CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761228Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 10, 2021

To: Nataliya Fesenko, Regulatory Project Manager
Division of Oncology 3 (DO3)

From: Lynn Panholzer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Comments for proposed Dear Healthcare Provider Letter for KIMMTRAK® (tebentafusp-tebn) injection, for intravenous use

BLA: 761228

In response to DO3's consult request dated December 9, 2021, OPDP has reviewed the proposed Dear Healthcare Provider (DHCP) Letter for KIMMTRAK® (tebentafusp-tebn) injection, for intravenous use (Kimmtrak). The purpose of the DHCP letter is to inform healthcare providers about the risk of cytokine release syndrome associated with use of Kimmtrak.

OPDP has reviewed the proposed DHCP Letter (attached) that was received via electronic mail from DO3 on December 7, 2021, and our comments are provided below. OPDP recommends that the information in the proposed DHCP letter be updated to be consistent with the final FDA-approved labeling.

GENERAL COMMENTS

Submission of Final DHCP Letter on Form FDA 2253

1. DHCP letters are considered promotional labeling. Therefore, please remind the sponsor, pursuant to 21 CFR 314.81 (b)(3)(i), to submit the final DHCP letter under cover of Form FDA-2253 at the time of initial dissemination.

Mailing of Important Information about Drugs

2. Please remind the sponsor to refer to 21 CFR § 200.5 (Mailing of important information about drugs) regarding the format for recommended mailing of important prescribing

information letters. We recommend that the distinctive box described in 21 CFR § 200.5 appear in the letter as well as on the envelope.

Guidances

3. OPDP recommends that the DHCP Letter be updated in accordance with the guidance titled, "Guidance for Industry and FDA Staff – Dear Healthcare Provider Letters: Improving Communication of Important Safety Information" (DHCP Letter Guidance) dated January 2014.

4. If sending the letter electronically, please remind the sponsor to disseminate the letter in accordance with the "Guidance for Industry – Using Electronic Means to Distribute Certain Product Information."

SPECIFIC COMMENTS

OPDP recommends the following revisions/edits provided in the attached copy of the draft DHCP letter, consistent with the DHCP letter guidance.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
12/10/2021 09:39:13 AM

Clinical Inspection - Addendum:

Date	Tuesday, December 7, 2021
From	Michele Fedowitz, MD Karen Bleich, MD Kassa Ayalew, MD, MPH Good Clinical Practice Assessment Branch (GCPAB)
To	Margaret Thompson MD, Clinical Reviewer Jamie Brewer MD, Clinical Team Leader MD, Division Director Nataliya Fesenko, Regulatory Project Manager Division of Oncology 3 (DO3)
BLA #	761228
Applicant	Immunocore LLC.
Drug	Kimmtrak (tebentafusp)
Therapeutic Classification	A bispecific glycoprotein 100 (gp100)-targeted T cell receptor fusion protein
Proposed Indication	Treatment of unresectable or metastatic uveal melanoma

The Office of Scientific Investigations received the response to the information request on November 19, 2021 to provide a listing of all adverse events and protocol deviations which resulted in changes to the EDC data from before the data cutoff, including at site 6401.: This CIS Addendum provides review of the sponsor's response to the information request.

There were not widespread unreported AEs or PDs. The unreported adverse events do not change the safety profile of the drug and the unreported protocol deviations were minor and typical for trials conducted during the Covid 19 pandemic. In addition, the ongoing updates of AEs are known to the review division as the safety information was updated in a post-BLA submission safety update of May 21, 2021 and an annual DSUR submitted October 12, 2021

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/s/

MICHELE B FEDOWITZ
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KAREN B BLEICH
12/07/2021 10:52:42 AM

KASSA AYALEW
12/07/2021 01:47:30 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 3, 2021
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761228
Product Name and Strength:	Kimmtrak (tebentafusp-tebn[a]) injection, 100 mcg/0.5 mL
Applicant/Sponsor Name:	Immunocore Ltd. (Immunocore)
OSE RCM #:	2021-500-2
DMEPA 2 Safety Evaluator:	Sarah Thomas, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on December 1, 2021 for Kimmtrak. The Division of Oncology 3 (DO3) requested that we review the revised carton labeling for Kimmtrak (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

The Applicant implemented all of our recommendations, and the revised carton labeling are acceptable from a medication error perspective at this time.

[a] The proposed nonproprietary name (tebentafusp-tebn) is only conditionally accepted for this product until the application is approved; see Mena-Grillasca, M. Suffix Review for Nonproprietary Name for Kimmtrak (BLA 761228). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 May 5. Nexus NPNS ID #: 2021-22.
[b] Thomas, S. Label and Labeling Review for Kimmtrak (BLA 761228). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 NOV 17. RCM No.: 2021-500-1.

APPENDIX A. IMAGES OF CARTON LABELING RECEIVED ON DECEMBER 1, 2021

Carton labeling

Sample Carton Labeling

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/s/

SARAH E THOMAS
12/03/2021 11:27:50 AM

ASHLEIGH V LOWERY
12/03/2021 02:06:42 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 29, 2021

To: Nataliya Fesenko, Regulatory Project Manager
Division of Oncology 3 (DO3)

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for KIMMTRAK® (tebentafusp-tebn) injection, for intravenous use

BLA: 761228

In response to DO3's consult request dated September 23, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original BLA submission for KIMMTRAK® (tebentafusp-tebn) injection, for intravenous use.

Labeling: OPDP's comments on the proposed PI are based on the draft PI received by electronic mail from DO3 on November 15, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review of the proposed PPI will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labels: OPDP has reviewed the attached proposed carton and container labels submitted by the Applicant to the electronic document room on October 26, 2021 and November 3, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
11/29/2021 10:44:30 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 29, 2021
To:	Nataliya Fesenko Regulatory Project Manager **Division of Oncology III (DO3)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Lynn Panholzer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	KIMMTRAK (tebentafusp-tebn)
Dosage Form and Route:	Injection, for intravenous use
Application Type/Number, Supplement Number:	BLA 761228
Applicant:	Immunocore Ltd.

1 INTRODUCTION

On June 23, 2021, Immunocore Ltd. submitted for the Agency's review an original Biologics License Application (BLA) 761228 for KIMMTRAK (tebentafusp-tebn) injection. The proposed indication is for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology III (DO3) on September 3, 2021 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for KIMMTRAK (tebentafusp-tebn) injection.

2 MATERIAL REVIEWED

- Draft KIMMTRAK (tebentafusp-tebn) injection PPI received on June 23, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and on November 15, 2021.
- Draft KIMMTRAK (tebentafusp-tebn) injection Prescribing Information (PI) received on June 23, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 15, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
11/29/2021 10:48:04 AM

LYNN M PANHOLZER
11/29/2021 11:09:00 AM

Clinical Inspection Summary

Date	11/23/2021
From	Michele Fedowitz, MD Karen Bleich, MD Kassa Ayalew, MD, MPH Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Margaret Thompson MD, Clinical Reviewer Jamie Brewer MD, Clinical Team Leader MD, Division Director Nataliya Fesenko, Regulatory Project Manager Division of Oncology 3 (DO3)
BLA #	761228
Applicant	Immunocore LLC.
Drug	Kimmtrak (tebentafusp)
NME (Yes/No)	Yes
Therapeutic Classification	A bispecific glycoprotein 100 (gp100)-targeted T cell receptor fusion protein
Proposed Indication	Treatment of unresectable or metastatic uveal melanoma
Consultation Request Date	7/02/2021
Summary Goal Date	11/22/2021
Action Goal Date	12/23/2021
PDUFA Date	2/23/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study IMCgp100-202 (NCT03070392) were submitted to the Agency in support of a New Biologics Application (BLA 761228) for tebentafusp (also known as IMCgp100) for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

Four clinical investigators, Drs Hassel (Site 3504), Piperno-Neumann (Site 6101), Rutkowski (Site 6401), and Kirkwood (Site 8705) were selected for clinical inspections. The Sponsor, Immunocore LLC., was inspected as this is the first marketing application for this sponsor and it is a new molecular entity. All inspections were conducted onsite.

There were updates to the electronic database involving efficacy and safety data generated at Site 6401 made after the database lock for the submitted application, apparently due to limited data cleaning prior to the submission. There was one change in the primary end point of overall survival (OS) for the control arm (Subject 6401-(b) (6)). Based on the sponsors report dated

November 19, 2021, changes impacting the primary efficacy endpoint of OS and secondary efficacy endpoints of PFS and BOR across all sites were reviewed and no changes to the OS endpoint occurred in any other patient besides 6401-(b) (6). Four additional patients treated at 4 different sites (other than 6401) had a change impacting either PFS and/or BOR. These changes and the extent of their impact are discussed under the review of Site 6401 below, but the changes after data cutoff do not appear to affect the endpoint of efficacy or safety in an important way. Based on the results of these inspections, the study appears to have been conducted adequately and the data generated by the inspected entities appear to be acceptable in support of this BLA.

II. BACKGROUND

Immunocore LLC., seeks approval of Tebentafusp for the proposed indication. In support of the BLA, the Applicant submitted clinical data from IMCgp100-202, a Phase II, open label, multi-center, randomized study comparing tebentafusp versus investigator's choice (dacarbazine, ipilimumab, or pembrolizumab) in adult HLA-A*02:01-positive patients with metastatic uveal melanoma (mUM) who had not received prior systemic therapy in the metastatic setting.

The primary objective of Study IMCgp100-202 is to compare the overall survival (OS) in all patients randomized to tebentafusp monotherapy versus all patients randomized to investigator's choice monotherapy. The primary endpoint is OS, defined as the time from randomization until death by any cause.

The key secondary endpoints progression free survival (PFS) and disease control rate (DCR) defined as CR or PR, or SD ≥ 12 weeks using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Key inclusion criteria include adult subjects with:

- Confirmed uveal melanoma (UM)
- HLA-A*02:01 positive by central assay1
- Metastatic disease
- Have not received prior treatment in the metastatic setting
- No prior regional liver-directed therapy
- Prior neoadjuvant or adjuvant therapy is allowed, provided it was administered in the setting of localized ocular disease with curative intent
- Measurable or non-measurable disease according to RECIST v1.1
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; and
- Life expectance of > 3 months based on investigator's judgement. any other medical conditions should be well-managed and stable in the opinion of the investigator for at least 28 days prior to the administration of the study drug

Subjects were randomized 2:1 to receive either tebentafusp or investigator's choice and were stratified by lactate dehydrogenase status. A treatment cycle lasted 3 weeks for both arms.

Arm 1, Tebentafusp, was administered weekly using an intra-patient dose escalation: 20 mcg on C1D1, 30 mcg on C1D8, and 68 mcg on C1D15 and weekly thereafter. Due to the possible cytokine release-associated toxicity with tebentafusp, patients were monitored overnight as an inpatient following the weekly doses at C1D1, C1D8, and C1D15.

Arm 2, Investigator's Choice (pembrolizumab, ipilimumab, or dacarbazine) were given on Day 1 of each 3 week cycle:

- Pembrolizumab 2mg/kg up to 200 mg,
- ipilimumab 3 mg/kg, or
- dacarbazine 1000 mg/m^2

Treatment continued until progression by RECIST v1.1, unacceptable toxicity, investigator decision, initiation of another anticancer therapy, or patient withdrawal of consent.

Subjects could continue to receive treatment beyond disease progression if they were clinically stable, deriving clinical benefit and showed no signs of unacceptable toxicity as determined by the investigator. Subjects who elected to continue treatment beyond the protocol-specified RECIST v1.1 progressive disease (PD) were to sign a separate consent to continue treatment after the initial assessment of PD.

Imaging assessments for the key secondary endpoints were performed at screening (within 28 days of C1D1) and every 12 weeks, using a reference to C1D1 and were not to follow delays incurred during the treatment period. Tumor response was determined locally by site according to RECIST v1.1. Local investigator's review of the imaging studies was used for efficacy assessment and treatment decision-making.

After treatment was discontinued, subjects had an end of treatment (EOT) visit and were followed for safety, survival status, subsequent cancer therapy, and quality of life, if they had not withdrawn consent to follow-up. Survival follow-up occurred every 12 weeks until death, or the end of the study. All subjects who discontinued treatment for reasons other than death, PD, withdrawal of consent, or study termination were followed for disease progression with continued imaging assessments until they had evidence of confirmed PD by RECIST v1.1.

This study was conducted at 58 study centers in 14 countries (US, Germany, France, United Kingdom, Poland, Canada, Australia, Belgium, Spain, Switzerland, Ukraine, Russia, Italy, and the Netherlands). For the study, 447 HLA-A*02:01-positive subjects were screened and 378 were randomized 2:1 to tebentafusp (252) or investigator's choice (126). The first subject was enrolled October 4, 2017 and the data cutoff for the current submission was October 13, 2020.

By the data cutoff 378 patients (252 tebentafusp, 126 investigator's choice) were randomly assigned to treatment, and 356 patients (245 tebentafusp, 111 investigator's choice) received at least 1 full or partial dose of study drug.

The Sponsor was sent an information request at on 11/19/2021, inquiring the extent of EDC changes for adverse events and protocol deviations at site 6401 and other sites. The request is

pending at the time of this report. (Please see the review of Site 6401 below.)

III. RESULTS

1. **Dr. John Kirkwood, (Site 8705)**
University of Pittsburgh Medical Center
UPMC Cancer Center
5150 Centre Ave., Suite 301
Pittsburgh, PA 15232

Inspection Dates: August 23-27, 2021

This investigator was inspected as an onsite surveillance inspection for Study IMCgp100-202. A previous inspection of this firm conducted 3/1/2010 was classified as no action indicated (NAI).

At the time of data cutoff, there were 18 subjects screened, 12 subjects enrolled, and 11 subjects treated at the site; one subject withdrew without receiving treatment (8705-(b) (6)). Of the 11 subjects treated, five died of progressive disease (Subjects 8705-(b) (6); and (b) (6)), five are off study and in follow-up (Subjects 8705-(b) (6)), and one subject (Subject 8705(b) (6)) continues the study drug.

The source documents for subjects 8705-(b) (6) were reviewed and compared to the subject data line listings. The reviewed subject records included medical records, including office notes and laboratory reports, informed consent, eligibility criteria, investigational product administration records, adverse events, SAEs, and protocol deviations. Study records were also reviewed including Form FDA 1572s, delegation of authority log, site monitoring log, IRB approvals, investigational test article accountability records, and site protocol with amendments.

Enrollment, subject disposition, overall survival, PFS, and DCR as reported in the data line listings was verified for all subjects by comparison with the source records. No unreported adverse events or protocol deviations were identified. No significant regulatory violations

2. **Dr. Jessica Hassel (Site 3504)**
Universitätsklinikum Heidelberg
NCT Heidelberg – Nationales Centrum für Tumorerkrankungen
Im Neurenheimer Feld 460
49120 Heidelberg

Inspection Dates: September 13-17, 2021

This investigator was inspected as an onsite surveillance inspection for Study IMCgp100-202. This was the first FDA inspection for this investigator.

At the time of the data cutoff, the investigator had screened 18 subjects, enrolled 16, and treated 15 (Subjects 3504[(b) (6)] and [(b) (6)] were screen failures and Subject 3504-[(b) (6)] withdrew consent.) There were no significant discrepancies between the source documents and the data line listings. At the time of inspection, six subjects had died (Subject 3504-[(b) (6)]) and five were still on treatment (Subjects 3504-[(b) (6)]). All other subjects were off treatment but in follow up, except Subject 3504-[(b) (6)], who withdrew consent for follow up.

The source documents for the 18 screened subjects were reviewed and compared to the subject data line listings. The reviewed subject records included medical records, including progress notes, imaging records, and laboratory evaluations, informed consent, eligibility criteria, investigational product administration records, concomitant medications, adverse events, SAEs, and protocol deviations. Study records were also reviewed including Non-US Investigator Information Form, financial disclosure forms, delegation of authority log, training log, monitoring site visit logs, IEC approvals, investigational test article accountability records, and the site protocol with amendments.

The source documentation the primary efficacy endpoint of overall survival (OS) was compared to the data listings and there were no discrepancies. The source data for the key secondary endpoints using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) were compared to the data listings and there were no significant discrepancies. No unreported adverse events or protocol deviations were identified. No significant regulatory violations.

3. **Dr. Sophie Piperno-Neumann (site 6101)**
Institut Curie Département d'oncologie
Médicale26 Rue d'Ulm
Paris, 75005
FRANCE

Inspection dates: September 13-17, 2021

This investigator was inspected as an onsite surveillance inspection for Study IMCgp100-202. This was the first FDA inspection for this investigator.

At the time of the data cutoff, 34 subjects screened, 28 were enrolled into the study. At the time of inspection, two subjects were still in the study. Subject 6101-[(b) (6)] is still receiving treatment with the study medication and subject 6101-[(b) (6)] is off treatment but still in the follow-up portion of the study. Two subjects had withdrawn consent, Subject 6101-[(b) (6)] withdrew consent prior to receiving the study drug and Subject 610-[(b) (6)] withdrew from the study after progressing. All other subjects either died while on treatment or after having progressed. There were no significant discrepancies between the source documents and the data line listings.

The source documents for the 28 enrolled subjects were reviewed and compared to the subject data line listings. The reviewed subject records included medical records, including physician

notes, laboratory results, pathology results, and imaging records, informed consent, concomitant medications, adverse events, SAEs, and protocol deviations. Study records were also reviewed including Form FDA 1572s, financial disclosures, delegation of authority log, site monitoring log and records, IEC approvals, investigational test article accountability records, site protocol with amendments, and the electronic data capture system.

The source documentation for the primary and secondary endpoints were reviewed for all 28 enrolled subjects. The survival documentation for the primary endpoint of overall survival (OS) was compared to the data listings and there were no discrepancies. The imaging source data (measurements and interpretations from the local radiologist on the radiology reports and from the study radiologist using RECIST criteria) were compared to the data listings and found no discrepancies. No unreported adverse events or protocol deviations were identified.

4. **Dr. Piotr Rutkowski (Site 6401)**
Centrum Onkologii - Instytut im. Marii
Sklodowskiej-Curie, W. K. Roentgena 5
Warszawa, 02-781
POLAND

Inspection dates: September 20-24, 2021

This investigator was inspected as an onsite surveillance inspection for Study IMCgp100-202. This investigator had a previous FDA inspection with a regulatory finding of voluntary action indicated (VAI) for failure to follow the protocol, namely, out of window ECG testing and failure to report concomitant medications correctly.

At the time of the data cutoff, there were 28 subjects screened, 21 were randomized, and 20 were treated; one subject transferred to another site in Ukraine (Subject 6401-(b) (6)).
One subject withdrew consent (Subject 6401-(b) (6)), one subject withdrew consent after a serious adverse event (Subject 6401-(b) (6)), and one subject early terminated due to an adverse event (subject (b) (6)), five subjects discontinued due to disease progression (Subjects 6401-(b) (6)), one subject discontinued due to death (Subject 6401-(b) (6)), and 11 subjects were treated beyond progression. There were no significant discrepancies between the source documents and the data line listings.

The source documents for the primary and key secondary endpoints for the 28 enrolled subjects were reviewed and compared to the subject data line listings. The reviewed subject records included medical records, including physician notes, laboratory results, pathology results, and imaging records, informed consent, concomitant medications, adverse events, SAEs, and protocol deviations. Study records were also reviewed including Form FDA 1572s, financial disclosures, delegation of authority log, site monitoring log and records, IEC approvals, investigational test article accountability records, and the site protocol with amendments.

The primary endpoint data (overall survival dates) and key secondary endpoint data (progression free survival date and best overall response) for all 21 randomized subjects were

reviewed and compare to the data listings. There were five subjects who had data discrepancies for the primary and secondary endpoint, as shown in the following Table 1:

Table 1: Endpoint data discrepancies Site 6401

Subject	Arm	Parameter	Date of Parameter according to submitted line listing	Date of Parameter in source record	Endpoint change
6401-(b) (6)	Pembrolizumab	OS	(b) (6)	(b) (6)	OS ↓46 days
6401-	IMCgp100	PFS	(b) (6)	(b) (6)	PFS ↑ 177 days
6401-	IMCgp100	PFS	(b) (6)	(b) (6)	PFS ↑ 182 days; BOR changed from PD to SD
		BOR			
6401-	IMCgp100	PFS	(b) (6)	(b) (6)	PFS ↑ 85 days
6401-	IMCgp100	PFS and BOR	(b) (6)	Non-evaluable for all timepoints	PFS (2.79 months) and BOR (PD) changed to Not evaluable

Reviewer's Comments:
Changes were made to the electronic database after the data cutoff date/ database lock due to a delay in monitoring, mostly due to Covid-19 restrictions. There were extenuating circumstances specific to Site 6401, which led to a back log of data monitoring ("cleaning") at the site. Specifically, some of the monitoring was done remotely as access to the hospital was restricted due to Covid-19 hospital policies. Additionally, three data managers at the site were prevented from entering data at the site (one was a contractor, and for a time was not allowed on site because he was not a hospital employee, one data manager was on maternity leave, and one was on extended sick leave due to Covid), which led to difficulty conducting remote monitoring. Furthermore, in June 2020, when the monitors were allowed back onsite, they were only allowed so in a limited capacity; therefore, there was, a backlog of data to monitor. Monitoring visits that occurred since the database lock have reviewed the source data and resulted in changes to the electronic database for data already turned into the FDA for review.

The updated survival data for Subject 6401-(b) (6) (pembrolizumab) would have made favored tebentafusp arm and the decrease is by less than 6 weeks. The updated PFS and BOR for Subjects 6401-(b) (6) appear to also favor the study drug, so neither update would likely impact the risk-benefit for the study drug. The sponsor inspection did not find a wide-spread problem of delays in data entry due to Covid and the delays at this site seem to have been exacerbated by site-specific personnel issues (personnel being unavailable).

An information request was sent to the sponsor inquiring the extent of changes to the EDC at other sites, and an accounting of these changes. The Sponsor responded on 11/19/2012 that there were delays in monitoring due to the Covid-19 pandemic. The Sponsor referenced September 3, 2020 meeting minutes, written response, question 39, (See attached) where they propose a tiered approach to data monitoring due to the impact of Covid-19. The FDA does not provide agreement but does reiterate that there is not "a requirement for 100% source data verification, however, the data necessary to assess safety and efficacy and inform product labeling should be accurate and reliable and submitted in the original BLA (and not post-marketing)." The Sponsor states they took a tiered approach to data cleaning prioritizing OS, demographics, dosing, adverse events, SAEs, safety laboratory values, and subsequent treatment.

There were 4 additional subjects across four sites with updates to either PFS or BOR made after the data lock according to the sponsor, as shown in the following Table 2:

Table 2: Endpoint data discrepancies at Other Sites (from IR response 11/22/2021)

Subject	Arm	Parameter	Date of Parameter according to submitted line listing	Date of Parameter in source record	Endpoint change
(b) (6)	Pembrolizumab	PFS	Censored (b) (6) (b) (6)	(b) (6)	PFS confirmed (b) (6)
	IMCgp100	PFS	(b) (6)	(b) (6)	PFS ↑ 30 days
	IMCgp100	BOR	Censored (SD)	(b) (6) (PD)	BOR confirmed (b) (6)
		PFS	(b) (6)	(b) (6)	PFS ↓ 84 days
	IMCgp100	BOR	(b) (6) (SD)	(b) (6) (PR)	BOR increase

Reviewer's Comments: According to the Sponsor, it appears that there are no other discrepancies with the primary endpoint of OS. The inspections at the 3 other inspected sites did not reveal changes to the primary endpoint (OS) made after the data cutoff. There were 4 subjects across 4 sites with changes that both increase and decrease the PFS for they study drug. The changes do not appear widespread or impactful to the efficacy of the study drug. They were all due to delays in data monitoring/ data cleaning due to the Covid-19 pandemic.

Additionally, there were discrepancies between the source data and the data listings for adverse events (AEs) and protocol deviations (PDs) at site 6401. It appears there were again changes

to the EDC after the data cutoff/ database lock. The Sponsor was sent an information request at on 11/19/2021, inquiring the extent of changes to the EDC at site 6401 and other sites, and an accounting of these changes.

Reviewer's Comments: The request is pending at the time of this report, but will be addended as necessary.

5. Immunocore, LLC (Sponsor)
Six Tower Bridge, Suite 200
181 Washington Street
Conshohocken, PA 19428

Inspection dates: October 4-8 and October 12 – 7, 2020.

(b) (4) was inspected as a surveillance inspection for Study IMCgp100-202. This is the first FDA inspection for the firm.

Records reviewed included organizational charts, standard operating procedures (SOPs), master service agreements (MSAs), vendor oversight plans, vendor transfer of regulatory obligation (TORO) agreements, clinicaltrials.gov study submissions, vendor meeting minutes and reports, independent data monitoring committee (IDMC) charter, pharmacovigilance (PV) plans, monitoring plan, safety plan, monitor visit reports, sponsor/monitor/investigator correspondence, monitor/investigator training records, financial disclosure forms, serious adverse events, 7/15 day report submissions, clinical supply chain agreement, and test article distribution records and certificates of analysis

Monitoring responsibility was transferred to (b) (4) and the TORO was reviewed. There were delays in monitoring due to Covid, however, the sponsor/monitor developed a Standard Operating Procedure for this and it was followed. There did not appear to be widespread delays in data entry due to Covid.

The sponsor appeared to follow their SOPs and had control of the conduct of the study.

{See appended electronic signature page}

Michele Fedowitz, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Karen Bleich, M.D.
Team Leader
Good Clinical Practice Assessment Branch
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CONCURRENCE: {See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

cc:

Review Division /Division Director/Steve Lemery, MD
Review Division /Project Manager/ Nataliya Fesenko
Review Division/Cross Discipline Team Lead/Jamie Brewer, MD
Review Division/Clinical Reviewer/ Margaret Thompson, MD
OSI/Office Director/Dave Burrow
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

ATTACHMENT September 3, 2020 meeting minutes, written response, question 39

IND 114314

MEETING REQUEST-
WRITTEN RESPONSES

Immunocore LLC
Attention: Sheetal Thakur, Ph.D., R.A.C.
Associate Director, Regulatory Affairs
Six Tower Bridge, 181 Washington Street, Suite 540
Conshohocken, PA 19428

Dear Dr. Thakur:[1]

Please refer to your pre-investigational new drug application (PIND) file for tebentafusp (IMCgp100).

We also refer to your submission dated July 6, 2020, containing a meeting request. The purpose of the requested meeting was to seek Agency feedback on the proposed structure and content of the planned BLA submission based on Clinical Study IMCgp100-102 and IMCgp100-202.

Further reference is made to our Meeting Granted letter dated July 10, 2020, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your August 3, 2020 background package.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call me at (240) 402-6376.

Sincerely,

{See appended electronic signature page}

Nataliya Fesenko, Pharm.D.
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO3
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

WRITTEN RESPONSES

Meeting Type:	Type C
Meeting Category:	Guidance
Application Number:	IND 114314
Product Name:	Tebentafusp (IMCgp100)
Indication:	Treatment of advanced uveal melanoma in HLA_A*02:01-positive patients
Sponsor Name:	Immunocore LLC (Immunocore)
Regulatory Pathway:	351(a) of the Public Health Service Act

BACKGROUND

On July 6, 2020, Immunocore requested a Type C meeting seeking Agency feedback on the proposed structure and content of a planned BLA submission based on Clinical Studies IMCgp100-102 and IMCgp100-202.

Regulatory

- January 21, 2016, FDA granted orphan drug designation to IMCgp100 for the treatment of uveal melanoma.
- October 12, 2018, a Type B meeting was held to discuss Agency feedback on the overall approach to support a potential regulatory submission seeking accelerated approval of IMCgp100 in patients with uveal melanoma based on the results of Study IMCgp100-102.
- April 01, 2019, FDA granted fast track designation for IMCgp100 for first-line treatment of metastatic uveal melanoma.
- March 3, 2020, a teleconference was held to discuss the clinical development plan of IMCgp100 for the treatment of patients with uveal melanoma.

Nonclinical

Tebentafusp is a bispecific fusion protein consisting of a soluble T cell receptor (TCR) targeting antigen gp100 fused to an antibody single-chain variable fragment (scFv) targeting CD3. Gp100 is a membrane-associated glycoprotein expressed on normal melanocytes and tumors derived from melanocytes. Immunocore states that once the

soluble TCR is engaged, the scFv effector can bind to CD3 on any T cell, redirecting the T cell to produce effector cytokines and/or kill the cell presenting the target peptide.

Nonclinical pharmacology data indicate that there is no relevant animal species in which to study tebentafusp. Immunocore describes extensive in vitro analyses that have been performed to characterize its pharmacologic activity including in vitro functional assays, T-cell activation and cytotoxicity assays, cytokine release assays, activity against uveal and cutaneous melanoma cell lines, epitope requirement studies, and off-target tissue cross-reactivity studies.

Clinical

Immunocore is proposing to submit a BLA for regular approval of IMCgp100 (tebentafusp) for the treatment of advanced uveal melanoma in HLA_A*02:01-positive patients. The main evaluation of efficacy and safety will be based on data from the prespecified interim analysis of Study IMCgp100-202 and the supportive final analysis of Study IMCgp100-102.

Study IMCgp100-102 is an open-label, single-arm, multi-center, dose finding with dose expansion study of IMCgp100 as a single agent in adult patients with metastatic uveal melanoma (mUM) in the second or third-line setting who received up to one prior liver-directed therapy regimen. The primary endpoint of the dose expansion portion of the study is confirmed objective response rate (ORR) based on RECIST v.1.1 as assessed by independent central review. The main secondary efficacy endpoints include overall survival (OS), progression free survival (PFS), disease control rate (DCR), time to response, and duration of response (DOR).

The study was closed to accrual February 2019 with 127 patients with mUM enrolled and treated in the expansion portion of the trial. As of data cutoff, all 127 patients had been followed for at least 12 months. The investigator-reported and independently-reviewed ORRs were 7.1% [9 partial responses (PR)] and 4.7% (6 PR), respectively. There were no complete responses (CR). The 1-year OS rate for UM in the study was 62%. The median DOR in the 6 patients who achieved PR was 8.7 months (95% CI: 5.6, 24.5).

In the 146 patients enrolled on IMCgp100-102 who received at least one dose of study drug, 100% had at least one treatment emergent adverse event (TEAE) with 63% having at least one Grade 3/4 TEAE and 36% having at least one serious TEAE. There were no deaths due to a TEAE. Six percent (6%) of patients had a TEAE that led to study drug discontinuation. The most frequently reported TEAEs (≥40%) were pyrexia (83%), pruritis (71%), nausea (70%), chills (67%), fatigue (65%), hypotension (46%), dry skin (44%), vomiting (43%), and peripheral edema (40%). The most common ≥ Grade 3 TEAEs (≥ 5%) were maculo-papular rash (11%), hypotension (9%), fatigue (5%), and pyrexia (5%).

Study IMCgp100-202 is a randomized, open-label, multi-center study of IMCgp100 compared to investigator's choice therapy (dacarbazine, ipilimumab, or pembrolizumab) in HLA A*201-positive patients with previously untreated advanced uveal melanoma. As of June 18, 2020, accrual is complete with 378 patients randomized and treated (253 received tebentafusp). Patients were randomly allocated in a 2:1 ratio to IMCgp100 vs. investigator's choice therapy with stratification based on LDH status. The primary endpoints are a) OS in patients randomized to IMCgp100 monotherapy as compared to patients randomized to investigator's choice monotherapy and b) OS in patients randomized to receive IMCgp100 monotherapy who develop rash within the first week of treatment as compared to OS for all patients randomized to investigator's choice arm. Secondary efficacy endpoints are ORR, PFS, DOR, time to response, and disease control rate (DCR) using RECIST v1.1. Radiologic assessments are performed every 12 weeks.

The 2-sided alpha of 0.05 is split into 0.045 for testing OS in the all randomized population and 0.005 for testing OS in the rash analysis population (RAS), with a fallback procedure.

Per the briefing package, in the all randomized population, assuming a 2:1 randomization ratio, 250 events (deaths) are needed to provide 80% power to detect a 0.645 hazard ratio (HR) for OS with a 2-sided significance level of 0.045. Immunocore states that assuming OS is exponentially distributed, this may translate to a median OS of 18.6 months in the tebentafusp treated arm and 12 months in the investigator's choice arm. In the RAS, assuming 50% of the patients treated with IMCgp100 develop a rash within the first week of treatment, 164 events are required to provide 89% power to detect an OS hazard ratio of 0.531 based on a 2-sided stratified log-rank test at the 0.005 significance level.

Two interim analyses are planned in this study; the first interim analysis will be based on approximately 60% of the events (150 events), and the second interim analysis will be based on approximately 80% of the events (200 events). At each interim analysis, the analysis of the RAS will be performed first, and depending on the significance of OS in the RAS, the alpha will be propagated to the analysis of OS in the all randomized population. The stopping boundaries, based on the O'Brien Fleming method, for the interim analyses in both analysis populations are provided in the Table below.

Analysis Set (allocated alpha)	Analysis Number	OS Events (IF)	Lower Z-Boundary	Upper Z-boundary	Nominal Alpha (2-sided)	Cumlative Alpha
RAS (α_{RAS}=0.005)	First Interim	99 (60%)	-3.732	3.732	0.0002	<0.001
	Second Interim	131 (80%)	-3.198	3.198	0.0014	0.001
	Final	164 (100%)	-2.838	2.838	0.0045	0.005
ITT	First Interim	150	-2.724	2.724	0.006	0.006
(α_{ITT}=0.045)		(60%)				
	Second Interim	200 (80%)	-2.336	2.336	0.019	0.021
	Final	250 (100%)	-2.073	2.073	0.038	0.045
ITT (α_{ITT}=0.05)	First Interim	150 (60%)	-2.669	2.669	0.008	0.008
	Second Interim	200 (80%)	-2.289	2.289	0.022	0.024
	Final	250 (100%)	-2.031	2.031	0.042	0.050

Note: The timing of the interim analysis will be driven by the number of events in the ITT population. Separate analyses will be carried out for each of the two primary objectives that will occur at the same time.

No efficacy results are available from Study IMCgp100-202 to date. The topline results of the first interim analysis are expected in October 2020. Final analysis of the primary endpoint of OS is projected for 2H2022.

Immunocore is proposing a rolling BLA submission broken into 2 submissions. The first submission would comprise CMC Module 3, Preclinical Module 4, and corresponding Module 2 Summaries. The second submission would comprise Clinical Module 5, all remaining summaries for Modules 1 and 2, and all SDTM and ADaM datasets, etc.

SPONSOR QUESTIONS AND FDA RESPONSES

Chemistry Manufacturing and Controls

1. Does the FDA agree that the proposed panel of tests are appropriate to control the Drug Substance and Drug Product?

   FDA Response: The proposed panel of tests presented in Table 6 appears reasonable to control IMCgp100 drug substance (DS) and drug product (DP). A final determination regarding the suitability of the proposed panel of tests will be a review issue based on the totality of information and data presented in the BLA (e.g., method validation reports and characterization of IMCgp100 critical quality attributes).

2. At the time of filing the BLA, stability data will be presented on three commercial scale, process validation batches (Drug Substance and Drug Product). Supportive stability data on two representative GMP batches and three non-GMP

(b) (4)

- Microbiological studies in support of the post-dilution storage conditions. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, bracket the drug product concentrations that would be administered to patients, and use the label-recommended diluents. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> *Antimicrobial Effectiveness Testing*, plus typical skin flora or species associated with hospital-borne infections. *In lieu* of this data, the product labeling should recommend that the post-dilution storage period is not more than 4 hours.

Additional Question

39. Taking into consideration the COVID-19 impact on clinical trials, does the FDA agree with adequacy of proposed prioritization of source data cleaning for Study IMCgp100-202 to support approval? If needed, additional data will be provided as a post-marketing commitment/requirement as an addendum to the study report.

FDA response: Based on the information provided and lack of high-level efficacy and safety data, FDA cannot provide agreement with the proposal at this time; however, consider the following high-level principles that may help facilitate the submission of the proposed BLA:

- Data necessary to assess safety and efficacy and inform product labeling should be accurate and reliable and submitted in the original BLA (and not post-marketing). This may include data identified by Immunocore as being lower priority.

- FDA does not have a requirement for 100% source data verification; however, it is the applicant's responsibility to submit accurate and reliable data. FDA regulation requires that sponsors are responsible for ensuring proper monitoring of investigations (21 CFR 312.50). Various approaches, including risk-based approaches, may be taken towards this aim.

- In the case of modifications to the initial monitoring plan necessitated by COVID-19, provide a description of the changes, justification for the changes, and impact of the changes in the appropriate section of the Clinical Study Report.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MICHELE B FEDOWITZ
11/23/2021 10:36:13 AM

KAREN B BLEICH
11/23/2021 12:11:29 PM

KASSA AYALEW
11/23/2021 12:31:54 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 17, 2021
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761228
Product Name and Strength:	Kimmtrak (tebentafusp-tebn[a]) injection, 100 mcg/0.5 mL
Applicant/Sponsor Name:	Immunocore Ltd. (Immunocore)
OSE RCM #:	2021-500-1
DMEPA 2 Safety Evaluator:	Sarah Thomas, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on October 26, 2021 and November 3, 2021 for Kimmtrak. The Division of Oncology 3 (DO3) requested that we review the revised container label and carton labeling for Kimmtrak (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

The Applicant implemented all of our recommendations, and the revised container label is acceptable from a medication error perspective at this time. However, we have a few remaining recommendations for the carton labeling to improve safe use of the product as described below in Section 3.

[a] The proposed nonproprietary name (tebentafusp-tebn) is only conditionally accepted for this product until the application is approved; see Mena-Grillasca, M. Suffix Review for Nonproprietary Name for Kimmtrak (BLA 761228). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 May 5. Nexus NPNS ID #: 2021-22.
[b] Thomas, S. Label and Labeling Review for Kimmtrak (BLA 761228). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 OCT 6. RCM No.: 2021-500.

3 RECOMMENDATIONS FOR IMMUNOCORE LTD. (IMMUNOCORE)

We recommend the following be implemented prior to approval of this BLA:

A. Carton Labeling

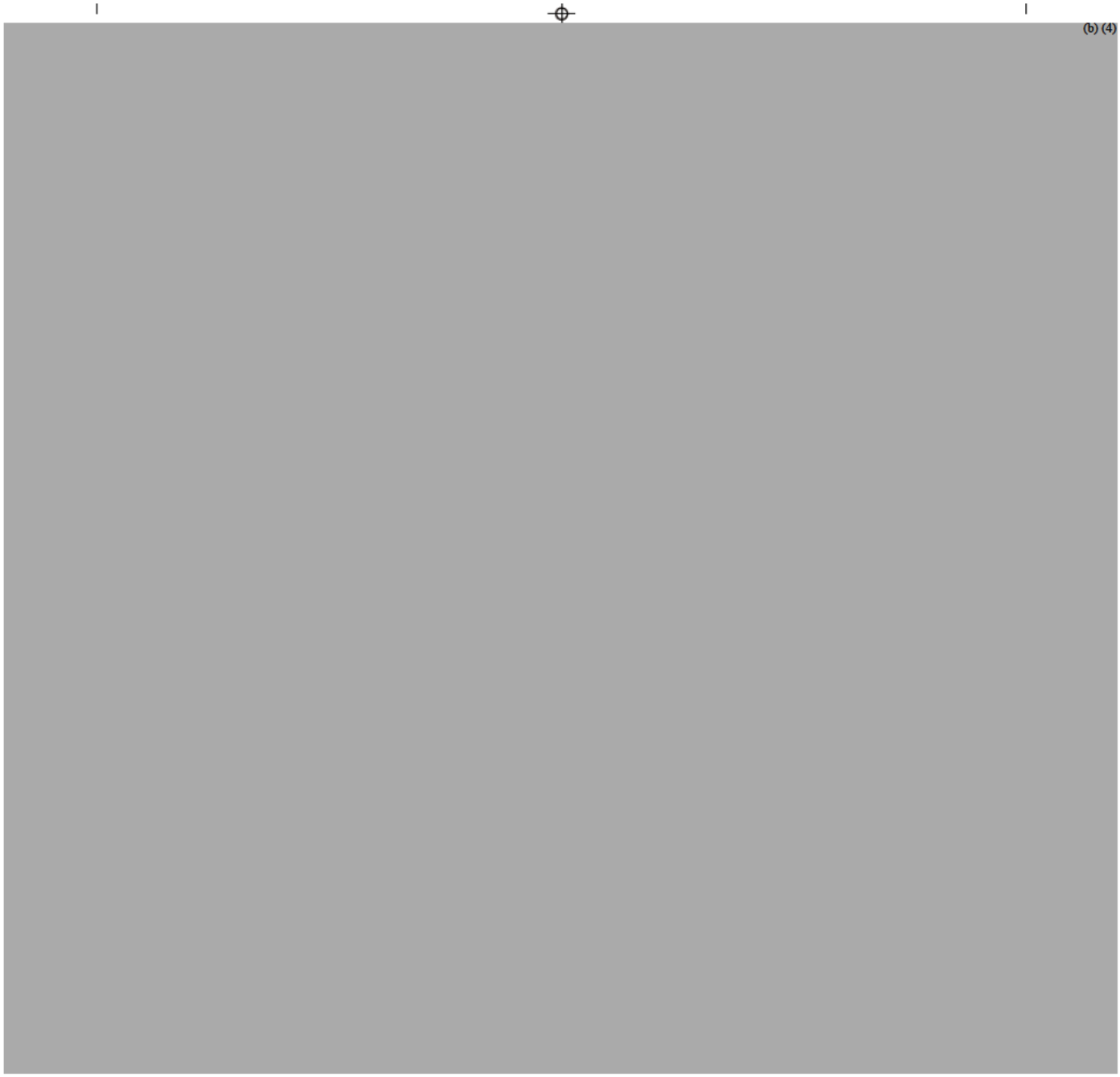
a. We recommend adding a space between "0.9%" and "Sodium" in the following statement on the side panel of the sample and commercial carton labeling: "Must be diluted before use in a prepared Albumin (Human) in 0.9%_Sodium Chloride Injection, USP solution."

b. Clarify why there are 2 sets of human-readable product identifiers provided on the sample and commercial carton labeling near the 2D data matrix barcode (please see below). In order to prevent confusion, we recommend only providing one set of human-readable product identifiers.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 26, 2021 AND NOVEMBER 3, 2021

Container label

Carton labeling



Sample Carton Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SARAH E THOMAS
11/17/2021 10:52:30 AM

ASHLEIGH V LOWERY
11/17/2021 03:25:01 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 6, 2021
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761228
Product Name, Dosage Form, and Strength:	Kimmtrak (tebentafusp-tebn[a]) injection, 100 mcg/0.5 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Immunocore Ltd. (Immunocore)
FDA Received Date:	June 23, 2021
OSE RCM #:	2021-500
DMEPA 2 Safety Evaluator:	Sarah Thomas, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

[a] The proposed nonproprietary name (tebentafusp-tebn) is only conditionally accepted for this product until the application is approved; see Mena-Grillasca, M. Suffix Review for Nonproprietary Name for Kimmtrak (BLA 761228). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 May 5. Nexus NPNS ID #: 2021-22.

1 REASON FOR REVIEW

As part of the approval process for Kimmtrak (tebentafusp-tebn) injection, the Division of Oncology 3 (DO3) requested in their September 3, 2021 consult that we review the proposed Kimmtrak prescribing information (PI), patient information, container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Label and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Upon review of the PI Dosage and Administration section 2.4 "Preparation and Administration", we had several questions for Immunocore regarding the preparation and administration instructions for the proposed tebentafusp product. Our preliminary questions were communicated to Immunocore, and then Immunocore emailed their responses to our preliminary questions back prior to the teleconference held on June 1, 2021 (please see Appendix F for full list of questions and preliminary responses from Immunocore). We received further clarification on our questions and Immunocore's preliminary responses at the teleconference.

We asked the following questions related to the proposed supplies required for preparation of tebentafusp:

1. Is there a recommended concentration of Albumin (Human) to be used for compounding the 100 mL infusion bag containing 0.9% Sodium Chloride Injection, USP plus Albumin (Human)?

2. Are the 1 mL sterile syringes with graduations of 2 decimal places required for the preparation of the proposed product readily available in the proposed settings of use (e.g., hospital pharmacies)? Are end-users able to accurately measure the amounts of albumin and tebentafusp required for preparing the proposed product with the 1 mL sterile syringes with graduations of 2 decimal places?

Immunocore responded that they do not recommend use of a specific concentration of Albumin (Human) for compounding. In the tebentafusp clinical trials, Immunocore reports that 5% Albumin (Human) was required for use, and the volumes for dose preparation were provided in study pharmacy manuals. Immunocore reports that the required 1 mL sterile syringes with graduations of 2 decimal places are readily available at local administration sites and are the standard syringes used for withdrawal of small volumes. In addition, Immunocore reports that throughout the tebentafusp clinical trials, end-users have been able to accurately measure the amounts of tebentafusp using 1 mL syringes with no issues reported.

Another important area of the preparation instructions that we clarified with Immunocore dealt with the first step of the dilution process, which involved preparation of the Albumin (Human) in 0.9% Sodium Chloride Injection, USP solution. We asked the following key questions related to this step:

1. How was the proposed volume or mcg amount of Albumin (Human) calculated in the clinical trials for tebentafusp? Is there a calculation equation that can be added to the prescribing information to assist end-users with calculating the volume or mcg amount of Albumin (Human)?
2. Why is a final intended concentration (b) (4)

Immunocore clarified that the first step of the dilution process involving preparation of the Albumin (Human) in 0.9% Sodium Chloride Injection, USP solution is necessary because albumin protects against adsorption of tebentafusp to the infusion bag. Immunocore reported that in the tebentafusp clinical trials, the Albumin (Human) volumes for dose preparation were provided in study pharmacy manuals, and there were no additional calculations to be carried out at the trial sites. Immunocore also stated that the target concentration of Albumin (Human) in the infusion bag should be approximately 250 mcg/mL (b) (4) In order to provide clarification in the labeling, Immunocore proposed to add a table displaying available concentrations of Albumin (Human) and their corresponding volume amounts for compounding of the Albumin (Human) in 0.9% Sodium Chloride Injection, USP solution, with or without an equation:

[redacted] we think that end-users will be able to measure the Albumin (Human) volumes needed to compound the target 250 mcg/mL Albumin (Human) in 0.9% Sodium Chloride Injection, USP solution concentration with a 1 mL syringe with graduations of 2 decimal places using the example Albumin (Human) concentrations of 5%, 20%, and 25%. Therefore, we add a recommendation below in Section 4.1 to revise the proposed table in the labeling [redacted] the required volume amounts of 5%, 20%, and 25% Albumin (Human) needed to compound a targeted concentration of 250 mcg/mL Albumin (Human) in 0.9% Sodium Chloride Injection, USP solution, [redacted]. This will help to [redacted] improve readability of the proposed table in the prescribing information.

We also noted confusing homogenization instructions provided in step 1b of the instructions, as well as unusual instructions to "[redacted] to ensure that any residual solution is released into the bulk solution." Immunocore reports that the homogenization process was developed throughout the clinical trials to ensure homogenous mixing of small transfer volumes of albumin and tebentafusp in the compounding process. We provide recommendations in Section 4.1 to revise the homogenization instructions for clarity. With regard to the unusual instructions to [redacted], we communicated to Immunocore that [redacted] We asked Immunocore if [redacted] to release residual solution into the bulk solution is necessary and unique for the preparation of the proposed product. Immunocore responded that tapping of the port tubing is important to ensure complete administration and homogenous mixing of the drug solution and that tapping of the port on the side of the tubing does not violate aseptic technique protocol. Immunocore proposed to edit the current text in the proposed prescribing information [redacted]. We find this proposal reasonable.

[redacted]

(b) (4)

Additionally, we clarified with Immunocore about the proposed 4-hour window for storage of the compounded tebentafusp infusion bag at room temperature and if this window includes the proposed 15-20 minutes infusion time. Immunocore responded that the 4-hour window includes the 15 to 20 minutes infusion time and that they will update the prescribing information accordingly. We find this proposal reasonable.

Last, upon review of the carton labeling, we noted that Immunocore submitted sample carton labeling with "NOT FOR SALE" provided on the principal display panel but no corresponding sample vial container label. We communicated an information request to Immunocore on June 25, 2021 confirming that they are proposing a professional sample product, and if so, encouraging them to submit an image of the professional sample container label. Immunocore responded on June 30, 2021 that they propose to use the same vial container label for both the commercial product and the professional sample product, as the proposed vial container label does not have sufficient space to enable addition of the "NOT FOR SALE" text. While we prefer for the sample container label to also be labeled as "sample" or "NOT FOR SALE", we understand the space limitations on the label. We do not have a medication safety concern with Immunocore's proposal to use the same container label for both the commercial and sample products.

Upon review of the proposed container label, carton labeling, patient information, and PI, we note areas of the label and labeling that could be improved to promote the safe use of this product. Thus, we provide related recommendations for the label and labeling in Section 4 below.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container label, carton labeling, patient information, and PI may be improved to promote the safe use of the product as described in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 3 (DO3)

A. Prescribing Information and Patient Information

1. General Recommendations

a. We note the use of "BRAND" in the PI and Patient Information instead of the conditionally acceptable proprietary name, Kimmtrak. We recommend replacing "BRAND" placeholder with the conditionally acceptable proprietary name, Kimmtrak, throughout the labeling.

b. We note the nonproprietary name description "tebentafusp" is missing the conditionally acceptable suffix "-tebn" in some locations within the PI and Patient Information. Revise the nonproprietary name description from "tebentafusp" to "tebentafusp-tebn" throughout the labeling.

B. Prescribing Information

1. General Recommendations

a. We note that the storage instructions for the diluted product provided in Sections 2 and 16 are not consistent and can be revised to improve clarity (please see below). We recommend revising the instructions as follows:

Section 2 instructions:

"The prepared infusion bag should be administered within 4 hours from the time of preparation including the duration of infusion. During the 4-hour window, the BRAND infusion bag should remain at room temperature."

"If not used immediately, store the BRAND infusion bag in a refrigerator at 2°C to 8°C (36°F to 46°F) (b) (4) and infuse within 24 hours from the time of preparation, which includes the storage time in the refrigerator, the time allowed for equilibration of the infusion bag to room temperature, and the duration of the infusion."

Section 16 instructions:

(b) (4)

2. Dosage and Administration Section, Highlights

a. We recommend adding the route of administration to the first bullet under the Dosage and Administration Section in the Highlights, as follows:
"(b) (4) 20 mcg intravenously on Day 1, 30 mcg intravenously on Day 8, 68 mcg intravenously on Day 15, and 68 mcg intravenously once every week thereafter (2.2)."

b. We recommend adding the following statement after the last bullet under the Dosage and Administration Section in the Highlights to alert end-users to additional dosing information for adverse reactions in the full PI: "Dosage modification is recommended in patients experiencing certain adverse reactions (b) (4)."

c. We recommend revising the third bullet under the Dosage and Administration Section in the Highlights to the following:
"See Full Prescribing Information for instructions on preparation and administration of the diluted solution for intravenous infusion (2.2, 2.4)"

3. Dosage and Administration Section, full PI

   a. We recommend adding the route of administration to the first sentence under the Dosage and Administration Section 2.2, as follows:
   "The recommended dose of BRAND is 20 mcg intravenously on Day 1, 30 mcg intravenously on Day 8, 68 mcg intravenously on Day 15, and 68 mcg intravenously once every week thereafter."

   b. We note error-prone abbreviations and symbols and undefined abbreviations in Section 2 of the full PI.[b] We recommend defining the CRS (b) (4) abbreviations as specified below. We also recommend replacing the > and < symbols and "IV" abbreviation with their meanings under Sections 2.2 (b) (4), as well as in the Management columns (b) (4) to prevent misinterpretation and confusion, as follows:

      - Section 2.2 Recommended Dosage: (b) (4)
      - (b) (4)
      - (b) (4)

[b] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2021 JULY 8]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

c. We recommend revising the following statements to specify using aseptic technique to compound intravenous infusion solutions, as follows:

- "Use aseptic technique for dilution and preparation of (b) (4) intravenous infusion solutions."

d. We recommend adding the route of administration to the following bullet under Section 2.4:

- (b) (4)

e. Consider adding the rationale for the first step of the dilution process involving preparation of the albumin/NS solution (e.g., to prevent adsorption of tebentafusp to the infusion bag and other components of the drug delivery system), as follows:

"Step 1- (b) (4) to prevent adsorption of tebentafusp to the infusion bag and other components of the drug delivery system, prepare an Albumin (Human) in 0.9% Sodium Chloride Injection, USP solution (b) (4) as follows:"

f. We recommend revising the description in Step 1 a. and Table 1 as shown below (b) (4) the target volume of Albumin (Human) required for each Albumin (Human) concentration to add to the 100 mL 0.9% Sodium Chloride Injection, USP bag to make a final target Albumin (Human) concentration of 250 mcg/mL, as we think the end-user will be able to accurately measure the required volumes of 0.5 mL, 0.13 mL, and 0.1 mL provided in the table with the intended 1 mL syringes with graduations of 2 decimal places. (b) (4)

a. Using a 1 mL syringe and a sterile needle, withdraw the calculated volume of Albumin (Human) into the syringe (see Table 1 below) and add to the 100 mL 0.9% Sodium Chloride Injection, USP bag to make a final Albumin (Human) concentration of 250 mcg/mL

Table 1: Examples of Albumin (Human) Concentrations and Volumes

Albumin (Human) concentration	Albumin (Human) volume for addition to a 100 mL 0.9% Sodium Chloride Injection, USP Infusion Bag to prepare a concentration of 250 mcg/mL Albumin (Human) in 0.9% Sodium Chloride Injection, USP
5% (50 g/L)	0.5 mL
20% (200 g/L)	0.13 mL
25% (250 g/L)	0.1 mL

g. We recommend revising the homogenization instructions used to describe mixing the Albumin (Human) in the bag of 0.9% Sodium Chloride Injection, USP and then the tebentafusp in the Albumin (Human) in 0.9% Sodium Chloride Injection, USP solution to improve clarity and consider providing corresponding illustrations, as the language as currently written does not provide clear direction to the end-user on how to mix the infusion bag.

    i. Consider revising the instructions such as:
    "b. Gently homogenize the prepared solution by completing the following steps:

        i. Invert the infusion bag so that the bag is upside down with the entry port positioned on top. Then tap the side of the port tubing to ensure that any residual solution is released into the bulk solution.

        ii. Next, mix the prepared solution by gently rotating the bag lengthwise (b) (4) degrees from the inverted position at least 5 times. Do not shake the infusion bag.

        iii. Repeat (i) and (ii) an additional three times."

h. We note the following warning provided in Step 2 of the dilution instructions: (b) (4) thus, we recommend removing this warning from the prescribing information.

i. We recommend revising the instructions provided in the first bullet under the Administration instructions to the following, in order to clearly specify that the prepared diluted solution should be administered by intravenous infusion: "Immediately administer the diluted solution via intravenous infusion over 15-20 minutes through a dedicated intravenous line…".

j. Under the Administration instructions, consider removing the statement, (b) (4) We recommend this revision due to (b) (4)

k. [redacted]

4. How Supplied/Storage and Handling Section, full PI

   a. We note the side panel of the carton labeling states the following: "The vial stopper is not made with natural rubber latex." We note this statement is missing in the PI. We defer to OPQ on determining the accuracy of the statement, and if accurate, consider adding the statement to Section 16 as well.[d]

   b. We recommend replacing the word "[redacted]" with "carton" in the description under Section 16.1 and the first bullet under Section 16.2, in order to more appropriately describe the outer packaging for the vial, as follows:

      -Section 16.1: "Each BRAND (tebentafusp) injection carton [redacted] (NDC 80446-401-01) contains:"

      -Section 16.2:

      - "Store BRAND vials in the original carton [redacted] refrigerated at 2°C to 8°C (36°F to 46°F) and protect from light until time of use. Do not freeze. Do not shake."

C. Patient Information

1. We recommend revising the instructions regarding pregnancy and breastfeeding for clarity, as follows:

   "For ~~F~~females who are able to become pregnant:

   - Your healthcare provider ~~should do~~ will administer a pregnancy test before you start treatment with BRAND.
   - [redacted] Use effective birth control during your treatment and for at least 1 week after the last dose of [redacted] BRAND."

   For females who are breastfeeding or plan to breastfeed:

[c] Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

[d] Guidance for Industry and Food and Drug Administration Staff: Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex. 2014. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommendations-labeling-medical-products-inform-users-product-or-product-container-not-made-natural.

- ~~Are breastfeeding or plan to breastfeed.~~ It is not known if BRAND passes into your breast milk. Do not breastfeed during the treatment.

2. We note the instructions provided to the patient regarding breastfeeding in the Patient Information do not necessarily match the information provided in Section 8.2, Lactation (e.g., recommendation to not breastfeed in the Patient Information but not in Section 8.2). We defer to the review team on determining the accuracy of the information provided in the Patient Information and Section 8.2 related to lactation, as well as making sure the recommendations related to breastfeeding are consistently communicated across the labeling.
3. We note the following potentially confusing instructions provided under the section titled "How will I receive BRAND?":

   - "Your healthcare provider may delay your (b) (4) of BRAND if you have certain side effects (b) (4) "

   We aren't clear what is meant by (b) (4) and how this relates to the first part of the sentence. We recommend clarifying what this instruction refers to in Section 2 and revising to improve clarity.

4. The "blood tests" mentioned in the following statement under the section titled "How will I receive BRAND?" are unclear:

   - "Your healthcare provider may do blood tests regularly during treatment with BRAND."

   We defer to the review team on the determination of the accuracy of this statement and including in this section of the Patient Information.

5. We recommend specifying why the 16-hour observation is needed following administration of tebentafusp (e.g., to monitor for cytokine release syndrome) in the following statement under the section titled "How will I receive BRAND?":

   - "Your healthcare provider will keep you under observation for at least 16 hours following first three BRAND treatments"

4.2 RECOMMENDATIONS FOR IMMUNOCORE LTD. (IMMUNOCORE)

We recommend the following be implemented prior to approval of this BLA:

A. General Comment for the Container Label, Carton Labeling, Prescribing Information, and Patient Information

   1. We note the manufacturer information provided across the label and labeling is inconsistent, and so we recommend revising the manufacturer information provided across the container label, carton labeling, prescribing information, and patient information to provide consistent information related to manufacturer name, address, and license number.

B. General Comments (Container Label & Carton Labeling)

1. To ensure consistency with the Prescribing Information, we recommend revising the usual dose statements on the container label and carton labeling, respectively, from (b) (4) to "Recommended Dosage: See Prescribing Information.".
2. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.[e]
3. Confirm there is enough white space around the linear barcodes on the container label and carton labeling to allow the barcodes to be read. The barcodes should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).

C. Container Label

1. We note the absence of a lot number and expiration date on the proposed container label. Provide the lot number in accordance with 21 CFR 201.10(i)(1), and the expiration date in accordance with 21 CFR 211.137.
    a. Ensure the lot number and expiration date are clearly differentiated from one another.[f]
    b. Also ensure that the lot number and expiration date are not located in close proximity to other numbers where the numbers can be mistaken as the lot number or expiration date.[g]

D. Carton Labeling

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[e] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf

[f] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert A cute Care. 2014;19(23):1-4.

[g] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

1. We note the nonproprietary name description “tebentafusp” on the side panel is missing the conditionally acceptable suffix “-tebn”. Revise the nonproprietary name description from “tebentafusp” to “tebentafusp-tebn”.
2. Consider decreasing the size of the graphic on the carton labeling near the proprietary name, as it currently competes in prominence with the proprietary name.[h]
3. We recommend revising the storage instructions provided on the side panel of the carton labeling to the following: “Must be refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake.” We also recommend bolding this statement as shown to increase the prominence of this important information and minimize the risk of the storage information being overlooked.
4. We recommend revising the statement “Must be diluted before use.” on the side panel of the carton labeling to include the specific solution required for dilution, as follows: “Must be diluted before use in a prepared Albumin (Human) in 0.9% Sodium Chloride Injection, USP solution.” This may help to avoid errors associated with using a wrong solution for dilution.
5. We note the 2D data matrix barcode is missing from carton labeling. The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier.
   The DSCSA guidance on product identifiers recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier.
   The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following:

   NDC: [insert NDC]
   SERIAL: [insert serial number]
   LOT: [insert lot number]
   EXP: [insert expiration date]

   We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product’s labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.[i]

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[h] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[i] When final, this guidance will represent FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Kimmtrak received on June 23, 2021 from Immunocore Ltd. (Immunocore).

Table 2. Relevant Product Information for Kimmtrak	
Initial Approval Date	N/A
Nonproprietary Name	tebentafusp-tebn
Indication	treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma
Route of Administration	intravenous
Dosage Form	injection
Strength	100 mcg/0.5 mL
Dose and Frequency	The recommended dose of BRAND is 20 mcg intravenously on Day 1, 30 mcg intravenously on Day 8 and 68 mcg intravenously on Day 15 and 68 mcg intravenously once every week thereafter.
How Supplied	One single-dose vial packaged in a carton
Storage	Store BRAND vials in the original package refrigerated at 2°C to 8°C (36°F to 46°F) and protect from light until time of use. Do not freeze. Do not shake. (b) (4)
Container Closure	2 mL Type (b) (4) clear glass injection vial (USP / Ph. Eur.) with a (b) (4) rubber stopper and an aluminum overseal with a flip-off cap.

APPENDIX F. OTHER

Preliminary Response to FDA Comments on Draft USPI Received on May 26, 2021:

2021-500 Kimmtrak (Tebentafusp) Respor

APPENDIX G. LABELS AND LABELING

G.1 List of Label and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[j] along with postmarket medication error data, we reviewed the following Kimmtrak label and labeling submitted by Immunocore Ltd. (Immunocore).

- Container label received on June 23, 2021
- Carton labeling received on June 23, 2021
- Professional Sample Carton Labeling received on June 23, 2021
- Prescribing Information and Patient Information (Image not shown) received on June 23, 2021, available from \\CDSESUB1\evsprod\bla761228\0012\m1\us\114-label\1141-draft-label\proposed.docx

G.2 Label and Labeling Images

Container Label

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[j] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SARAH E THOMAS
10/06/2021 11:19:59 PM

ASHLEIGH V LOWERY
10/13/2021 10:42:38 AM

Clinical Consult Review
Division of Hematologic Malignancies 1

Referenced File:	**BLA 761228**
Applicant:	**Immunocore Ltd.**
Drug(s):	**Tebentafusp-xxxx**
Consult Requested:	**8/9/21**
Desired Completion Date:	**9/27/21**
Primary Reviewer:	Emily Jen, MD, PhD
Team Leader:	Donna Przepiorka, MD, PhD
Division Director:	R. Angelo de Claro, MD

1. Product Information

Tebentafusp is a T-cell engager targeting a gp100 (melanocyte protein PMEL) 9-mer peptide presented by HLA-A*02:01 on the cell surface. The 77 kDa heterodimeric protein is comprised of a soluble form of a TCR for the cognate ligand joined via peptide linker to the scFv domain of an anti-CD3 antibody.

In clinical studies, tebentafusp was reported to have a volume of distribution approximating the blood volume (5.3 L), clearance of 4.33 L/d and terminal half-life of 6-8 hours. For the proposed indication, treatment consists of tebentafusp 20 mcg Day 1, (b) (4) mcg Day 8, 68 mcg on Day 15 and 68 mcg weekly thereafter for as long as the patient is deriving clinical benefit and in the absence of unacceptable toxicity.

Cytokine release syndrome (CRS) is an expected class safety issue for T-cell engagers.

2. Reason for Consultation (from the DO3 consult request)

On June 23, 2021, we have received BLA 761228 for Tebentafusp (IMCgp100), Injection for Intravenous Use. Please provide a consult to discuss 1) tocilizumab use for tebentafusp-related CRS and 2) evaluation of CRS safety events in context of tocilizumab use. See the section titled Questions for the Consultant for responses from DHM1.

3. Materials Reviewed

- BLA 761228 – ISS, ISS dataset \\cdsesub1\evsprod\BLA761228\0012\m5\datasets\iss\analysis\adam, patient narratives, Pharmacology Written Summary, Summary of Clinical Pharmacology Studies, Study 102 and Study 202 Clinical Study Reports
- Response to 25 August 2021 Request for Information
- Response to 17 Sept 2021 Request for Information
- Relevant literature
- Other publicly available information

4. Clinical Trials of Tebentafusp in the ISS

The safety population in the ISS included 502 patients with melanoma who received at least one dose of tebentafusp monotherapy in five trials (See Table 1). The ISS also included data from 111 patients treated with investigator's choice of therapy on a control arm and 3 patients treated with tebentafusp + another immunotherapy. However, data for the algorithmic adjudication of CRS are available only from Studies 102 and 202. The majority of this consult review therefore focuses on the 391 patients treated with tebentafusp in Studies 102 and 202.

Table 1. Table of Clinical Trials of Tebentafusp

Study Number Study Status	Study Design	Patient Population	Treatment	Patient Sample Size	Analysis Cutoff Dates
Pivotal Efficacy and Safety Study					
IMCgp100-202 (Study 202) Enrollment completed, treatment and follow-up ongoing	Phase 3, open-label, randomized, controlled, multi-center	HLA-A*02:01-positive advanced UM previously untreated in the metastatic setting (1L)	Tebentafusp monotherapy Investigator's choice (ipilimumab, pembrolizumab, dacarbazine)	252/245 [a] 126/111 [a]	Interim/primary DCO date: 13Oct2020 Interim/primary CSR date: 13 April 2021 BLA DCO date: 13Oct2020
Supportive Efficacy and Safety Study					
IMCgp100-102 (Study 102) Enrollment completed, treatment and follow-up ongoing	Phase 1/2, open-label, uncontrolled, multi-center	Previously treated (2L+) HLA-A*02:01-positive advanced UM	Tebentafusp monotherapy, dose escalation (Phase 1) Tebentafusp monotherapy, dose expansion (Phase 2)	19 127	Primary DCO date: 20Mar2020 Primary CSR date: 08Feb2021 BLA DCO date: 20Mar2020
Other Supportive Studies					
IMCgp100-01 (Study 01) Completed	Phase 1, FIH, open-label, uncontrolled, dose-finding	Previously treated HLA-A*02:01-positive advanced melanoma	Tebentafusp monotherapy	84 (n = 19 with mUM)	Final DBL date: 11Aug2017 Final CSR date: 09Feb2018 BLA DCO date: 11Aug2017
IMCgp100-201 (Study 201) Enrollment completed, treatment and follow-up ongoing	Phase 1b/2, open-label, uncontrolled, multi-center	Previously treated unresectable stage III or metastatic stage IV CM	Tebentafusp monotherapy Tebentafusp + immunotherapy	27 85	No CSR BLA DCO date: 13Oct2020

Source: BLA 761228 Summary of Clinical Safety

5. Review

5.1 Background: Cytokine Release Syndrome (CRS)

- Drug-induced CRS is a clinical diagnosis based on fever ≥ 38.0° C with or without hypotension and/or hypoxia with a temporal relationship to a treatment with a drug mechanistically known to provoke production of proinflammatory cytokines.[1]

- CRS can start within minutes or hours of the first dose up to 14 days after infusion depending on the product.

- Constitutional symptoms (headache, fatigue, arthralgias, myalgias), nausea or rash are common but not required for diagnosis of CRS. Severe cases may include respiratory failure, hypotension requiring vasopressors, cardiac dysfunction, renal failure, elevated transaminases, and disseminated intravascular coagulation. CRS may result in fatal multi-organ failure.

- Laboratory findings can include cytopenias, elevated creatinine and liver enzymes, abnormal coagulation parameters, and elevated CRP and ferritin. However, the laboratory abnormalities can be highly variable and nonspecific or may lag after clinical changes, so diagnosis of CRS does not rely on laboratory findings.

- Inflammatory cytokines (TNFα, IL-6, IFNγ) are elevated, but these data are often not available in real time for diagnosis. Interleukin-6 is the main pro-inflammatory cytokine produced in drug-induced CRS.

    - In patients with acute lymphoblastic leukemia treated with short-acting blinatumomab, mean (+/- SD) peak IL-6 levels were 826 (+/- 2390) pg/mL in the first week of treatment.[1] Any-grade CRS was reported in 7% - 15%, and it was severe in 3%. The use of tocilizumab in clinical trials of blinatumomab was rare. Labeling includes premedications but no recommendations for tocilizumab for treatment of blinatumomab-induced CRS.[2]

    - For patients with severe CRS after chimeric antigen receptor T-cell therapy, peak IL-6 levels were approximately 1-2 logs higher (median IL-6 level of 122 pg/mL [0.4-20892, range] in patients with CRS Grade 0-3, and median IL-6 level of 8,309 pg/mL [480-102476, range] in patients with Grade 4-5) and could be sustained for days.[3] Any-grade CRS was reported in 74% -94%, and it was severe in 2% - 48%. Tocilizumab was used for treatment of CRS in 17% - 54% of patients treated

[1] Shimabukuro-Vornhagen A, et al. (2018) Cytokine release syndrome. J Immunother Cancer 6: 56.
[1] Zhu M, et al. (2018) Blinatumomab pharmacodynamics and exposure–response relationships in relapsed/ refractory acute lymphoblastic leukemia. J Clin Pharm 58:168-179.
[2] See USPI.
[3] Teachey DT, et al. (2016) Identification of Predictive Biomarkers for Cytokine Release Syndrome after Chimeric Antigen Receptor T-cell Therapy for Acute Lymphoblastic Leukemia. Cancer Discov 6; 664–79.

with CAR T cells. Labeling includes premedications to prevent CRS and tocilizumab for treatment of moderate to severe CRS.

- Drug-induced CRS can occur via multiple mechanisms.[2]

  - When engaged with cognate antigen, therapeutic antibodies with an intact Fc may cross-link the Fc-receptor and activate monocytes and macrophages, resulting in cytokine production. Tebentafusp does not have an Fc, but tebentafusp-ADA complexes may induce immune cell activation through the Fc receptor.

  - T-cell agonists, including T-cell engagers, activate T-cells directly with subsequent secretion of cytokines that may cascade to other inflammatory cells.

- There are multiple grading systems for CRS in use (see Appendix A). Grading is frequently based on the presence of fever not attributable to other cause with or without hypoxia and/or hypotension in addition to the level of intervention required for hypoxia or hypotension.

5.2 CRS with Tebentafusp - Proof of Concept

Nonclinical

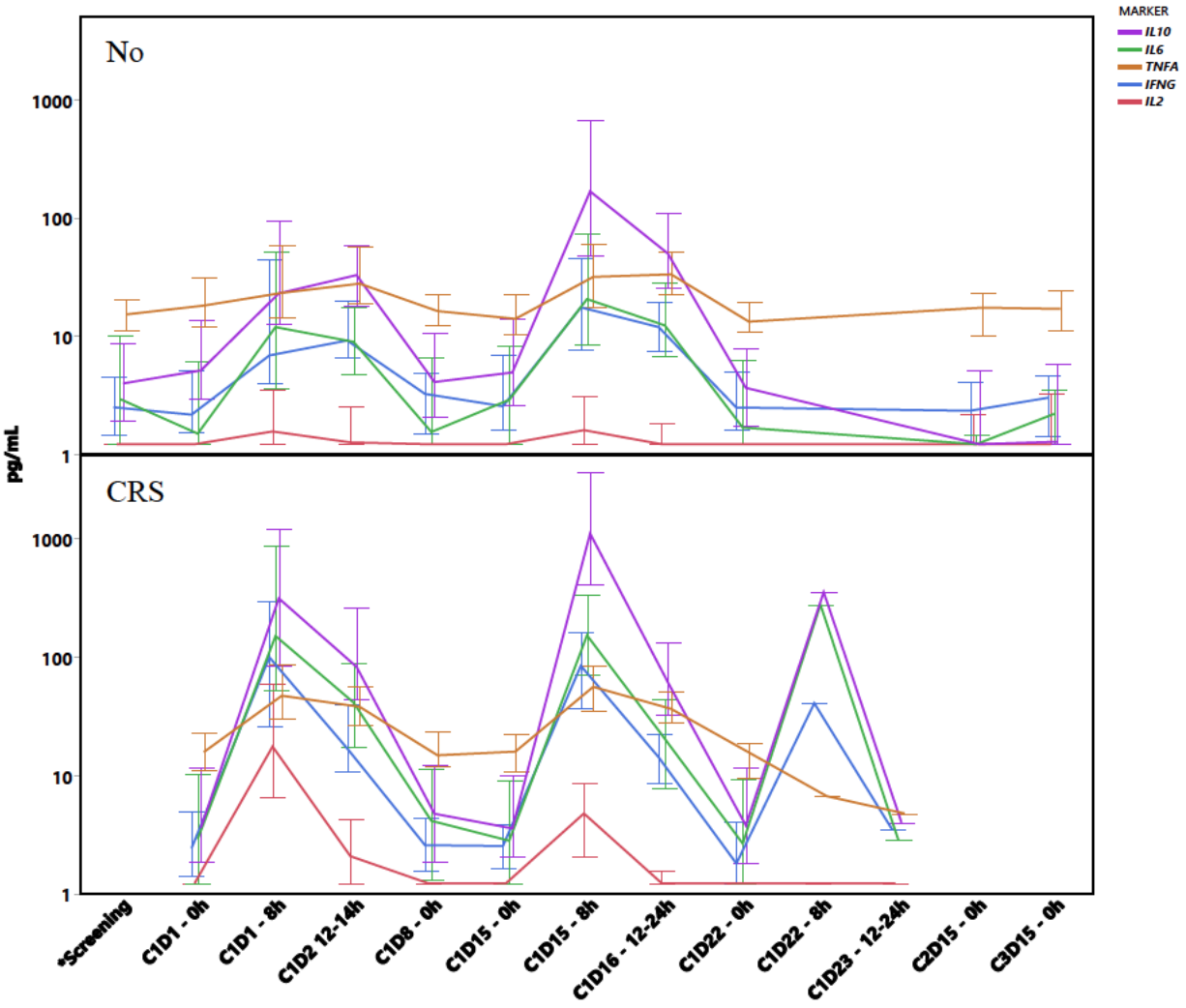
In the Pharmacology Written Summary (Module 2.6.2), the Applicant included data from studies of cutaneous melanoma cell lines that express HLA-A*02:01 and gp100 co-cultured with PBMCs as effector cells. The data demonstrated that tebentafusp can potently redirect T cells from PBMCs against CM target cell lines, leading to release proinflammatory cytokines such as TNFα, IL-2, and IL-6. Cultures of whole blood with tebentafusp did not show evidence of cytokine release in the absence of target cells.

Clinical

The Applicant provided data on cytokine levels collected before, during, and after treatment with tebentafusp for patients treated in Study 102 (Response to 17 Sept 2021 IR). In patients with CRS, cytokine levels peak 8 to 24 hours post treatment and return to baseline levels prior to the subsequent dose (see Figure 1). This cytokine increase was also seen after the third and fourth doses. Section 4.2.2 of the Summary of Clinical Pharmacology confirms that samples were not analyzed after the second dose.

[2] Bugelski PJ, et al. (2009) Monoclonal antibody-induced cytokine-release syndrome. Expert Rev Clin Immunol 5:499 - 521.

Figure 1. Study 102 – Change in Serum Cytokine Levels after Treatment with Tebentafusp



Error bars represent upper and lower quartiles
Source: DHM1 Reviewer Analysis

Reviewer Comment: The nonclinical and clinical data confirm that tebentafusp stimulates release of cytokines.

5.3 CRS with Tebentafusp - Clinical Characterization

Investigator-Reported CRS

Safety data were available for 616 patients in the ISS. Of these patients, 502 were treated with tebentafusp monotherapy, 3 were treated with tebentafusp + immunotherapy (Study 201), and 111 were treated with Investigator's Choice (Study 202). No cases of CRS were reported in patients who received Investigator's Choice. No cases of CRS were reported in 30 patients from the on-going Study 201 (including the 3 with combination therapy). Among the remaining 475 patients treated with tebentafusp on Studies 01, 102 and 202, CRS was reported as an adverse event for 63 (13%) patients. The median time to first CRS event was 1 day (range 1-529 days; 25%-75%

interquartile range 1 - 2 days). Table 2 shows the incidence of investigator-reported CRS by CTCAE grade for each protocol.

Table 2. Investigator-Reported CRS in Patients Treated with Tebentafusp

Max CRS Grade*	Study		
	IMCGP100-01 (n=84)	**IMCGP100-102 (n=146)**	**IMCGP100-202 (n=245)**
1	1 (8%)	3 (2%)	20 (8%)
2	0	5 (3%)	29 (12%)
3	1 (8%)	2 (1%)	2 (<1%)
4	0	0	0
5	0	0	0

Source: FDA analysis
*CTCAE v4.03

Limitations of CRS Clinical Assessment in the Tebentafusp Trials

Diagnosis and grading of CRS used in clinical trials changed over the course of tebentafusp drug development. Early studies started with CTCAE grading (v3.0 or 3.04), followed by a transition to Lee 2014 criteria in 2017. None of the studies utilized a case report form that included specific reporting of CRS characteristics other than as an individual term on the adverse event page.

For this BLA submission, the Applicant retrospectively classified CRS events in Study 102 and Study 202 using an algorithmic approach based on fever, hypotension and hypoxia according to the ASTCT 2019 consensus grading (see Appendix A). Potential CRS events were reviewed by the study physician to ensure alignment with the grading criteria. These adjudications are provided in the data file iadcrs.xpt. An integrated vital sign data file was not included in the ISS, but iadcrs.xpt included flags for pyrexia AE, fever, hypotension, and hypoxia and columns for maximum temperature within 2 days of dose and minimum blood pressure.

Fever $\geq 38.0^{o}$ C is a hallmark of CRS and is required for diagnosis based on ASTCT criteria. Given the timing of the cytokine changes observed in patients treated with tebentafusp, the choice of maximum temperature within 2 days may be reasonable. However, there are discrepancies between the flags, vital signs on the corresponding rows in iadcrs.xpt, and ASTCT grading (e.g., in patients adjudicated as having CRS 19 rows (17 patients) have Fever Flag = N and maximum temperature $< 38.0^{o}$ C; 45 rows (35 patients) had a documented maximum temperature $< 38.0^{o}$ C and Pyrexia AE Flag = N but Fever Flag = Y). By ASTCT consensus grading criteria, these patients would not have met criteria for CRS. All were classified as Grade 1 or 2 CRS except for one patient with Grade 3 CRS for whom a narrative was provided and T 38.0^{o} C was described in the text. Some events are recorded as Hypotension Flag = N while the blood pressure measurements indicate hypotension or vice versa (Flag = Y when vital signs do not show a corresponding decrease in BP).

It is worth noting that the incidence of rashes in studies with tebentafusp is very high given expression of the target epitope in melanoma. The Applicant reports that almost 60% of patients on Study 102 and 202 had an AE that fell under the SOC Skin and subcutaneous tissue disorder during the time period that CRS was reported. Although rash can be a manifestation of CRS as

well as hypersensitivity reactions, the potential for rash due to on-target effects of the drug precludes determination of relationship to CRS.

Additionally, the data for key elements of CRS grading (e.g., oxygen use) were not collected in Study 01 (dose-finding) and Study 201 (cutaneous melanoma); therefore, the incidences of CRS in those studies by current criteria are unknown.

Reviewer comment: We will limit our review to the data presented in iadcrs.xpt for Studies 102 and 202, and the narratives when available. However, due to the incompleteness of the raw data for vital signs, concomitant medications, and patient narratives in all trials, there will remain some uncertainty regarding the true rate of CRS with tebentafusp.

Incidence of CRS in Study 102 and Study 202

Using the algorithmic approach, the Applicant identified 1,308 CRS events in 344 patients treated with tebentafusp monotherapy in Study 102 and Study 202. Table 3 shows percentage of cases by ASTCT grade as reported by the Applicant.

Table 3. Applicant-Adjudicated CRS by Maximum Grade

Parameter	Study 102 Phase 1 All Doses (N = 19)	Study 102 Phase 2 20/30/68 mcg (N = 127)	Study 202 20/30/68 mcg (N = 245)	All Studies (N = 391)
CRS Grade (ASTCT CRS Consensus Grading), n (%)				
Grade 0	1 (5.26%)	18 (14.17%)	28 (11.43%)	47 (12.02%)
Grade 1	3 (15.79%)	43 (33.86%)	29 (11.84%)	75 (19.18%)
Grade 2	15 (78.95%)	61 (48.03%)	186 (75.92%)	262 (67.01%)
Grade 3	0	4 (3.15%)	2 (0.82%)	6 (0.02%)
Grade 4	0	1 (0.79%)	0	1 (0.002%)

ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome
Number missing = 11

Source: BLA 761228 Summary of Clinical Safety, Table 24

Eight Grade ≥ 3 CRS events were reported in 7 patients (seven Grade 3 and one Grade 4). Narratives were available for all but 2 Grade ≥ 3 CRS events. One patient without a narrative had a documented C1D1 temperature of 39.7° C and hypoxia treated with oxygen. This patient meets the criteria for at least Grade 2. The other event without a narrative occurred on C1D8 in a patient with prior Grade 3 CRS on C1D1 (narrative provided). Iadcrs.xpt shows no documented fever (by AE, flag, or max temp 36.4° C) but indicates hypotension treated with a vasopressor and steroids. In the absence of a documented fever, this would not meet criteria for CRS.

Reviewer comment: The true incidence of CRS with tebentafusp treatment is unknown. The algorithm is likely to have overcalled the number of CRS events, especially Grade 1 which requires only fever without hypotension or hypoxia which may be nonspecific. Additionally, based on iadae.xpt and the few available narratives, it appears at least some cases of low-grade CRS identified by the algorithm are likely IRR rather than CRS. Based on the Applicant's adjudication of CRS and the information provided regarding interventions used in Study 102 and

Study 202 (see section on Treatment of CRS), the incidence of Grade ≥2 CRS with tebentafusp may range from 50-77%. Grade ≥ 3 CRS occurred in 2% of patients treated with tebentafusp in these two studies, including one patient considered to have had fatal CRS (see discussion of Subject (b) (6) *later in this review). Thus, although infrequent, serious, life-threatening or fatal CRS does occur after treatment with tebentafusp.*

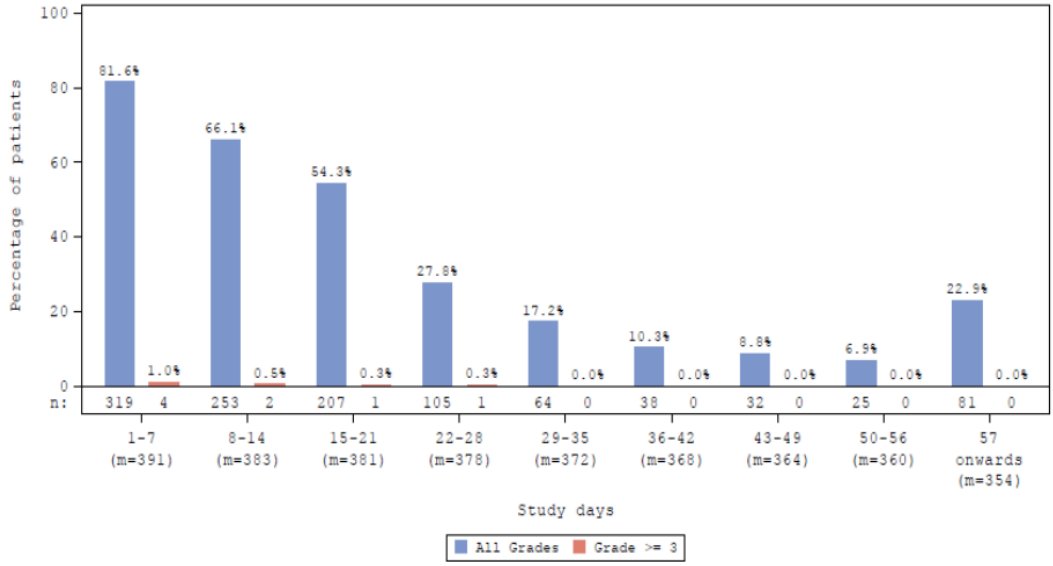
Also, of note, CRS was underreported by investigators, including some Grade 3 events which required escalating intervention. Given the potential for serious and life-threatening CRS, a communication REMS informing providers about the risk of CRS is warranted. For the initial approval of the blinatumomab application in November 2014, the approval included a communication REMS due to the safety issues of CRS (all grade 11%, Grade 3 and higher 1%), neurotoxicity, and administration/preparation errors observed with blinatumomab. For details of the communication REMS framework and experience to date, please refer to the REMS review for blinatumomab under BLA 125557 specifically REMS review on 11/12/2014, and REMS periodic reviews (5-year review completed on 9/4/2020).

Characterization of CRS

Time to Onset: Data elements for the study day of start of a CRS event were not available in iadcrs.xpt for all patients. Of 344 patients with a Grade ≥ 1 CRS event reported, a study day for the first CRS event was available for 327 patients. The median time to first CRS event was 1 day from start of tebentafusp treatment (interquartile range: 1-2 days). For CRS events without a study day for start of the event, the Analysis Visit may have been available. For the 17 patients without an AE start date listed in iadcrs.xpt, 71% had the earliest CRS event recorded on Analysis Visit = Cycle 1 Day 1. Four (24%) additional patients had an earliest CRS event during Cycle 1 (2 on Day 8, 2 on Day 15). Of the 7 patients considered to have had a possible Grade ≥ 3 event confirmed by narrative or other documentation, the median time to start of CRS was 1 day (range 1-22 days). The latest start of a Grade 3 event was on Cycle 2 Day 1. The only Grade 4 event occurred on Cycle 1 Day 1.

Recurrences of CRS: Of 391 patients treated with tebentafusp monotherapy, 300 (77%) had > 1 CRS event by algorithm, and 184 patients (47%) had at least one Grade ≥ 2 CRS and one other CRS event by algorithm. The Applicant's assessment of incidence of CRS by time period is shown in Figure 2. Priming doses are given on Cycle 1, Weeks 1 and 2. The target dose begins on Week 3.

Figure 2. Incidence of CRS by CTCAE Grade and Time Period



Source: BLA 761228 Summary of Clinical Safety

Duration of CRS: The median duration of CRS (DoCRS) was 2 days (range 1-198). The high end of the range for DoCRS is likely due to inaccurate recording of the AE stop date (e.g., one patient had an AE stop date 14 days after start of CRS, but the narrative indicated CRS resolved on day 2). The interquartile range for DoCRS was 1-2 days. Grade 3 events had a median DoCRS of 2 days (range 2-3 days [*high end of range confirmed by narrative]). The Grade 4 event lasted 14 days according to iadcrs.xpt, is listed in the narrative as having resolved on Day 3, and it is noted that the patient had ongoing multiorgan failure from CRS when he died on Day 27.

Reviewer comment: CRS occurs early after start of treatment with tebentafusp, with a median time to CRS of 1 day, and is of relatively short duration. Except for the fatal CRS event, the Grade ≥ 3 events resolved within 3 days. The algorithm identified recurrent CRS in a majority of patients, but no data are available to confirm this observation. Although some patients may have had more than one CRS event, it is notable that the algorithm identified 14 patients with 10 or more CRS events (up to a maximum of 39 events). It is very unlikely that all of these events were true cases of CRS. It is more likely that some of these patients had repeated mild infusion reactions.

5.4 CRS Management in Tebentafusp Trials

Mitigation Instructions

Table 4. Tebentafusp Administration Instructions Per Protocol

	Study 102	***Study 202 Pivotal Trial***
Hospitalization		
Overnight hospitalization and predose and Q4 vital signs after C1D1, C1D8, C1D15 – monitor at least 16 hours after dosing for 1st 3 doses	✓	✓
If no AR involving Grade ≥ 2 hypotension, C1D22 and subsequent doses may be given outpatient	✓	✓
Premedication		
Due to risk of hypotension, IV fluids may be administered prior to IMCgp100	✓	
Pruritis is common so premedication with antihistamine may be considered	✓	
No premedications prior to 1st infusion. If a patient experiences an IRR, for subsequent infusions: paracetamol/acetaminophen and an antihistamine. Corticosteroid premedication should be avoided unless other premedications are not effective.	✓	✓

Source: DHM1 Reviewer Analysis

As shown in Table 4, premedications were not prespecified in protocols across the clinical development program. As noted in the section above, the indications for concomitant medications are not included in iadcm.xpt; therefore, the proportion of patients receiving premedication for CRS prophylaxis cannot be accurately determined. An attempt was made to describe medications listed as given prior to tebentafusp infusion.

- Study 102 Protocol:
    - No entries with [CMINDC = Premedication] were reported for Study 102.
    - Sodium chloride infusion (CMDECOD = Sodium chloride, CMROUTE = Intravenous, CMINDC = prophylaxis) was reported for 18 (12%) patients.
    - Systemic corticosteroids were reported as prophylaxis in 11 (8%) patients.

- Study 202 Protocol:
    - Entries with [CMINDC = Premedication] included:
    - Paracetamol/acetaminophen and/or an antihistamine was reported as pre-medication in 58 (24%) patients.
    - Corticosteroid was reported as premedication in 26 (11%) patients.
    - Sodium chloride infusion was reported as prophylaxis for 41 (17%) patients (this protocol did not include instructions for pretreatment IV fluids).

- Systemic corticosteroids were reported as prophylaxis in 10 (4%) patients.

Reviewer comment:

- *As noted in the table above, patients were hospitalized overnight/at least 16 hours after the first 3 doses (step-up dosing with maximum dose on Week 3). Subsequent doses could be given outpatient in the absence of Grade ≥ 2 hypotension. The draft USPI reflects these instructions.*

- *Only 12% of patients in Study 102 and 17% in Study 202 received IV fluids as prophylaxis.* (b) (4) *However, this was not a specified premedication in the pivotal trial Study 202 and a minority of patients received IV fluid prophylaxis. The numbers of patients are too small to conclude that pretreatment with IV fluids is necessary or safe.*

- *Some patients received premedication with paracetamol/acetaminophen and/or antihistamines prior to later doses of tebentafusp. These would not prevent CRS as they do not address the mechanism of cytokine release, but they may have a role in mitigation of IRR.*

- *Premedication with corticosteroids can be used to reduce the incidence of CRS, but the protocol specified that corticosteroid premedication should be avoided and few patients received premedication with corticosteroids in these studies.*

Treatment of CRS

The Applicant-identified interventions administered for treatment of CRS in Study 102 and Study 202 are shown below (Table 5). It should be noted that there are no corresponding indications for treatment in the iadcm.xpt data file. According to the Applicant, corticosteroid use in this table was derived programmatically and defined as any use of systemic corticosteroids within 3 days of the last tebentafusp dose preceding a CRS episode.

Table 5. Interventions for CRS in Patients Receiving the Labeled Dose of Tebentafusp in Study 102 and Study 202

Treatment Group	Medication Received	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Study 102 20/30/68 mcg (N=133)	Tocilizumab	1 (0.8%)	0	0	1 (0.8%)	2 (1.5%)
	Vasopressors	0	0	1 (0.8%)	1 (0.8%)	2 (1.5%)
	Steroids	7 (5.3%)	19 (14.3%)	3 (2.3%)	1 (0.8%)	27 (20.3%)
	Oxygen	0	5 (3.8%)	4 (3.0%)	1 (0.8%)	10 (7.5%)
	IV Fluids	3 (2.3%)	49 (36.8%)	2 (1.5%)	0	53 (39.8%)
	Antipyretics	68 (51.1%)	57 (42.9%)	3 (2.3%)	1 (0.8%)	104 (78.2%)
Study 202 20/30/68 mcg (N=245)	Tocilizumab	0	2 (0.8%)	0	0	2 (0.8%)
	Vasopressors	0	1 (0.4%) [a]	1 (0.4%)	0	2 (0.8%)
	Steroids	17 (6.9%)	46 (18.8%)	1 (0.4%)	0	57 (23.3%)
	Oxygen	0	19 (7.8%)	1 (0.4%)	0	20 (8.2%)
	IV Fluids	1 (0.4%)	93 (38.0%)	1 (0.4%)	0	93 (38.0%)
	Antipyretics	89 (36.3%)	158 (64.5%)	1 (0.4%)	0	192 (78.4%)

IV = intravenous; CRS = cytokine release syndrome.
[a] Subject (b) (6) had intramuscular epinephrine listed as a concomitant medication for contrast allergy and not for CRS, which was never used. Post DCO for the ISS, site has since removed the entry from the database.
Source: Module 5.3.5.3, Table ISS 02.03.08.15.

Source: BLA 761228 Summary of Clinical Safety

Of patients the 330 patients identified by the algorithm as having CRS, iadcrs.xpt indicates that:

- 82 (21%) patients received at least one pressor and/or oxygen support and/or steroids. Addition of IV fluids to these interventions brings the total to 102 (31%).
- 134 (41%) were managed with IV fluids alone or IV fluids and antipyretics.

Compliance with CRS Management Instructions

- Early drug development between 2010 and 2017 (Study 01, Study 102 Phase 1) assessed adverse events based on CTCAE v4.0 or 4.03. Adverse events of acute allergic reactions, anaphylaxis, acute infusion reactions and cytokine release syndrome were grouped together as "acute systemic reactions" and management instructions were provided generally for supportive care with corticosteroids and antihistamines only recommended for severe acute systemic reactions.
- In October 2017, one patient on Study 102 experienced Grade 4 CRS requiring tocilizumab, pressors, intubation, and multiple organ failure requiring dialysis. Due to this event, the protocol was revised to incorporate CRS grading criteria based on Lee, 2014 in Study 102 Protocol Version 7.0, and the management guidelines were updated to include general instructions to "consider adding further immunosuppression or additional interventions … (e.g., anti-IL-6, tocilizumab)" for Grade 3 CRS.

- These instructions were used through Study 202 version 5.0 which further defined the maximum acceptable duration of ongoing Grade 2 CRS before immunosuppressive therapy was indicated (if not resolved within 2-3 hours of onset) and added tocilizumab dosing instructions: 8 mg/kg IV (not to exceed 800 mg/infusion) "per institutional guidelines". However, no patients received tocilizumab according to these instructions.

Using the dates of the Dear Investigator Letters sent to inform physicians of the revised management guidelines (Response to 25 August 2021 IR), we reviewed CRS incidence and treatment by time period.

Table 6. CRS in Study 102 and Study 202 by Management Guideline Time Period

Time period of tebentafusp exposure followed by CRS	ASTCT CRS – Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Before 10/12/17 Steroids recommended only for Grade 3 or 4 (CTCAE v4)	33	28 1 rec'd steroids	19 6 rec'd steroids	0	1 Rec'd steroids + tocilizumab @12h
10/13/17 – 4/21/20 *Lee 2014 criteria for CRS grading and revised management: HD IV steroids @ Grade 2 if not resolved w/fluids Tocilizumab @ Grade 3 (no dose specified)	357	207 22 rec'd steroids	232 60 rec'd steroids 2 rec'd tocilizumab w/in ~3 hours of onset	6 4 rec'd steroids	0
After 4/21/20 *HD IV steroid ± Tocilizumab 8 mg/kg @ Grade 2 if not resolved in 2-3h)	28	15 2 rec'd steroids	17 4 rec'd steroids 0 rec'd tocilizumab	0	0

*See Appendix B for details on management instructions
Source: DHM1 Reviewer Analysis

Reviewer comment: Based on the analysis above, it does not appear that treatment with tocilizumab changed according to the incorporation of instructions for use in the protocols. None of the 3 instances of tocilizumab use are consistent with the management guidelines of the respective time periods.

Use of Tocilizumab for CRS in Tebentafusp Trials

Five patients in the ISS had tocilizumab recorded as a concomitant medication. One was reported to have tocilizumab listed as a PRN medication for a history of arthritis, and the other had

tocilizumab listed as PRN without a corresponding indication. The Applicant states that neither patient received tocilizumab for any indication during study treatment (see Response to 25 Aug 2021 IR #1a).

The Applicant reports that the remaining 3 patients received tocilizumab for CRS. The narratives for these events are reviewed below.

Study 102

(b) (6) 53yo F, baseline weight (IADSL) = 70.2kg

- **Applicant: Grade 4 CRS**
- Tebentafusp dose: 20 mcg Day 1, 30 mcg Day 8, 68 mcg QW starting Day 15
- Timeline:
- C1D1 – T 38.1C, constitutional symptoms, vomiting starting 90 minutes after completion of dose 1 (infusion 12:15-12:30p 10/5/17)
- Hypotension failed to respond to fluids.
- Dexamethasone 10 mg IV, hydrocortisone 50 mg IV x 2, phenylephrine 20 mg
- BP failed to stabilize; patient was admitted to ICU
- At 12 hours post-dose, **tocilizumab 640 mg x 1 dose (~5 mg/kg – RA dosing?)** was administered, and corticosteroid therapy escalated to include methylprednisolone 1000 mg IV
- 12-24 hours post-infusion: BP remained low, pressor therapy with epinephrine/ vasopressin/norepinephrine 1 mcg/min initiated
- C1D2 – patient experienced Grade 4 multiple organ dysfunction including AKI, respiratory failure, "shock liver" – Grade 4 increases in AST, ALT, Grade 3 hyperbilirubinemia (meeting potential Hy's Law Criteria)
- Worsening AKI and acidosis managed with CVVH; patient intubated for respiratory support ~15 hours post-infusion
- Hydrocortisone, lidocaine, phytomenadione, and albumin for multiple organ dysfunction syndrome (MODS)
- ~24 hours post-tebentafusp, acidosis improved, and BP stabilized
- Epi discontinued 30 hours post-infusion, ABG pH normalized ~36 hrs post-infusion, norepinephrine and vasopressin wean initiated ~72 hrs post-infusion
- "On (b) (6), the event of cytokine release syndrome resolved." (C1D3)
- (b) (6), patient extubated and transitioned to hemodialysis
- (b) (6), 27 days after the 1st (only) dose of tebentafusp, the patient died.
  - Primary COD reported as disease progression
  - MODS was "ongoing at time of death"

Study Visit	Date	Time	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Body Temperature (°C)
C1D1	(b) (6)	11:54 (pre-dose)	106	70	37
		12:43 (post-EOI)	107	68	36.7
		13:15	118	76	36.7
		14:00 (approximate)	*Not reported*	*Not reported*	*38.1*
		16:15	122	82	37.2
		20:15	70	52	36.8
		20:30 (approximate)	*41*	*23*	*Not reported*
C1D2		00:12	71	56	36.8
		12:15	97	56	39.9
Unscheduled		*Unknown*	*100*	*65*	*35.8*
Unscheduled		*Unknown*	*92*	*64*	*37.0*
Unscheduled		*Unknown*	*81*	*55*	*36.0*
Unscheduled		*Unknown*	*79*	*51*	*36.5*
Unscheduled		*Unknown*	*124*	*74*	*37.4*

Note: the infusion was started at 12:15 and completed at 12:30.
BP = blood pressure; C#D# = Cycle # Day #; EOI = end of infusion.

Serum chemistry findings relevant to the events of multiple organ dysfunction syndrome and potential Hy's Law included:

Study Visit	Date	Creatinine, ULN: 79.56 µmol/L	ALT, ULN:46 IU/L	AST, ULN: 39 IU/L	Bilirubin, ULN: 22.23 µmol/L
C1D1	(b) (6)	80 HT1	108 HT1	111 HT1	27.4 HT1
Unscheduled		229 HT2	1428 HT4	4477 HT4	77.0 HT3
Unscheduled		126 HT2	1260 HT4	2305 HT4	92.3 HT3
Unscheduled		116 HT1	786 HT3	656 HT3	77.0 HT3
Unscheduled		107 HT1	635 HT3	428 HT3	83.8 HT3
Unscheduled		112 HT1	501 HT3	302 HT3	87.2 HT3
Unscheduled		225 HT2	366 HT3	218 HT3	82.1 HT3
Unscheduled		538 HT4	171 HT2	144 HT2	97.5 HT3
Unscheduled		359 HT3	145 HT2	143 HT2	121.4 HT3
Unscheduled		403 HT3	91 HT1	165 HT2	191.5 HT3

Note: C1D1 labs were performed 1 day prior to the C1D1 visit.
C#D# = Cycle # Day #; H = high, T# = toxicity grade #; ULN = upper limit of normal.
*= Potential Hy's Law criteria met

Source: Study 102 CSR Narratives

*Reviewer comment: This narrative is consistent with worsening CRS resulting in multiple organ failure. We consider this patient's death in the setting of ongoing multiple organ failure to be at least possibly related to CRS **(i.e. Grade 5 CRS)**. The CRS management guidelines at this time in drug development did not include instructions for use of tocilizumab. The patient received a ~5 mg/kg dose (possibly based on rheumatoid arthritis dosing?) 12 hours after the start of the CRS after failure to respond to fluids and low doses of steroids. The dose/timing of tocilizumab were not effective at managing this patient's CRS. Additionally, it is possible that progression of the patient's clinical course could have been mitigated by earlier intervention with high dose corticosteroids and more aggressive management of hypotension. High dose steroids were not administered until ~12 hours post-infusion (concurrent with tocilizumab) and pressors are described as having been given "12-24 hours" post-infusion.*

Study 202

(b) (6) 64yo M; baseline weight 121kg

- **Applicant: Grade 2 CRS**
  - C1D1 - Grade 1 CRS within 3.5 hours post-infusion? – shivers and abdominal discomfort – received paracetamol

- Fever, shivering, abdominal pain, hypertension = (b) (6) received methylprednisolone 200 mg IV, tocilizumab 800 mg IV once, and oxygen 2L NC
- "He had neither hypotension nor decrease in oxygen"

Study Visit	Date	Time	Body Temperature (°C)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse rate (beats per minute)
C1D1	(b) (6)	11:58 (Pre-dose)	36.3	139	91	85
		15:47	37.2	151	93	83
		16:17	37.1	155	95	95
		17:17	37.7	154	88	102
		18:00	38.8	158	110	130
		18:30	39.0	204	139	140
		18:50	39.5	222	136	140
		19:14	39.1	190	112	128
		19:27	39.3	182	117	125
		19:55	39.3	178	115	110
		20:18	39.7	171	113	120
		20:50	39.4	167	115	125
		21:35	39.2	166	112	125
		22:05	38.6	154	118	NR
		22:36	28.5	153	101	115
		23:09	38.1	149	99	111
		23:35	36.8	150	05	104
C1D2	(b) (6)	01:07	35.6	131	92	94
		02:11	36.2	130	95	86
		03:36	35.5	135	95	92
		04:19	35.9	125	93	103
		06:39	36.5	128	101	73
		08:17	36	144	89	75
		12:16	35.7	121	67	86

Source: Study 202 CSR Narratives

- "Additional medication given around the time of the event of cytokine release included sodium chloride." Timing not specified.
- On (b) (6), the event of CRS was reported as resolved.

Reviewer comment: The Applicant classified this as Grade 2 CRS given the reported use of oxygen 2L NC. However, the report specifies that the patient had neither hypotension nor decrease in oxygen (but received oxygen and IV fluids). Based on the narrative and the vital signs shown above, this case does not appear to fulfill the criteria for CRS. The description is consistent with an IRR.

In the Applicant's Response to 17 Sept 2021 IR they assert that this event is CRS because "the management of the event appeared consistent with treatment of CRS" and that the patient had a post treatment decrease in SBP and DBP relative to pre-dose vitals despite observed hypertension. They also note that this patient was rechallenged on Day 8 and had a similar event with no increase in severity which resolved without corticosteroids or tocilizumab. There are 4 CRS events for this patient in iadcrs.xpt: C1D8 is listed as Grade 2 based on fever and hypotension, C1D15 and C2D1 Grade 1. No premedications are listed in iadcm.xpt for doses after C1D1. Given the narrative above and the lack of premedication for subsequent doses, this is consistent with a patient having repeated IRR with each dose.

(b) (6) 63yo M; baseline weight 81.2kg

- **Applicant: Grade 2 CRS**
- C1D8 – Grade 2 CRS after second dose (dose infused 12-12:15p)
- Treated with IV diphenhydramine, hydromorphone, tocilizumab IV 330 mg (~4mg/kg) once; no corticosteroid use reported

Study Visit	Date	Time	Body Temperature (°C)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse rate (beats per minute)
C1D8	(b) (6)	11:52 (predose)	36.5	131	80	82
		12:34	37	139	81	76
		15:15	38.6	119	77	121
		17:44	37.2	116	77	109
		19:48	37.1	104	66	97
		22:45	36.6	120	71	76
		23:33	36.6	109	65	89
C1D9	(b) (6)	03:42	37.2	123	68	76
		06:31	36.6	125	77	73

Source: Study 202 CSR Narratives

- On (b) (6) the event of CRS was resolved. No action was taken with study drug.
- Around the time of the event of cytokine release syndrome, the patient also experienced additional non-serious adverse events of Grade 1 rash erythematous (face/upper chest), transaminases increased, and pyrexia (treated with paracetamol). Additional concomitant medications that were given around the time of the event of cytokine release syndrome included famotidine and IV sodium chloride "for prophylaxis"

Reviewer comment: No description of signs/symptoms are provided in the narrative, but the patient has fever documented ~3 hours post-infusion and hypotension w/tachycardia. This would meet criteria for Grade 2 CRS.

Reviewer comment re: use of tocilizumab for tebentafusp-related CRS: Of the three patients who received tocilizumab, one patient is considered to have Grade 5 CRS. Only this patient had a narrative consistent with use of tocilizumab for CRS not responding to other management. However, the dose/timing of tocilizumab she received were not effective, and escalation of care for CRS was slow after failure to respond to initial treatment with low-dose steroids. There is no indication that either of the other two events (one considered an IRR and one Grade 2 CRS) merited the use of tocilizumab and use of tocilizumab in those cases did not follow the protocol management guidelines at the time of the events.

Questions for the Consultant:

1. Discuss evaluation of CRS safety events in context of tocilizumab use.

DHM1 Response to DO3:

Cytokine release syndrome (CRS) is a class effect of T-cell engagers. Both nonclinical and clinical data indicate that treatment with tebentafusp resulted in elevated IL10, IL-6, TNFa, and IFNg levels. In the clinical trials included in this BLA, CRS requiring intervention such as

steroids, pressors, and oxygen supplementation did occur following treatment with tebentafusp, one patient required intubation and dialysis, and it was fatal in one patient.

However, it is not possible to fully describe the incidence and severity of CRS in the population due to missing information (see section on Limitations of CRS Clinical Assessment in Tebentafusp Trials) and the fact that fever alone may be nonspecific. Based on the Applicant's algorithm and available narratives, we estimate that the rate of CRS with hypotension or hypoxemia (ASTCT Grade 2 or higher) following tebentafusp treatment is 52-77%. Life-threatening and fatal CRS, though rare, has occurred after treatment with tebentafusp. The median time to onset of the first event is 1 day, the median duration is 2 days, and it can recur in later cycles (although the incidence is lower in later cycles).

2. Discuss tocilizumab use for tebentafusp-related CRS.

DHM1 Response to DO3:

Regarding the use of tocilizumab, the Applicant reports that 3 patients received tocilizumab for treatment of CRS. Of the 3 patients, based on the narratives only two met criteria for CRS (documented fever with or without documented hypotension and/or hypoxia), one with Grade 2 and one with Grade 5 CRS. Use of tocilizumab in the former may have been premature, since the event was only Grade 2. No patients with Grade 3 CRS were treated with tocilizumab. For the patient with Grade 5 CRS, treatment for CRS was not escalated to include high dose steroids for at least 12 hours and pressors were not started until the 12 to 24-hour post-infusion time period. The dose/timing of tocilizumab administered to this patient was not effective for management of CRS. Therefore, there are no data showing that tocilizumab is effective in the treatment of tebentafusp-related ASTCT Grade 3 or 4 CRS.

Based on our review, we have the following recommendations:

CRS Labeling Considerations (see attached draft USPI)

(b) (4)

Management of CRS

- Based on the data in this BLA submission [redacted] (b) (4) .

- Management guidelines in the USPI [redacted] (b) (4) should provide instructions based on the clinical signs and symptoms of CRS.

Warning for CRS

- The warning for CRS in Section 5.1 should note that tebentafusp-related CRS may be fatal. See proposed text.

Additional recommendations for mitigation of CRS risk

Communication REMS

- See Tables 2 and 3 of this consult review for differences in CRS rates reported by investigators and by the Applicant. Since the results of the study suggest that even the trained investigators may not have been able to recognize CRS, there is a risk of late diagnosis when used by the community oncologists. We recommend education for providers on the risks, diagnosis, and management of CRS after treatment with tebentafusp as a means to mitigate severe CRS.

Medication Guide

- [redacted] (b) (4) CRS events were also reported on C1D22 (dose 4) and in subsequent cycles of therapy which would be given outpatient. We recommend a Medication Guide to inform patients about the signs and symptoms of CRS for which they should contact their healthcare provider.

Additional recommendations for revisions to Study IMC-gp100-201

We recommend that the protocol for the ongoing Study IMC-gp100-201 be revised to address the following:

- Consider adding premedications to mitigate the high rate of ASTCT Grade 2 CRS.

- Revise the instructions for CRS management to be consistent with the comments on the draft USPI.

- If tocilizumab is included in the CRS management plan, add tocilizumab PK sampling in order to allow estimation of tocilizumab clearance and determination of the appropriate tocilizumab dose and schedule for tebentafusp labeling.

- Add parameters in the CRF to capture information about characteristics of CRS to allow for accurate evaluation of CRS in this study.

Appendix A. Grading Systems for CRS[3,45,]

CTCAE v.3

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.						

Lee, 2014

CRS Grade	Toxicity (Grade CTCAE v4.0)
Grade 1	Symptoms are not life-threatening and require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgias, malaise)
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement < 40% or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40% or Hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
Grade 5	Death

ASTCT Consensus Grading for CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[†]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With either:		
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or		
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

[†]Fever = temperature ≥ 38C not attributable to any other cause
CRS grade determined by more severe event: hypotension or hypoxia not attributable to any other cause

[3] Available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50
[4] Adapted from Lee DW, et al. (2014) Current concepts in the diagnosis and management of cytokine release syndrome. Blood 124(2):188-192
[5] Adapted from Lee DW, et al. (2019) ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 25:625-638.

Appendix B. CRS Management Guidelines in the Tebentafusp Development Program Including Use of Tocilizumab

CRS Grading*	Study 102 Protocol / Version 7.0 15Dec2017	Study 202 Protocol / Version 5.0 31March2020
Grade 1	Admit for inpatient monitoring (unless already hospitalized per protocols) and manage according to individual symptoms. Assess for potential infection and treat fever and neutropenia. Initiate bolus and/or maintenance intravenous fluids and carefully monitor fluid balance Consider prophylactic electrolyte supplementation for patients receiving intravenous fluids with low-normal serum electrolyte levels Vigilantly monitor for escalation to grade 2 cytokine release syndrome with frequent vital signs (e.g., every-hour vital signs). Strongly consider early, high-dose corticosteroid therapy with changes in vital signs (see grade 2 below)	Same as Study 102 Protocol / Version 7.0 15 Dec 2017
Grade 2	Management as above (grade 1) and include the following measures:	**NOTE:** Same as Study 102 Protocol / Version 7.0 15 Dec 2017 except for below:
	Increase monitoring with continuous cardiac and pulse oximetry monitoring and continue or increase vital sign monitoring (e.g., every hour vital signs) To manage hypotension, administer bolus intravenous fluids (recommended rate of approximately 1 L per hour). If not rapidly resolved with fluids, high-dose intravenous corticosteroid therapy should be considered, e.g., methylprednisolone 2 mg/kg initial dose (or equivalent) until symptoms (e.g., hypotension) resolve Consider prophylactic electrolyte supplementation for patients receiving intravenous fluids with low-normal serum electrolyte levels Manage respiratory distress and oxygen requirement with supplemental oxygen and additional respiratory support as needed	If not rapidly resolved (i.e., within 2–3 hours of onset) with fluids, high dose IV corticosteroid therapy, e.g., methylprednisolone 2 mg/kg initial dose or equivalent and/or tocilizumab 8 mg/kg IV (not to exceed 800mg/infusion) per institutional guidelines should be administered until symptoms (e.g., hypotension) resolve ***Rationale for Change**: Study 202 protocol more precisely defined the maximal acceptable duration of ongoing hypotension (i.e., 2-3 hours) before considering administration of high-dose intravenous corticosteroid therapy. In addition, it permitted earlier administration of tocilizumab (i.e., for persistent Grade 2 CRS) rather than waiting for onset of Grade 3 CRS)*

Grade 3	Management as above (grade 2) and include the following measures: Maximize immunosuppression with continued high-dose intravenous corticosteroid (e.g., methylprednisolone 2 mg/kg/day or equivalent) Consider adding further immunosuppression measures or additional interventions according to the institutional cytokine release protocol (e.g., anti-IL6, tocilizumab) Continue to manage symptoms and vigilantly monitor for escalation Patient may restart IMCgp100 if symptoms resolve and only after discussion and written approval of Sponsor Medical Monitor	Same as current Study 102 Protocol / Version 7.0 15 Dec 2017
Grade 4	Management as above (grade 3) and include the following measures: Additional immunosuppression recommended (e.g., anti-IL6, tocilizumab) with continued high-dose intravenous corticosteroid therapy as described above (e.g., methylprednisolone 2 mg/kg/day or equivalent) If appropriate, consider additional measures according to the institutional cytokine release protocol Permanently discontinue all study medications	Same as current Study 102 Protocol / [Version 7.0 15 Dec 2017

*CRS grading: Study 102 & 202 (Lee, 2014); USPI (ASTCT consensus grading - Lee, 2019)

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