ORO/DROOD
Cross-disciplinary Team Lead	Jamie Brewer	OND/OOD/DOI
Medical Officer	Margaret Thompson	OND/OOD/DOIII
Pharmacology/Toxicology	Elizabeth Spehalski/Matt Thompson (TL)	OND/OOD/DHOT
Clinical Pharmacology	Huiming Xia/Hong Zhao (TL)	OTS/OCP/DCPII
Statistics	Sirisha Mushti/Joyce Cheng (TL)	OTS/OB/DBV

1. Names:

a. Proprietary Name: KIMMTRAK
b. Trade Name: KIMMTRAK
c. Non-Proprietary Name/USAN: Tebentafusp-tebn
d. CAS Name: 1874157-95-5
e. Common Name: IMCgp100
f. INN Name: Tebentafusp
g. OBP systematic name: FUS: MABFRAG HUMANIZED (IGG1) ANTI P07766 (CD3E_HUMAN); RPROTFRAG P0DTU4 (TRBR2_HUMAN); RPROTFRAG P0DTU3 (TRAR2_HUMAN) [IMCGP100]

Submissions Assessed:

Submission(s) Assessed	Document Date
STN 761228/0004	03/31/2021
STN 761228/0007 (response to IR#1 OPMA)	04/26/2021
STN 761228/0008 (response to IR#2 OBP)	05/03/2021
STN 761228/0010 (response to IR#3 OBP)	06/02/2021
STN 761228/0011 (response to IR#4 OPMA)	06/09/2021
STN 761228/0014 (response to IR#5 OPMA)	06/28/2021
STN 761228/0015 (response to IR#6 OPMA)	07/06/2021
STN 761228/0016 (response to IR#7 OBP)	07/09/2021
STN 761228/0017 (response to IR#8 OPMA)	07/26/2021
STN 761228/0019 (response to IR#9 OPMA)	08/11/2021
STN 761228/0021 (response to IR#10 OBP)	09/03/2021
STN 761228/0024 (response to IR#11 OBP)	09/30/2021
STN 761228/0028 (response to IR#12 OBP)	11/03/2021
STN 761228/0030 (response to IR#13 OBP)	11/11/2021

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)
2. Related/Supporting Documents:

   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Assessment Completed
(b) (4)	III		(b) (4)	2	Adequate	N/A
	III			2	Adequate	N/A
	III					
	III			2	Adequate	N/A
	III			2	Adequate	N/A

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows: 2- Assessed previously and no revision since last assessment; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be assessed.

   B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	114314	Immunocore Ltd.-sponsored IND under which IMCgp100 was developed and meetings were held

3. Consults: None.

4. Environmental Assessment of Claim of Categorical Exclusion:

   Immunocore Ltd. claims a categorical exclusion from the requirements of environmental assessment for tebentafusp under the provisions of 21 CFR 25.31(b and c). Tebentafusp is a biodegradable product, and when exposed to the environment, is not expected to significantly alter the concentration or distribution of the active substance, its metabolites or degradation products in the environment. Categorical Exclusion is appropriate for this product and the claim is accepted.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Product Quality (OPQ), CDER, recommends approval of STN BLA 761228 for KIMMTRAK manufactured by Immunocore Ltd. The data submitted in this application are adequate to support the conclusion that the manufacture of KIMMTRAK is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance (DS): AGC Biologics A/S
    Vandtaamsvej 83B,
    DK-2860 Soeborg, Copenhagen, Denmark
    FEI: 3004708748

  - Drug Product (DP): Baxter Oncology GmbH
    Kantstraβe 2
    33790 Halle/Westfalen, Germany
    FEI: 3002806419
- Fill size and dosage form:
  0.1 mg/0.5 mL (0.2 mg/mL) Tebentafusp in a single-dose glass vial as a sterile, preservative-free, clear colorless or slightly yellowish solution for intravenous infusion.

- Dating Period:
  - Drug Product: 18 months: 2-8 °C
  - Drug Substance: (b) (4) months: (b) (4)
  - For packaged products: “not packaged”
  - Stability Option:
    We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

- Exempt from lot release:
  - Yes
  - Rationale, if exempted: specified product
    Note: KIMMTRAK is exempted from lot release per FR notice 95-29960.

C. Benefit/Risk Considerations:

KIMMTRAK received orphan drug designation, breakthrough therapy designation, and priority review status for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma (mUM). UM is a rare type of melanoma, representing approximately 5% of all melanoma cases. UM represents the most common intraocular malignancy in adults,

accounting for approximately 85% of all ocular neoplasms arising from the melanocytes of the iris, ciliary body, or choroid of the eye. Approximately half of the patients with UM will experience metastasis within 2 to 10 years of diagnosis. The median survival after metastasis is < 12 months. No therapy has been shown to improve overall survival. There are currently no systemic treatments approved specifically for mUM and this indication presents a significant unmet medical need. Tebentafusp is a bispecific gp100-targeted T cell receptor fusion protein. The TCR domain of tebentafusp recognizes a gp100 peptide fragment, a melanocyte-lineage antigen expressed exclusively in normal melanocytes and overexpressed on melanocytic tumors, when presented by HLA-A*02:01 on the cell surface. When the TCR domain binds to UM cells and the CD3 effector domain binds to polyclonal T cells, an immune synapse is formed resulting in redirection, proliferation, and activation of polyclonal T cells regardless of their native TCR specificity. Tebentafusp-activated polyclonal T cells release inflammatory cytokines and cytolytic proteins, which result in direct lysis of UM tumor cells. In addition, tebentafusp-mediated lysis may prime an endogenous antitumor immune response via epitope spreading.

The overall control strategy includes control of raw materials, facilities, and equipment, manufacturing process, and adventitious agents. The conditions used in manufacturing have been sufficiently validated, and the data submitted in this application support the conclusion that the manufacture of tebentafusp is well controlled and yields a consistently high-quality product.

The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective. And the OPMA assessors are also recommending approval of the commercial manufacture of tebentafusp DS at AGC Biologics A/S, Copenhagen, Denmark FEI: 3004708748 and KIMMTRAK DP at Baxter Oncology GmbH, Halle/Westfalen, Germany FEI: 3002806419.

The OBP assessments including DS quality, DP quality, and validation of immunogenicity assays. OPMA DS and DP microbiological and facility technical assessments are located as separate documents in Panorama.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

The following PMCs were proposed by OBP and accepted by the Applicant:

PMC-1: Monitor [redacted] (b) (4) the next three commercial batches of tebentafusp drug substance [redacted] (b) (4). Submit the finalized report after evaluation of these results, along with potential updates of the control strategy on [redacted] (b) (4) to FDA.
Final report submission date: Q1 2024

PMC-2: Develop methods for extraction and quantitation of extractables/ leachables from the primary CCS in the presence of tebentafusp DS. Once methods have been developed and validated, incorporate the methods into the long-term stability study program [redacted] (b) (4) for monitoring of the level of extractables/ leachables in the process

performance qualification (PPQ) batches over the duration of shelf-life. Submit the study results to FDA as part of the annual update.
Final report submission date: Validated method by Q4 2022 and study results reported by Feb 2023

PMC-3: Implement (b) (4) monitoring (b) (4) of tebentafusp-tebn drug product and update Sections 3.2.P.3.3 and 3.2.P.3.4 of the BLA with (b) (4) as a Critical Process Parameter.
Implementation Date: Q2 2022

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and the associated control strategies for attributes that are relevant to both Drug Substance and Drug Product. For additional information, see the primary reviews, including the Drug Substance Quality Review and Drug Product Quality Review by OBP/DBRRII and the Drug Substance Microbiology Review and the Drug Product Microbiology Review by OPMA/DBM.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
Binding to gp100 peptide and binding to CD3. (Potency)	Efficacy	Intrinsic to molecule	(b) (4)	SPR testing against HLA and CD3 was performed for characterization
T cell activation and cytokine release (Potency)	Efficacy	Intrinsic to molecule		Cytokine release tested by MSD and inhibition assay using the IFNγ ELISpot assay were performed for characterization

CQA (type)	Risk	Origin	(b) (4)	Other
Primary Structure and PTM	Efficacy and immunogenicity	Intrinsic to molecule		Disulfide bonds, deamidation, acetylation, carbamylation, phosphoglucon-oylation, variants and oxidation were detected in characterization. In vitro testing indicated these variants are at low level and do not impact binding activity or non-specific reactivity.
Aggregation (dimer, higher and IMCgp100(scFv)) (product-related impurity)	Efficacy, pharmacokinetics and immunogenicity IMCgp100(scFv) species indicate potential off target activity due to cross-reactivity *in vitro* not *in vivo*.	Manufacturing process and storage conditions. Can form due to agitation, temperature, or light exposure.		IMCgp100 (scFv) is characterized as tebentafusp ligated to an additional fragment of anti-CD3-scFv. IMCgp100(scFv) is not a degradation product
Fragmentation (product-related impurities)	Efficacy, pharmacokinetics and immunogenicity	Manufacturing process and storage conditions. fragmentation may be caused by agitation, temperature, or light		
Acidic variants (product related impurity)	Efficacy, pharmacokinetics and immunogenicity	DS manufacturing process and storage conditions		Caused by deamidation and acetylation.

CQA (type)	Risk	Origin	Control Strategy	Other
Basic variants (product-related substance)	Efficacy, pharmacokinetics and immunogenicity	DS manufacturing process and storage conditions	(b) (4)	
Higher order structure	Efficacy, immunogenicity	Intrinsic to molecule		

B. Drug Substance [tebentafusp-tebn] Quality Summary

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	Risk	Origin	Control Strategy
Appearance, color and clarity (general)	Safety	Manufacturing process	(b) (4)
Protein Concentration (general)	Efficacy, pharmacokinetics, safety	Manufacturing process	
pH (general)	Efficacy, safety	Formulation and stability	
Host Cell Proteins (process-related impurity)	Safety and immunogenicity	Derived from host cell line	
Host Cell DNA (process-related impurity)	Safety	Derived from host cell line	
Osmolality (general)	Safety	Manufacturing process	
(b) (4) (b) (4) (process-related impurity)	Safety	(b) (4)	
Bacterial Endotoxin (contaminant)	Safety, Purity	Endotoxin can be introduced by raw materials and throughout the	

CQA (type)	Risk	Origin	Control Strategy
		manufacturing process.	(b) (4)
Microbial enumeration test (Bioburden) (contaminant)	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Bioburden can be introduced by raw materials and throughout the manufacturing process	
(b) (4)	Safety	Added during manufacture	
(b) (4) (general)	Safety, stability	Manufacturing process	
(b) (4)	stability	(b) (4)	
(b) (4)	Stability	(b) (4)	

- Description: Tebentafusp is a bispecific protein composed of a soluble human T cell receptor (TCR) domain and a single-chain variable fragment (scFv) domain of an anti-CD3 antibody. The TCR portion consists an alpha chain and a beta chain subunit. The beta subunit is fused with the scFv. The alpha chain is composed of 195 amino acids and the beta chain is composed of 500 amino acids. The two chains are linked via a disulfide bond between cysteine α157 and β427. Post-translational modifications of tebentafusp include oxidation, deamidation and N-terminal acetylation. The theoretical molecular weight of tebentafusp calculated from the mass of the polypeptide chains combined is 76145 Da. The main peak isoelectric point is 6.3.

- Mechanism of Action (MoA): The TCR domain of tebentafusp specifically binds to the gp100 peptide presented by the HLA:A*02:01 on the melanoma cancer cell surface. The anti-CD3 scFv activates local T cells via interaction with CD3 on the surface of T cells. The activated T cells kill the target tumor cells directly and trigger an augmentation of a local tumor-directed immune response, such as increase in inflammatory cytokines, T cell proliferation and migration from peripheral blood.

- Potency Assay:

    - Activity Enzyme-Linked Immunosorbent Assay (ELISA): A sandwich based colorimetric ELISA is used to assess the binding potency of tebentafusp to gp100. The HLA molecules loaded with the gp100 peptide is used as the capture reagent to coat a 96-well plate; tebentafusp is added to bind to HLA-A2 gp100. Detection is achieved through the binding of a horseradish peroxidase (HRP) conjugated CD3 to the anti-CD3 scFv section of tebentafusp with final colorimetric detection through addition of HRP substrate Turbo TMB. tebentafusp binding directly correlates with its concentration.

  - Cell based potency assay: the assay determines the bioactivity of tebentafusp samples using a cell-based bioactivity assay with an interleukin-2 (IL-2) ELISA for detection of response. A surrogate melanoma cell line (T2 cells pulsed with the gp100 peptide) is cultivated with a surrogate T-lymphocyte cell line (jurkat). Tebentafusp DS is serially diluted and added to the assay plate to bind to T2 gp100 cells in a dose-dependent manner. The assay plate is incubated in an incubator at 37°C, 5% CO_2 for 18 hours. The supernatant from the assay plate is transferred to the ELISA plate. Biotinylated anti-IL-2 antibody is added to each well and incubated. Streptavidin-HRP conjugate is added to each well and final colorimetric detection is through addition of TMB substrate. The relative activity of the sample is calculated by comparing the cell responses induced by the different tebentafusp concentrations of the test item to those of cells treated with the reference item concentrations.

- Reference Materials: A two-tiered reference material system is in place as per ICH Q6B recommendations. The current primary reference standard (PRS) was derived from (b) (4) The PRS will be used to quality future WRS batches. The WRS will be used for release, stability and characterization testing of tebentafusp DS and DP. The current reference standards are suitable for their intended use in tebentafusp testing. The reference standards are stored at (b) (4) and the PRS is tested (b) (4). The WRS will be assigned (b) (4) retest date (b) (4) based on review of in use trended stability data. The testing methods, acceptance criteria and testing time points of the stability protocol are adequate, and the stability data will be updated while available. A protocol is provided for the qualification of future working reference standards and the protocol contains adequate testing and acceptance criteria. The implementation of a new reference standard will be reported in annual report. (b) (4)

- Critical starting materials or intermediates: The Master Cell Bank (MCB) was prepared from a *E.coli* cell line (b) (4) (b) (4)

(b) (4)

Raw materials used in commercial manufacture are animal- and human-component free. All compendial raw materials and excipients comply with the requirements of the relevant Ph. Eur., USP or USP-NF monographs and are purchased from qualified suppliers with Certificates of Analysis. All non-compendial materials are purchased from approved suppliers and are tested against the defined set of acceptance criteria.

- Manufacturing process summary: (b) (4)

Three consecutive lots were executed at commercial scale to demonstrate that the manufacturing process is well-controlled and reproducibly yields a pure and potent product with the expected quality attributes.

There is no reprocessing of the tebentafusp DS.

- Container closure: The drug substance container closure system is (b) (4)

The container closure for stability program is (b) (4) .

- Dating period and storage conditions: The applicant conducted real-time stability studies at (b) (4) for 2 clinical batches and 3 process validation batches. These data are also supported by accelerated and stressed stability studies. These data support a dating period of (b) (4) months at (b) (4). The applicant committed to place one batch of tebentafusp DS on stability at (b) (4) each year that the product is manufactured. The stability testing program is adequate and consistent with ICH Q5C recommendations.

C. Drug Product [KIMMTRAK] Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy
Appearance, color and clarity (general)	Safety	Manufacturing process	(b) (4)
Particulate matter (subvisible and visible)	Safety	Manufacturing process, product degradation	
Extractable volume (general)	Safety, efficacy	Manufacturing process, storage conditions	
Protein concentration (general)	Efficacy	Manufacturing process	
pH (general)	Safety, efficacy	Formulation	
Osmolality (general)	Safety, stability	Formulation	
Bacterial Endotoxin (contaminant)	Safety, purity and immunogenicity	Raw materials; microbial contamination during the manufacturing process	
Sterility (contaminant)	Safety, purity, efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced during DP manufacture or through a container closure integrity failure	
Container closure integrity	Safety (maintenance of sterility during shelf-life)	Container closure breaches during storage. May be	

CQA (type)	Risk	Origin	Control Strategy
		impacted by storage conditions.	

- Potency and Strength: Kimmtrak drug product contains tebentafusp drug substance of 0.1 mg in a 0.5 mL solution (0.2 mg/mL). The potency assays are the same assays as those described in the Drug Substance section of this review.

- Summary of Product Design: Kimmtrak is supplied as a sterile, preservative-free clear, colorless or slightly yellowish solution in a single-dose 2 mL Type (b) (4) clear glass injection vial, containing tebentafusp DS of 0.1 mg in a nominal volume of 0.5 mL solution. Kimmtrak is further diluted in sterile 0.9% Sodium Chloride Injection, USP containing albumin (Human) for intravenous infusion.

- List of Excipients: Excipients include polysorbate 20 (0.1 mg), citric acid monohydrate (0.95 mg), di-sodium hydrogen phosphate (2.91 mg), mannitol (5 mg), trehalose (25 mg) and water for injection.

- Reference Materials: The same reference standard is used for Drug Product as for Drug Substance. Refer to the Drug Substance reference standard section above.

- Manufacturing process summary: The manufacturing process for Drug Product includes the following steps: (b) (4) The commercial batch size is approximately (b) (4) vials.

  Three consecutive batches at the commercial scale were manufactured and analyzed to validate the manufacturing process. Manufacturing process parameters were within pre-specified parameters, and product quality attributes were within specification limits. These data support a well-controlled process that will consistently produce a high-quality product and that is adequate from a product quality review perspective.

  (b) (4) Bioburden and endotoxin are tested during manufacture, and endotoxin are tested at DP lot release. Sterility and container closure integrity test are included in the DP release and stability specifications. OPMA recommends approval of the DP manufacturing process from a product quality microbiology and sterility assurance perspective.

- Container closure: The primary packaging material for Kimmtrak Drug Product consists of a 2 mL Type (b) (4) clear glass injection vial with a (b) (4) rubber stopper and an aluminum overseal with a flip-off cap.

- Dating period and storage conditions: The sponsor conducted real-time, accelerated, and thermal-stressed stability studies on 3 PPQ lots and 1 clinical Drug Product lot. These data support a dating period of 18 months when stored at 2 to 8°C.

- List of co-package components, if applicable: None.

D. Biopharmaceutics Considerations: None.

E. Novel Approaches/Precedents: None

F. Any Special Product Quality Labeling Recommendations: None

G. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug substance manufacture. DS Release and stability testing DP release and stability testing (description/ID, purity, quantity, potency (activity) and endotoxins)	AGC Biologics A/S Vandtaamsvej 83B, DK-2860 Soeborg, Copenhagen, Denmark	307169677/ 3004708748	VAI	A two-item FDA Form 483 was issued on May 10, 2021. Deficiencies were adequately addressed in the firm's responses to the FDA-483 Inspectional Observations.	Approve
DS and DP Potency release and stability testing	(b) (4)		-----	Waived	Approve
Storage of DS Labeling of primary packaging Secondary packaging and labeling Storage and distribution			-----	Waived	Approve

MCB and WCB manufacture and storage Testing (growth and identity)	(b) (4)		-----	Waived	Approve
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP manufacture Primary packaging DP release testing DP stability testing (description/ID, sterility, endotoxin) DS Stability testing (subvisible particles) Storage of DS	Baxter Oncology GmbH Kantstraβe 2 33790 Halle/Westfalen Germany	344276063/ 3002806419	-----	Waived	Approve

H. Facilities: A pre-license inspection for tebentafusp drug substance manufacture was conducted on May 3-7, 10, 2021 at AGC Biologics, Inc. a 2-item FDA Form 483 was issued and the initial recommendation is approval for the BLA. The final classification of the AGC pre-license inspection was acceptable.

The pre-license inspection of the drug product site Baxter Oncology GmbH was waived because of the site's compliance status and its recent FDA surveillance inspection.

I. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
- Stability protocol for the extension of drug substance shelf life
- annual post-approval stability protocol
- stability protocol for master cell banks
- annual stability protocol for primary reference standard.
- Qualification of new working reference standards.
- Protocols for concurrent validation of resins lifetime at commercial scale

ii. Outstanding assessment issues/residual risk: None.
iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:
- stability protocol for the extension of drug product shelf life
- annual stability protocol

ii. Outstanding assessment issues/residual risk: None.
iii. Future inspection points to consider: None.

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/s/

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