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APPLICATION NUMBER:

761228Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

[FDA will complete this section.]

Application Type	BLA
Application Number(s)	761228
Priority or Standard	Priority
Submit Date(s)	June 23, 2021
Received Date(s)	June 23, 2021
PDUFA Goal Date	February 23, 2022
Division/Office	OOD/DO3
Review Completion Date	January 21, 2022
Established Name	Tebentafusp-tebn
(Proposed) Trade Name	Kimmtrak
Pharmacologic Class	Bispecific gp100 peptide-HLA-directed CD3 T-cell engager
Code name	IMCgp100
Applicant	Immunocore, LLC
Formulation(s)	Injection, Solution, 100 mcg in 0.5 mL, Intravenous Infusion
Dosing Regimen	20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter, via intravenous infusion
Applicant Proposed Indication(s)/Population(s)	For the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma

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Kimmtrak (tebentafusp)

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Kimmtrak (tebentafusp)

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Stats	

OPO=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GLP	good laboratory practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

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OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Tebentafusp-tebn (referred to as tebentafusp) is a bispecific gp100 peptide-HLA-directed CD3 T cell engager. The tumor cell receptor arm of tebentafusp binds to a gp100 peptide presented by human leukocyte antigen-A*02:01 (HLA-A*02:01) on the cell surface of uveal melanoma tumor cells. Tebentafusp exerts its anti-tumor effect by redirecting T cells to attack gp100-expressing tumor cells.

At the time of submission of the current BLA 761228 on June 23, 2021, tebentafusp was not yet approved for any indication in the United States. The Applicant's proposed indication at the time of BLA submission was as follows:

Tebentafusp is a bispecific gp100- (b) (4) T cell (b) (4) for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma

The proposed dosing regimen is 20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter, via intravenous infusion over 15-20 minutes.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team has determined that the results of Study 202, an open-label, randomized, multi-center study in 378 adult HLA-A*02:01-positive patients with unresectable or metastatic uveal melanoma (mUM) demonstrate a statistically significant and clinically meaningful improvement in overall survival (OS) in patients treated with tebentafusp. This trial is ongoing and has enrolled patients with histologically or cytologically confirmed mUM who had not received prior systemic therapy in the metastatic setting or prior regional liver-directed therapy. Patients were randomized 2:1 to receive tebentafusp or investigator's choice of therapy (dacarbazine, ipilimumab, or pembrolizumab) until radiographic progression (except for patients receiving ipilimumab), unacceptable toxicity, investigator decision, or patient withdrawal of consent. The primary study endpoint was overall survival (OS), and key secondary endpoint was investigator-assessed progression free survival (PFS) per RECIST 1.1.

The data submitted by the Applicant has provided substantial evidence for the effectiveness of tebentafusp administered at 20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma and supports regular approval for this indication. This conclusion is based on results from Study 202 which demonstrates a clinically and statistically significant improvement in OS in patients who received tebentafusp compared to

those who received investigator's choice of therapy (HR of 0.51 [95% CI: 0.37, 0.71], $p < 0.0001$).

The safety of tebentafusp has been adequately characterized by data submitted from Study 202 and by supportive data submitted from other studies in the tebentafusp development program. The review team believes that the magnitude of improvement in OS provides a benefit that outweighs the risks associated with systemic treatment with tebentafusp for this patient population with no FDA approved therapies for mUM.

Therefore the review team recommends granting regular approval to tebentafusp for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Uveal melanoma is a rare subset that accounts for <5% of all cases of melanoma in the United States but represents the most commonly occurring intraocular malignancy in adults (Sayan 2020, Kaliki 2017). There are no FDA approved therapies for the treatment of uveal melanoma. Patients with uveal melanoma who have systemic disease are treated with therapies approved for cutaneous melanoma, which have demonstrated limited efficacy in this population. In the metastatic uveal melanoma setting, the National Comprehensive Cancer Network (NCCN) guidelines version 2.2021 recommends participation in a clinical trial as the preferred management option with consideration of monotherapy or combination regimen consisting of liver-directed therapies (e.g. ablative procedures, embolization, isolation of perfusion, resection or radiation), systemic therapies (e.g. immune-oncology agents, cytotoxic regimens or trametinib), resection or radiation treatment for limited or symptomatic extrahepatic disease, or palliative care. Despite responses as high as 90% to treatment options for localized uveal melanoma, as many as 50% of patients will develop metastatic disease (Nichols 2016). The prognosis in patients who develop metastatic uveal melanoma is very poor with median overall survival less than 6 months (Rantala 2019).

The Applicant has submitted data from Study 202 to support the approval of tebentafusp for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. A favorable benefit-risk assessment has been established for tebentafusp based on demonstration of a clinically meaningful and statistically significant improvement in OS in patients who received tebentafusp compared to those who received Investigator's choice of therapy which include dacarbazine, pembrolizumab or ipilimumab (HR of 0.51 [95% CI: 0.37, 0.71], $p < 0.0001$).

The data submitted to support the safety review of tebentafusp is adequate to characterize toxicity in patients with uveal melanoma. The toxicity profile of tebentafusp in patients with HLA-A*02:01 unresectable or metastatic uveal melanoma was comparable with the toxicity observed in patients treated with Investigator's choice of therapy in Study 202. Although there was a slightly higher incidence of SAEs observed in patients treated with tebentafusp, overall tebentafusp appeared to be well tolerated. Fatal adverse events and permanent treatment discontinuation in patients on tebentafusp are rare. Adverse events of special interest (AESIs) were identified in patients treated with tebentafusp. These AESI included cytokine release syndrome (CRS), skin reactions (which includes the subcategories of rash, pruritis, pigment change, erythema, edema, dry skin, and other changes) and elevated hepatic enzymes. Risk minimization strategies have been instituted via

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current management guidelines included in the product labeling and a Medication Guide. In addition, health care providers that will be responsible for prescribing or managing patients on tebentafusp will receive a “Dear Health Care Provider” letter to increase awareness of the risk of CRS, which can be serious or fatal, associated with tebentafusp.

The review team recommends that tebentafusp be approved for the treatment of patients with HLA-A*02:01-positive unresectable or metastatic uveal melanoma.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Uveal melanoma is a rare subset of melanoma and accounts for <5% of all cases of melanoma in the United States. - The incidence of uveal melanoma is estimated to be 4 to 5 cases per million per year (Sayan 2020; Kaliki 2017). - Localized disease may be treated with radiation or surgery, however almost half of patients will develop systemic disease (Sayan 2020).	Uveal melanoma is a serious and life-threatening condition. Patients diagnosed with metastatic disease have a poor prognosis with median survival <6 months (Rantala 2019).
Current Treatment Options	- Non-metastatic disease can be treated with radiation or surgery depending on the size of the lesion. - Patients with advanced and metastatic uveal melanoma are encouraged to participate in clinical trials. Other options for management include a combination approach liver-directed therapies, systemic therapies, and resection or radiation for limited or symptomatic extrahepatic disease (NCCN 2021). - Uveal melanoma is treated with the same systemic therapies used for the management of cutaneous melanoma; however these therapies have shown limited benefit in patients with uveal melanoma.	There are no approved therapies specifically for uveal melanoma and no effective therapy options once disease has metastasized. Given the poor prognosis, there remains an unmet medical need.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Benefit</u>	In Study 202, tebentafusp demonstrated a clinically and statistically significant improvement in OS compared to investigator choice of dacarbazine, pembrolizumab or ipilimumab (HR of 0.51 [95% CI: 0.37, 0.71], $p < 0.0001$).	The study met its primary objective with tebentafusp demonstrating superiority over investigator's choice therapy. OS is the preferred endpoint to demonstrate clinical meaningfulness and effectiveness of new therapeutics across oncology indications.
<u>Risk and Risk Management</u>	- The safety profile of tebentafusp for the treatment of HLA-A*02:01-positive metastatic or unresectable uveal melanoma appears acceptable for a therapy used for the treatment of a serious and life-threatening disease. - Rates of AEs were comparable (to slightly higher) on the tebentafusp arm with those observed on the Investigator's Choice arm. Fatal adverse events and permanent treatment discontinuation in patients on tebentafusp are rare. - Tebentafusp has been associated with adverse events of special interest (AESIs) which include cytokine release syndrome, skin reactions, and elevated liver enzymes.	The safety data submitted was sufficient to characterize the toxicity profile of tebentafusp and the risks are considered acceptable in the context of the clinical efficacy in the advanced or metastatic disease setting. The USPI has been appropriately amended to provide guidance for the management of AESIs, Routine pharmacovigilance for late toxicities is warranted.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
☒	Patient reported outcome (PRO)	Section 8.1.2

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	☐	Observer reported outcome (ObsRO)	
	☐	Clinician reported outcome (ClinRO)	
	☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify)	
	☐	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Uveal melanoma is a rare and highly malignant subset of melanoma, representing < 5% of all melanoma cases in the United States (US; [McLaughlin, 2005](#)). Uveal melanoma is the most frequent primary intraocular malignancy of the adult eye (~85%; [Patel, 2011](#); [Maio, 2013](#)). The incidence varies by geography, race, and age, ranging from 5.3 to 10.9 cases per million ([Singh, 2011](#)). Uveal melanoma arises exclusively from melanocytes of the uvea, and it is biologically, clinically, and genetically distinct from cutaneous melanoma (CM; [Jager, 2020](#)). *BRAF* and *NRAS* mutations dominate the landscape in CM, whereas mutations in guanine nucleotide binding protein, q polypeptide, and alpha 11 dominate in UM ([Shoushtari, 2014](#)). The mode of disease spread is distinct between the 2 diseases, with hematogenous spread being most common in UM while lymphatic predominates in CM. Moreover, UM has a highly immunosuppressive tumor microenvironment ([Jager, 2020](#); [Rothermel, 2016](#)). Cutaneous melanoma has one of the highest tumor mutational burdens (TMB), whereas the TMB of UM is among the lowest of all cancers ([Lee, 2019](#); [Yarchoan, 2017](#)). The low TMB in UM results in few neoantigens, which limits natural antitumor immunity ([Violanti, 2019](#)), making UM less sensitive to immune checkpoint inhibitors than CM.

Uveal melanoma is a life-threatening disease with no effective therapy once it metastasizes. Despite local therapy (radiation and surgery), up to 50% of patients with UM develop systemic metastases, predominantly to the liver (~90% of patients) and less commonly to the lungs and bones ([Nathan, 2015](#)). Once patients develop metastatic UM (mUM), the prognosis and outcomes are dismal, with a median survival of ≤ 12 months ([Rantala, 2019](#); [Khoja, 2019](#)). Over the past 40 years, there has been no significant improvement in survival for patients with mUM.

The FDA's Assessment:

FDA agrees with the Applicant's characterization and assessment of the disease.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

No products are formally approved by FDA for the treatment of metastatic uveal melanoma.

Current Treatment Landscape for Uveal Melanoma

In contrast to other melanomas, particularly CM, current treatment options for mUM are limited and deemed ineffective. Metastatic UM responds poorly to cytotoxic chemotherapy, radiotherapy, and immunotherapy ([Buder, 2013](#); [Pereira, 2013](#)). No systemic or local therapies are approved specifically for the treatment of mUM ([Carvajal, 2014](#); [Luke, 2013](#); [Maio, 2013](#)). Treatments introduced for CM over the past decade have not significantly benefited patients with UM, reflecting the distinct biology, genetics, and clinical course of UM. The standard of care for mUM is enrollment in a clinical trial ([Carvajal, 2017](#)). When clinical trials are not available, therapies for advanced CM are used.

Representative multicenter clinical studies or case series of at least 20 patients with mUM who received available therapies are summarized in **Error! Reference source not found..** Studies with single-agent chemotherapy arms showed a median overall survival (OS) of approximately 10 months ([Buder, 2013](#)). Single-agent immune checkpoint inhibitors (anti-cytotoxic T-lymphocyte associated antigen-4 [CTLA-4] or anti-programmed cell death-1 [PD-1]) exhibited median OS similar to that of cytotoxic therapy in mUM (approximately 6 to 10 months). These data are generally consistent with a global meta-analysis that included > 900 patients in Phase 2 trials in mUM, demonstrating a median OS of approximately 9 months and 1-year OS rate of 43% across treatment modalities and lines of therapy in the metastatic setting ([Khoja, 2019](#)). In a meta-analysis of > 2400 first line (1L) mUM patients, median OS was about 12 months with a 1-year OS rate of 52% ([Rantala, 2019](#)). Although the combination of anti-CTLA-4 and anti-PD-1 has a numerically higher objective response rate (ORR), this combination has a 1-year OS rate similar to checkpoint monotherapy ([Pelster, 2021](#); [Piulats, 2021](#)). Together, these data suggest that a new treatment option with different mechanism of action (MoA) to those used for other melanomas is essential to improve outcomes in mUM, a serious and life-threatening disease.

Table 1: Efficacy of Current Therapies for Patients with Metastatic Uveal Melanoma

Clinical Study ^a	N ^b	Median Prior Tx Lines (range)	LDH (%)	Response Criteria	ORR n (%)	Median OS (months)	1-yr OS rate (%)	Median PFS (months)
Khoja, 2019	912	(0->3)	NR	Multiple	NR	8.9 (IT) ^e 9.2 (CT) ^e	43	2.8 (IT) ^e 2.6 (CT) ^e
Rantala, 2019	2494	1 (NR)	NR	NR	NR	12.8	52	NR

Table 1: Efficacy of Current Therapies for Patients with Metastatic Uveal Melanoma

Clinical Study ^a	N ^b	Median Prior Tx Lines (range)	LDH (%)	Response Criteria	ORR n (%)	Median OS (months)	1-yr OS rate (%)	Median PFS (months)
Single-agent chemotherapy								
<u>Buder, 2013</u>	768	(0-8)	NR	WHO/RECIST	34 (4.4)	9.3	NR	NR
Anti-CTLA-4 (ipilimumab) monotherapy								
<u>Zimmer, 2015</u>	53	1 (0->3)	NR	RECIST	0	6.8	22	2.8
<u>Luke, 2013</u>	39	1 (0-5)	63	irRECIST	2 (5.1)	9.6	45 ^c	NR
<u>Maio, 2013</u>	82	NR (≥ 1)	45	irRC	4 (5.0)	6.0	31	3.6
Anti-PD-1 monotherapy								
<u>Algazi, 2016</u>	56	1 (0->4)	70	ir/RECIST ^d	2 (3.6)	7.6	45 ^c	2.6
<u>Karydis, 2016</u>	25	1 (0->3)	72	irRC	2 (8.0)	>225 days	28	91 days
Ipilimumab + nivolumab combination therapy								
<u>Pelster, 2021</u> ^f	33	NR (0-4)	43	RECIST	6 (18.2)	19.1	56	5.5
<u>Najjar, 2020</u>	89	3 (0->4)	45	NR	10 (11.6)	15.0	NR	2.7
<u>Piulats, 2021</u>	52	0	37	RECIST	6 (11.5)	12.7	52	3.0

CT = chemotherapy; CLTA-4 = cytotoxic T-lymphocyte-associated antigen-4; ir = immune-related; irRC = immune-related Response Criteria; IT = immunotherapy; LDH = lactate dehydrogenase; NR = not reported; ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death-1; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; Tx = treatment; UM = uveal melanoma; WHO = World Health Organization.

^a Studies included if conducted in a multicenter approach and reporting efficacy in at least 20 patients.

^b Number of UM patients who were evaluable for efficacy, as reported by the publication cited.

^c OS/PFS rate estimated from published Kaplan-Meier curve.

^d RECIST implemented with 1 or 2 responses reported following treatment beyond initial RECIST progression.

^e Meta-analysis (Khoja, 2019) reported some efficacy parameters (median PFS, OS) based on therapy groups (IT or CT).

^f Single institution study.

The FDA's Assessment:

FDA agrees with the Applicant's characterization and assessment of current treatment landscape. There is no FDA approved therapy for metastatic uveal melanoma. There is no effective standard of care for metastatic uveal melanoma.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

No prior marketing applications have been submitted to the US Food and Drug Administration (FDA) for tebentafusp for any indication, including metastatic uveal melanoma. No prior application has been submitted to any other Health Authority globally for tebentafusp for any indication. No marketing application has been rejected or deemed not approvable in the US by FDA or any other Health Authority globally.

The FDA's Assessment:

FDA agrees with the Applicant.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

All clinical studies of tebentafusp were conducted in accordance with Good Clinical Practice, the Declaration of Helsinki, and local requirements. Furthermore, all studies were conducted in accordance with applicable regulatory guidance, including the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance.

The Applicant sought regulatory and scientific advice from health authorities, including the FDA and EMA, throughout the tebentafusp clinical development program for UM. Table 2 provides a summary of key regulatory interactions with FDA that occurred during the tebentafusp clinical development program for UM that are relevant to the BLA application.

Table 2: Summary of Key FDA Regulatory Interactions During the Tebentafusp Clinical Development Program for Uveal Melanoma

Regulatory Event	Date	Description
Key Interactions with FDA		
Orphan Drug Designation granted	21Jan2016	Orphan Drug Designation received for UM (File #15-5036).
Fast Track Designation granted	01Apr2019	FDA granted Fast Track Designation for mUM first line patients.
Breakthrough Designation Approval	18Feb2021	Breakthrough Designation Request was granted for treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic UM.

Table 2: Summary of Key FDA Regulatory Interactions During the Tebentafusp Clinical Development Program for Uveal Melanoma

Regulatory Event	Date	Description
Pre-BLA Type B meeting	12Mar2021	Discussed content and format of the planned submission of a BLA for tebentafusp for the treatment of patients with unresectable or metastatic UM. FDA agreed to the proposed RTOR submission plan and Assessment Aid submission for the BLA.
Initial Agreed iPSP	23Mar2021	FDA agreed with the iPSP with a full waiver for the use of tebentafusp in pediatric patients from birth to 18 years.

BLA = Biologics License Application; BTB = breakthrough therapy designation; HLA = human leukocyte antigen; HTA = Health Technology Assessment; IND = Investigational New Drug; iPSP = initial Pediatric Study Plan; mUM = metastatic uveal melanoma; OS = overall survival; RTOR = Real-time Oncology Review; UM = uveal melanoma.

The FDA's Assessment:

In addition to the interactions summarized above, FDA highlights the following:

- January 9, 2012, FDA received initial IND submission for IMCgp100-01.
- February 8, 2012, FDA issued Study May Proceed letter.
- October 14, 2015, StudyIMCgp100-102 was submitted to FDA.
- January 21, 2016, FDA granted Orphan Drug designation to IMCgp100 for the treatment of uveal melanoma.
- November 14, 2016, End of Phase 2 meeting was held. The purpose of the meeting was to discuss the design of the proposed pivotal Study IMCgp100-202, entitled, "A Phase 2 Open-Label, Multi-Center, Randomized, Active Comparator Trial in Patients with Advanced Uveal Melanoma (UM) Without Prior Treatment in the Advanced or Metastatic Setting".
- October 12, 2018, Type B meeting was held. The purpose of this meeting was to discuss the Applicant's development plan and registrational strategy for tebentafusp that included a proposal to submit ORR data (with a target lower 95% confidence limit of $\geq 5\%$) from Study 102 and supportive data from Study 202, available at the time of the planned interim analysis of Study 102, to support a BLA submission for accelerated approval. FDA stated that it was unclear whether the targeted treatment effect that excludes a lower 95% confidence limit of $\geq 5\%$ for confirmed ORR meets the threshold for reasonably likely to predict clinical benefit and that it was also unclear whether that target treatment effect would demonstrate a favorable risk:benefit analysis considering the observed toxicities of tebentafusp.
- April 1, 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.
- February 18, 2021, FDA granted Breakthrough Therapy designation to tebentafusp (IMCgp100) for treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

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- March 12, 2021, a Pre-BLA meeting was held to discuss the RTOR submission plan for the tebentafusp BLA and to gain feedback on the timing of the PAI inspections, planned ISS/post-submission data update content and cutoffs, and proposed regulatory plans for an HLA genotype assay submission.
- On March 23, 2021, FDA issued an initial agreement with the iPSP requesting full waiver (birth to 17 years) for tebentafusp for the proposed indication of unresectable or metastatic uveal melanoma.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division of Oncology 3 consulted OSI to discuss an audit of overall trial conduct. Four clinical investigators were selected for audit. These were Dr. Hassel (Site 3504), Dr. Piperno-Neumann (Site 6101), Dr. Rutkowski (Site 6401), and Dr. Kirkwood (Site 8705). The Applicant, Immunocore LLC., was also inspected as this is the first marketing application from the Applicant and a new molecular entity. All inspections were conducted onsite. During the inspection of Site 6401 it was noted that updates to the electronic database involving efficacy and safety data had been made after the database lock for the submitted application which were reportedly to be due to limited site resources affecting their ability to complete data cleaning prior to the submission. There was one change in the primary end point of overall survival (OS) for the control arm (USUBID 6401-^{(b) (6)}). A request for information dated November 10, 2021, was sent to the Applicant to determine the extent of changes impacting the primary efficacy endpoint of OS and secondary efficacy endpoints of PFS and BOR across all sites. The Applicant reported that 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. After FDA review, it was determined that these updates were unlikely to change the analysis of OS or PFS or to have a significant impact on interpretation of the study results. The other inspectional findings verified the Applicant's reported clinical data with source records at these study sites. No significant GCP compliance deviations were observed at these sites. Based on the inspectional findings, the OSI review team considers the submitted data from this study reliable for this NDA and the respective indication.

Product Quality

There were no significant issues.

4.2. Clinical Microbiology

There were no significant issues.

4.3. Devices and Companion Diagnostic Issues

All tebentafusp-tebn trials used the SeCore[®] HLA Sequencing System and uTYPE[®] Dx v1.0 HLA Sequence Analysis Software developed by Thermo Fisher Scientific to identify HLA-A*02:01 positive patients. The accuracy of this assay for detecting the specific HLA-A*02:01 allele has not been adequately demonstrated ^{(b) (4)}. A PMC will be issued

requesting the Applicant to conduct an assay validation study to demonstrate that the assay can accurately differentiate HLA-A*02:01 from other HLA A alleles. See Section 13.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Tebentafusp (IMCgp100) is a bispecific fusion protein that consists of a soluble T cell receptor (TCR) fused to an anti-cluster of differentiation 3 (anti-CD3) single-chain variable fragment (scFv). The TCR domain binds a gp100 peptide (peptide fragment derived from the melanoma associated antigen glycoprotein 100, position 280-288, YLEPGPVT A):human leukocyte antigen (HLA)-A*02:01 complex. Glycoprotein 100 (gp100) is a type 1 transmembrane glycoprotein that is enriched in melanosomes. The established pharmacologic class (EPC) is bispecific gp100 peptide-HLA-directed CD3 T-cell engager.

In an in vitro assay, tebentafusp bound the gp100 peptide:HLA-A*02:01 complex with a mean K_D value of 24 pM. Tebentafusp bound CD3 with a mean K_D value of 38 nM. Average bifunctional binding of tebentafusp to gp100 peptide-HLA-A*02:01 and soluble CD3 was 88%. Tebentafusp exhibited binding specificity towards the HLA-A*02:01 subtype, with EC_{50} values ranging from ~30 to 60 pM for HLA-A*02:01-positive cell lines. Comparatively, tebentafusp bound other HLA-A subtypes with EC_{50} values of ≥ 166 pM. In HLA-A*02:01-positive cutaneous and uveal melanoma cell lines co-incubated with peripheral blood mononuclear cells (PBMCs), tebentafusp treatment led to a dose-dependent increase in IFN γ release with EC_{50} values ranging from 0.89 to 121 pM. T cell activation by tebentafusp increased cytokines IFN γ , TNF- α , IL-6, IL-2, and MIP-1 β . In vivo, the anti-tumor activity of tebentafusp was evaluated in mice engrafted with HLA-A*02:01/gp100-positive Mel526 human melanoma cancer cells mixed with PBMCs isolated from human whole blood. In this study, administration of 5 doses of tebentafusp resulted in tumor growth inhibition compared to controls.

There are no pharmacologically relevant animal species to evaluate tebentafusp toxicity. In vitro, the scFv portion of tebentafusp bound to T cells in human PBMCs but did not bind PBMCs from mouse or monkey. Tebentafusp was evaluated in a series of in vitro studies to characterize potential cross-reactivity in 35 normal human tissues by immunohistochemistry (IHC) and the potential for organ-specific toxicities in functional assays using 13 normal human tissues. Tebentafusp did not show off-target/cross-reactivity in tissues outside of melanocytes, and alloreactivity and platelet activation were not observed.

Genotoxicity and carcinogenicity studies were not warranted.

Tebentafusp was not evaluated in embryofetal toxicity studies. In the reproductive toxicity assessment provided by the Applicant, the following points are considered: (1) gp100 is expressed embryonically in melanocytes found in the skin, inner ear, and eyes by 7 weeks of gestation; (2) MHC Class I classical proteins (including HLA-A*02:01) and transporter-associated-with-antigen-processing (TAP) proteins required for presentation of antigen on the cell surface are expressed early in embryonic development; and (3) CD3-positive T cells begin to populate the periphery and are capable of being activated by around 12 weeks of gestation.

Fusion proteins may cross the placenta. In an embryo-fetal development study in mice, a murine surrogate of blinatumomab, which has a similar molecular weight and mechanism of action as tebentafusp, crossed the placental barrier and fetal exposure occurred at pharmacologically active concentrations.

Based on its size and mechanism of action, tebentafusp may cross the placenta and cause fetal harm, particularly the skin, inner ear, and eye, if the developing fetus is exposed to tebentafusp.

There are no approvability issues from a pharmacology/toxicology perspective.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

No prior BLAs have been submitted for tebentafusp for any indication, including metastatic uveal melanoma. No DMFs are utilized by any of the Contract Manufacturing Organizations (CMOs) that produce the drug substance (AGC in Copenhagen, Denmark) or finished product (Baxter, Germany), nor any other processing provider.

5.3. Pharmacology

Primary pharmacology

In vitro studies

Surface plasmon resonance (SPR) was used to assess binding (Study IMC 1022). The mean K_D value of tebentafusp for the gp100 peptide-HLA-A*02:01 complex was 24 pM. The mean K_D value of tebentafusp for CD3 was 38 nM. When SPR was used to evaluate the bifunctional binding of tebentafusp, 88% of gp100 peptide-HLA-A*02:01 complex-bound tebentafusp bound soluble CD3.

The Applicant also used SPR to assess the ability of tebentafusp to bind the gp100 peptide complexed with other HLA-A2 subtypes (HLA-A*02:02, 03, 05, 06, and 07; Study IMC 1040). In this study, tebentafusp was affinity enhanced to bind a heteroclitic (e.g., sequence-modified) version of the gp100 peptide, in which the C-terminal amino acid was substituted from an alanine to a valine to provide binding stability on HLA-A*02. As shown in Table 3, the binding of IMCgp100 (tebentafusp) was reduced with other A2 subtypes as compared to HLA-A*02:01, as measured by relative residence half-life values.

Table 3: Relative residence half-life for tebentafusp (IMCgp100) across HLA-A*02 subtype heavy chains

Heteroclitic gp100 Peptide Complex	IMCgp100 Relative Residence Half-life
A*0201	1
A*0202	0.68
A*0203	0.02
A*0205	0.71
A*0206	0.31
A*0207	0.16

(Source: Applicant table reproduced from Study IMC 1040)

The Applicant conducted cellular assays to support the HLA-A*2 subtype binding data. Briefly, plasmids encoding the subtypes HLA-A*02:01, HLA-A*02:02, HLA-A*02:04, HLA-A*02:05, and HLA-A*02:06 were generated under the control of a human promoter. These plasmids were transduced into the SK-Mel28 HLA-A*02-negative cutaneous melanoma cell line and cells were incubated overnight with increasing concentrations of tebentafusp in the presence of PBMCs. T cell activation was assessed via IFN γ production ELISPOT (Study IMC 1061).

Table 4: Potency of tebentafusp-driven T cell response against cutaneous melanoma cell lines expressing HLA-A*02 subtypes

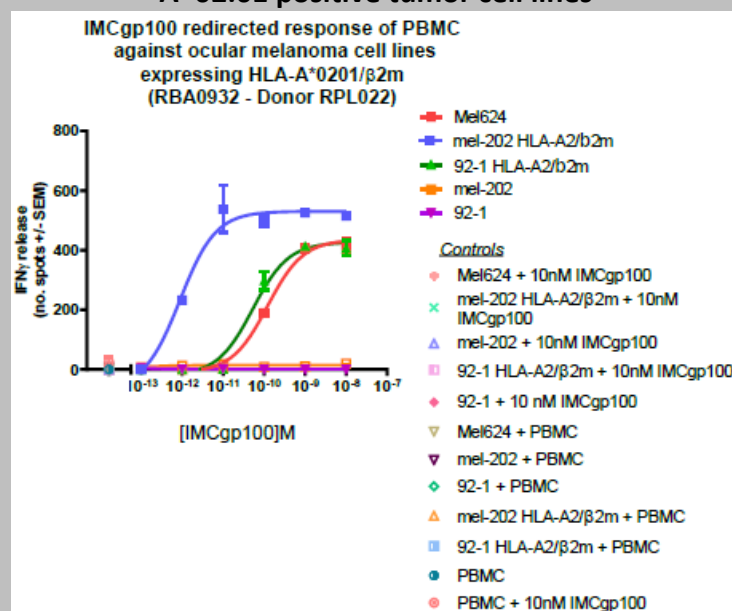
Cell line - HLA-A*02 subtype	Donor TS-016 EC ₅₀ (pM)	R ²	Donor TS-017 EC ₅₀ (pM)	R ²
Mel624	29.6	0.97	18.8	0.97
SK-MEL28 non transduced	ND	ND	ND	ND
SK-MEL28 A*0201	60.3	0.99	40	0.98
SK-MEL28 A*0202	166	0.99	175	0.99
SK-MEL28 A*0204	971	0.99	630	0.99
SK-MEL28 A*0205	ND	ND	ND	ND
SK-MEL28 A*0206	ND	ND	ND	ND

(Source: Applicant Table reproduced from Study IMC 1061)

The Applicant assessed the ability of tebentafusp to inhibit the proliferation of tumor cells that are positive for HLA-A*02:01, including the HLA-A*02:01-positive cutaneous melanoma (CM) cell line, Mel624, and the uveal melanoma (UM) cell lines, mel-202 and 92-1 (Study IMC 1061). Due to limited cell line availability for UM, the two HLA-A*02:01-negative cell lines (92-1 and mel-202) were transduced with a construct to express HLA-A*02:01 and β 2M under the control of a human promoter to allow for physiological levels of HLA-A*02:01 expression. Tumor cells were incubated with non-tumor specific PBMCs from healthy human donors and increasing concentrations of tebentafusp. T cell activation was determined by measuring IFN γ release (ELISPOT), while tumor cell killing was determined by the IncuCyte cell killing assay. Briefly, NucView is a DNA dye-based reagent that is membrane permeable and does not fluoresce unless bound to DNA. In its native state, NucView contains a substrate that prevents binding to DNA. However in the presence of active caspase-3/7, this substrate is cleaved to release the dye to bind DNA. Upon binding to DNA, the dye will emit fluorescence at 488 nm counts are the number of objects that are fluorescing per unit area.

Data from the IFN γ ELISPOT assay (representative data from one PMBC donor) is shown in Figure 1. Incubation of tumor cell lines with PMBCs and tebentafusp led to a dose-dependent increase in IFN γ release, indicating a tebentafusp-mediated redirected PMBC response against the HLA-A*02:01-positive tumor cell lines. The EC₅₀ values for Mel624, mel-202 HLA-A*201/ β 2M, and 92-1 HLA-A*201/ β 2M were 121, 0.89, and 53 pM, respectively.

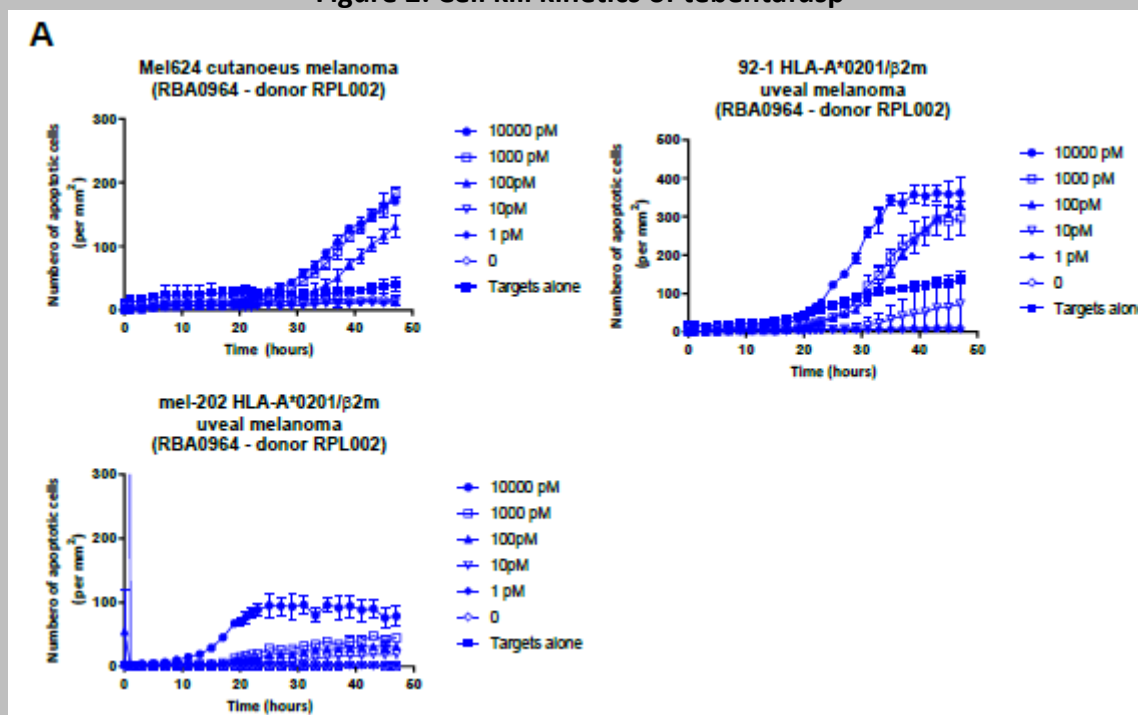
Figure 1: PMBCs release IFN γ following incubation with tebentafusp (IMCgp100) and HLA-A*02:01 positive tumor cell lines



(Source: Applicant figure reproduced from Study IMC 1061)

Representative data from the IncuCyte killing assay is shown in Figure 2. The graphs show the accumulation of apoptotic target cells over a 47 hour time course. Uveal melanoma cells were killed with faster kinetics than cutaneous melanoma cells at doses as low as 10 pM tebentafusp.

Figure 2: Cell kill kinetics of tebentafusp

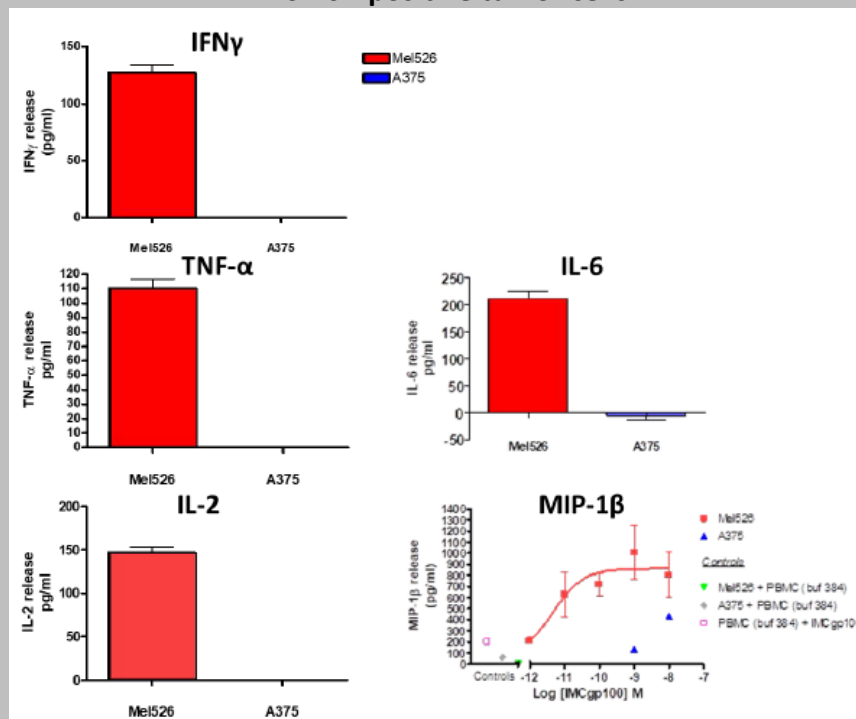


(Source: Applicant figure reproduced from Study IMC 1061)

Similar IFN γ and T cell killing data were seen when antigen-positive cutaneous melanoma cell lines were incubated with tebentafusp in the presence of CD4 $^{+}$ and CD8 $^{+}$ T cells from healthy human donors as well as donor PBMCs from patients with stage 4 melanoma (Study IMC 1014, IMC 1015, IMC 1017, IMC 1020).

The Applicant performed an assay to determine if T cell activation by tebentafusp induced release of proinflammatory cytokines (Study IMC 1020). In this study, tebentafusp was incubated with HLA-A*02:01-positive Mel526 CM cells and HLA-A*02:01-negative A375 melanoma cells co-cultured with PBMCs as effector cells. Cytokine release was measured via the Luminex assay. HLA-A*02:01-positive Mel526 cells incubated overnight with 1 nM tebentafusp showed release of proinflammatory cytokines, while HLA-A*02:01-negative A375 cell lines did not (Figure 3).

Figure 3: Tebentafusp (IMCgp100)-mediated proinflammatory cytokine release by HLA-A*02:01-positive tumor cells

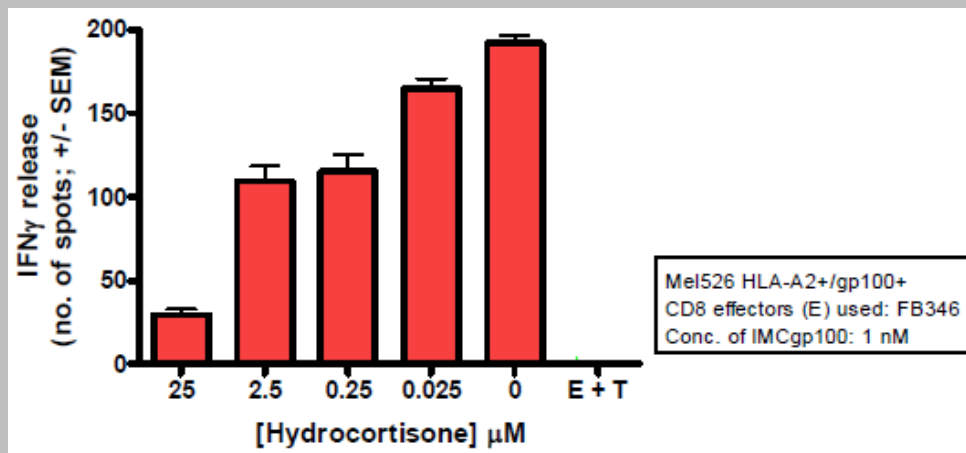


(Source: Applicant figure reproduced from Study IMC 1020)

Comparable results were seen in co-culture assay with PMBCs isolated from patients with cutaneous melanoma (Study IMC 1046).

Tebentafusp exhibits its pharmacologic activity through the redirected activation of CD3+ T cells. To test whether the activity of tebentafusp could be blocked by corticosteroids, tebentafusp-mediated T cell activation assays (IFN γ ELISPOT) were performed (Study IMC 1018). Mel526 cells were co-incubated with CD8+ T cells and 1 nM tebentafusp, with increasing concentrations of hydrocortisone. As shown in Figure 4, tebentafusp-mediated T cell activity (via measurement of IFN γ release) was inhibited by hydrocortisone in a dose-dependent manner.

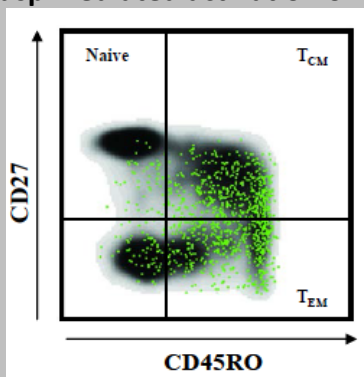
Figure 4: Hydrocortisone inhibition of CD8+ T cell activation by tebentafusp



(Source: Applicant figure reproduced from Study IMC 1018)

Tebentafusp redirects T cell activity through its anti-CD3 scFv effector domain. The Applicant performed studies to evaluate the kinetics of tebentafusp T cell redirecting capacity and to analyze the subsets of T cells that are activated. To determine the effects of tebentafusp on activation of specific T cell subsets, polychromatic flow cytometry was performed on T cells using gp100 peptide-pulsed PBMCs as target cells. The phenotypic profile of CD8+ T cells activated with tebentafusp is shown in Figure 5 (tebentafusp at a concentration of $\sim 10^{-11}$ M in the presence of gp100 peptide-pulsed PBMC target cells). Activated cells undergoing degranulation are depicted in green (CD107a staining). The major T cell populations activated in these experiments were the effector memory (T_{EM}) and central memory (T_{CM}) subsets as determined by CD45RO and CD27 staining.

Figure 5: Tebentafusp mediated activation of T_{EM} and T_{CM} subsets

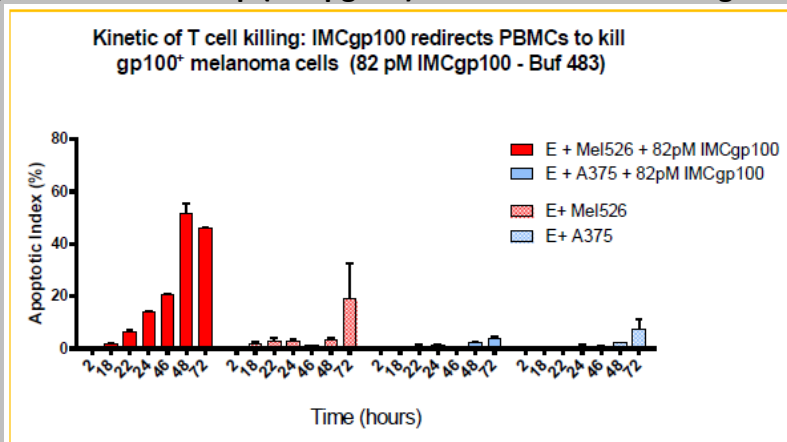


(Source: Applicant figure reproduced from Study IMC 1027)

To determine the tebentafusp killing kinetics sustained by PBMCs, CD8+, and CD4+ T cell subpopulations, Mel526 cells were treated with a clinically relevant concentration of

tebentafusp (82 pM), co-cultured with effector cell subsets, and cell killing was assessed using the IncuCyte platform (Study IMC 1045). As shown in Figure 6, apoptotic events using PMBCs begin around 22 hours with a peak at ~48 hours.

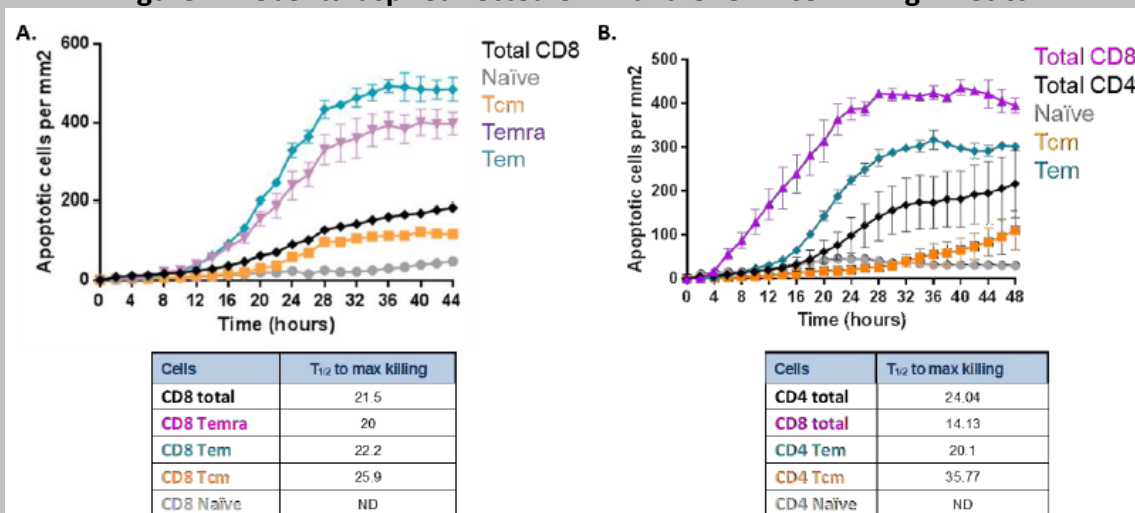
Figure 6: Tebentafusp (IMCgp100) redirected PBMC killing kinetics



(Source: Applicant figure reproduced from Study IMC 1045)

In this assay, tebentafusp also redirected CD8⁺ and CD4⁺ T cells to kill gp100-positive melanoma cells. CD8⁺ cell subset kinetics are shown in Figure 7A and CD4⁺ cell subset kinetics are shown in Figure 7B. Killing by tebentafusp-redirected CD4⁺ T cells was delayed compared to CD8⁺ T cells but with similar total activity. In both CD4⁺ and CD8⁺ T cells, TEM and TEMRA (effector memory T cells re-expressing CD45RA) subsets were the most effective and fastest at mediating tumor cell killing.

Figure 7: Tebentafusp redirected CD4⁺ and CD8⁺ T cell killing kinetics

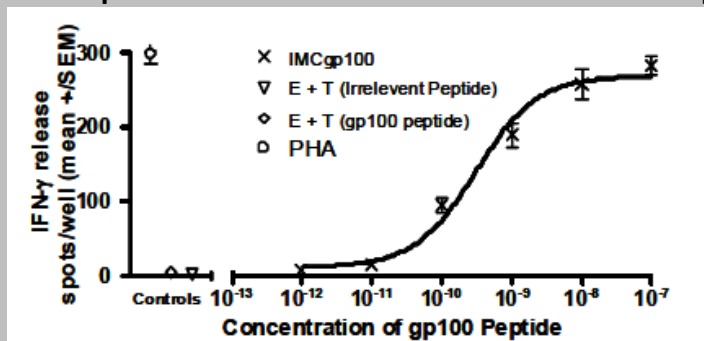


(Source: Applicant figure reproduced from Study IMC 1045)

The Applicant next assessed the threshold of epitope density necessary for tebentafusp-mediated T cell activation and whether the activity of tebentafusp was epitope density-dependent (Study IMC 1030). Briefly, the TCR domain of tebentafusp was tagged with biotin to allow a fluorescently labeled streptavidin to detect a single TCR-peptide:HLA interaction. Microscopy was used to quantify the number of gp100 antigens presented on CM cell lines and T2 cells (a lymphoma-derived cell line that expresses low levels of HLA-A2) that had been exogenously pulsed with increasing levels of the target gp100 peptide. To determine the relationship between the level of gp100 antigen presentation on target cells and tebentafusp-mediated T cell activation, the T2 cells were pulsed with increasing concentrations of gp100 antigen in the presence of 0.1 nM tebentafusp and CD 8+ T cells. IFN γ ELISPOT assays were then used to measure T cell activation.

CM cell lines Mel526 and Mel624 exhibited an average of 33 epitopes and 30 epitopes, respectively (data not shown). In the T2 cells incubated with tebentafusp and the target gp100 peptide epitope, IFN γ release was observed starting at ~100 pM peptide and reached its maximum between 1 and 10 nM of target gp100 peptide. These results suggest that T cell activation is correlated with epitope density. According to the Applicant, these results correspond to a minimum of ~5 epitopes per cell for T cell activation, with maximum activation observed beginning at a concentration of 10^{-9} M gp100 peptide, corresponding to approximately 18 epitopes per cell.

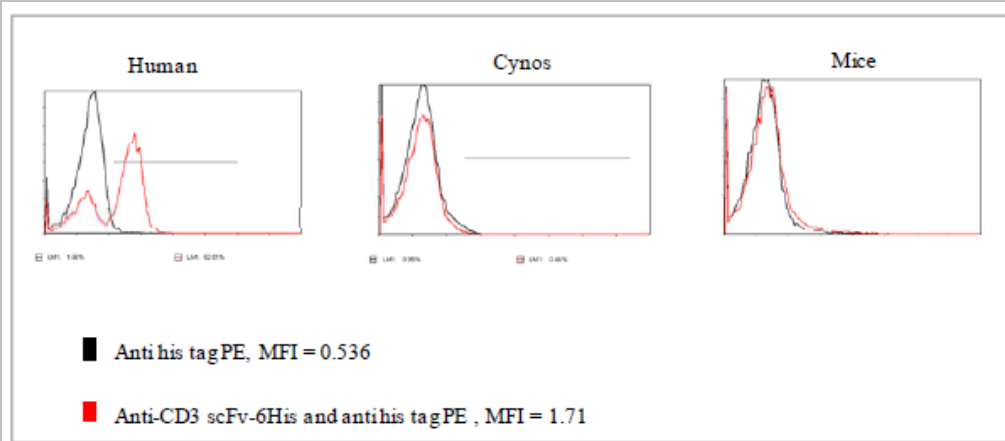
Figure 8: Tebentafusp-mediated T cell activation correlates with epitope density



(Source: Applicant figure reproduced from Study IMC 1030)

The Applicant performed a study to determine if the scFv portion of tebentafusp (UCHT1) binds to T cells in human, mouse, and monkey PBMCs (Study IMC 1029). Briefly, PBMCs were isolated from blood from human donors, cynomolgus monkeys, and mice (strain unspecified). Samples were stained with UCHT1-his scFv protein, an IgG1 PE (isotype control), and species specific anti-CD3 antibodies. Binding was assessed via flow cytometry. Comparison of staining of PBMCs from human, monkey, and mouse indicated that UCHT1 binds to CD3 on human T cells only (Figure 9).

Figure 9: Tebentafusp binding to CD3 on human, monkey, and mouse T cells

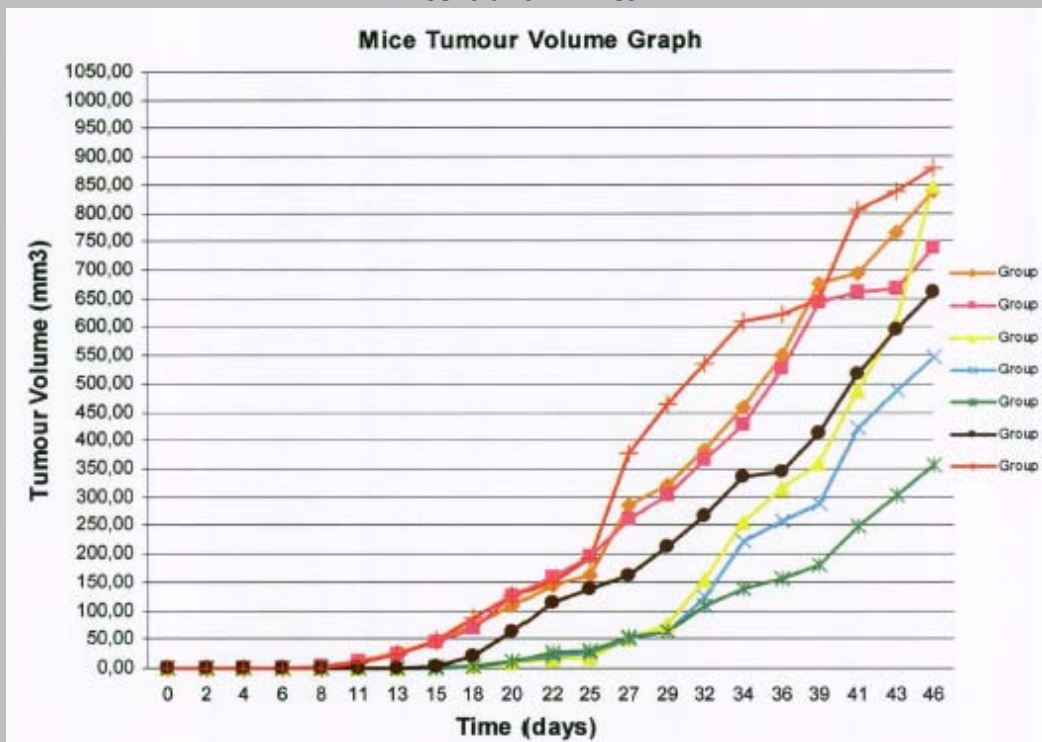


(Source: Applicant figure reproduced from Study IMC 1029)

In vivo studies

To evaluate the anti-cancer activity of tebentafusp, HLA-A*02:01/gp100-positive Mel526 human melanoma cancer cells mixed with PBMCs isolated from human whole blood were engrafted subcutaneously into female Beige/severe combined immune deficiency (SCID) mice on Day 0 (Study CAM 018). On Days 1 to 5, tebentafusp was administered to the mice via intravenous tail injection once daily, at doses ranging from 0.004 to 0.1 mg/kg. Control animals received vehicle or a molecule that consisted of a TCR recognizing the HLA-A*02:01 presenting an HIV-GAG peptide fused to an anti-CD3 scFv. Tumor size was assessed using caliper measurements three times weekly. As shown in Figure 10, tebentafusp inhibited tumor growth compared to controls.

Figure 10: Tumor volume of tebentafusp treated SCID mice engrafted with human melanoma cells and PBMCs



(Source: Applicant figure reproduced from Study CAM 018)

Group 1: vehicle control, no PBMCs, Group 2: vehicle control, Group 3: 0.1 mg/kg tebentafusp, Group 4: 0.04 mg/kg, Group 5: 0.01 mg/kg, Group 6: 0.004 mg/kg, Group 7: Control molecule 0.04 mg/kg

Secondary Pharmacology

The Applicant's Position:

There is no relevant species in which tebentafusp pharmacology can be tested. Therefore, extensive in vitro analysis of secondary pharmacodynamics was performed to characterize both on-target/off-tumor and off-target/off-tumor effects of tebentafusp using a range of functional activity assays. The results of these can be summarized as follows:

- Assessment in normal cells:** In vitro assessments of redirected T cell activity were performed with tebentafusp in the presence of a range of normal cells from 13 tissue types. These studies showed no reactivity of tebentafusp against normal cells at ≤ 1 nM, except for epidermal melanocytes. Tebentafusp demonstrated reactivity against melanocyte lots at concentrations between 10 to 100 pM (10-100 $\times$ MABEL). This activity was deemed to be on-target due to the confirmation of gp100 transcript and protein expression in the reactive cell lots, which is consistent with reports of gp100 expression in melanocytes. Given the low doses required to elicit an on-target on-tumor response, tebentafusp showed a window between normal cells and the reference

CM or UM cell line tested. This activity against melanocytes was not changed when tebentafusp was combined with durvalumab and/or tremelimumab. Tebentafusp demonstrated broad loss of specificity for the target pHLA complex from 1 nM (1,000× MABEL), where consistent evidence of T cell activation (IFN γ release) and/or redirected killing (GrB release) was observed across the different normal cells tested.

- **Alloreactivity:** Most human TCRs only recognize and bind effectively to self-HLA molecules loaded with peptides. A small proportion (less than 10%) of TCRs have the ability to recognize non-self HLA molecules and can induce allojection. This phenomenon is termed alloreactivity (Murphy, 2016). Tebentafusp was specifically engineered and selected for high affinity binding to the HLA-A*02:01-gp100 peptide complex. Therefore, binding to a non-HLA-A*02 Class I molecule is unlikely to occur or, if it does, would occur at much reduced affinity than that for the target HLA-A*02 molecule. Alloreactivity was assessed by IFN γ in ELISPOT in a panel of Epstein-Barr virus-transformed B cell lines representing a large proportion of the target market Class I HLA genotypes, as targets, in the presence of tebentafusp. These studies were non-GLP. These studies were non-GLP. Tebentafusp demonstrated no evidence of alloreactivity when tested against panels of cells displaying other Class I HLA types (inclusive of rare alleles).
- **Activity in whole blood and potential for cytokine release syndrome:** The potential for cytokine release syndrome (CRS) was assessed in blood from 6 healthy HLA-A*02:01-positive donors incubated with increasing concentrations of tebentafusp, and samples were analyzed for evidence of cytokine release by multiplex. These studies were non-GLP. Tebentafusp did not show evidence for increased release of 5 key cytokines in the presence of whole blood at < 1 nM. Combining tebentafusp with durvalumab and/or tremelimumab did not enhance tebentafusp-mediated cytokine release in whole blood.
- **Platelet activity:** Given that platelets have been reported to have very high levels of HLA on their surface (Rowley, 2011; Chapman, 2012), they are a potential target for cross-reactivity of the TCR portion of tebentafusp. Since platelets play a key role in hemostasis, tebentafusp was examined in platelet-activation assays. Platelet activation assays were performed with whole blood from 6 healthy HLA-A*02:01-positive donors and samples were assessed by flow cytometry for the presence of the platelet activation marker CD62P. Additionally, to assess the ability of tebentafusp to interfere with blood-clotting, blood from one healthy HLA-A*02:01-positive donor was incubated with increasing concentrations of tebentafusp and the time to clotting was measured. These studies were non-GLP. Tebentafusp did not give any evidence of adversely affecting platelet activation or function.

The FDA's Assessment:

The Applicant performed a number of functional cross-reactivity experiments to determine if there is a concentration of IMCgp100 at which a loss of target specificity is observed. Of note, at the recommended clinical dose, the steady-state C_{max} of IMCgp100 is 13 ng/mL and AUC_{0-7d} is 4.6 ng·day/mL.

- Assessment in normal cells: To determine potential reactivity of tebentafusp, levels of cytokine (IFN γ) or enzyme (GrB) released by redirected effector cells from PBMCs or purified CD8+ T cells were examined in a cell panel from 13 normal human tissues in the presence of increasing concentrations of tebentafusp up to 10 nM (Study IMC 1001-IMC 1013). FDA agrees with the Applicant's position with respect to melanocyte findings. Additionally, tebentafusp showed activity at <1 nM in 1 of 5 donors when tested on human astrocytes (Study IMC 1001). The Applicant states: *"Based on these [astrocyte and melanocyte] data, skin rash and potentially vitiligo were expected as the primary TCR mediated on-target, off-tumor toxicities."*
- Alloreactivity: FDA agrees. The tested concentrations were 1 nM tebentafusp (Study IMC 1021), 200 pM (Study IMC 1057).
- Activity in whole blood and potential for cytokine release syndrome: In some samples, IL-6, TNF α , and IFN γ were detectable in whole blood at concentrations of 10 and 100 nM tebentafusp (Study IMC 1023). Levels were 2 to 10-fold below the levels of cytokine release observed with positive controls.
- Platelet activity: FDA agrees.
- Impurity Assessment: IMCgp100 contains an identified active impurity (IMCgp100 +scFv fragment), typically at a level of < 1% when tested across multiple batches. The Applicant performed in vitro experiments to assess the impact (Module 4.2.1.2; Study IMCgp100-IMC 1058) on specificity of a batch of tebentafusp spiked with an artificially high (~6.7%) level of the IMCgp100 (+scFv fragment) impurity. Briefly, GMP reference standard batch of tebentafusp was compared with the spiked sample and assessed for specificity by screening for redirected T cell activity by IFN γ release (IFN γ ELISpot) with antigen positive and antigen negative normal cells derived from high risk tissue types and for cytokine release in whole blood (Study IMC 1058).

Higher levels of IFN γ and TNF α release were detected at 0.2 – 1 nM of the tebentafusp spiked sample when compared to non-spiked tebentafusp. This data indicates that high levels of impurity may alter the activity of tebentafusp.

Safety Pharmacology

The Applicant's Position:

Tebentafusp can only recognize human HLA; therefore, all nonclinical toxicology studies were conducted in vitro. Therefore, no specific safety pharmacology studies were conducted.

The FDA's Assessment:

FDA agrees.

5.4.ADME/PK

The Applicant's Position:

Tebentafusp can only recognize human HLA; therefore, all nonclinical toxicology studies were conducted in vitro. Therefore, conventional in vivo animal models used to evaluate drug distribution, bioavailability, mechanism(s) of elimination, and potential risks of specific tissue toxicity are considered limited. Nevertheless, the nonclinical pharmacokinetics (PK) of tebentafusp were evaluated in four animal studies: non tumor-bearing and tumor-bearing severe combined immune deficiency (SCID) mice, C57BL/6 mice, and CD57 or HDD mice. These studies were non-GLP, PK and /or biodistribution studies and administered as single intravenous (IV) or subcutaneous (SC) dose.

Preclinical biodistribution studies demonstrate that tebentafusp is being retained in the melanoma tumor for a significantly longer timeframe compared to other non-target tissues, with a half-life of tumour retention of approximately 24 hours.

Observed pharmacokinetics for tebentafusp after IV administration were generally linear across dose levels tested in different strains of mice. Maximum concentrations (C_{max}) and exposure (AUC) increased in an approximately dose proportional manner for dose levels from 0.005 to 0.05 mg/kg. The maximum concentrations were recorded at 15 minutes, as well as a secondary concentration peak at 1 hour, while the radioactivity was detectable in all samples up to 72 hours. The terminal half-lives calculated from the plasma radioactivity concentrations were also similar at each dose level. Tebentafusp exposure was maintained at measurable levels for 72 hours. Following SC administration of [³H]-tebentafusp to CD57 mice at 0.05 mg/kg, the maximum mean plasma radioactivity concentration was lower and measured later than that measured after the IV dose route at the same dose level, as expected due to the dose route. Concentrations then decreased and were still detectable in all samples at 72 hours. The terminal half-live calculated from the plasma radioactivity concentrations was similar to that calculated following the intravenous administration.

The FDA's Assessment:

Serum tebentafusp PK parameters following a single IV bolus administration to C57BL/6 mice:

Compound	Tebentafusp		
Dose (mg/kg)	0.0001	0.01	0.1
Administration Method	IV	IV	IV
Mouse strain	C57BL/6	C57BL/6	C57BL/6
C ₀ (ng/mL)	19.6	193	2155
C _{max} (ng/mL)	-	-	-
T _{max} (hr)	0	0	0
T _{1/2} (hr)	2.4	1.8	1.7
AUC _{0-t} (ng equiv*hr/g)	53	464	4942
AUC _{0-∞} (ng equiv*hr/g)	55	469	4978

(Source: Applicant table reproduced from Study C85954)

Plasma tebentafusp PK parameters following an IV bolus infusion in SCID mice after single and repeated dosing:

Parameters	Units	Single Dose	Multiple Dose
		Tumor bearing SCID mice 0.01 mg/kg I.V.	Tumor bearing SCID mice 0.01 mg/kg I.V
$T_{1/2\alpha}$	hours	1.92	1.82
Clearance	mL/hour	0.891	0.743
$T_{1/2\beta}$	hours	44.49	27.33
AUC	$\mu\text{Ci/mL/hour}$	25.54	7.747

(Source: Applicant table reproduced from Study IM-CH-01-09)

Study IM-CH-01-09	Major Findings
Distribution studies of one binding ^{125}I -mTCR fusion and one negative control ^{125}I -mTCR fusion given intravenously in a mouse tumor model	Distribution The $t_{1/2}$ in mice: 1.5 hours in blood, 20 hours in tumor For other organs, $t_{1/2}$ ranged from 6 to 10 hours Excretion Less than 10% radioactivity of injected dose found in feces over 7 days. 90% of radioactivity found in urine in the first 24 hours.

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

Tebentafusp can only recognize human HLA; therefore, all nonclinical toxicology studies were conducted in vitro. Human tissue and cell-based in vitro approaches were taken to understand potential organ-specific toxicities that may arise in the clinical setting with tebentafusp. These approaches considered the on-target/off-tumor potential effects, as well as the off-target/off-tumor effects (cross-reactivity) of tebentafusp. These studies are detailed in Secondary Pharmacology Section above.

Tebentafusp was also investigated in toxicology studies to assess its cross-reactivity with normal tissues in a GLP-compliant tissue cross-reactivity study. The ability of tebentafusp to bind to a panel of 35 normal human tissues from 3 healthy donors was assessed using immunohistochemistry (IHC). Staining with tebentafusp was observed in the membrane and cytoplasm of lymphocytes throughout the human tissue panel examined. Similar staining was observed with the individual anti-CD3 component of tebentafusp, while no staining was observed with the individual TCR component, indicating that this staining was attributable to the binding of tebentafusp to CD3. As CD3 is a T lymphocyte marker, this staining was expected. No other staining was observed across the panel of tissues tested, indicating no unexpected cross-reactivity. It should be noted that the TCR targeting domain of tebentafusp recognizes very low target pHLA complexes (>5 pHLA complexes per cell), which are expected to be outside the normal range of sensitivity of the IHC method and would therefore inform on cross-reactivity above the threshold of detection of IHC only. Overall, the results of this study are consistent with published reports of gp100 being specific to melanocytes and melanoma cells, and not in other.

The FDA's Assessment:

In general, and as noted by the Applicant, the use of IHC has limitations based on the low number of target complexes (i.e., IHC is not as sensitive a measure for this cross-reactivity assessment). Tebentafusp staining was observed in the membrane and cytoplasm of lymphocytes in the mammary gland, gastrointestinal tract (colon, esophagus, small intestine, and stomach), kidney, liver, lung, lymph node, fallopian tube, prostate, salivary gland, skin, spleen, thymus, thyroid, tonsil, ureter, urinary bladder, and cervix (Study IM 1861). FDA agrees that this appears to be attributable to CD3 binding. Of note, brain was negative for staining, indicating tebentafusp activity at <1nM in 1/5 human astrocyte samples is likely of low clinical risk (Study IMC 1001).

5.5.2. Genetic Toxicology

The Applicant's Position:

Tebentafusp can only recognize human HLA; therefore, all nonclinical toxicology studies were conducted in vitro. Therefore, no genetic toxicology studies were conducted. The indication is for patients with unresectable or metastatic uveal melanoma whose life expectancy is limited and the risk of death from their uveal melanoma outweighs the risk. This is consistent with requirements of ICH 6, and ICH 9.

The FDA's Assessment:

Based on the biologic properties of tebentafusp, a fusion protein, genetic toxicology studies are not warranted.

5.5.3. Carcinogenicity

The Applicant's Position:

Tebentafusp can only recognize human HLA; therefore, all nonclinical toxicology studies were conducted in vitro. Therefore, no carcinogenicity toxicology studies were conducted. The indication is for patients with unresectable or metastatic uveal melanoma whose life expectancy is limited and the risk of death from their uveal melanoma outweighs the risk. This is consistent with requirements of ICH 6, ICH 9, and S1.

The FDA's Assessment:

Carcinogenicity studies were not warranted for the proposed indication.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

Tebentafusp is a bispecific fusion protein for the treatment of unresectable or metastatic uveal melanoma. The targeting end is an affinity-enhanced T cell receptor (TCR) that binds a human peptide fragment of the melanoma associated antigen glycoprotein 100 (gp100) presented by human leukocyte antigen-A*02:01 (HLA-A*02:01), which is expressed on the surface of melanoma cells. The effector end is a single chain variable fragment (scFv) that binds specifically to human CD3 on T cells. Once administered, tebentafusp is expected to bind to melanoma tissue and stimulate the immune system to attack the target tissue. Due to the specificity for human targets, embryo-fetal development (EFD) studies cannot be conducted in nonclinical species. Therefore, a weight of evidence assessment was conducted to evaluate the risk of tebentafusp administration on pregnancy and embryo-fetal development. A literature search revealed that gp100 is expressed embryonically in melanocytes found in the skin, inner ear, and eyes by 7 weeks of gestation, and MHC Class I classical proteins (including HLA-A*02:01) and transporter-associated-with-antigen-processing (TAP) proteins required for presentation of antigen on the cell surface are expressed very early in embryonic development. In addition, CD3-positive T cells begin to populate the periphery and are capable of being activated by around 12 weeks of gestation.

However, tebentafusp's ability to directly affect embryo-fetal development requires that tebentafusp crosses the placenta and gains access to the fetus. The molecular weight of tebentafusp is 77 kDa, therefore, it is much too large to cross the placenta by diffusion. It also does not contain an Fc domain and, therefore, cannot bind to the neonatal Fc receptor (FcRn), which facilitates transfer of IgG molecules across the placenta, nor does it have domains that could bind to other placental transporters. Thus, tebentafusp would not be able to gain access to or elicit pharmacologic activity directly in the embryo/fetus. There is also no evidence that

tebentafusp could interfere with implantation or the maintenance of pregnancy through its mechanism of action.

Based on the results of this weight of evidence assessment, tebentafusp would not be expected to adversely affect embryo-fetal development or the maintenance of pregnancy when administered during pregnancy.

The FDA's Assessment:

Biologics of this molecular weight may cross the placenta. Based on its mechanism of action, tebentafusp may cause fetal harm, particularly the skin, inner ear, and eye, if the developing fetus is exposed to tebentafusp.

5.5.5. Other Toxicology Studies

The Applicant's Position:

None conducted.

The FDA's Assessment:

No additional toxicology studies were warranted.

X

X

Primary Reviewer

Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

Tebentafusp is a bispecific gp100 peptide-HLA-A*02:01 directed CD3 T cell engager. The applicant is seeking approval of tebentafusp for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. The proposed dosing regimen is 20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter, via intravenous infusion over 15-20 minutes.

The primary efficacy and safety evidence supporting the proposed dosage regimen results from the pivotal Phase 2 study IMCgp100-202, a randomized, open-label trial demonstrating improvements in overall survival (median of 21.7 months for Tebentafusp arm vs 16 month for Investigator's choice arm, with HR of 0.73 and p-value of 0.0139) and an overall acceptable safety profile in Tebentafusp arm.

The dose selection is supported by the results from study IMCgp100-102 and study IMCgp100-01. Study IMCgp100-01 suggested that the flat dosing is preferable given more adverse events (AEs) observed in patients with higher body weight receiving body weight based dosing. Study IMCgp100-01 also showed no clinically meaningful differences in safety or efficacy between the weekly and daily dosing regimens. The maintenance dose selection is supported by the results from study IMCgp100-102, in which a higher 73 mcg dose was not well tolerated as indicated by elevations in hepatic transaminases with concurrent low-grade increases in bilirubin. No dose-limiting toxicities nor significant liver enzyme elevations were observed at the maintenance dose of 68 mcg.

Cytokine release syndrome (CRS) is one of the most common adverse reactions, occurred in 89% of patients in Study IMCgp100-202 who received tebentafusp. CRS led to permanent treatment discontinuation in 1.2% of patients. The priming dosing strategy (20 mcg on Day 1, 30 mcg on Day 8) was adopted to mitigate CRS.

Treatment-emergent anti-drug antibodies (ADA) against tebentafusp were detected in 33% and 29% of patients receiving tebentafusp across all doses in study IMCgp100-102 and study IMCgp100-202, respectively. The median onset time to ADA formation was 6-9 weeks after tebentafusp treatment. Tebentafusp concentration decreased in patients with ADA positivity. Ratio of tebentafusp concentration of ADA+/ ADA- at cycles 5-13 ranged between 0.01 to 0.5. High-titer (>Median titer of 8192) ADAs increased tebentafusp clearance by 35-fold. Exploratory subgroup analysis does not show evidence of clinically meaningful ADA impact on efficacy or safety. Information regarding the presence and impact by neutralizing ADA (Nab) on pharmacokinetics (PK), safety and efficacy was not included in current submission. A Post

marketing commitment (PMC) will be issued to request assessing the presence of Nab in all patient samples that tested positive for binding antibodies and evaluating its clinical impact on PK, safety and efficacy.

The clinical pharmacology review focused on the evaluation of dose selection and the clinical impact of immunogenicity on PK, safety and efficacy.

6.1.1. Recommendations:

The Office of Clinical Pharmacology has reviewed the information submitted in BLA761228. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below in Table 5.

Table 5: Key Clinical Pharmacology Review Issues and Recommendations by FDA

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness comes from the pivotal study IMCgp100-202. The proposed dosage regimen (20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter) is supported by improvements in overall survival (median of 21.7 month for Tebentafusp arm vs 16 month for Investigator's Choice arm), with HR of 0.51 and p value of < 0.0001), in HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.
General dosing instructions	The proposed dosage regimen (20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter) is selected with the following rationale: • Body weight (BW) based dosing regimen: higher BW patients experienced more severe AEs with BW-based dosing. • Weekly dosing: There are no clinically meaningful differences between weekly dosing as compared to daily dosing. • Priming dosing: Cytokine Release Syndrome (CRS) occurred during the first 3 weeks • Maintenance dose of 68 mcg: ○ 73 mcg dose was not tolerated (hepatic transaminases elevation, concurrent low-grade bilirubin elevation). ○ no dose-limiting toxicities and no significant liver enzyme elevations were observed at 68 mcg during dose finding.
Dosing in patient subgroups	No dose adjustment is needed in patient subgroups. The effect of severe renal impairment to end-stage renal disease (CLcr < 30 mL/min) and moderate to

Review Issue	Recommendations and Comments
(intrinsic and extrinsic factors)	severe hepatic impairment (total bilirubin > 3 to 10x ULN, any AST) is not known.
Labeling	Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement with the FDA recommended revisions to the labeling.

Proposed Post Marketing Commitment (PMC)

Information regarding the presence and impact by neutralizing anti-drug antibodies (Nab) on pharmacokinetics (PK), safety and efficacy was not included in the current submission. This following PMC is to be issued to request assessing the presence of Nab in all patient samples that tested positive for binding antibodies and evaluating its impact on PK, safety and efficacy.

Conduct an assessment to determine the presence of neutralizing anti-drug antibodies against tebentafusp in all patient samples that tested positive for binding anti-drug antibodies in studies IMCgp100-202 and IMCgp100-102 by using the validated neutralizing anti-drug antibody assay. Assess the clinical impact of the neutralizing anti-drug antibodies on pharmacokinetics, efficacy and safety of tebentafusp in the final report. Include datasets and analyses in the final study report.

The applicant proposed final report submission date is February 2022.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Table 6: Population Pharmacokinetic Parameter

Parameter	Units	Estimate	Standard Error
CL	L/day	4.33	2.8
V ₁	L	5.25	0.5
Q	L/day	11.4	3.1
V ₂	L	470	79.9
eGFR ~ CL	mL/min/1.73m ²	3.32	1.4
ADA Titer ≥ 8192 ~ CL	-	46.2	8.5

Parameter	Units	Estimate	Standard Error
Interindividual Variability			
CL	CV%	78.5	46.9
V ₁		32.5	10.1
Q		40.9	7.3
V ₂		174.2	13.5
Residual Error			
Additive	ng/mL	0.24	0.081

ADA = antidrug antibody; CL = clearance; CV = coefficient of variation; eGFR = estimated glomerular filtration rate; Q = intercompartment clearance between compartments 1 and 2; V₁ = central volume of distribution; V₂ = peripheral volume of distribution

Clearance is estimated by the following equation: $CL = 4.33 * (eGFR/120)^{3.32} * 46.2^{ADA}$

Source: Module 5.3.3.5, Population PK Modeling Report and Exposure-Response Analysis for Tebentafusp;

(b) (4) Report No. (b) (4) 8472E4.01, Table 8

The Applicant's Position:

Noncompartmental analysis of tebentafusp from study IMCgp100-102 in mUM patients indicated dose-proportional PK with a terminal t_{1/2} of 6.8 to 7.5 hours. The estimated systemic CL and central volume of distribution of tebentafusp in melanoma patients were 4.33 L/d and 5.25 L, respectively. In population PK modeling, the eGFR and high-titer ADA (≥ median titer) were identified as significant covariates impacting CL.

Exposure-response analysis revealed there were no clinically significant trends between tebentafusp exposure and key safety or efficacy endpoints over the dose range investigated (QW IV infusion of 5 ng/kg to 68 µg of tebentafusp). In the final population PK model tebentafusp CL slightly decreased with decreasing renal function. However, CL values in renally impaired patients were essentially within the range observed in patients with normal renal function. Additionally, no impact on safety or efficacy parameters was identified in patients with mild to moderate renal impairment. Therefore, no dose adjustment is recommended in renally impaired patients. There is no information available in patients with severe renal impairment.

The FDA's Assessment:

FDA agrees with the sponsor's position. The tebentafusp clinical pharmacology program includes three clinical studies (Table 7). The results from these three studies generally provide adequate characterization of tebentafusp PK properties, exposure-response relationships and immunogenicity assessment. The Applicant's population PK (PPK) model is generally acceptable with minor change to the definition of immunogenicity. FDA's position is that ADA status should be treated as time-varying covariates. Please refer to section 19.5.4 for detail. Impact of ADA

Titer ≥ 8192 on exposure was re-estimated and USPI was updated (refer to section 12.3).

Table 7: Tebentafusp Clinical Studies with PK and ADA Assessments

Study Number Study Status	Key Study Objectives	Study Design	Patient Population	Treatment Arm and Dosing Regimen	Patients Enrolled/ Treated (N)
IMCgp100-202 (Study 202) Enrollment completed, treatment and follow-up ongoing	Efficacy, safety, PK, and IM	Phase 3, open-label, randomized, controlled, multicenter	Previously untreated (1L) HLA-A*02:01-positive patients with advanced UM	<u>Arm 1: Tebentafusp</u> 20 mcg on C1D1, 30 mcg on C1D8, and 68 mcg on C1D15 and weekly thereafter <u>Arm 2: Investigator's choice</u> <i>Dacarbazine</i> (1000 mg/m ² on D1 of each 21-day cycle) <i>Ipilimumab</i> (3 mg/kg on D1 of each 21-day cycle for maximum of 4 doses) <i>Pembrolizumab</i> (2 mg/kg up to maximum of 200 mg or 200 mg IV, where locally approved, on D1 of each 21-day cycle)	252/245 126/111 7/7 16/13 103/91
IMCgp100-102 (Study 102) Enrollment completed, treatment and follow-up ongoing	Safety, efficacy, PK, and IM	Phase 1/2, open-label, uncontrolled, multi-center	Previously treated (2L+) HLA-A*02:01-positive patients with advanced UM	<u>Phase 1 dose-escalation cohorts</u> Tebentafusp 20 mcg on C1D1, 30 mcg on C1D8, and the respective cohort dose below on C1D15 and weekly thereafter: <i>Cohort 1: 54 mcg</i> <i>Cohort 2: 64 mcg</i> <i>Cohort 3: 73 mcg</i> <i>Cohort 4: 68 mcg</i> <u>Phase 2 dose-expansion cohort</u> Tebentafusp 20 mcg on C1D1, 30 mcg on C1D8, and 68 mcg on C1D15 and weekly thereafter	19/19 3/3 6/6 4/4 6/6 127/127
IMCgp100-01 (Study 01) Completed	Safety, PK, efficacy, and IM	Phase 1, FIH, open-label, uncontrolled, dose-finding	Previously treated HLA-A*02:01-positive patients with advanced melanoma	<u>Arm 1 (weekly dosing)</u> Tebentafusp by weight dose: <i>5 ng/kg</i> <i>15 ng/kg</i> <i>45 ng/kg</i> <i>135 ng/kg</i> <i>270 ng/kg</i> <i>405 ng/kg</i> <i>600 ng/kg</i> <i>900 ng/kg</i> Tebentafusp flat dose: <i>20 mcg intra-patient dose escalation</i> <i>30 mcg intra-patient dose escalation</i> <i>50 mcg</i> <u>Arm 2 (daily dosing)</u> Tebentafusp by weight dose: <i>10 mcg</i> <i>20 mcg</i> <i>30 mcg</i> <i>40 mcg</i> <i>50 mcg</i>	66/66 3/3 3/3 3/3 3/3 3/3 6/6 20/20 4/4 7/7 3/3 11/11 18/18 3/3 3/3 3/3 4/4 5/5

1L = first line; 2L+ = second line or greater; C = Cycle; D = Day; FIH = first-in-human; HLA-A*02:01 = human leukocyte antigen-A*02:01; IM = immunogenicity; IV = intravenous; PK = pharmacokinetic(s); UM = uveal melanoma

NDA/BLA Multi-disciplinary Review and Evaluation BLA 761228
Kimmtrak (tebentafusp)

Source: Summary of Clinical Pharmacology, Table 1, Page 15.

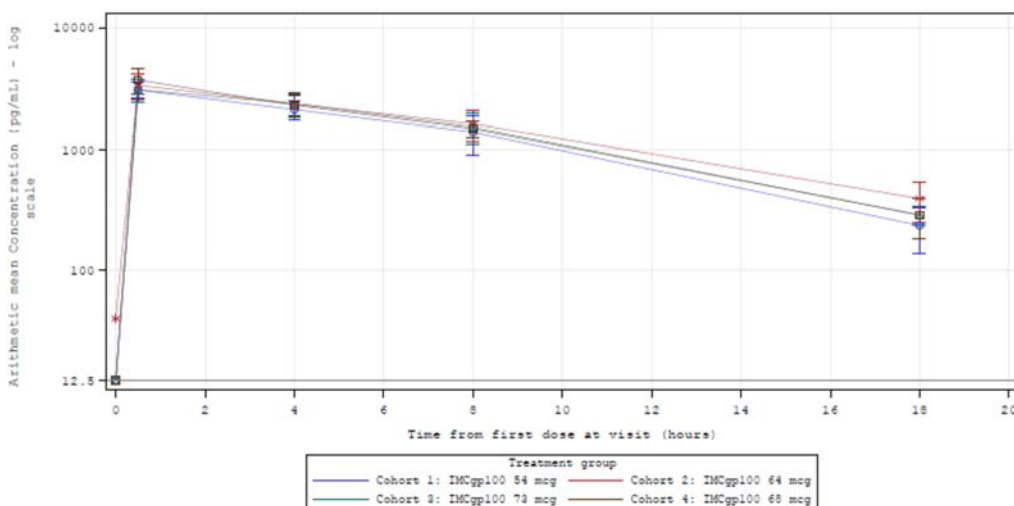
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6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

Figure 11 Tebentafusp Serum Concentration Versus Time (Log Scale): Phase 1 Cycle 1 Day 1 (Safety Analysis Set)



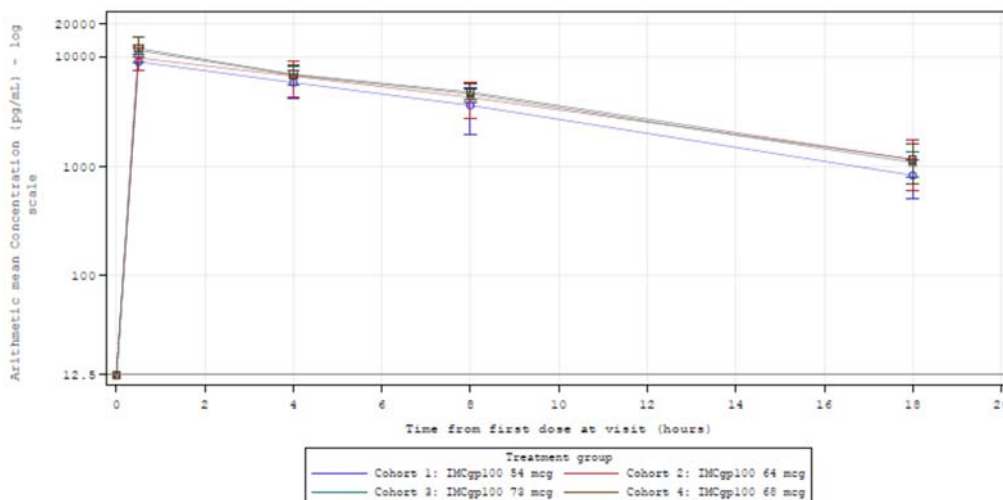
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Lower limit of quantification (LLOQ) = 25 pg/mL

Concentrations below the LLOQ were plotted as 12.5 pg/mL (half the LLOQ)

Source: IMCgp100-102 Clinical Study Report Figure 15

Figure 12 Tebentafusp Serum Concentration Versus Time (Log Scale): Phase 1 Cycle 1 Day 15 (Safety Analysis Set)

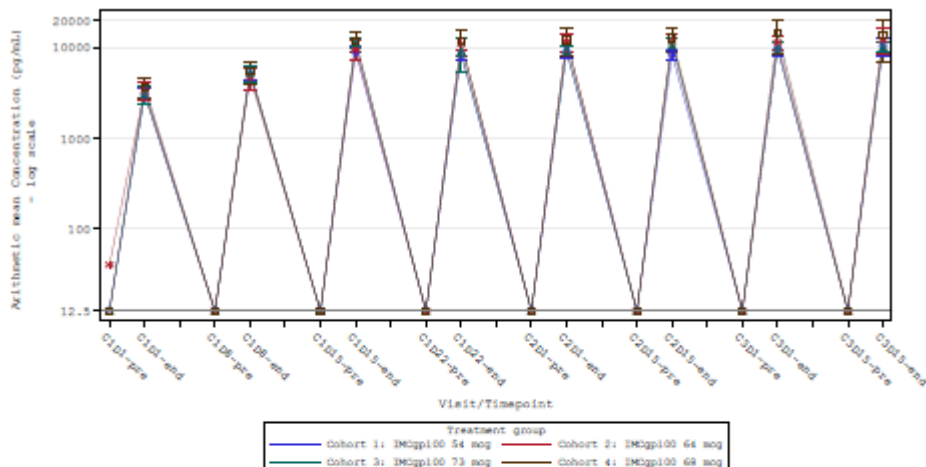


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Lower limit of quantification (LLOQ) = 25 pg/mL
Concentrations below the LLOQ were plotted as 12.5 pg/mL (half the LLOQ).
Source: IMCgp100-102 Clinical Study Report Figure 16

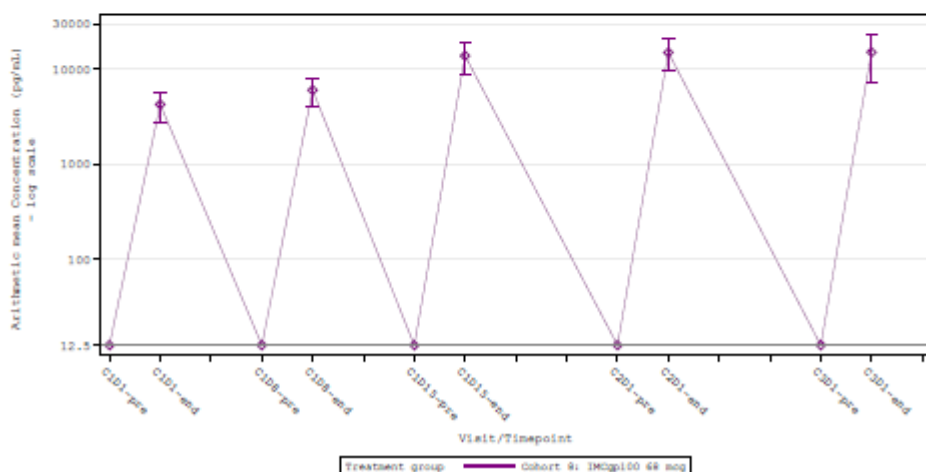
Figure 13 Tebentafusp Mean Concentration Versus Time Profile Cycle 1 Day 15 (Safety Analysis Set)

Phase = Phase 1 dose escalation cohorts (N=19)



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Phase = Phase 2 dose expansion cohort (N=127)



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Top Panel: Phase 1 dose escalation cohorts (N=19)

Bottom Panel: Phase 2 dose expansion cohort (N=127)

Lower limit of quantification (LLOQ) = 25 pg/mL

Concentrations below the LLOQ were plotted as 12.5 pg/mL (half the LLOQ)

Source: IMCgp100-102 Clinical Study Report Figure 17

The Applicant's Position:

The recommended dosing regimen of tebentafusp is 20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter. Tebentafusp is administered via IV infusion over 15 to 20 minutes. The selection of intra-patient dose escalation over the first 3 weeks was

identified in Study 01 and the actual doses were selected during the Phase 1 portion of Study 102. The final, recommended dosing regimen was then studied in the Phase 2 portion of Study 102 and the Phase 3 Study 202.

Study 01: Several key observations in the first-in-human, Phase 1 study (Study 01) led to recommending an intra-patient escalation regimen using fixed doses. First, in Study 01, patients with higher body weights who received higher absolute doses of tebentafusp experienced more severe treatment-related toxicity. Consequently, fixed doses, rather than weight-based doses, were incorporated during the study. Second, given no clinically meaningful differences in safety or efficacy were identified between the weekly and daily dosing regimens, and in light of the easier utility of a weekly regimen, subsequent evaluation focused on weekly dosing. Third, the emerging safety profile of tebentafusp suggested that CRS (and associated hypotension) was more likely to occur during the first 2 weeks, after which tachyphylaxis occurred. Therefore, as has been used for other T cell-engaging bispecifics, an intra-patient escalation regimen during Weeks 1 and 2 (ie, 20 and 30 mcg, respectively) prior to dosing 50 mcg was selected as the preferred regimen to evaluate further in the subsequent single-arm, Phase 1/2 Study 102.

Study 102: In Study 102, the intra-patient escalation regimen based on fixed dosing identified in Study 01 was further optimized by evaluating higher Week 3 doses (54 to 73 mcg) to achieve greater exposure. During the Phase 1 portion of this study, which employed a standard 3+3 dose-escalation design, the 73 mcg dose level was not tolerated due to elevations in hepatic transaminases with concurrent low-grade increases in bilirubin in 2 of 4 treated patients. These hepatic events were reversible without administration of corticosteroids, and all patients who experienced dose-limiting toxicities remained on treatment. After a dose reduction to 68 mcg, 6 patients were treated with no dose-limiting toxicities and no significant liver enzyme elevations. As a result, a dose of 68 mcg was identified as the maximum tolerated dose and selected for further evaluation as part of the intra-patient escalation regimen during the Phase 2 portion of the study.

Study 202: The efficacy and safety of the intra-patient escalation regimen from Study 102, ie, 20 mcg on Day 1 and 30 mcg on Day 8, followed by the escalated dose of 68 mcg on Day 15 and weekly thereafter, were confirmed in the Phase 3 Study 202 in which all patients randomly allocated to tebentafusp received this regimen. In Study 202, this tebentafusp dosing regimen delivered convincing OS benefit and statistically significant PFS, and acceptable safety with a low discontinuation rate and no treatment-related deaths. Additionally, data from Study 102 revealed pharmacodynamic biomarkers consistent with the MoA including cytokine induction and T cell trafficking into the tumor.

Blood samples were taken for PK assessment in patients at pre-dose-, the end of infusion, and 12 - 24 hours post end of infusion for each QW dose for the first cycle, pre-dose and at the end of infusion on the first dose of each cycle thereafter, and at the End of Treatment (EOT) visit.

PK parameters calculated by noncompartmental methods from the Phase 1 dose escalation cohorts after dosing on C1D1 were comparable due to the dose range evaluated. Serum concentrations were measurable up to 24 hours after dosing but were below the LLOQ at subsequent timepoints

between 24 and 168 hours. The C_{max} was achieved immediately after the end of infusion (median 0.5 hours), with a geometric mean C_{max} of 4063 pg/mL for C1D1 (20 mcg dose; Figure 11) and 13040 pg/mL for C1D15 (68 mcg dose; Figure 12). The increase in geometric mean PK exposure (C_{max}) of tebentafusp was approximately dose proportional between the 20 mcg dose administered on C1D1 and the 68 mcg dose administered on C1D15. From the dose escalation data, the observed terminal $t_{1/2}$ was 6.8 to 7.5 hours. Subsequent mean C_{max} values after C1D15 ranged from 10000 to 20000 pg/mL, and mean pre-dose concentrations were undetectable, indicating no accumulation with QW dosing at the 68 mcg dose (Figure 13).

The FDA's Assessment:

FDA agrees with the Applicant's position that the proposed dosing regimen of tebentafusp for the general patient population (20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter, refer to as 20/30/68 mcg) is acceptable. The dosing regimen selection is based on the following rationale:

- Priming dosing regimen: Cytokine release syndrome (CRS) mainly occurs within the first 3 weeks of dosing.
- Weekly dosing regimen: No clinically meaningful differences in safety or efficacy were identified between the weekly and daily dosing regimens. The weekly dosing regimen was adopted given the easier utility.
- Flat dosing regimen: Patients with higher body weights who received higher absolute doses of tebentafusp experienced more severe treatment-related toxicity. Analysis of PK data indicated that tebentafusp C_{max} is directly proportional to the absolute dose. As a result, heavier patients tended to have higher serum IMCgp100 concentrations. The data thus indicated that heavier patients were being unduly exposed to risk, which warranted a move from weight dosing to flat dosing.
- Maintenance dose of 68 mcg: 73 mcg was not well tolerated (elevations in hepatic transaminases with concurrent low-grade increases in bilirubin); furthermore, there were no dose-limiting toxicities and no significant liver enzyme elevations at the selected dosing regimen (20/30/68 mcg) in study 102 (N=6).

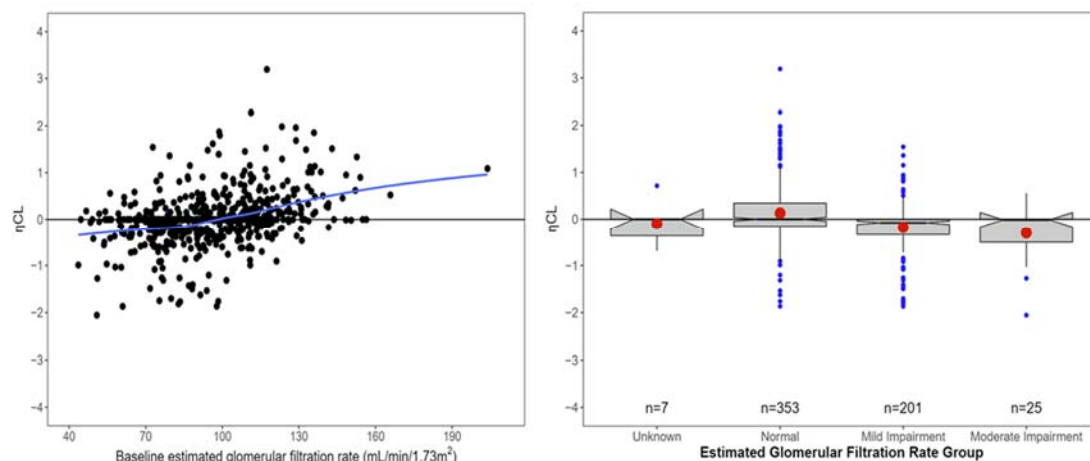
Although only one priming dosing regimen (20 mcg on Day 1, 30 mcg on Day 8) was evaluated, the FDA considers further priming dose optimization effort is not necessary or feasible based on the following information:

- The rate of grade 3+ CRS is low (0-0.5%).
- Grade 2 CRS was transient and mainly occurred during the first 3 weeks of dosing.
- Small number of patients (n=3) were treated with tocilizumab to mitigate CRS.
- The observed low ORR of 9% posts challenge for further priming dose optimization.

6.2.2.2. Therapeutic Individualization

Data:

Figure 14 Population PK Plots: Estimated Glomerular Filtration Rate



η_{CL} = interindividual variability clearance; PK = pharmacokinetic(s)

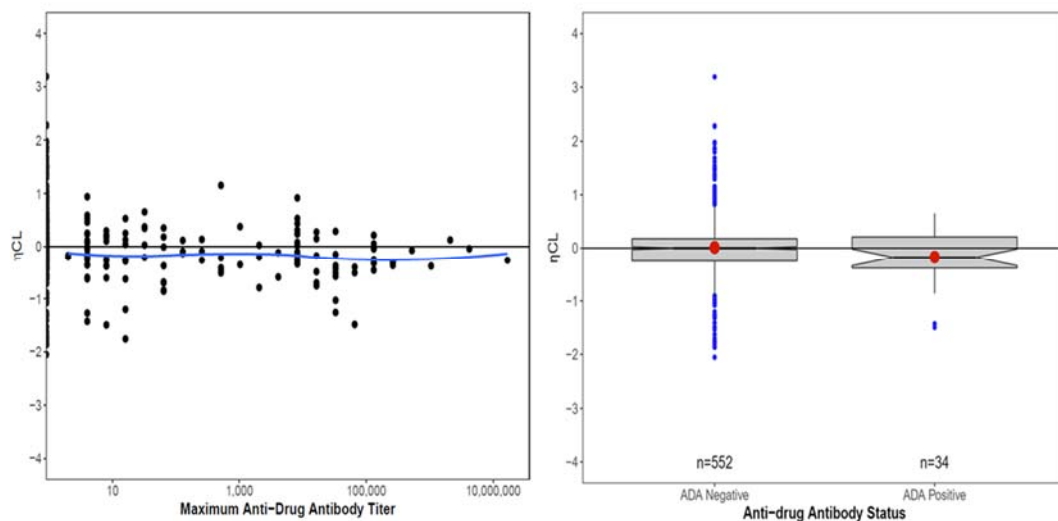
Left Panel: Continuous eta plots of interindividual variability of CL versus eGFR

Right Panel: Categorical eta plots of interindividual variability of CL versus eGFR

Source: Module 5.3.3.5, Population PK Modeling Report and Exposure-Response Analysis for Tebentafusp;

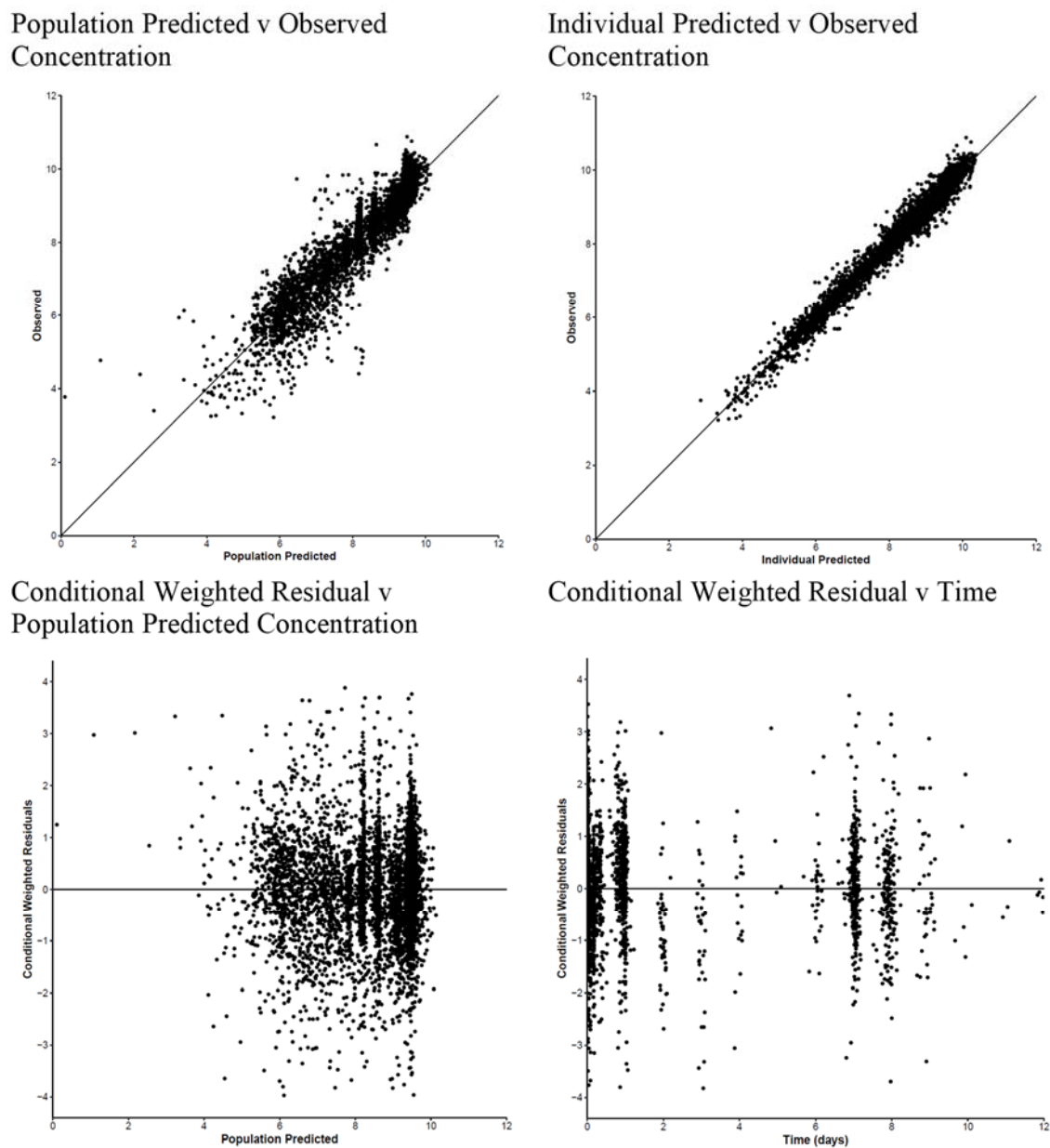
Report No. (b) (4) 8472E4.01 Appendix Figure 7

Figure 15 Population PK Plots: Maximum ADA Titer



η_{CL} = interindividual variability clearance; ADA = anti-drug antibody; PK = pharmacokinetic(s)
Left Panel: Continuous eta plots of interindividual variability of CL versus maximum ADA titer; Right Panel: Categorical eta plots of interindividual variability of CL versus ADA status (negative or positive)
Source: Module 5.3.3.5, Population PK Modeling Report and Exposure-Response Analysis for Tebentafusp;
(b) (4) Report No. (b) (4) 8472E4.01 Appendix Figure 7

Figure 16 Population PK Goodness of Fits – Final Model



Top Left Panel: Population prediction of tebentafusp serum concentrations versus observed tebentafusp serum concentrations; Top Right Panel: Individual prediction of tebentafusp serum concentrations versus observed tebentafusp serum concentrations; Bottom Left Panel: Population prediction of tebentafusp serum concentrations versus conditional weighted residuals; Bottom Right Panel: Time versus conditional weighted residuals.
Note: Observed and Predicted concentration values are presented as log transformed values.

Source: Module 5.3.3.5, Population PK Modeling Report and Exposure-Response Analysis for Tebentafusp;
(b) (4) Report No. (b) (4) 8472E4.01, Figure 3.

The Applicant's Position:

Effects on the PK of tebentafusp by the baseline characteristics were visually assessed by comparing the distributions of the interindividual variability estimates from the base PK model with tebentafusp. Baseline characteristics included, but were not limited to, age, weight, body mass index, eGFR, renal function, ADA titer, maximum ADA titer, ADA status, sex, race, melanoma stage, sum of tumor diameters, percent change from baseline sum of tumor diameters, and largest liver lesion group. Visual inspection of covariate versus eta (inter-individual variability) plots demonstrated that baseline renal function (eGFR) and ADA (titer>8192) were the only statistically meaningful covariates on final PK model fit.

Estimated tebentafusp CL slightly decreased (3.32 L/d) in patients with moderate renal impairment (eGFR ranging from 30 to 59 mL/min; Figure 14 ,Table 6). High interpatient variability was observed (78 %CV) and CL values in renal impaired patients were essentially within the range observed in patients with normal renal function. No impact on safety or efficacy parameters was identified in patients with mild to moderate renal impairment and no dose adjustments are recommended. There is no information available in patients with severe renal impairment (eGFR less than 30 mL/min).

Estimated CL considerably increased when an ADA titer greater than 8192 was present (Figure 15; Table 6). However, ADA status was not associated with safety or efficacy and thus, monitoring of ADA is not necessary.

Assessment of goodness of fit plots (Figure 16) was conducted to evaluate the performance of the final PK model. The model diagnostic plots indicate that the final PK model adequately describes the observed concentration data. No absolute value of conditional weighted residual error was greater than 4, and no recorded concentrations, were excluded based on poor fitting in model development.

The PK of tebentafusp in patients with melanoma enrolled in these trials was adequately described by a two-compartment model with a first-order elimination from the central compartment. Only eGFR and the presence of high titer ADA were identified as relevant PK covariates. The estimated CL slightly decreased in patients with moderate renal impairment. However, CL values in renal impaired patients were essentially within the range observed in patients with normal renal function. Additionally, no impact on safety or efficacy parameters was identified. Therefore, no dose adjustment is recommended in renally impaired patients. Tebentafusp exposure was considerably decreased when an ADA titer greater than 8192 was present. Because ADA status was not associated with safety or efficacy of tebentafusp, monitoring of ADA is not necessary. Age, sex, weight, and race had no impact on the PK of tebentafusp in patients with melanoma.

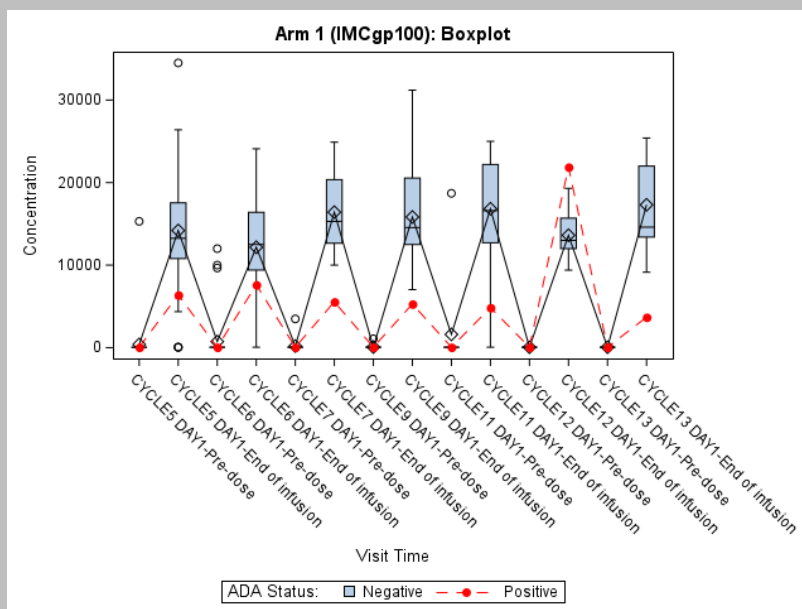
No dose modification are required for intrinsic or extrinsic factors.

The FDA's Assessment:

FDA agrees with the Applicant's position that no dose adjustment is necessary for patients with mild and moderate renal impairment although the estimated CL slightly decreased in this subpopulation.

The tebentafusp clearance increased in patients with high titer ADAs. There was clear evidence of time-dependent impact of ADA on PK at the end of the infusion after Cycle 5. Mean Ratio of geometric mean tebentafusp concentration in ADA+/ ADA- patients during Cycle 6-13 in study 102 ranged between 0.01-0.55 and during cycle 5-13 for study 202 ranged between 0.01-0.5 (Figure 17). ADA status should be treated as time-varying covariates. Please refer to section 19.5.4 for details. The impact of ADA Titer ≥ 8192 on exposure was re-estimated and the USPI was updated as described in section 12.3. The figures (Figure 15, Figure 48) visualizing the ADA effect on PK provided by the applicant treated ADA status or titer as a fixed factor; therefore, FDA does not agree with the applicant's presentation of these data.

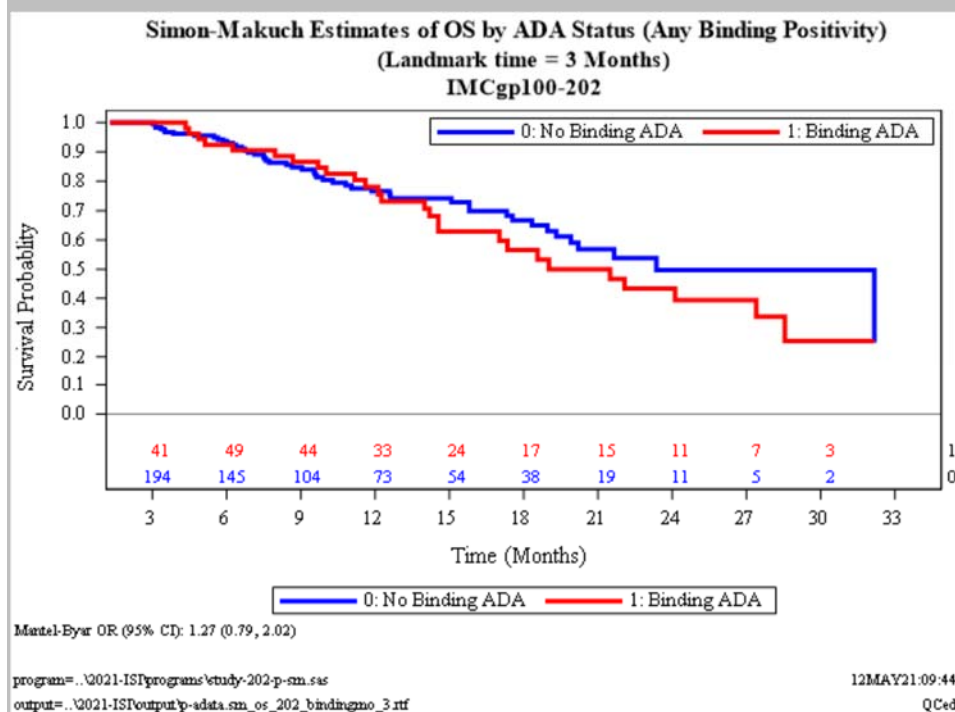
Figure 17. Tebentafusp concentration in ADA+/ ADA- Patients in Study 202



Source: FDA's independent analysis

Exploratory subgroup analyses comparing the efficacy (OS, Figure 18) in patients who were ADA+ or ADA- did not show clinically significant differences.

Figure 18. Association of Overall Survival with ADA Status, IMCgp100-202



Source: Figure 44, summary of clinical pharmacology, page 80.

Since ADA formation has the potential to induce type I-III hypersensitivity events, the impact of tebentafusp treatment emergent ADA on patient safety was evaluated using reported AEs from IMCgp100-102 and IMCgp100-202 filtered for hypersensitivity-associated events. No clinically relevant association was identified between hypersensitivity AEs and ADA onset (Table 8).

Table 8: ADA Onset Versus Hypersensitivity Adverse Events

	Frequency	Hypersensitivity After ADA					
		IMCgp100-102			IMCgp100-202		
		No	Yes	Total	No	Yes	Total
Hypersensitivity Before ADA	No	18	1	19	24	1	25
	Yes	18	3	21	32	4	36
	Total	36	4	40	56	5	61

Source: Table 20, summary of clinical pharmacology, page 110.

FDA considers such retrospective analyses exploratory in nature and may be affected by confounding factors. Taking into consideration the totality of data, there is insufficient evidence suggesting a need to recommend monitoring or dose adjustment for patients who develop anti-drug antibodies.

6.2.2.3. Outstanding Issues

Data:

Not Applicable

The Applicant's Position:

None based on applicant's assessment.

The FDA's Assessment:

The presence and the assessment of clinical impact of neutralizing anti-drug antibodies (ADA) on PK, safety, and efficacy was not included in the BLA submission; however, such information can still inform labeling. Therefore, a PMC is to be issued to request such an assessment to determine the presence and clinical impact of the of neutralizing ADA on PK, efficacy, and safety of tebentafusp.

6.3. Comprehensive Clinical Pharmacology Review

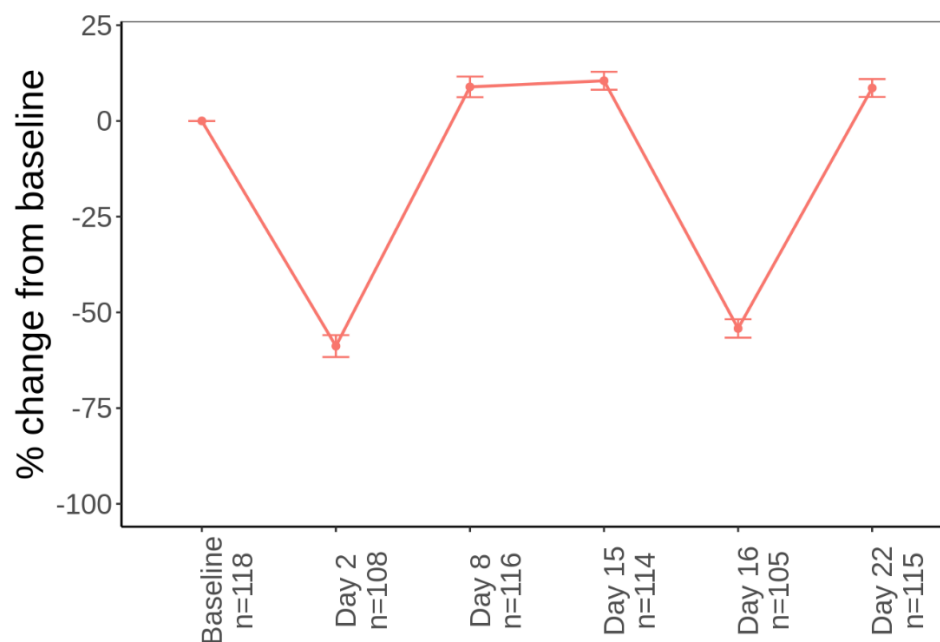
6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Lymphocyte Re-distribution

As anticipated based on other T-cell engagers, blood lymphocyte levels decreased by 60% within 24 hours of the first dose of tebentafusp and returned to baseline by Day 8 after the first dose (Figure 19). This pattern was repeated after the third dose of tebentafusp on Day 15. Samples were not collected after the second dose (Day 8). These results are consistent with activation of lymphocytes followed by their margination and re-distribution into tumors and tissues.

Figure 19 Change in Blood Lymphocytes Over Time



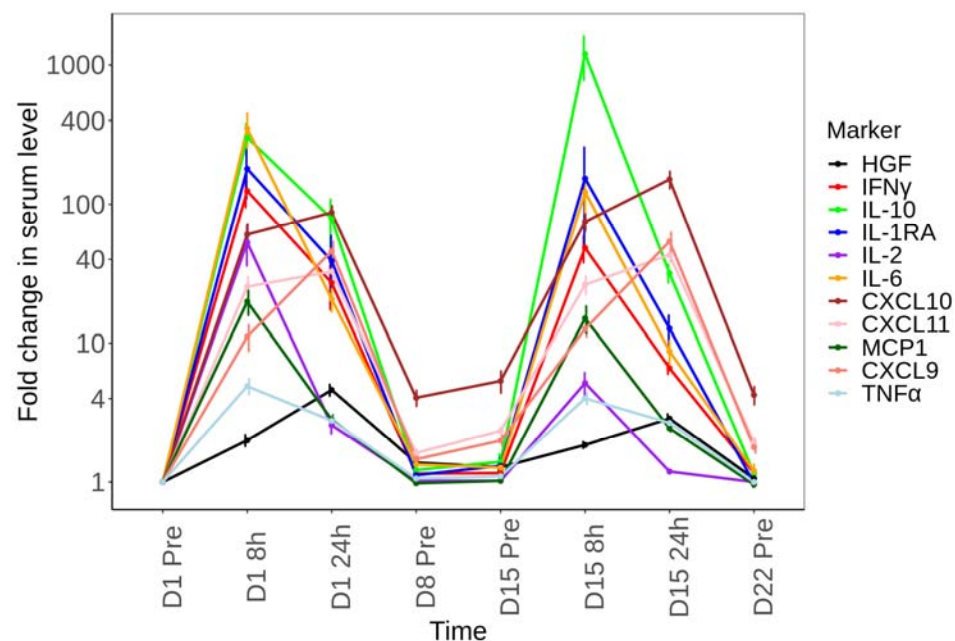
1.1. Serum Biomarkers

Consistent with other T cell engagers, all patients exhibited a treatment-induced increase in all cytokines and chemokines measured after the first dose. Levels of 11 immune markers associated with inflammatory responses (IFN- γ , tumor necrosis factor [TNF]- α , IL-2, and IL-6), immune modulation (IL-10 and IL-1RA), and chemotaxis (C-X-C motif ligand [CXCL]9[MIG], CXCL10 [IP-10], CXCL11[I-TAC], hepatocyte growth factor (HGF), and monocyte chemoattractant

protein-1 [MCP-1]) were measured in patient serum samples collected at baseline and on-treatment.

Serum biomarker changes were transient, peaking at 8 to 24 hours post treatment. Biomarkers returned to baseline levels as measured in samples collected at Day 8, prior to patients receiving the second dose. The treatment-induced increase was seen again after the third dose, where the magnitude of increase was higher for certain markers, notably IL-10 and CXCL10 (Figure 20). Samples were not analyzed after the second dose (Day 8).

Figure 20 Change in Serum Cytokine Levels Over Time

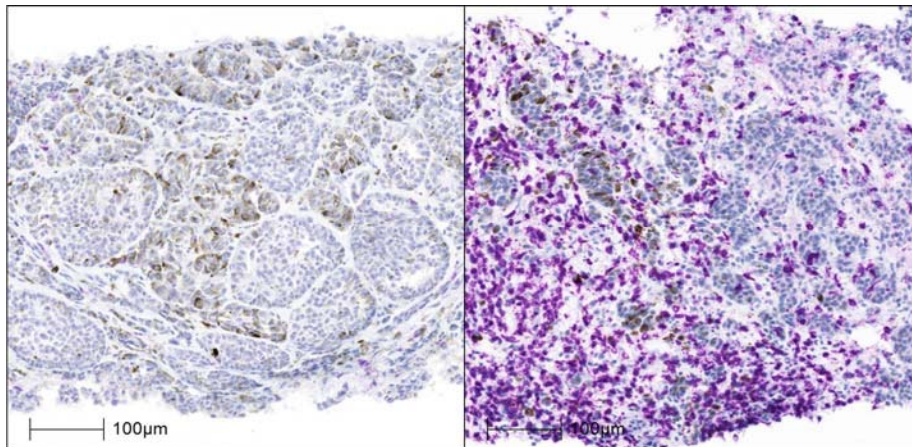


CXCL = C-X-C motif Ligand; D = Day; HGF = hepatocyte growth factor; IL = interleukin; MCP = monocyte chemoattractant protein; TNF – tumor necrosis factor

1.2. T-cell Infiltration into Tumors

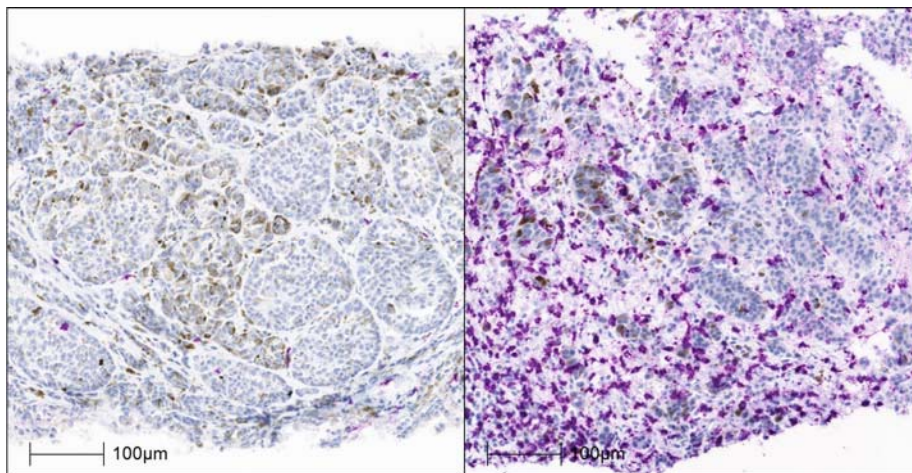
Consistent with other T-cell engagers, increases in CD3 (median 3.2-fold; Figure 21), CD8 (median 2.3-fold; Figure 22) and CD4 (median 2.1-fold; Figure 23) T cells within the tumor microenvironment were observed 16 days after the first dose. Biopsies were collected prior to treatment initiation and 16 days post first dose, (i.e., after the third dose) and analyzed for CD3, CD4 and CD8 T cells by immunohistochemistry. The majority of biopsies (68%) had a ≥ 1.5 -fold increase in CD3 T cells by Day 16, after 3 doses of tebentafusp.

Figure 21 CD3 T Cells Infiltrate Tumors after 3 Doses of Tebentafusp



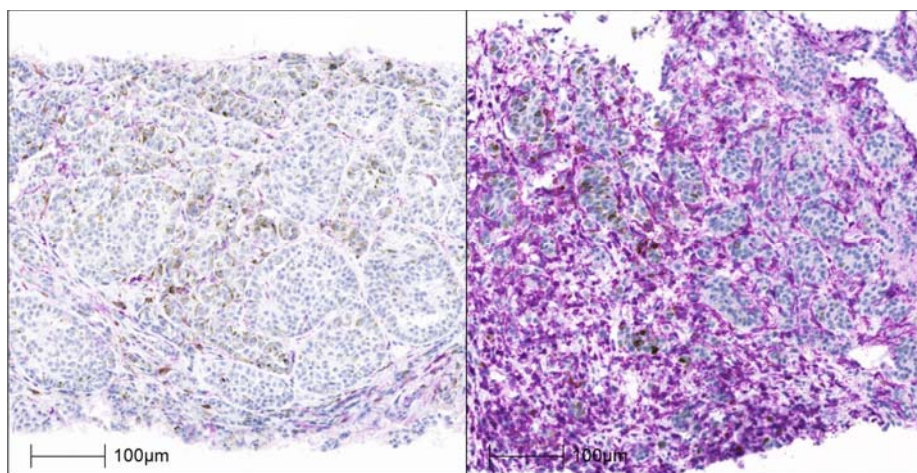
Left Panel: Pre-treatment; Right Panel: After 3 doses of tebentafusp

Figure 22 CD8 T Cells Infiltrate Tumors after 3 Doses of Tebentafusp



Left Panel: Pre-treatment; Right Panel: After 3 doses of tebentafusp

Figure 23 CD4 T Cells Infiltrate Tumors after 3 Doses of Tebentafusp



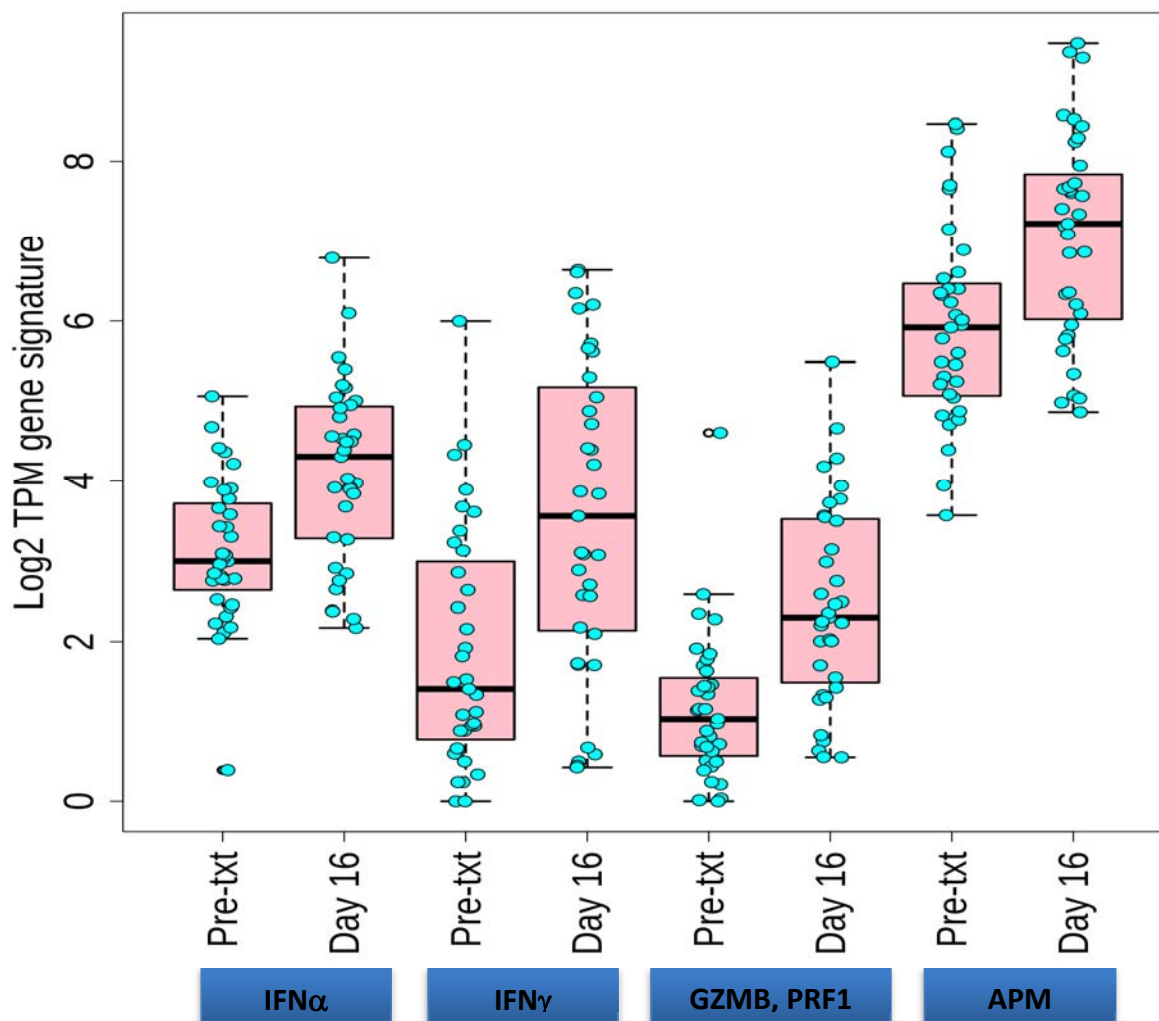
Left Panel: Pre-treatment; Right Panel: After 3 doses of tebentafusp

1.3. T-cell Activation and Down-regulation of Melanoma Genes in Tumor Biopsies

As shown in Figure 24, consistent with the gp100-dependent activation of T cells by tebentafusp, gene expression analyses of paired baseline and on-treatment tumor biopsies collected at Day 16 revealed the following increases in messenger RNA (mRNA) levels after 3 doses of tebentafusp:

- Interferon alpha (type 1 IFN) and gamma (type 2 IFN) pathway genes (2- and 3-fold respectively)
- HLA class 1, transporter associated with antigen processing (TAP)1, TAP2 and Proteasome 20S Subunit Beta 8 (PSMB8) (2-fold).
- Cytotoxic CD8 genes, granzyme B and perforin, that are required for tumor cell killing (2- to 3-fold).

Figure 24 Increased Expression of IFN alpha, IFN gamma, Granzyme B, Perforin 1, and Antigen Presenting Machinery in Tumor Biopsies by Day 16 After First Dose of Tebentafusp



APM = antigen presenting machinery; GZMB = granzyme B; IFN = interferon; PRF1 = perforin 1; TPM = transcripts per million

Taken together, these results demonstrate that tebentafusp induced a broad and potent anti-tumor immune response in metastatic uveal melanoma patients enrolled in the Phase 2 trial and support the proposed mechanism of action for tebentafusp.

The Applicant's Position:

The mechanism of action and pharmacodynamic effects of tebentafusp were explored in the Phase 1 (Study IMCgp100-01, primarily cutaneous melanoma) and Phase 2 trials (Study IMCgp100-102). The analysis below is focused on Study IMCgp100-102 because it enrolled

uveal melanoma patients who were treated at the 68 mcg dose after IE dose escalation, a regimen that was identical to that used in the Phase 3 study IMCgp100-202. Similar trends were observed in the Phase 1 trial (Middleton et al., 2020). The key pharmacodynamic effects of tebentafusp observed in study IMCgp100-102 are summarized here:

- Tebentafusp induced transient reductions in blood lymphocyte levels which were accompanied by transient increases in serum inflammatory cytokines and chemokines.
- Tebentafusp increased CD3, CD4 and CD8 T cells levels in the tumor, consistent with T cell trafficking into the tumor microenvironment.
- Tebentafusp induced Type 1 (IFN α) and Type 2 (IFN γ) interferon pathways in tumors.

The FDA's Assessment:

FDA considers the above biomarker assessments as supportive information to understand tebentafusp's mechanism of action.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

6.3.3. See General Pharmacology and Pharmacokinetic Characteristics Above

The Applicant's Position:

Yes, the mechanism of action and pharmacodynamic effects of tebentafusp were explored in the Phase 1 (Study IMCgp100-01, primarily cutaneous melanoma) and Phase 2 trials (Study IMCgp100-102). The analysis below is focused on Study IMCgp100-102 because it enrolled uveal melanoma patients who were treated at the 68 mcg dose after IE dose escalation, a regimen that was identical to that used in the Phase 3 study IMCgp100-202. Similar trends were observed in the Phase 1 trial (Middleton et al., 2020). The key pharmacodynamic effects of tebentafusp observed in study IMCgp100-102 are summarized here:

- Tebentafusp induced transient reductions in blood lymphocyte levels which were accompanied by transient increases in serum inflammatory cytokines and chemokines.
- Tebentafusp increased CD3, CD4 and CD8 T cells levels in the tumor, consistent with T cell trafficking into the tumor microenvironment.

- Tebentafusp induced Type 1 (IFN α) and Type 2 (IFN γ) interferon pathways in tumors.

The FDA's Assessment:

FDA considers the above assessments of tebentafusp pharmacodynamic effects as supportive information to understand tebentafusp's mechanism of action.

6.3.4. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

The Applicant's Position:

Justification for the Phase 3 tebentafusp dose and regimen is based on clinical data driven by safety, tolerability, and clinical activity from the dose escalation phases of study IMCgp100-01 and study IMCgp100-102 with supporting data from the expansion phase of study IMCgp100-102 rather than tebentafusp exposure-response. Validation of the tebentafusp regimen is provided by the Phase 3 results, including high OS (Hazard Ratio 0.51 for OS) and overall tolerability (low rate of tebentafusp-related discontinuations [3.1% Phase 2, 2.0% Phase 3] and no tebentafusp-related deaths).

The FDA's Assessment:

FDA agrees with the Applicant's position that the proposed dosing regimen of tebentafusp for the general patient population (20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter) is selected based on safety, tolerability and clinical activity from study IMCgp100-01 and study IMCgp100-102 and confirmed by the Phase 3 results.

From a safety perspective, data from study IMCgp100-202 showed that CRS mainly occurred within the first 3 weeks of dosing, with the majority of the CRS events being grade 2 or below (Table 9). From an efficacy perspective, partial responses were observed in patients receiving 40 mcg weekly dosing and in 1 patient receiving 20 mcg IMCgp100 daily dosing, suggesting potential activity at 20- 30 mcg dose.

FDA considers that no further dose optimization on priming dose is considered necessary or feasible, given that CRS occurred during the first 3 weeks and with low rate of grade 3+ CRS (Table 9), and that the overall response rate (ORR) was low making the dose optimization effort challenging. In addition, a small number of patients (n=3) used tocilizumab, suggesting general

acceptable tolerability (with respect to CRS).

Table 9: Study IMCgp100-202 Summary of weekly CRS incidence rates over time

Week/Dose	Any Grade CRS	Grade ≥ 2 CRS	Grade ≥ 3 CRS*
Week 1 (20 mcg) (N=245)	84.5%	69.8%	0.4%
Week 2 (30 mcg) (N=225)	74.2%	55.1%	0.0%
Week 3 (68 mcg) (N=225)	58.2%	42.2%	0.4%
Week 4 (68 mcg) (N=221)	29.0%	11.3%	0.5% ⁺
Week 5 (68 mcg) (N=222)	18.5%	8.6%	0.0%
Week 6 (68 mcg) (N=221)	9.5%	4.1%	0.0%
Week 7 (68 mcg) (N=212)	8.5%	1.9%	0.0%
Week 8 (68 mcg) (N=219)	8.2%	3.2%	0.0%
$\geq$ Week 9 #	0.8%	0.1%	0.0%

Source: Table 2, Response to FDA IR, SDN22, Page 3.

The selection of flat dosing strategy is based on result from study IMCgp100-01. The MTD for weekly tebentafusp dosing was identified as 600 ng/kg. Patients dosed with 600 ng/kg tebentafusp received an average dose of 49.3 mcg; however, experience with study drug identified the potential for higher serum concentrations to occur in heavier patients with body weight dosing. As a result, a flat dosing was selected over body weight based dosing.

The selection of weekly dosing is supported by results from study IMCgp100-01 showing no clinically meaningful differences in safety or efficacy between the weekly and daily dosing regimens. From efficacy perspective, the profile of responses to tebentafusp treatment was comparable for patients treated with weekly dosing and daily dosing (9.3% vs 6.7%, Table 10). Partial responses were seen in 4 patients receiving 600 ng/kg and 1 patient receiving 40 mcg tebentafusp weekly dosing in Arm 1 and in 1 patient receiving 20 mcg tebentafusp daily dosing in Arm 2. In particular, all partial responses seen in patients with uveal melanoma were for those treated with the weekly dosing regimen. The overall response rate was 20.0% (3/15) (95% CI: 4.3% to 41.8%) for weekly dosing as compared to 0% (0/3) for daily dosing.

Table 10: Best Tumour Response Based on RECIST 1.1/Efficacy Population

	Arm 1 (weekly dosing) n (%) [95% CI]	Arm 2 (daily dosing) n (%) [95% CI]	Total n (%) [95% CI]
Number of patients	54 (100.0)	15 (100.0)	69 (100.0)
Partial response ¹	5 (9.3)	1 (6.7)	6 (8.7)
Minor response ²	4 (7.4)	1 (6.7)	5 (7.2)
Stable disease ³	26 (48.1)	7 (46.7)	33 (47.8)
Progressive disease	17 (31.5)	6 (40.0)	23 (33.3)
Not evaluable	2 (3.7)	0 (0.0)	2 (2.9)
Overall response rate	5 (9.3) [3.1, 20.3]	1 (6.7) [0.2, 31.9]	6 (8.7) [3.3, 18.0]
Disease-control rate at 16 weeks	13 (24.1) [13.5, 37.6]	4 (26.7) [7.8, 55.1]	17 (24.6) [15.1, 36.5]
Disease-control rate at 24 weeks	10 (18.5) [9.3, 31.4]	3 (20.0) [4.3, 48.1]	13 (18.8) [10.4, 30.1]

Source: table 28, IMCgp100-01 Clinical study report, page 102.

An overview of TEAEs in the overall study population and in both treatment arms is presented in Table 11. **Error! Reference source not found.** No clinically significant difference on the rate of adverse events was noticed between the weekly dosing as compared to the daily dosing.

Table 11: Summary of Treatment-emergent Adverse Events/Safety Population

AE category¹	Arm 1 (weekly dosing) n (%) [no. of AEs]	Arm 2 (daily dosing) n (%) [no. of AEs]	Total n (%) [no. of AEs]
Number of patients	66 (100.0)	18 (100.0)	84 (100.0)
Treatment-emergent AEs	66 (100.0) [1678]	18 (100.0) [446]	84 (100.0) [2124]
Treatment-related ² AEs	65 (98.5) [1299]	18 (100.0) [364]	83 (98.8) [1663]
AEs of CTCAE Grade ≥3	36 (54.5) [99]	12 (66.7) [28]	48 (57.1) [127]
Treatment-related ² AEs of CTCAE Grade ≥3	27 (40.9) [77]	9 (50.0) [18]	36 (42.9) [95]
SAEs	24 (36.4) [39]	5 (27.8) [5]	29 (34.5) [44]
Treatment-related ² SAEs	11 (16.7) [22]	1 (5.6) [1]	12 (14.3) [23]
SAEs leading to death	1 (1.5) [1]	1 (5.6) [1]	2 (2.4) [2]
Discontinuation due to AEs	5 (7.6) [8]	1 (5.6) [1]	6 (7.1) [9]
Discontinuation due to treatment-related ² AEs	2 (3.0) [4]	0 (0.0) [0]	2 (2.4) [4]
CTCAE Grade			
Grade 1	66 (100.0) [1272]	18 (100.0) [324]	84 (100.0) [1596]
Grade 2	58 (87.9) [307]	18 (100.0) [94]	76 (90.5) [404]
Grade 3	35 (53.0) [89]	12 (66.7) [25]	47 (56.0) [114]
Grade 4	6 (9.1) [9]	2 (11.1) [2]	8 (9.5) [11]
Grade 5	1 (1.5) [1]	1 (5.6) [1]	2 (2.4) [2]
Action taken with respect to study drug			
None	66 (100.0) [1656]	18 (100.0) [441]	84 (100.0) [2097]
Changed	1 (1.5) [1]	0 (0.0) [0]	1 (1.2) [1]
Temporarily stopped	7 (10.6) [13]	4 (22.2) [4]	11 (13.1) [17]
Discontinued ³	5 (7.6) [8]	1 (5.6) [1]	6 (7.1) [9]
Relationship to study drug			
Not related	62 (93.9) [379]	14 (77.8) [82]	76 (90.5) [461]
Possibly related	60 (90.9) [321]	17 (94.4) [96]	77 (91.7) [417]
Probably related	47 (71.2) [341]	6 (33.3) [18]	53 (63.1) [359]
Definitely related	48 (72.7) [637]	17 (94.4) [250]	65 (77.4) [887]

Source: table 38, IMCgp100-01 Clinical study report, page 128.

The selection of the maintenance dose of 68 mcg dose is mainly based on results from study IMCgp100-102, in which the different maintenance dose was compared by evaluating fixed low doses of tebentafusp at C1D1 (20 mcg) and C1D8 (30 mcg), followed by an escalated cohort-specified QW dose administered at C1D15 and beyond (i.e., 54, 64, 73 and 68 mcg). Two out of four patients at the 20/30/73 mcg experienced dose limiting toxicities (DLT) (Grade 4 AST increased, and ALT increased in one patient and Grade 2 and Grade 3 AST increased and Grade 1 hyperbilirubinemia in another patient). All 3 patients recovered, and all resumed tebentafusp treatment at a reduced dose with no recurrence of toxicity. Given the DLTs reported at 73 mcg, a lower dose level of 68 mcg was tested. No DLTs were reported at this dose level, which was considered the MTD/RP2D for Phase 2 dose expansion.

6.3.2.2 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:

See Therapeutic Individualization Section Above

The Applicant's Position:

No, See Therapeutic Individualization Section Above

The FDA's Assessment:

FDA agrees with the Applicant's position that no dose adjustment is needed in subpopulations based on intrinsic patient factors or ADA status. Although the ADA formation increased the tebentafusp clearance and decreased tebentafusp exposure, exploratory exposure-response analyses do not suggest any clinically meaningful differences in efficacy or safety between the ADA+ versus ADA- patient populations.

6.3.2.3 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

Not Applicable – iv infusion.

The Applicant's Position:

Not Applicable – iv infusion.

The FDA's Assessment:

Tebentafusp can cause transient release of cytokines that may potentially suppress CYP450 enzymes. Based on evaluation of the totality of data, FDA considers the risk of drug interaction to be low. FDA's conclusion is based on the following considerations:

- Tebentafusp's half-life of 6-8 hours is relatively short.
- The elevations of specific pro-inflammatory cytokines observed after the tebentafusp infusions are transient in nature, and attenuate with repeat dosing.
- The highest drug-drug interaction risk is following the first three doses of tebentafusp.
- Label recommends that patients are required to be observed after dosing for at least 16 hours, which alleviate the risk of potential drug interaction related AEs.

This conclusion is supported by the observed clinical data. In study IMCgp100-202, twenty (20/392, 5.1%) tebentafusp-treated patients with metastatic uveal melanoma were identified as receiving concomitant medications with narrow therapeutic index within a 2-week period of a CRS episode. The rate of Grade 3 and 4 TEAEs in the selected population was comparable to the overall tebentafusp population and none of these patients had QTcF prolongation > 500 msec during the susceptible period.

Table 12: Grade 3+ TEAEs that occurred within two weeks of CRS in patients who experience at least one episode of CRS within two weeks of administration of a concomitant medication with a narrow therapeutic index

System Organ Class/ Preferred Term (MedDRA v23.1)	Received a Concomitant medication with a Narrow Therapeutic Index within 2 weeks of a CRS* episode (N=20) n (%)
Blood and lymphatic system disorders	1 (5.0%)
Lymphopenia	1 (5.0%)
Cardiac disorders	2 (10.0%)
Atrial flutter	1 (5.0%)
Tachycardia	1 (5.0%)
General disorders and administration site conditions	1 (5.0%)
Pyrexia	1 (5.0%)
Hepatobiliary disorders	1 (5.0%)
Hypertransaminasaemia	1 (5.0%)
Investigations	2 (10.0%)
Gamma-glutamyl transferase increased	1 (5.0%)
Lymphocyte count decreased	1 (5.0%)
Musculoskeletal and connective tissue disorders	1 (5.0%)
Back pain	1 (5.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (5.0%)
Tumour pain	1 (5.0%)
Respiratory, thoracic and mediastinal disorders	2 (10.0%)
Hypoxia	1 (5.0%)
Dyspnoea	1 (5.0%)
Pulmonary embolism	1 (5.0%)
Dyspnoea at rest	1 (5.0%)
Pulmonary oedema	1 (5.0%)
Skin and subcutaneous tissue disorders	2 (10.0%)
Rash maculo-papular	2 (10.0%)
Vascular disorders	5 (25.0%)
Hypertension	3 (15.0%)
Hypotension	2 (10.0%)

Source: Table 2, Response to FDA IR, SDN22, Page 13.

Given the technical challenges of conducting a dedicated drug-drug interaction study to coincide with the peak of cytokine release and expected variance in degree of cytokine increase for individual patients, no formal drug-drug interaction study is considered feasible to assess the drug interaction potential due to cytokine release after tebentafusp treatment .

X

X

Primary Reviewer

Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

The clinical development program of tebentafusp in melanoma includes 5 Immunocore-sponsored clinical studies, 2 completed studies (Phase 1 Study 01 and Phase 2 rollover Study 401) and 3 ongoing studies (Phase 1/2 Study 102, Phase 1b/2 Study 201, and Phase 3 Study 202) (Table 13). Across these clinical studies, 587 patients with melanoma, including 410 patients with UM, have been exposed to tebentafusp monotherapy.

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Table 13: Listing of Clinical Trials Relevant to this BLA

Trial Identity/ NCT No. (Trial Status)	Trial Design	Regimen/ Schedule/ Route	Primary and Key Secondary Study Endpoints	Treatment Duration/ Follow-up	No. of Patients Randomized/ Treated	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
IMCgp100-202 (Study 202)/ NCT03070392 (Ongoing)	Phase 3, open-label, randomized, controlled, multi-center	<u>Tebentafusp monotherapy (IV) at RP2D-IE:</u> • 20 mcg on C1D1 • 30 mcg on C1D8 • 68 mcg on C1D15 and weekly thereafter <u>Investigator's choice:</u> • Dacarbazine 1000 mg/m² q3w • Ipilimumab 3 mg/kg q3w • Pembrolizumab 2 mg/kg (up to maximum of 200 mg) or 200 mg q3w	Primary: OS Secondary: PFS, BOR, DCR (CR, PR and SD ≥ 24 wks) by RECIST v1.1	Until radiographic progression (except for patients receiving ipilimumab), unacceptable toxicity, investigator decision, or patient withdrawal of consent	Tebentafusp: 252/245 Investigator's choice: 126/111	HLA-A*02:01-positive advanced UM previously untreated in the metastatic setting (1L)	58 centers in 14 countries
Studies to Support Efficacy and Safety							
IMCgp100-102 (Study 102)/ NCT02570308 (Ongoing)	Phase 1/2, open-label, uncontrolled, multi-center	<u>Phase 1 dose escalation - tebentafusp monotherapy (IV):</u> • 20 mcg on C1D1 • 30 mcg on C1D8 • 54, 64, 68, or 73 mcg on C1D15 and weekly thereafter <u>Phase 2 expansion - tebentafusp monotherapy at RP2D-IE (IV):</u> • 20 mcg on C1D1 • 30 mcg on C1D8 • 68 mcg on C1D15 and weekly thereafter	Primary: ORR by RECIST v1.1 (ICR) Secondary: tolerability, PK, tumor response (PFS, DCR, DOR, TTR, rate and duration of MinR) by RECIST v1.1, OS	Until occurrence of unacceptable toxicity, PD per modified irRECIST, and/or treatment discontinuation at the discretion of the investigator or patient	Phase 1: 19 Phase 2: 127	Previously treated (2L+) HLA-A*02:01-positive advanced UM	26 centers in 5 countries

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Table 13: Listing of Clinical Trials Relevant to this BLA

Trial Identity/ NCT No. (Trial Status)	Trial Design	Regimen/ Schedule/ Route	Primary and Key Secondary Study Endpoints	Treatment Duration/ Follow-up	No. of Patients Randomized/ Treated	Study Population	No. of Centers and Countries
<i>Other Studies Pertinent to the Review of Safety</i>							
IMCgp100-01 (Study 01)/ NCT01211262 (Completed)	Phase 1, FIH, open-label, uncontrolled, dose-finding	Tebentafusp monotherapy (IV) Arm 1 (qw doses): 5, 15, 45, 135, 270, 495, 600, 900 ng/kg Arm 2 (4 daily doses q3w): 10, 20, 30, 40, 50 mcg	Primary: DLT, safety, tolerability Secondary: tumor response, PK, ADA	For as long as, in opinion of investigator, the patient derived clinical benefit and benefit-risk ratio remained favorable	84 (n = 19 with mUM)	Previously treated HLA-A*02:01- positive advanced melanoma	9 centers in 2 countries
IMCgp100-401 (Study 401)/ NCT02889861 (Completed)	Phase 2, open-label, multi-center, rollover	Tebentafusp monotherapy (IV): according to defined regimen in parent study	Primary: safety Secondary: tolerability, ADA	Until loss of clinical benefit for the patients, unacceptable toxicity, withdrawal of consent, loss to follow-up, or death	3	Previously treated HLA-A*02:01- positive advanced melanoma	Not applicable
IMCgp100-201 (Study 201)/ NCT02535078 (Ongoing)	Phase 1b/2, open-label, uncontrolled, multi-center	Tebentafusp monotherapy (IV): at doses > 68 mcg weekly or 68 mcg 3 times per week Tebentafusp + immunotherapy	Primary: DLT (Phase 1b), ORR per RECIST v1.1 (Phase II) Secondary: safety, tolerability, PK, PFS, ADA	Until disease progression as defined by RECIST v1.1	Tebentafusp monotherapy: 27 Tebentafusp + immunotherapy: 85	Previously treated unresectable stage III or metastatic stage IV CM	23 centers in 6 countries

1L = first line; 2L+ = second line and greater; ADA = antidrug antibody; BLA = Biologics License Application; BOR = best overall response; C = Cycle; CM = cutaneous melanoma; CR = complete response; D = Day; DCR = disease control rate; DLT = dose-limiting toxicity; DOR = duration of response; FIH = first-in-human; HLA = human leukocyte antigen; ICR = independent central review; IV = intravenous(ly); MinR = minor response; mUM = metastatic uveal melanoma; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; q3w = every 3 weeks; qw = once weekly; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D-IE = recommended Phase 2 dose-intra-patient escalation; SD = stable disease; TTR = time to response; UM = uveal melanoma.

The Applicant's Position:

The efficacy and safety evaluation of tebentafusp for the proposed indication is based primarily on data from the ongoing pivotal, Phase 3 Study 202 and ongoing supportive, Phase 1/2 Study 102 that evaluated the proposed dosing regimen of tebentafusp in HLA-A*02:01-positive patients with mUM in the 1L and 2L+ settings, respectively. The remaining 3 studies contributed safety data only. Studies included in the safety dataset are presented in Section 8.2 of this document.

The FDA's Assessment:

FDA agrees with the Applicant's summary of clinical trials relevant to the application. For this BLA application, the clinical data for FDA's analysis of efficacy and safety were based on data from Study 202.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Pivotal Study 202

Trial Design

The Applicant's Description:

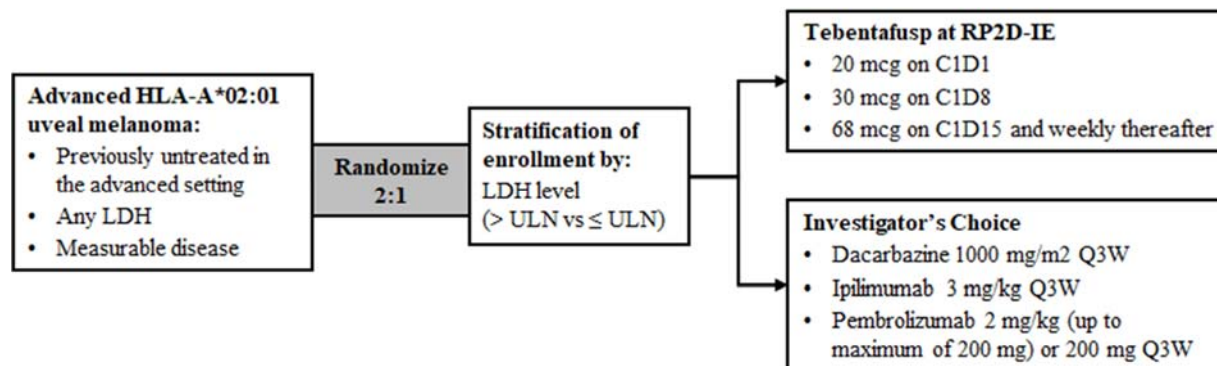
Overall design

This is an ongoing open-label, randomized, multi-center study to evaluate the efficacy and safety of tebentafusp versus investigator's choice (dacarbazine, ipilimumab, or pembrolizumab) in adult HLA-A*02:01-positive patients with mUM who had not received prior systemic therapy in the metastatic setting. Enrolled patients were randomized 2:1 to receive either tebentafusp (Arm1) or investigator's choice (Arm 2), the latter of which was selected prior to randomization. Randomization was stratified by LDH status. The study schema is depicted in Figure 25.

Arm 1 (tebentafusp): All patients randomized to Arm 1 received tebentafusp by intravenous (IV) infusion following the intra-patient escalation regimen. Patients received 20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter. Due to the anticipated cytokine release-associated toxicity with tebentafusp following the first 3 doses, patients were monitored for at least 16 hours after dosing as an inpatient following the weekly doses on Days 1, 8, and 15.

Arm 2 (investigator's choice): All patients randomized to Arm 2 received investigator's choice of one of the following 3 options: dacarbazine at the standard dosing regimen in UM of 1000 mg/m² given on Day 1 of each 21-day cycle; ipilimumab at the dosing regimen for unresectable or metastatic melanoma of 3 mg/kg given on Day 1 of each 21-day cycle for a maximum of 4 doses; or pembrolizumab at the dosing regimen of 2 mg/kg up to a maximum of 200 mg or 200 mg administered IV where approved locally given on Day 1 of each 21-day cycle. The preferred investigator's choice agent was selected prior to randomization. No extended monitoring after dosing was required in Arm 2.

Figure 25 Study 202 Design



C#D# = Cycle # Day #; HLA = human leukocyte antigen; LDH = lactate dehydrogenase; Q3W = every 3 weeks;
RP2D-IE = recommended Phase 2 dose intra-patient escalation regimen; ULN = upper limit of normal.

Treatment continued until radiographic progression (except for patients receiving ipilimumab), unacceptable toxicity, investigator decision, or patient withdrawal of consent. Patients receiving tebentafusp, pembrolizumab, or ipilimumab experiencing disease progression per RECIST could continue with treatment beyond initial RECIST progression if they met the prespecified criteria.

Choice of control group

Prior to this study, no therapy has demonstrated a survival benefit in UM (Ramaiya, 2007; Augsberger, 2009; Khattak, 2013). In the absence of standard of care, options for UM patients have included PD-1 inhibitors, ipilimumab, or chemotherapy. Therefore, the comparator arm for this randomized study was an investigator's choice with 3 options that included pembrolizumab, ipilimumab, and dacarbazine.

Eligibility criteria

Key inclusion criteria included:

- ≥ 18 years of age at the time of informed consent.
- Histologically or cytologically confirmed mUM.
- No prior systemic therapy in the metastatic or advanced setting.
- No regional liver-directed therapy.
- HLA-A*02:01 positive by central assay.
- ECOG performance status score of 0 or 1.

Key exclusion criteria included:

- Systemic or untreated CNS metastases.
- History of severe hypersensitivity reactions to other iologic drugs or mAbs.
- Clinically significant cardiac or impaired cardiac function.
- Active infection that required systemic antibiotic therapy.
- Known HIV.

- Active hepatitis B virus or hepatitis C virus infection.
- History of adrenal insufficiency.
- History of interstitial lung disease.
- History of pneumonitis requiring corticosteroid treatment or current pneumonitis.
- History of colitis or inflammatory bowel disease.
- Treatment with systemic steroid therapy or any other immunosuppressive medication at any dose level.
- Radiotherapy within 2 weeks of first dose of study drug.
- Use of hematopoietic colony-stimulating growth factors.

Dose selection

Tebentafusp

The dosing regimen of tebentafusp used in Study 202 was 20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter. Tebentafusp is administered via IV infusion over 15 to 20 minutes. The selection of intra-patient dose escalation over the first 3 weeks was identified in FIH, Phase 1 Study 01 and the actual doses were selected during the Phase 1 portion of Study 102. The final, recommended dosing regimen was then studied in the Phase 2 portion of Study 102 and Study 202.

Several key observations in Study 01 led to recommending an intra-patient escalation regimen using fixed doses. First, in Study 01, patients with higher body weights who received higher absolute doses of tebentafusp experienced more severe treatment-related toxicity. Consequently, fixed doses, rather than weight-based doses, were incorporated during the study. Second, given no clinically meaningful differences in safety or efficacy were identified between the weekly and daily dosing regimens, and in light of the easier utility of a weekly regimen, subsequent evaluation focused on weekly dosing. Third, the emerging safety profile of tebentafusp suggested that CRS (and associated hypotension) was more likely to occur during the first 2 weeks, after which tachyphylaxis occurred. Therefore, as has been used for other T cell-engaging bispecifics, an intra-patient escalation regimen during Weeks 1 and 2 (ie, 20 and 30 mcg, respectively) prior to dosing 50 mcg was selected as the preferred regimen to evaluate further in the subsequent single-arm, Phase 1/2 Study 102.

In Study 102, the intra-patient escalation regimen based on fixed dosing identified in Study 01 was further optimized by evaluating higher Week 3 doses (54 to 73 mcg) to achieve greater exposure. During the Phase 1 portion of this study, which employed a standard 3+3 dose-escalation design, the 73 mcg dose level was not tolerated due to elevations in hepatic transaminases with concurrent low-grade increases in bilirubin in 2 of 4 treated patients. These hepatic events were reversible without administration of corticosteroids, and all patients who experienced dose-limiting toxicities remained on treatment. After a dose reduction to 68 mcg, 6 patients were treated with no dose-limiting toxicities and no significant liver enzyme elevations. As a result, a dose of 68 mcg was identified as the maximum tolerated dose and selected for further evaluation as part of the intra-patient escalation regimen during the Phase 2 portion of Study 102 and was subsequently also incorporated into Study 202.

Investigator's choice

The investigator's choice options (pembrolizumab, ipilimumab, or dacarbazine) were administered at approved doses and regimens for the treatment of metastatic melanoma.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the pivotal trial, Study 202. The comparator arm consisting of Investigator's choice of dacarbazine, ipilimumab or pembrolizumab is considered appropriate and consistent with current standard of care for the systemic treatment of unresectable and metastatic uveal melanoma.

Study Endpoints

The Applicant's Description:

Primary endpoint

The primary endpoint of Study 202 was OS, defined as the time from randomization until death by any cause. The endpoint of OS had dual primary objectives relating to: (1) OS in all patients randomized to tebentafusp versus all patients randomized to investigator's choice (ITT Analysis Set); and (2) OS in all patients randomized to tebentafusp who developed a rash during the first week of treatment versus all patients randomized to investigator's choice (RAS).

Secondary endpoints

Secondary endpoints were:

- Safety and tolerability (AEs, SAE, laboratory parameters, vital signs, ECGs)
- PK (serum concentrations over time)
- PFS
- Tumor response (BOR, DOR, TTR, DCR [defined as CR or PR, or SD $\geq$ 24 weeks])
- HRQoL (assessed using EQ-5D, 5L and EORTC QLQ-C30)

The FDA's Assessment:

FDA agrees with the applicant's summary of study endpoints. It should be noted that although OS in the RAS analysis population was one of the primary objectives in this study, FDA's risk:benefit assessment of tebentafusp was only based on the OS in all patients randomized (ITT Analysis population).

Statistical Analysis Plan and Amendments

The Applicant's Description:

Analysis populations

Four analysis sets were used in this study, as defined in Table 14.

Table 14: Study 202: Analysis Populations

Analysis Set	Definition
ITT Analysis Set	The ITT Analysis Set comprised all patients assigned to treatment analyzed by the treatment assignment whether or not the patient received the assigned treatment. All patients randomized in the study were analyzed in the ITT population. The ITT Analysis Set was used for all summaries and analyses of demography, baseline characteristics, disposition, medical history, prior anticancer therapy, and efficacy data summaries and analyses.
RAS	The RAS comprised all patients assigned to tebentafusp who developed a rash within the first week of treatment (ie, Study Days 1 to 7 and prior to the second dose in case the second dose was received early) and all patients randomized to investigator's choice regardless of rash. If the analysis for the RAS crossed the pre-specified stopping boundaries and stopping boundaries for the ITT Analysis Set at the same planned analysis were not crossed, then this analysis set was also to be used for demography, baseline characteristics, efficacy, and safety data summaries and analyses. If the stopping boundaries for the RAS OS analysis were crossed, then summaries of demographics, baseline characteristics, and safety were also to be run on this analysis set.
Safety Analysis Set	The Safety Analysis Set included all randomized patients who received at least 1 full or partial dose of tebentafusp or investigator's choice. Patients were classified in this set according to initial treatment received. The Safety Analysis Set was used for all safety summaries.
PK Analysis Set	The PK Analysis Set included patients in the Safety Analysis Set who had at least 1 measurable PK concentration and who had the relevant date, time, and dosing data for the sample.

ITT = Intent-to-treat; OS = overall survival; PK = pharmacokinetics; RAS = Rash Analysis Set.

Multiple testing strategy

To provide strong control of the type I error rate, the primary endpoint of OS and key secondary endpoints of PFS and BOR were to be tested in this sequential order for the ITT analyses. If any previous analysis in the sequence was not statistically significant, the alpha could not be transferred to subsequent analyses. Since neither PFS nor BOR were tested on an interim basis, both endpoints were tested at an overall alpha level of 0.045 (2-sided) or 0.05 if the alpha from the RAS analysis was transferred to the ITT analyses.

The final analysis of PFS was to be based on 274 progression and death events. Assuming a median PFS of 5 months in the tebentafusp arm and 3.3 months in the investigator's choice arm, an HR of 0.66, and the same accrual and drop-out assumptions described earlier for OS, the analysis of PFS was expected to have 90% power to demonstrate a difference in the survival distributions between the 2 arms. Due to the higher hazard of progression events relative to death events, the required number of PFS events was expected to occur prior to the first interim analysis of OS. If the required number of events did not occur at the time of the first OS interim analysis, then the PFS analysis was to occur at a later time when 274 progression events had occurred.

The analysis of BOR was to occur after all 369 randomized patients were followed for approximately 9 months (ie, at least 3 planned on-treatment assessments) for response. It was to be formally tested for statistical significance only if the null hypotheses for OS and PFS in the ITT Analysis Set were both rejected.

Interim analyses

Two interim analyses were to be performed using a 3-stage group sequential design. Separate analyses were to be performed for each of the 2 primary objectives, but the analyses were to occur at the same time and the timing would be driven by the number of events in the ITT Analysis Set. The first interim analysis was based on approximately 60% of the events (150 events). The second interim analysis was to be based on approximately 80% of the events (200 events). Analyses of OS were based on O'Brien-Fleming boundaries (O'Brien, 1979). The Lan-DeMets approach (Lan, 1983) that approximates the O'Brien-Fleming spending function was used to adjust for situations where the actual number of events up to the DCO date for a given interim analysis did not match the planned number.

For the first interim analysis, the RAS analysis was conducted first. If the stopping boundaries were crossed, then the full alpha for that analysis ($\alpha = 0.005$) was added to the alpha allocated for the ITT analyses ($\alpha = 0.045$), resulting in a total $\alpha_{ITT} = 0.05$. If, at a particular interim analysis, stopping boundaries were crossed for the RAS analysis but not the ITT analysis, then the ITT alpha allocation for future analyses was adjusted, as described by Maurer and Bretz (Maurer, 2013). Therefore, stopping boundaries for the ITT analyses were adjusted accordingly. Secondary endpoints such as PFS and BOR were not formally tested in the RAS and were not tested on an interim basis.

SAP amendments

The first version of the SAP was released on 19 April 2017 and amended. The changes in each amendment are summarized in Table 15.

Table 15: Study 202: SAP Amendments Summary

SAP Version	Date	Major Changes
2	12 June 2020	Further clarification of endpoints and analysis methods following the protocol amendment
3	27 October 2020	• Removed PK parameter from secondary endpoint • Deleted subgroup "prior surgery for management of oligometastatic disease (Yes/No)" • Added post-treatment anticancer therapy start date imputation rule • Changed ORR/DCR analysis method from logistic regression to CMH test • Added time to QLQ-C30 sustained deterioration censoring rule • Added time to onset of each AESI and time to resolution of each AESI summaries/analysis • Added additional lab CTCAE shift summaries • Added vital signs shift from pre-dose to post-dose at each dosing schedule

Table 15: Study 202: SAP Amendments Summary

SAP Version	Date	Major Changes

AESI = adverse event of special interest; CMH = Cochran-Mantel-Haenszel; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; ORR = objective response rate; PK = pharmacokinetics.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the statistical analysis plan of Study 202. In addition to what is included in the Applicant's summary, additional details on sample size determination and analysis methods for the primary and key secondary endpoints are provided below.

Analysis Methods:

The difference in OS between the treatment arms was tested using a 2-sided log-rank test stratified by LDH status (LDH > ULN versus LDH ≤ ULN; measured centrally). The OS HR was estimated using a stratified Cox-proportional hazards model using the Efron approach for handling ties, along with corresponding 95% CIs for the HR. The analysis method for PFS was the same as that of OS. ORR was compared between treatment arms using a stratified Cochran Mantel-Haenszel (CMH) test adjusting for baseline LDH status.

Sample Size:

The sample size in Study 202 was driven by OS in the all randomized population. Assuming a 2:1 randomization ratio of tebentafusp versus investigator's choice, 250 events (deaths) were required to provide 89% power to detect an OS HR of 0.645 at 2-sided significance level of 0.045. Assuming OS was exponentially distributed and a median OS of 12 months in the investigator's choice arm, the HR of 0.645 corresponds to a median OS of 18.6 months in the tebentafusp arm resulting in a difference of 6.6 months in median OS between the arms. Considering a non-uniform recruitment of about 33 months and 10% annual drop-out rate, 369 patients were to be randomized in a 2:1 ratio to the 2 arms to observe 250 events after 51 months as follows. This sample size accounts for two formal interim analyses of OS.

Protocol Amendments

The Applicant's Description:

The original protocol was dated 12 January 2017. The global protocol was amended 4 times. Amendments 1 and 2 were instituted before the first patient was enrolled. The global protocol amendments are summarized in Table 16.

Table 16: Study 202: Global Protocol Amendments Summary

Amendment Number, Version Number (Date of Approval)	Key Details of Amendment	Rationale for Amendment
Amendment 1, Version 2 (28 March 2017)	Detailed the statistical methods for the primary analysis of OS.	To provide additional detail to statistical methods section.
	Removed extent of liver metastatic disease as a prespecified covariate. Added a multiple testing strategy to provide strong control of the type I error rate.	
	Added exclusion criteria for patients with autoimmunity including pneumonitis, interstitial lung disease, and inflammatory bowel disease.	To limit the risk of immune-related AEs associated with study drug.
	Explained that corticosteroids prior to the start of treatment were exclusionary.	Corticosteroids prior to the start of treatment may interfere with the mechanism of action of study drug.
Amendment 2, Version 3 (11 April 2017)	Throughout the protocol, revised the target tebentafusp dose at C1D15 and beyond from 75 to 68 mcg.	Given information indicating that the actual dose administered and defined as the RP2D in the Phase I study (IMCgp100-102) was 68 mcg.
Amendment 3, Version 4 (20 December 2018)	Revised the single-agent dosing regimen of tebentafusp.	Given data from a Phase I study (IMCgp100-102) identifying an escalated dose and regimen.
	Revised dosing of pembrolizumab in the investigator's choice arm.	To be consistent with approved dosing for treatment of advanced melanoma.
	Updated guidance on dose modifications and follow-up for toxicities to include additional guidance on management of hypotension and CRS events, including a CRS grading scale.	To provide clarification to the recommended toxicity and dose modification guidance for tebentafusp based on investigator notification letter for hypotension and CRS.
	Updated prohibited concomitant medications section to permit treatments for hypotension and CRS.	To provide additional guidance for patient management.
	Revised the requirements for reporting of irAEs to include hypotension and CRS events. In addition, revised the guidelines for management of irAEs to include events of hypotension and CRS.	Given that these events are included in the Reference Safety Information for tebentafusp as expected events.
	Made the following changes to the statistical analysis section: removed the Per-protocol Set analysis; corrected PFS definition regarding subsequent therapy; removed confirmation of response and clarified analyses of ORR; added	To reflect the statistical analysis plan.

Table 16: Study 202: Global Protocol Amendments Summary

Amendment Number, Version Number (Date of Approval)	Key Details of Amendment	Rationale for Amendment
	secondary endpoints to the multiple testing strategy and clarified the definition of exploratory efficacy endpoints.	
	Updated prohibited medications to allow treatment with denosumab, tocilizumab, or bisphosphonates during the study if required.	To provide additional guidance for patient management.
	Described the 0.2 mg/mL formulation of tebentafusp.	To introduce a new formulation of tebentafusp for use in clinical development.
	Updated exclusion criteria to clarify that a patient may have had a contraindication to 1 or 2 of the investigator's choices if he/she was a candidate for dosing with at least 1 investigator's choice and met all other study eligibility criteria. Patients who were institutionalized due to official or judicial order were excluded. Additionally, patients who were related to the investigator or any sub-investigator, research assistant, pharmacist, study coordinator, or other staff thereof, directly involved in the conduct of the study were excluded.	To ensure that appropriate patients are included in the study.
	Removed 1-hour post-dose serum blood sample at C1D1, C1D8, and C1D15, and refined PK and ADA sampling time points after 3 months of treatment.	Based on review of PK and biomarker data collected to date in tebentafusp program.
	Indicated that all cytokine assessments, including those done in the event of suspected CRS, would be assessed centrally. Removed local cytokine assessment and replaced with additional, as needed, pharmacodynamic assessment of cytokines.	To allow a better understanding of the cytokine response with treatment.
	Added reference to a sub-study that would be introduced via a separate protocol at select sites to evaluate ECGs, PK, and biomarkers.	To further supplement existing safety, PK, and pharmacodynamic assessments.
Amendment 4, Version 5 (31 March 2020)	Removed sample size re-estimation planned to occur at 55 events. Increased target sample size to N = 369 based on new assumptions and without a formal sample size re-estimation.	Given the limited information that would have been available at the time of the sample size re-estimation.

Table 16: Study 202: Global Protocol Amendments Summary

Amendment Number, Version Number (Date of Approval)	Key Details of Amendment	Rationale for Amendment
	Added an additional primary objective: comparison of OS among patients randomized to tebentafusp monotherapy who developed a rash within the first week of treatment versus all patients randomized to investigator's choice monotherapy.	Given data from a Phase I study (IMCgp100-102) that confirmed an association between rash, an early and on-target pharmacodynamic biomarker, and tebentafusp activity (as demonstrated by tumor shrinkage, PFS, and OS).
	Increased overall power of the study for the primary endpoint of OS.	Given the addition of another primary endpoint (see above).
	Permitted enrolled patients at a given site who had been receiving at least 2 months of tebentafusp to switch between tebentafusp formulations.	To allow for greater operational flexibility, while maintaining safe conduct of the study.
	Allowed patients who received pembrolizumab on the investigator's choice arm to switch from weight-based to flat dosing where locally approved.	
	Revised Inclusion Criterion 4 to allow prior surgical resection of oligometastatic disease outside liver.	To better reflect standard of care for patients with oligometastatic disease.
	Updated Exclusion Criterion 1 to redefine out-of-range value for absolute lymphocyte count from $1.0 \times 10^9/L$ to $< 0.5 \times 10^9/L$.	Based on emerging data suggesting no adverse impact on treatment in either arm.
	Revised wording around the mandatory hold of antihypertensive drugs 24 hours before and after the tebentafusp administration during at least the first 3 weeks of treatment.	To allow greater flexibility by the treating investigators to adjust medications safely based on clinical context.
	Adjusted hypotension and CRS management guidelines to allow the earlier use of steroids and/or tocilizumab in the setting of either prolonged Grade 2 events (ie, hypotension) despite the initial interventions or in response to initial onset of Grade 3 or 4 events.	To institute a more proactive approach to AE mitigation before allowing further worsening in patient's condition.
	Removed the option to conduct an ECG sub-study at select sites. Instead, indicated that all participating sites may have been asked to provide ECGs already being collected as part of the current study to a central ECG vendor for storage.	To allow for prospective central collection within the primary study.

ADA = anti-drug antibody; AE = adverse event; C#D# = Cycle# Day #; CRS = cytokine release syndrome; ECG = electrocardiogram; irAE = immune-related adverse event; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RP2D = recommended Phase II dose.

The FDA's Assessment:

FDA agrees with the Applicant's summary of Study 202 amendment history. FDA considers these protocol amendments unlikely to alter study conclusions.

8.1.2. Study 202 Results

Compliance with Good Clinical Practices

Data:

Not applicable.

The Applicant's Position:

The study was conducted in accordance with the protocol, the ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences ethical guidelines, applicable ICH GCP guidelines, and applicable laws and regulations, as described in the following sections of Protocol Version 5:

- Ethical consideration and administrative procedures: Protocol Section 11
- Data handling and management: Protocol Section 10
- Study drug compliance and accountability: Protocol Section 6.9.4

Immunocore Clinical Quality Assurance group or designee conducted audits at 2 study centers. No critical audit findings were observed. For all audit findings, appropriate corrective and preventive actions were undertaken.

The FDA's Assessment:

FDA concurs.

Financial Disclosure

Data:

Not applicable.

The Applicant's Position:

Financial disclosures for Study 202 are addressed in Section 19.2 of this assessment aid.

The FDA's Assessment:

Study 202 was a covered trial for this application. No investigator had any interests or arrangements to disclose. See Section 19.2.

Patient Disposition

Data:

From 04 October 2017 to 18 June 2020, 447 HLA-A*02:01-positive patients were screened, of whom 378 patients were randomly assigned (2:1) to tebentafusp (n = 252) or investigator's choice (n = 126; Figure 26) at 58 sites in 14 countries (US, Germany, France, United Kingdom, Poland, Canada, Australia, Belgium, Spain, Switzerland, Ukraine, Russia, Italy, and the Netherlands). Treatment choices available in the investigator's choice arm were pembrolizumab (n = 103; 81.8%), ipilimumab (n = 16; 12.7%), and dacarbazine (n = 7; 5.6%).

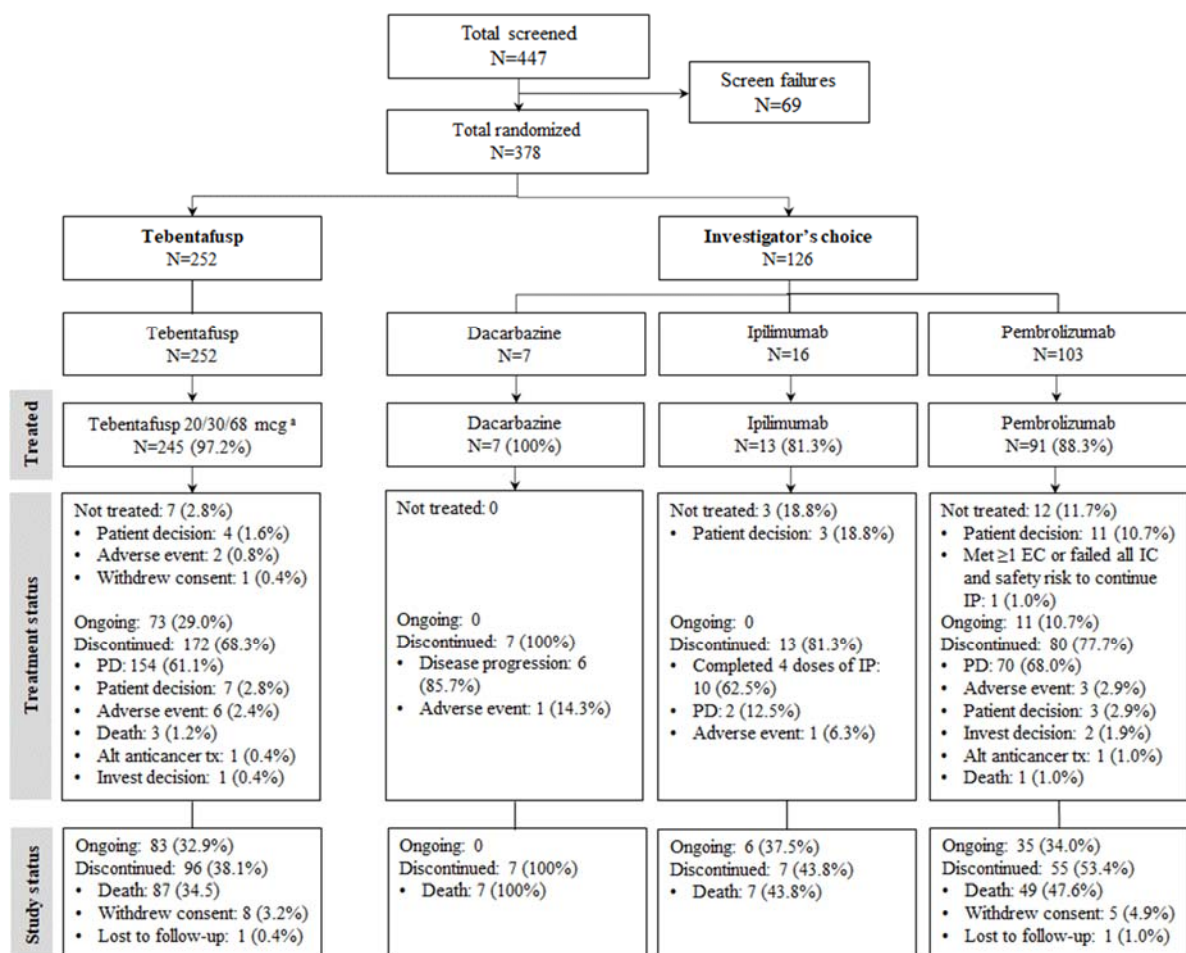
As of 13 October 2020, the DCO date of the primary analysis, the median duration of follow-up for all patients was 14.1 months (range, 12.7 to 15.6 months).

A total of 245 patients (97.2%) in the tebentafusp arm and 111 patients (88.1%) in the investigator's choice arm received at least 1 dose of study drug (Figure 26). Seven patients (2.8%) in the tebentafusp arm and 15 patients (11.9%) in the investigator's choice arm were randomized but not treated, with the main reason being patient decision (1.6% and 11.1%, respectively). Of the patients who were randomized but not treated, 3 patients (42.9%) in the tebentafusp arm and 10 patients (66.7%) in the investigator's choice arm continued to be followed for survival at the DCO. At least 6 of 10 patients (60.0%) in the investigator's choice arm received anti-PD-L1/cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) therapy, of whom 5 patients received anti-PD-L1/CTLA-4 combination therapy.

A total of 172 patients (68.3%) in the tebentafusp arm and 100 patients (79.4%) in the investigator's choice arm had discontinued treatment, while 73 patients (29.0%) continued to receive tebentafusp and 11 patients (8.7%) continued to receive investigator's choice (Figure 26). The most common reason for permanent discontinuation of study drug was PD, which occurred in 154 patients (61.1%) in the tebentafusp arm and 78 patients (61.9%) in the investigator's choice arm.

A total of 83 patients (32.9%) in the tebentafusp arm and 41 patients (32.5%) in the investigator's choice arm discontinued study treatment but remained on study (Figure 26). Study discontinuation was reported for 96 patients (38.1%) in the tebentafusp arm and 69 patients (54.8%) in the investigator's choice arm, with the main reason for discontinuation being death (87 and 63 patients, respectively).

Figure 26 Study 202: Patient Disposition (ITT Analysis Set)



Alt = alternative; Invest = investigator; IP = investigational product; ITT = Intent-to-treat; PD = progressive disease; tx = therapy.

^a 20/30/68 mcg refers to the dosing regimen applied throughout the study. The proposed dosing regimen is 20 mcg at Cycle 1 Day 1, 30 mcg at Cycle 1 Day 8, and 68 mcg at Cycle 1 Day 15 and weekly thereafter.

Source: Module 5.3.5.1, Study 202 CSR, Table 14.1.1 and Table 14.1.2.

The Applicant's Position:

The causes of study treatment discontinuation were generally consistent with the disease under study.

The FDA's Assessment:

FDA agrees with the Applicant's summary of patient disposition based on the data cutoff date of 13 October 2020. Ninety-four percent of randomized participants received study treatment. Proportionally, more patients on the Investigator's choice arm discontinued study treatment than on the tebentafusp arm. The majority of treatment discontinuations on both arms were

due to disease progression. Overall, the breakdown and percentages of participant disposition in the study were acceptable.

Protocol Violations/Deviations

Data:

At least 1 type of important protocol deviation was reported in 99 patients (39.3%) in the tebentafusp arm and 36 patients (28.6%) in the investigator's choice arm (Table 17). The most common (> 10% of patients) important protocol deviations in both treatment arms were related to trial procedures (22.6% and 11.1%, respectively).

Table 17: Study 202: Important Protocol Deviations (ITT Analysis Set)

Category	Tebentafusp (N=252) n (%)	Investigator's Choice (N=126) n (%)	Overall (N=378) n (%)
Patients with ≥1 type of important protocol deviation	99 (39.3)	36 (28.6)	135 (35.7)
Trial procedures	57 (22.6)	14 (11.1)	71 (18.8)
Informed consent/HIPAA	18 (7.1)	12 (9.5)	30 (7.9)
SAE reporting	15 (6.0)	7 (5.6)	22 (5.8)
Inclusion/exclusion criteria	11 (4.4)	4 (3.2)	15 (4.0)
IP intervention	15 (6.0)	0	15 (4.0)
Discontinuation criteria	6 (2.4)	3 (2.4)	9 (2.4)
Prohibited medications	1 (0.4)	0	1 (0.3)

HIPAA = Health Insurance Portability and Accountability Act; IP = investigational product; ITT = Intent-to-treat; SAE = serious adverse event.

Source: Module 5.3.5.1, Study 202 CSR, Table 14.1.3.

The Applicant's Position:

Overall, the higher rate of protocol deviations in the tebentafusp arm compared with the investigator's choice arm is related to more frequent dosing (weekly vs every 3 weeks) and an intensive schedule of assessments and visits in the tebentafusp arm. Given the number of patients enrolled and the volume of data collected over the study duration, the deviations were determined to not impact the interpretation of the study results as they pertain to the study's relevant objectives and endpoints. Moreover, the COVID-19 pandemic had no substantial impact on the assessment of the study objectives.

Protocol deviations were managed according to the protocol deviation guidance provided by the Sponsor and were reviewed by the Sponsor.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of important protocol deviations. The dataset

included 213 important violations (166 occurring on the tebentafusp arm, 45 occurring in the IC arm, and 2 involving use of incorrect versions of the informed consent document (ICD) occurring in patients not enrolled). Important protocol violations were categorized as violations in:

- Discontinuation criteria, including treatment past progression without signing specific treatment past progression informed consent form, or treatment past confirmed progression;
- Inclusion/ Exclusion criteria, including laboratory assessments not meeting criteria, missing ECG records, no measurable disease, randomization prior to baseline testing, failure to screen and inform patients of childbearing potential of contraception requirements.
- Informed Consent/ HIPAA, including use of wrong ICD or failure to re-consent with updated ICF, screening/ screening labs prior to signing ICD,
- Investigational Product, including patient refusal to stay overnight in hospital as required by protocol, product administered beyond 4 hours (all < 10 minutes), missed doses due to freezer or other technical problem with product, incorrect storage or freezer failure, administration of incorrect dose (2 events involving incorrect dosing of 68 mg instead of 20 mg on day 1 cycle 1).
- Prohibited medication, specifically administration of pre-medication which was not allowed per protocol prior to administration of C1D1 for 1 patient.
- Delayed SAE reporting.
- Trial procedures including missed laboratory assessments, scan completed outside of window, missed post dose vital signs, incorrect timing of laboratory assessments.

There were more Trial Procedure violations in the tebentafusp arm than occurred in the IC arm. This can be explained by the increased frequency of treatment, increased complexity of administration and monitoring, and lack of familiarity with the investigational product. The violations do not necessitate removal of any patients from the analysis. The protocol deviations described above are unlikely to have had a meaningful impact on interpretation of the study results.

Table of Demographic Characteristics

Data:

Overall, the majority of patients were White (87.0%) and approximately half were male (50.3%), with a median age of 64.0 years (range, 23 to 92 years) (Table 18). Approximately half of the patients were ≥ 65 years of age. Nearly two-thirds of patients were from the non-North American region (63.5%). By country, most patients were enrolled in the US (31.7%) and Germany (15.6%). The vast majority of patients (94.5%) had an ECOG performance status score of 0 or 1 at baseline. One patient, in the investigator's choice arm, had an ECOG performance status score of 2, which is an eligibility criteria deviation and was accounted for in the important protocol deviations.

Table 18: Study 202: Demographics and Baseline Characteristics (ITT Analysis Set)

Characteristic	Tebentafusp (N=252)	Investigator's Choice (N=126)	Overall (N=378)
Age, years			
n	252	126	378
Mean (Std)	61.3 (11.9)	63.6 (10.7)	62.1 (11.6)
Median (Min, Max)	63.5 (23, 92)	65.5 (25, 88)	64.0 (23, 92)
Age group, n (%)			
<65	130 (51.6)	61 (48.4)	191 (50.5)
≥ 65	122 (48.4)	65 (51.6)	187 (49.5)
Gender, n (%)			
Female	124 (49.2)	64 (50.8)	188 (49.7)
Male	128 (50.8)	62 (49.2)	190 (50.3)
Region, n (%)			
Non-North America	166 (65.9)	74 (58.7)	240 (63.5)
North America	86 (34.1)	52 (41.3)	138 (36.5)
Country, n (%)			
United States	72 (28.6)	48 (38.1)	120 (31.7)
Germany	40 (15.9)	19 (15.1)	59 (15.6)
France	24 (9.5)	13 (10.3)	37 (9.8)
United Kingdom	26 (10.3)	7 (5.6)	33 (8.7)
Poland	14 (5.6)	6 (4.8)	20 (5.3)
Canada	14 (5.6)	4 (3.2)	18 (4.8)
Australia	9 (3.6)	8 (6.3)	17 (4.5)
Belgium	11 (4.4)	5 (4.0)	16 (4.2)
Spain	11 (4.4)	5 (4.0)	16 (4.2)
Switzerland	6 (2.4)	6 (4.8)	12 (3.2)
Ukraine	8 (3.2)	2 (1.6)	10 (2.6)
Russia	8 (3.2)	0	8 (2.1)
Italy	6 (2.4)	1 (0.8)	7 (1.9)
Netherlands	3 (1.2)	2 (1.6)	5 (1.3)
Race, n (%)			
American Indian/Alaska Native	0	1 (0.8)	1 (0.3)

Table 18: Study 202: Demographics and Baseline Characteristics (ITT Analysis Set)

Characteristic	Tebentafusp (N=252)	Investigator's Choice (N=126)	Overall (N=378)
White	222 (88.1)	107 (84.9)	329 (87.0)
Not reported	23 (9.1)	14 (11.1)	37 (9.8)
Not allowed as per local regulatory	5 (2.0)	3 (2.4)	8 (2.1)
Unknown	1 (0.4)	1 (0.8)	2 (0.5)
Other	1 (0.4)	0	1 (0.3)
Ethnicity, n (%)			
Hispanic or Latino	3 (1.2)	6 (4.8)	9 (2.4)
Not Hispanic or Latino	217 (86.1)	102 (81.0)	319 (84.4)
Not reported	29 (11.5)	16 (12.7)	45 (11.9)
Unknown	3 (1.2)	2 (1.6)	5 (1.3)
ECOG performance status, n (%)			
0	192 (76.2)	85 (67.5)	277 (73.3)
1	49 (19.4)	31 (24.6)	80 (21.2)
2	0	1 (0.8)	1 (0.3)
Missing	11 (4.4)	9 (7.1)	20 (5.3)

ECOG = Eastern Cooperative Oncology Group; ITT = Intent-to-treat; Max = maximum; Min = minimum; Std = standard deviation.

Source: Module 5.3.5.1, Study 202 CSR, Table 14.1.4.

The Applicant's Position:

The demographic and baseline characteristics of the study population were generally well balanced between the 2 treatment arms.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the patients' demographic characteristics and agrees that they were generally balanced across the treatment groups. The median age of patients in the study was 64, slightly older than what has been cited in the literature as (59 to 62 years) (Kaliki 2017). The study included very few patients of American Indian/Alaskan Native race and Hispanic or Latino ethnicity. No patients were reported to be Black/African American or Asian, however this appears to be consistent with observed incidences of uveal melanoma in different racial and ethnic groups.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Baseline disease characteristics of the Study 202 population are summarized in Table 19. For most patients, the choroid was the initial UM site (75.7%) and metastasis was not observed at initial diagnosis (92.3%). Approximately one-third of patients had LDH > ULN 250 U/L (36.0%), a poor prognostic factor for advanced UM, and more than half of the patients' largest

metastatic lesion recorded at baseline was ≤ 3 cm (55.3%). For the majority of patients (79.9%), the pre-randomization choice of therapy was pembrolizumab. Most patients did not receive prior surgery for metastatic disease (91.3%).

Table 19: Study 202: Baseline Disease Characteristics (ITT Analysis Set)

Characteristic	Tebentafusp (N=252)	Investigator's Choice (N=126)	Overall (N=378)
Site of initial uveal melanoma, n (%)			
Iris	3 (1.2)	5 (4.0)	8 (2.1)
Ciliary body	25 (9.9)	13 (10.3)	38 (10.1)
Choroid	193 (76.6)	93 (73.8)	286 (75.7)
Unknown	30 (11.9)	14 (11.1)	44 (11.6)
Missing	1 (0.4)	1 (0.8)	2 (0.5)
Stage of initial diagnosis, n (%)			
I	48 (19.0)	14 (11.1)	62 (16.4)
II	89 (35.3)	40 (31.7)	129 (34.1)
III	56 (22.2)	34 (27.0)	90 (23.8)
IV	23 (9.1)	7 (5.6)	30 (7.9)
Missing	36 (14.3)	31 (24.6)	67 (17.7)
Was metastasis observed at initial diagnosis, n (%)			
Yes	17 (6.7)	10 (7.9)	27 (7.1)
No	234 (92.9)	115 (91.3)	349 (92.3)
Missing	1 (0.4)	1 (0.8)	2 (0.5)
Baseline LDH, U/L ^a			
n	234	117	351
Mean (Std)	361.9 (476.2)	281.2 (187.5)	335.0 (405.1)
Median (Min, Max)	207.0 (119, 5572)	204.0 (133, 1199)	207.0 (119, 5572)
Randomization stratum, n (%)			
LDH ≤ULN 250 U/L	162 (64.3)	80 (63.5)	242 (64.0)
LDH >ULN 250 U/L	90 (35.7)	46 (36.5)	136 (36.0)
Largest metastatic lesion at baseline, n (%)			
≤3 cm	139 (55.2)	70 (55.6)	209 (55.3)
3.1-8.0 cm	92 (36.5)	46 (36.5)	138 (36.5)
≥8.1 cm	21 (8.3)	10 (7.9)	31 (8.2)
Pre-randomization choice of treatment, n (%)			
Pembrolizumab	199 (79.0)	103 (81.7)	302 (79.9)
Ipilimumab	40 (15.9)	16 (12.7)	56 (14.8)
Dacarbazine	13 (5.2)	7 (5.6)	20 (5.3)
Prior surgery for metastatic disease ^b			
Yes	24 (9.5)	9 (7.1)	33 (8.7)
No	228 (90.5)	117 (92.9)	345 (91.3)

ITT = Intent-to-treat; LDH = lactate dehydrogenase; Max = maximum; Min = minimum; Std = standard deviation; ULN = upper limit of normal.

^a LDH value is based on central laboratory.

^b Prior surgery for metastatic disease is based on a medical review.

Source: Module 5.3.5.1, Study 202 CSR, Table 14.1.5.

The Applicant's Position:

Baseline disease characteristics were generally well balanced between the 2 treatment arms and representative of a 1L mUM population.

The FDA's Assessment:

FDA agrees with Applicant's summary of patients' disease characteristics at baseline.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Data are presented below as part of the applicant's position.

The Applicant's Position:

Treatment compliance

The median relative dose intensity was similar in both treatment arms: 100.0% (range, 95% to 100%) in the tebentafusp arm and 100% (range, 100% to 100%) in the investigator's choice arm.

Concomitant medications

Concomitant medications were defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug (or, started at the time of or after the first dose of study drug) up to 90 days following the last dose.

A total of 245 patients (97.2%) in the tebentafusp arm and 108 patients (85.7%) in the investigator's choice arm received at least 1 concomitant medication. The most common classes of concomitant medications received (by > 50% of patients in either the tebentafusp arm or investigator's choice arm) were analgesics (89.7% vs 41.3%), antihistamines for systemic use (86.1% vs 18.3%), blood substitutes and perfusion solutions (56.7% vs 14.3%), and corticosteroids, dermatological preparations (54.0% vs 14.3%). The drug classes of analgesics, antihistamines, blood substitutes, anti-inflammatory products, and corticosteroids were received by a notably higher percentage of patients in the tebentafusp arm because they were used as preventive or therapeutic interventions for management of rash and CRS, which are AEs associated with the mechanism of action of tebentafusp.

Subsequent anticancer therapies

After discontinuation of study drug, 109 patients (43.3%) in the tebentafusp arm and 55 patients (43.7%) in the investigator's choice arm received other systemic anticancer therapies. The median duration of subsequent anticancer treatment was 110.0 and 70.0 days, respectively.

The FDA's Assessment:

FDA agrees with the Applicant's assessments.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Overall survival – ITT Analysis Set

In the ITT Analysis Set, based on a median follow-up duration of 14.1 months and 150 death events (87 [34.5%] in the tebentafusp arm and 63 [50.0%] in the investigator's choice arm), the primary endpoint of OS favored tebentafusp with a HR of 0.51 (95% CI: 0.37, 0.71; $p < 0.0001$; Table 20 and Figure 27). Although not yet mature, the Kaplan-Meier estimates of median OS was longer in the tebentafusp arm (21.7 months; 95% CI: 18.6, 28.6) compared with the investigator's choice arm (16.0 months; 95% CI: 9.7, 18.4). Kaplan-Meier estimates of OS at 12 and 24 months were 73.2% and 44.8%, respectively, for tebentafusp, and 58.5% and 20.3%, respectively, for investigator's choice (Table 20).

Table 20: Study 202: Summary of Overall Survival (ITT Analysis Set)

Parameter	Tebentafusp (N=252)	Investigator's Choice (N=126)
Patients with events, n (%)		
Deaths	87 (34.5)	63 (50.0)
Survival, months		
Median (95% CI), months	21.7 (18.6, 28.6)	16.0 (9.7, 18.4)
Survival probability, % (95% CI)		
6 months	88.8 (84.1, 92.2)	78.1 (69.6, 84.6)
9 months	81.1 (75.3, 85.7)	63.2 (53.4, 71.5)
12 months	73.2 (66.4, 78.8)	58.5 (48.3, 67.3)
18 months	61.5 (53.3, 68.7)	42.9 (31.5, 53.8)
24 months	44.8 (34.9, 54.2)	20.3 (9.1, 34.7)
30 months	33.6 (20.2, 47.6)	10.2 (1.1, 31.1)
Median follow-up time, months (95% CI) ^a	14.1 (12.5, 16.1)	14.3 (10.9, 17.0)
Combined median follow-up time, months (95% CI) ^a	14.1 (12.7, 15.6)	
Stratified analysis		
Hazard ratio (95% CI) ^b	0.51 (0.37, 0.71)	NA
p value ^c	<0.0001	NA

CI = confidence interval; ITT = Intent-to-treat; LDH = lactate dehydrogenase; NA = not applicable.

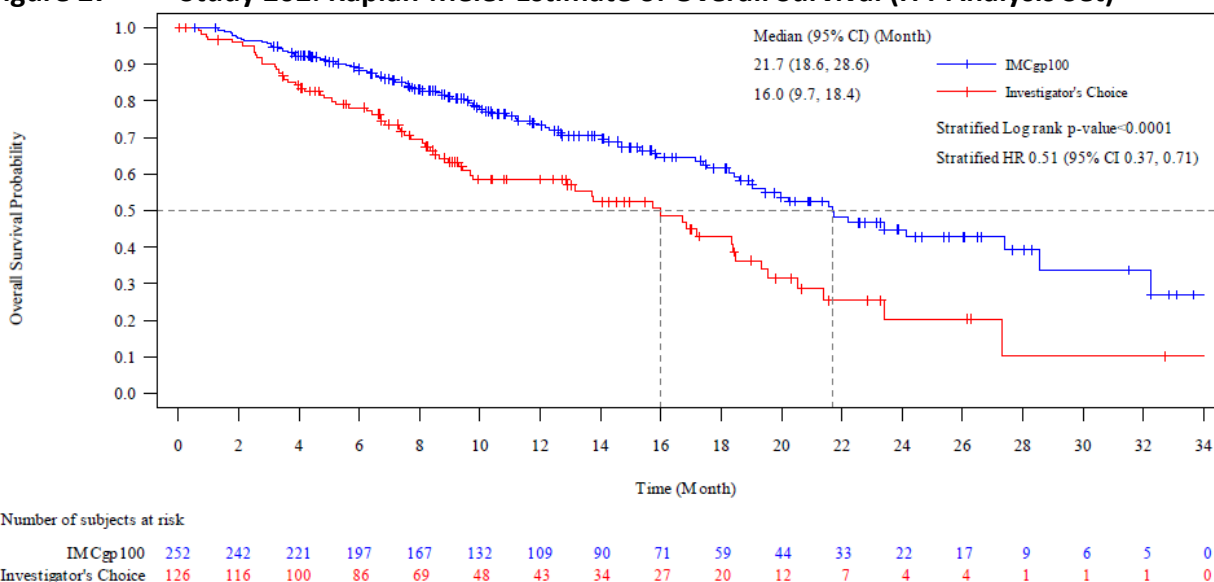
^a Reverse Kaplan-Meier estimate.

^b Hazard ratio is from a stratified proportional hazards model stratified by LDH status. A hazard ratio <1 favors tebentafusp.

^c P value is from a stratified log-rank test stratified by LDH status.

Source: Module 5.3.5.1 Study 202 CSR, Table 14.2.1.1.

Figure 27 Study 202: Kaplan-Meier Estimate of Overall Survival (ITT Analysis Set)



CI = confidence interval; HR = hazard ratio; IMCgp100 = tebentafusp; ITT = Intent-to-treat.

Source: Module 5.3.5.1, Study 202 CSR, Figure 14.2.1.1.

Overall survival sensitivity analysis

Overall survival results were consistent across all prespecified sensitivity analyses.

The Applicant's Position:

Tebentafusp demonstrated a significant improvement in OS, compared with investigator's choice, in HLA-A*02:01-positive patients with mUM who had not received prior systemic therapy in the metastatic setting. Tebentafusp reduced the relative risk of death by 49%, compared with investigator's choice (HR 0.51; 95% CI: 0.37, 0.71; $p < 0.0001$). Based on a median follow-up duration of 14.1 months, treatment with tebentafusp resulted in a 6-month improvement in estimates of median OS compared with investigator's choice (21.7 vs 16.0 months), and an approximate 15% increase in 1-year OS (73.2% vs 58.5%). Overall survival results were consistent across all prespecified sensitivity analyses.

The FDA's Assessment:

Primary analysis of OS:

FDA generally agrees with Applicant's summary of the primary analysis results of OS in the all-randomized population. FDA notes that with 150 OS events observed at this interim analysis (60% of the total 250 events required for final OS analysis), the corresponding stopping boundary was 0.006. FDA also notes that, while all the landmark/milestone rates presented for OS were validated by the FDA reviewers, these were considered as supportive information only.

Sensitivity analysis of OS:

FDA acknowledges and agrees with the Applicant's position that OS results were consistent across all prespecified sensitivity analyses. FDA notes that, as per SAP, the only planned sensitivity analysis of OS included considering a stratified analysis based on strata determined by the central LDH results if there are >10% discrepancies observed in LDH results when compared to the strata recorded at the time of randomization in the IRT system, which was the prespecified source of stratification that to be used in the primary analysis of OS. The Applicant noted that fewer than 10% of patients had inconsistencies between their randomized LDH stratum and their appropriate LDH stratum per the central lab data and therefore no additional sensitivity analysis were performed based on this criteria. In addition to this prespecified sensitivity analysis, the Applicant also reported the OS results in the RAS analysis set and safety analysis set.

Subgroup Analyses of OS:

Forest plots for OS by subgroups for Study 202 are presented in Figure 39, Section 8.1.6. FDA notes that all subgroup analyses are considered exploratory. In subgroups with adequate sample sizes, the OS results were consistent with the overall OS results. For further discussion on OS subgroup analysis refer to FDA's Assessment on Page-156 of this Assessment Aid.

Data Quality and Integrity

Data:

Not applicable.

The Applicant's Position:

No issues were identified that could potentially impact data integrity, prevent an adequate assessment of the data, and change the conclusions drawn.

The FDA's Assessment:

Data and reports for this BLA were submitted electronically in CDISC format. The data quality was acceptable. No data integrity issues were identified.

Efficacy Results – Secondary and other relevant endpoints

Data:

Progression-free survival

Based on a median follow-up duration of 11.4 months and 295 PD or death events (198 [78.6%] in the tebentafusp arm and 97 [77.0%] in the investigator's choice arm), PFS favored tebentafusp and met statistical significance (HR 0.73; 95% CI: 0.58, 0.94; $p = 0.0139$) (Table 21 and Figure 28). Median PFS was 3.3 months in the tebentafusp arm and 2.9 months in the investigator's

choice arm. Kaplan-Meier estimates of PFS rates at 6 months were 30.9% and 18.9%, respectively (Figure 37).

Table 21: Study 202: Summary of Progression-free Survival (ITT Analysis Set)

Parameter	Tebentafusp (N=252)	Investigator's Choice (N=126)
Patients with events, n (%)		
PFS events	198 (78.6)	97 (77.0)
Progressive disease	183 (72.6)	83 (65.9)
Death	15 (6.0)	14 (11.1)
PFS, months		
Median (95% CI), months	3.3 (3.0, 5.0)	2.9 (2.8, 3.0)
PFS probability, % (95% CI)		
6 months	30.9 (25.0, 37.0)	18.9 (12.0, 27.2)
9 months	19.8 (1.7, 25.5)	11.7 (6.1, 19.2)
12 months	14.1 (9.5, 19.5)	6.2 (2.3, 13.0)
18 months	11.5 (7.2, 16.9)	6.2 (2.3, 13.0)
24 months	9.2 (5.1, 14.8)	0.0 (--, --)
30 months	9.2 (5.1, 14.8)	0.0 (--, --)
Median follow-up time, months (95% CI) ^a	13.8 (10.9, 16.8)	11.3 (8.3, 16.9)
Combined median follow-up time, months (95% CI) ^a	11.4 (11.1, 1.6)	
Stratified analysis		
Hazard ratio (95% CI) ^b	0.73 (0.58, 0.94)	NA
p value ^c	0.0139	NA

-- = missing; CI = confidence interval; ITT = Intent-to-treat; LDH = lactate dehydrogenase; NA = not applicable;

PFS = progression-free survival.

^a Reverse Kaplan-Meier estimate.

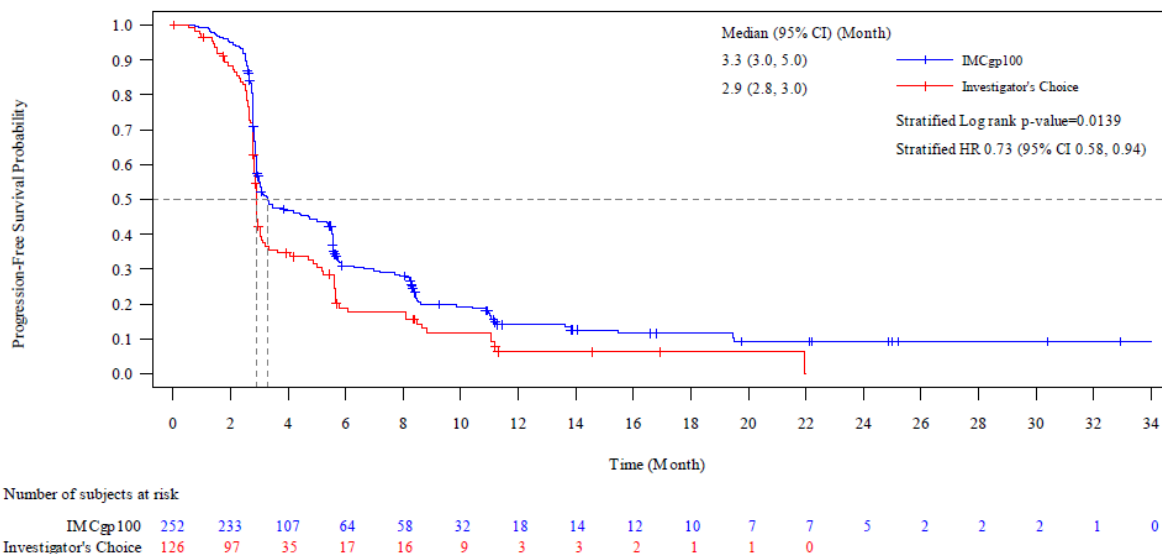
^b Hazard ratio is from a stratified proportional hazards model stratified by LDH status. A hazard ratio < 1 favors tebentafusp.

^c P value is from a stratified log-rank test stratified by LDH status.

Source: Module 5.3.5.1, Study 202 CSR, Table 14.2.2.1.

Figure 28 Study 202: Kaplan-Meier Estimate of Progression-free Survival (ITT Analysis Set)

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CI = confidence interval; HR = hazard ratio; IMCgp100 = tebentafusp; ITT = Intent-to-treat.
Source: Module 5.3.5.1, Study 202 CSR, Figure 14.2.2.1.

Progression-free survival results were consistent across both prespecified sensitivity analyses of evaluation-time bias and attrition bias.

Best overall response, objective response rate, disease control rate

Best overall response, ORR, and DCR are summarized in Table 22. **Error! Reference source not found..**

In the tebentafusp arm, BORs were 1 CR (0.4%) and 22 PRs (8.7%); 92 patients (36.5%) had SD and 131 (52.0%) had PD. In the investigator's choice arm, there were no CRs; 6 patients (4.8%) had PRs, 28 (22.2%) had SD, and 78 (61.9%) had PD.

The ORR was numerically higher in the tebentafusp arm (9.1%; 95% CI: 5.9, 13.4) compared with the investigator's choice arm (4.8%; 95% CI: 1.8, 10.1). The prespecified time point for statistical comparison of BOR has not yet been reached.

Disease control rate (defined as CR + PR + SD $\geq$ 12 weeks) favored the tebentafusp arm compared with the investigator's choice arm, with rates of 45.6% (115 of 252 patients; 95% CI: 39.4, 52.0) and 27.0% (34 of 126 patients; 95% CI: 19.5, 35.6), respectively.

Table 22: Study 202: Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate (ITT Analysis Set)

Parameter	Tebentafusp (N=252)	Investigator's Choice (N=126)
Best overall response, n (%)		
Complete response	1 (0.4)	0
Partial response	22 (8.7)	6 (4.8)
Stable disease	92 (36.5)	28 (22.2)

Table 22: Study 202: Summary of Best Overall Response, Objective Response Rate, and Disease Control Rate (ITT Analysis Set)

Parameter	Tebentafusp (N=252)	Investigator's Choice (N=126)
Progression of disease	131 (52.0)	78 (61.9)
Not evaluable	6 (2.4)	14 (11.1)
Not evaluable post-baseline tumor assessments and no death recorded	6 (2.4)	10 (7.9)
All post-baseline assessments have an overall response of not evaluable	0	1 (0.8)
SD recorded prior to Week 12 ^a from randomization	0	3 (2.4)
Objective response rate (CR/PR)		
n (%)	23 (9.1)	6 (4.8)
95% CI ^b	5.9, 13.4	1.8, 10.1
Stratified odds ratio (tebentafusp/investigator's choice)	1.98	NA
95% CI of odds ratio ^c	0.79, 4.97	NA
Disease control rate (CR/PR/SD ≥12 weeks)		
n (%)	115 (45.6)	34 (27.0)
95% CI ^b	39.4, 52.0	19.5, 35.6
Stratified odds ratio (tebentafusp/investigator's choice)	2.33	NA
95% CI of odds ratio ^c	1.45, 3.75	NA

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete response; ITT = Intent-to-treat; LDH = lactate dehydrogenase; PR = partial response; SD = stable disease.

^a Defined as disease assessment conducted prior to Day 77.

^b 95% CIs are calculated for the rate using the exact Clopper-Pearson method.

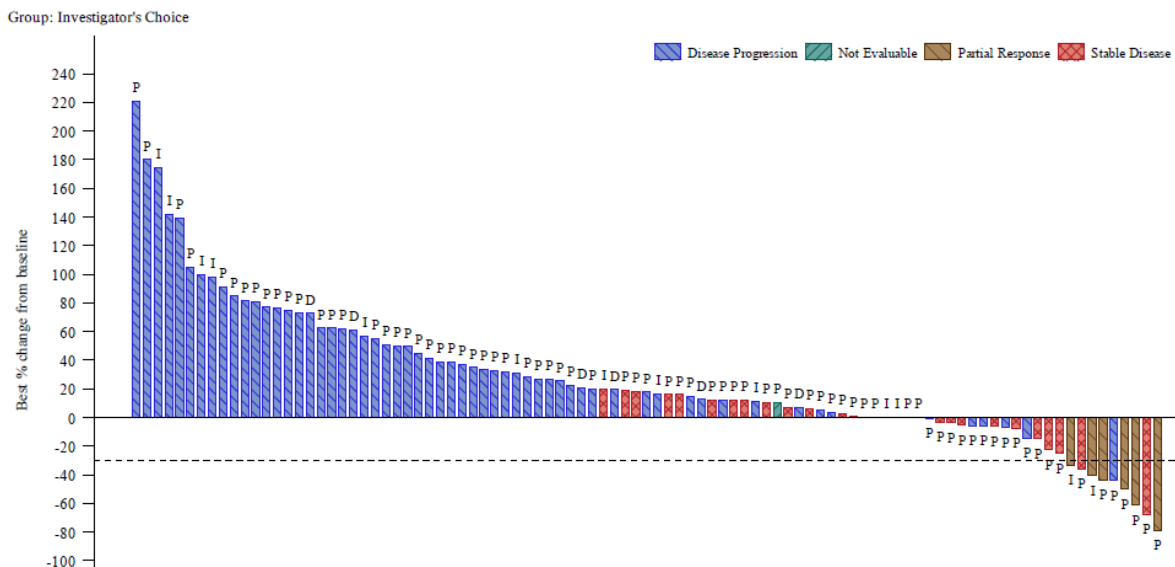
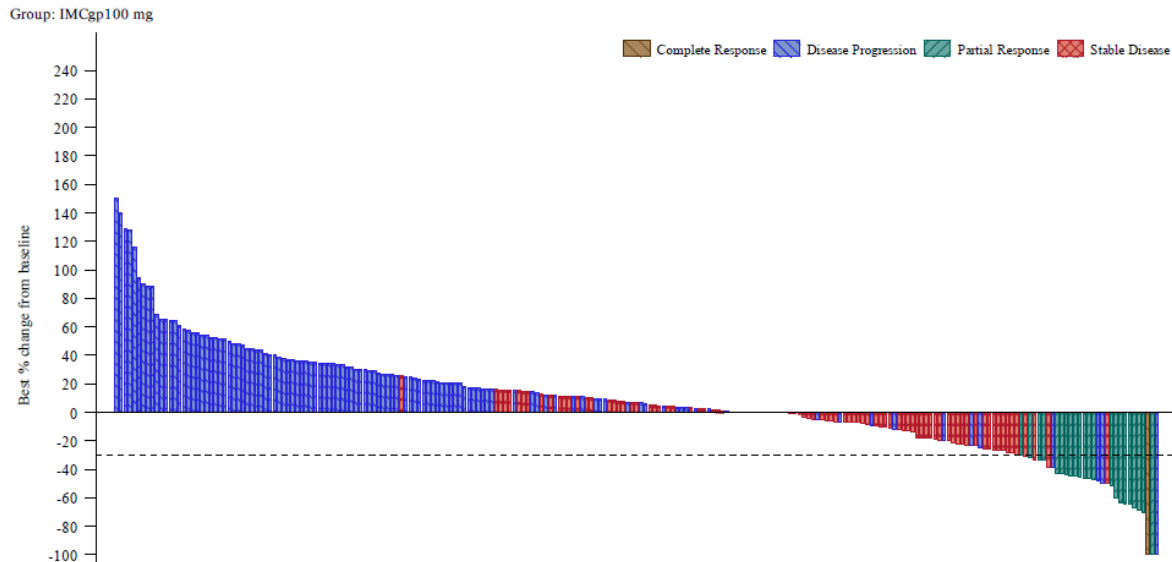
^c Stratified CMH test stratified by LDH status.

Source: Module 5.3.5.1, Study 202 CSR, Table 14.2.3.

The waterfall plot shows that the rate and degree of tumor shrinkage were much more pronounced in patients treated with tebentafusp than those treated with investigator's choice; 32.5% and 17.5% of patients, respectively, had a reduction in tumor size (Figure 29).

Figure 29 Study 202: Waterfall Plot of Best Percentage Change from Baseline in Tumor Size by Treatment Arm (ITT Analysis Set)

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D = dacarbazine; I = ipilimumab; IMCgp100 = tebentafusp; ITT = Intent-to-treat; P = pembrolizumab; RECIST = Response Evaluation Criteria in Solid Tumors.

Tumor size was measured as the sum of longest diameters or short axis of the target lesions according to RECIST v1.1.

Source: Module 5.3.5.1, Study 202 CSR, Figure 14.2.3.

Duration of response

The median DOR was 9.9 months for tebentafusp and 9.7 months for investigator's choice (Table 23). The Kaplan-Meier estimates for DOR at 6 months were 60.6% and 50.0%, respectively.

Table 23: Study 202: Summary of Duration of Response (ITT Analysis Set – Subset of Responders)

Parameter	Tebentafusp (N=23)	Investigator's Choice (N=6)
DOR, months ^a		
PFS events, n (%)	9 (39.1)	4 (66.7)
PD	9 (39.1)	4 (66.7)
Death	0	0
Median (95% CI), months	9.9 (5.4, --)	9.7 (2.7, --)
Kaplan-Meier estimates for DOR (95% CI) [No. at risk]		
3 months	84.8 (59.5, 94.9) [n=14]	50.0 (11.1, 80.4) [n=2]
6 months	60.6 (34.2, 7.2) [n=10]	50.0 (11.1, 80.4) [n=2]
9 months	54.5 (28.9, 74.4) [n=7]	50.0 (11.1, 80.4) [n=2]
12 months	46.8 (21.8, 68.4) [n=4]	50.0 (11.1, 80.4) [n=2]
Median follow-up time, months (95% CI) ^a	10.8 (2.8, 13.8)	9.3 (2.8, --)

-- = missing; CI = confidence interval; DOR = duration of response; ITT = Intent-to-treat; PD = progressive disease; PFS = progression-free survival.

^a Duration of response is defined as the time from the date of first documentation of PR or better to the date of first documentation of PD or death due to any cause, whichever comes first.

^b Reverse Kaplan-Meier method.

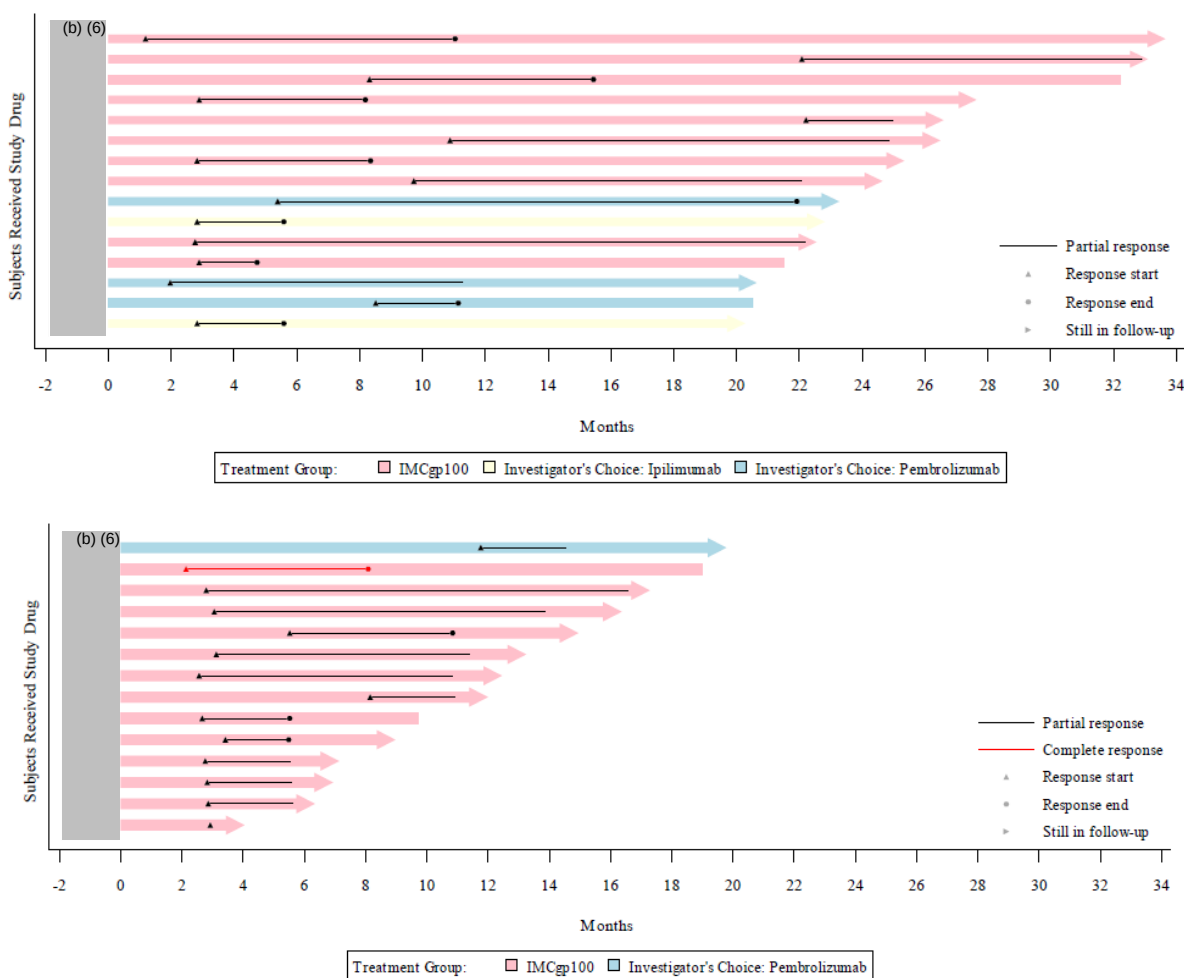
Only patients who have a complete or partial response are included.

Source: Module 5.3.5.1, Study 202 CSR, Table 14.2.4.

Time to response

In the subset of responders (23 in the tebentafusp arm and 6 in the investigator's choice arm), TTR occurred earlier in the tebentafusp arm than the investigator's choice arm, with a median of 2.9 months (range, 1.2 to 22.2) and 4.1 months (range, 2.0 to 11.8), respectively (Figure 30).

Figure 30 Study 202: Swimmer Plot for Time to Response (ITT Analysis Set)



IMCgp100 = tebentafusp; ITT = Intent-to-treat.
Source: Module 5.3.5.1, Study 202 CSR, Figure 14.2.5.1.

The Applicant's Position:

Tebentafusp demonstrated a statistically significant improvement in the secondary endpoint of PFS, compared with investigator's choice. Tebentafusp reduced the relative risk of disease progression or death by 27%, compared with investigator's choice (HR 0.73; 95% CI: 0.58, 0.94; $p = 0.0139$). Disease control rate at 12 weeks was numerically higher with tebentafusp than investigator's choice (45.6% vs 27.0%). The point estimate for ORR was higher with tebentafusp than investigator's choice (9.1% vs 4.8%). Best overall response will be formally tested in a later analysis after all patients have undergone at least 3 planned on-treatment tumor assessments.

The FDA's Assessment:

While FDA generally agrees with the Applicant's summary of the secondary endpoint results, FDA has the following assessments regarding these results:

- FDA does not agree with the Applicant's conclusion that tebentafusp demonstrated a clinically significant improvement in PFS over IC in Study 202. Although the HR of 0.73 (95% CI: 0.58, 0.94) for PFS favored the tebentafusp arm, the improvement in median PFS was only 0.4 months, and while the p-value of 0.0139 would be considered statistically significant, FDA does not consider an improvement of less than 2 weeks to be clinically meaningful. The tumor responses were assessed every 12 weeks. In addition, the 95% CI for the PFS probability at all landmark timepoints for the tebentafusp and IC arms overlap. The lack of benefit with respect to PFS can also be noted from the KM plot of PFS curves, where separation between the curves over the entire follow-up period was very marginal.
- The tumor response rates observed in Study 202 are marginal and effectively the same for both arms. The 95% CI's overall with the lower bound of the 95% CI is under 6% for both arms.

FDA also has the following additional comments :

- As per the SAP, PFS was planned to be tested only once after observing at least 275 events and therefore, the observed p-value of 0.0139 for PFS analysis was compared to an alpha of 0.05 to demonstrate statistical significance.
- FDA acknowledges that ORR was not formally tested at this interim analysis.
- FDA does not object to the Applicant's inclusion of DCR in their summary in this review; however, this endpoint was not considered as part of the overall benefit:risk assessment (b) (4).
- All the landmark/milestone rates presented for PFS and DOR were validated by the FDA reviewers but these were considered as supportive information only.

Dose/Dose Response

Data:

Not applicable.

The Applicant's Position:

Justification for the Phase 3 tebentafusp dose and regimen is based on clinical data driven by safety, tolerability, and clinical activity from the dose escalation phases of Study 01 and Study 102 with supporting data from the expansion phase of Study 102 rather than tebentafusp exposure-response. Validation of the tebentafusp regimen is provided by the Phase 3 results, including high OS (hazard ratio [HR] 0.51 for OS; Table 20) and overall tolerability (low rate of tebentafusp-related discontinuations [2.4% Phase 2, 2.0% Phase 3] and no tebentafusp-related

deaths.

The FDA's Assessment:
See Section 6.3.

Durability of Response

Data:

Data are presented below as part of the applicant's response.

The Applicant's Position:

The median DOR was 9.9 months for tebentafusp and 9.7 months for investigator's choice (Table 23). The Kaplan-Meier estimates for DOR at 6 months were 60.6% and 50.0%, respectively.

The FDA's Assessment:
FDA agrees with Applicant's position above.

Persistence of Effect

Data:

Data are presented below are part of the applicant's position.

The Applicant's Position:

The Phase 3 Study 202 is an ongoing open-label, randomized, multi-center study to evaluate the efficacy and safety of tebentafusp versus investigator's choice (pembrolizumab, ipilimumab, or dacarbazine) in adult HLA-A*02:01-positive patients with mUM who had not received prior systemic therapy in the metastatic setting. All patients randomized to tebentafusp received the intra-patient escalation regimen of 20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter. Tebentafusp was administered via intravenous infusion over 15 to 20 minutes. Treatment continued until radiographic progression, unacceptable toxicity, investigator decision, or patient withdrawal of consent. Patients who received tebentafusp, pembrolizumab, or ipilimumab and experienced disease progression per RECIST could continue with treatment beyond initial RECIST progression until confirmed RECIST progression, if they met the prespecified criteria.

In the ITT Analysis Set, based on a median follow-up of 14.1 months, the median duration of treatment was 163.0 days (range, 1 to 1016 days) with tebentafusp and 65.0 days (range, 1 to 658 days) with investigator's choice. A total of 172 patients (68.3%) in the tebentafusp arm and 100 patients (79.4%) in the investigator's choice arm had discontinued treatment, while 73 patients (29.0%) continued to receive tebentafusp and 11 patients (8.7%) continued to receive investigator's choice. The most common reason for permanent discontinuation of study drug was

disease progression, which occurred in 154 patients (61.1%) in the tebentafusp arm and 78 patients (61.9%) in the investigator's choice arm.

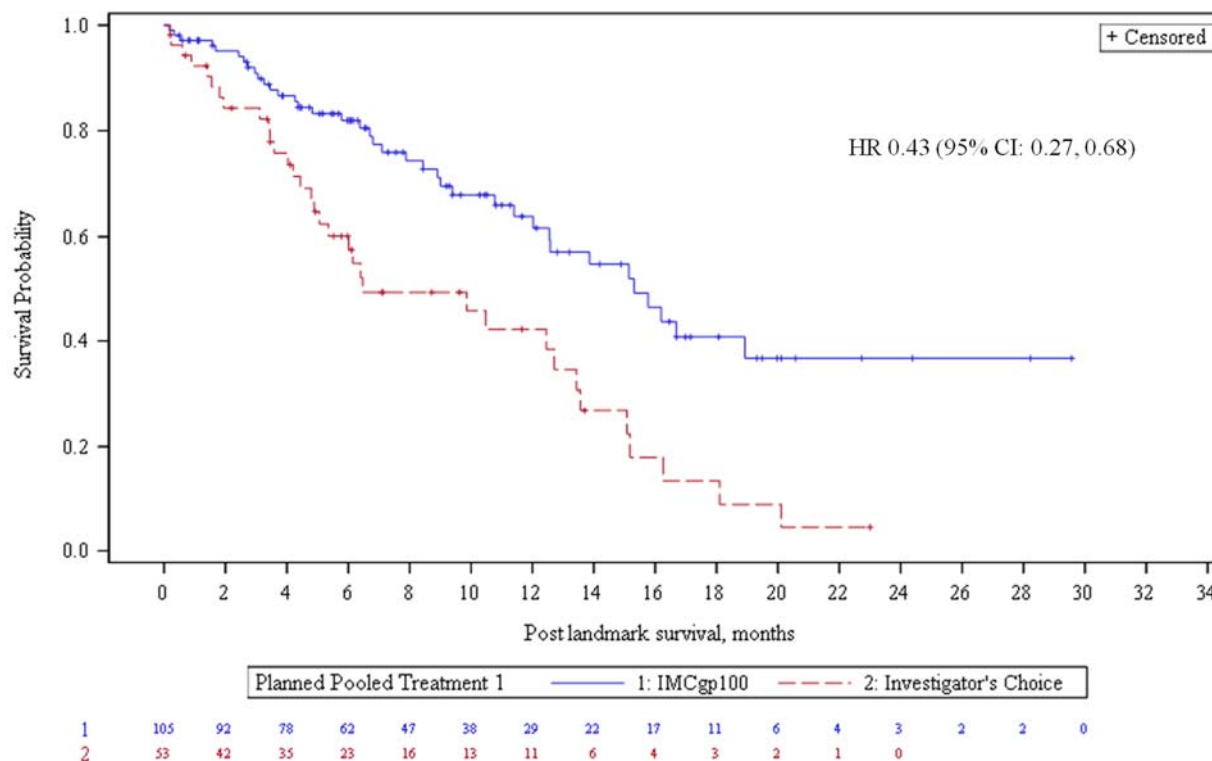
In Phase 3 Study 202, only patients receiving tebentafusp and, in the investigator's choice arm, only patients receiving pembrolizumab were treated beyond initial RECIST progression and included in the treatment beyond progression analyses. No crossover to tebentafusp was permitted; investigators were free to choose subsequent therapy. In the ITT Analysis Set, the incidence of treatment beyond initial RECIST progression was higher in patients randomized to the tebentafusp arm compared with those randomized to the investigator's choice arm (43.3% [109/252] vs 14.3% [18/126]).

To better understand the role of treatment beyond progression, a post-hoc exploratory analysis was conducted in the subset of patients who had a BOR of PD. Among patients with a BOR of PD, the incidence of treatment beyond initial RECIST progression was higher with tebentafusp than pembrolizumab (53.4% [70/131] vs 17.5% [11/63]). In these patients, the median duration of treatment beyond progression was longer with tebentafusp than pembrolizumab (1.7 vs 0.8 months).

To eliminate immortal time bias and to capture the majority of PD patients after the first tumor assessment at Day 84 ($\pm$ 7 days), a landmark OS analysis was conducted that was limited to patients with a BOR of PD alive at Day 100. Patients with a BOR of PD are traditionally considered to not be benefitting from therapy and by definition, do not have indolent SD, and so OS could not be confounded by slow growing tumor.

In this landmark OS analysis, 105 of 252 patients (41.7%) in the tebentafusp arm versus 53 of 126 patients (42.1%) in the investigator's choice arm were alive and had a best response of PD by Day 100. In these patients, OS was superior for tebentafusp compared with investigator's choice (HR 0.43; 95% CI: 0.27, 0.68; Figure 31), even when considering key baseline covariates. These data provide a potential explanation for why tebentafusp can have a low RECIST-based response rate but dramatic OS benefit and suggest that radiographic-defined PD for tebentafusp may not always equate with lack of benefit or a reason for treatment discontinuation.

Figure 31 Post-landmark Overall Survival in Patients with Best Overall Response of Progressive Disease in Study 202



CI = confidence interval; HR = hazard ratio; IMCgp100 = tebentafusp.

Source: Module 2.7.3, Figure 5.

The FDA's Assessment:

Post hoc analyses, including those of the responder-analysis of treatment past progression, were not considered as part of FDA's overall risk:benefit assessment of tebentafusp.

In general, FDA does not agree that the argument presented above supports the Applicant's conclusion. A comparison of patients in the tebentafusp arm who were treated past progression with patients in the pembrolizumab arm who were treated past progression does not support a conclusion that any observed benefit was due to treatment past progression. Any improvement in OS observed in patients in the tebentafusp arm who were treated past progression when compared to patients in the pembrolizumab arm could have been derived before being treated past progression. To assess whether treatment past progression provides benefit to the patients, the Applicant must demonstrate that patients in the tebentafusp arm who were treated past progression had superior outcome to patients in the tebentafusp arm who were not treated past progression by randomly assigning the patients to these two groups.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Health-related quality of life

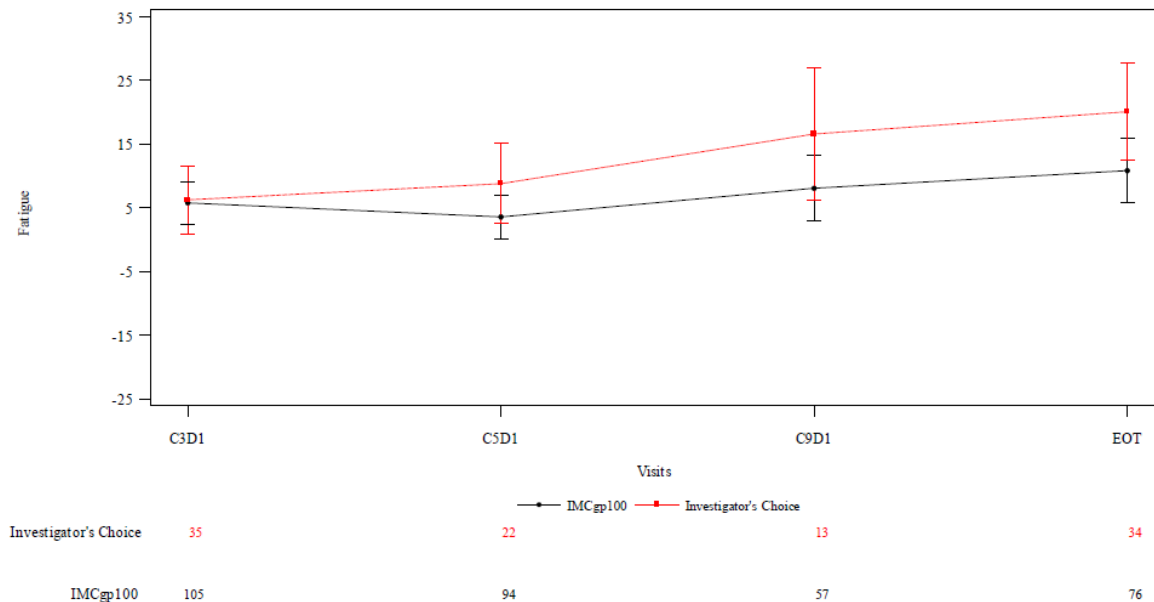
Health-related quality-of-life data were collected using the EORTC QLQ-C30 and EQ-5D,5L PRO instruments.

EORTC-QLQ-C30

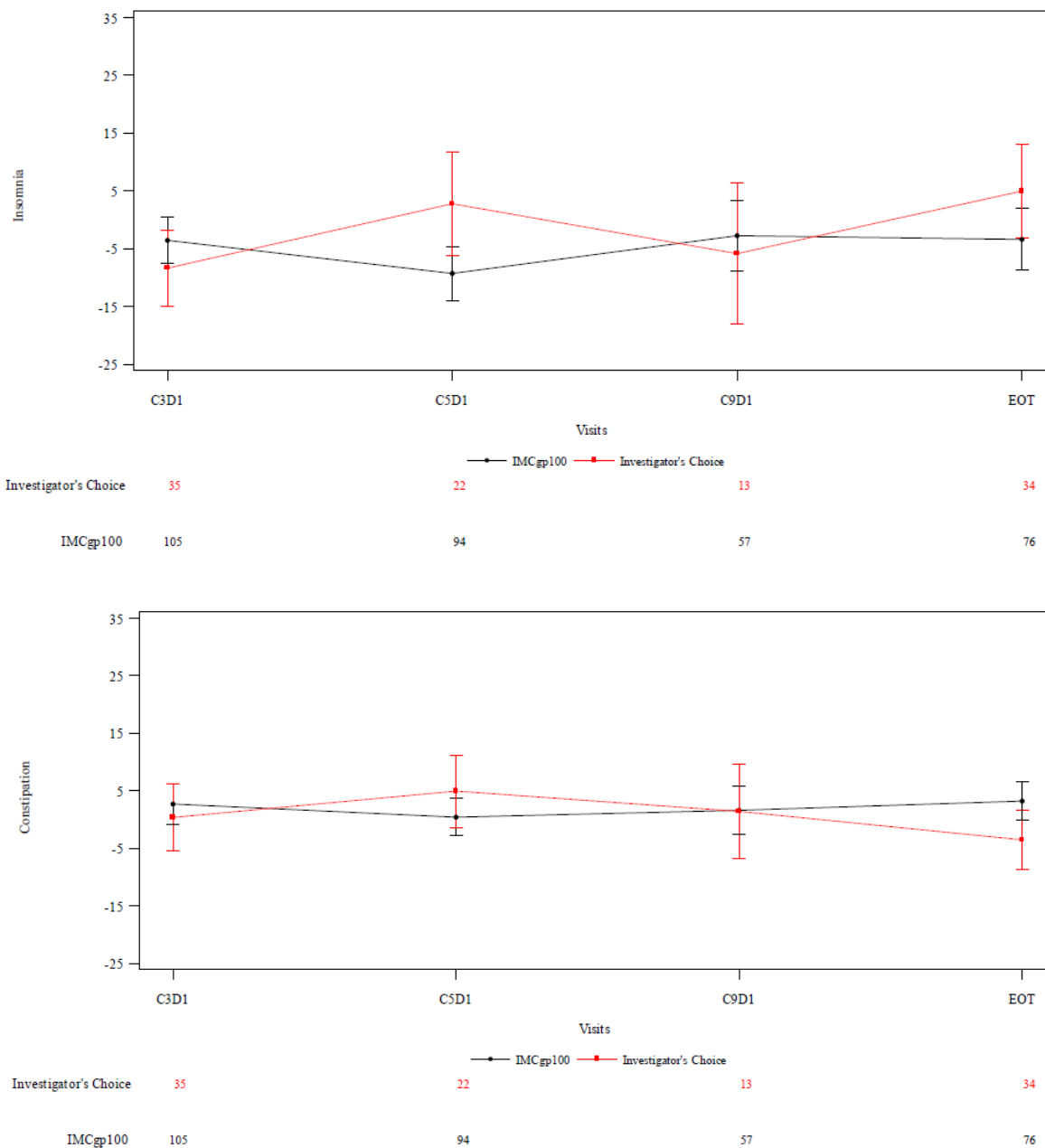
In both the tebentafusp and investigator's choice arms, patients were considered to be domain compliant (ie, completed at least 50% of the EORTC QLQ-C30 items) through C17D1, with generally similar rates between the arms. Subsequently, patients in the tebentafusp arm remained domain compliant through C29D1, whereas compliance in the investigator's choice arm decreased to approximately 33% at C29D1.

At baseline, no differences in EORTC-QLQ-C30 scores were observed between the treatment arms for any of the domains. In general, throughout the study, the EORTC-QLC-C30 scores were similar between the treatment arms and remained stable for most domains. However, statistically significant and clinically meaningful LS mean improvements from baseline were observed for fatigue at EOT (10.9 vs 20.1; $p = 0.0445$) and insomnia at C5D1 (-9.3 vs 2.8; $p = 0.0176$), both favoring tebentafusp, and for constipation at EOT (3.2 vs -3.5; $p = 0.0296$), favoring investigator's choice. LS mean scores over time are illustrated in Figure 32 for PRO symptoms of fatigue, insomnia, and constipation.

Figure 32 Study 202: LS Mean Scores Over Times for Selected PRO Symptoms – EORTC-QLQ-C30 (ITT Analysis Set)



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C#D# = Cycle # Day #; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire; IMCgp100 = tebentafusp; ITT = Intent-to-treat; LS = least squares; PRO = patient-reported outcome. Source: Module 5.3.5.1, Study 202 CSR, Figure 14.2.7.1.

Overall, there was no significant difference between the tebentafusp and investigator's choice arms for time to sustained deterioration across the different EORTC-QLQ-C30 domains.

EQ-5D, 5L

In both the tebentafusp and investigator's choice arms, patients were considered to be domain compliant through C17D1, with generally similar rates between the arms. Subsequently, patients in the tebentafusp arm remained domain compliant through C29D1, whereas compliance in the investigator's choice arm decreased to 40.0% at C21D1 and 33.3% at each of C25D1 and EOT.

At baseline, no differences in EQ-5D, 5L scores were observed between the treatment arms for any of the domains. In general, throughout the study, mean change from baseline was similar between the treatment arms for all domains.

The Applicant's Position:

Health-related quality of life, as assessed by the EORTC-QLQ-C30 and EQ-5D,5L PRO instruments, was generally similar between the 2 treatment groups, with some symptoms showing improvement in the tebentafusp group.

The FDA's Assessment:

PROs were included as secondary endpoints in Study 202; however, no PRO endpoints were included in the formal testing plan, so all PRO analyses are considered to be exploratory and no claims can be made based on these analyses. Thus, FDA does not agree with the Applicant's conclusion of "statistically significant and clinically meaningful LS mean improvements from baseline" for specific PRO domains such as fatigue, insomnia, and constipation. FDA also does not agree with the Applicant's conclusion of "no significant difference between the tebentafusp and investigator's choice arms for time to sustained deterioration across the different EORTC QLQ-C30 domains" and the Applicant's statement that health related quality of life was generally similar between the two treatment groups. Such claims in particular cannot be made as the trial was not powered to show non-inferiority and was not designed with pre-specified non-inferiority margins for the domains.

FDA has the following additional comments regarding the PRO analyses for this trial:

- The EORTC-QLQ-C30 and EQ-5D, 5L instruments are completed at baseline, at C1D1, at Day 1 of every other cycle through C5D1, then every 4th cycle thereafter beginning with C9D1 until (and including at) end of treatment (during the treatment period).
- FDA agrees with the Applicant's summary of the completion rates and the domain compliant rates as presented.
- While EORTC-QLQ-C30 maybe a reasonable choice to assess some functional impacts, the Global Health Status/QoL metric does not necessarily reflect a meaningful assessment of core disease, treatment symptoms, and their associated impact.
- The EQ-5D-5L is a composite that incorporates self-reported ability to function, pain, and general health status as filled out by the patient. This instrument is a generic preference based measure intended to provide a health utility index value for use in economic analyses and lacks content validity for use in estimating clinical benefit for the

purposes of labeling claims, though FDA acknowledges that this instrument is often used by other regulatory authorities and/or payers.

Additional Analyses Conducted on the Individual Trial

Data:

Data are presented below as part of the applicant's position. These data were also presented above to support persistence of effects.

The Applicant's Position:

There is accumulating evidence in the field of immuno-oncology, initially described for ipilimumab, that some patients treated with checkpoint inhibitors may develop immune-related response patterns beyond traditional RECIST response. While the most widely cited example of this is tumor regression despite the appearance of new lesions, other examples include a slow, steady decline in tumor burden and initial PD of the tumor prior to subsequent disease stabilization (Wolchok, 2009). The practical implication is that survival benefit may still occur despite initial disease progression, and thus, progression should be confirmed prior to discontinuation of immunotherapy (Hodi, 2016).

Examples of the immune-related response patterns to tebentafusp were noted in Phase 1, with predominantly a slow, steady decline in tumor burden and some patients who had initial PD followed by disease stabilization (Middleton, 2015; Middleton, 2016). In Study 102 Phase 2 expansion, a low RECIST response rate but promising OS coupled with examples again of these types of immune responses suggested that immune-related response may predominate for tebentafusp. Intriguingly, approximately 42% of patients (25/60) with a best RECIST response of PD, including some with an increase in tumor burden as best change on treatment, had survival longer than 1 year.

In clinical practice, standard of care for checkpoint inhibitors includes the option for treatment beyond initial progression because of the concept of immune-related responses. However, no Phase 3 study with checkpoint inhibitors has demonstrated that immune-related responses are sufficiently high to account for an OS benefit.

In Phase 3 Study 202, only patients receiving tebentafusp and, in the investigator's choice arm, only patients receiving pembrolizumab were treated beyond initial RECIST progression and included in the treatment beyond progression analyses. No crossover to tebentafusp was permitted; investigators were free to choose subsequent therapy. In the ITT Analysis Set, the incidence of treatment beyond initial RECIST progression was higher in patients randomized to the tebentafusp arm compared with those randomized to the investigator's choice arm (43.3% [109/252] vs 14.3% [18/126]).

To better understand the role of treatment beyond progression, a post-hoc exploratory analysis was conducted in the subset of patients who had a BOR of PD. Among patients with a BOR of

PD, the incidence of treatment beyond initial RECIST progression was higher with tebentafusp than pembrolizumab (53.4% [70/131] vs 17.5% [11/63]). In these patients, the median duration of treatment beyond progression was longer with tebentafusp than pembrolizumab (1.7 vs 0.8 months).

To eliminate immortal time bias and to capture the majority of PD patients after the first tumor assessment at Day 84 ($\pm$ 7 days), a landmark OS analysis was conducted that was limited to patients with a BOR of PD alive at Day 100. Patients with a BOR of PD are traditionally considered to not be benefitting from therapy and by definition, do not have indolent SD, and so OS could not be confounded by slow growing tumor.

In this landmark OS analysis, 105 of 252 patients (41.7%) in the tebentafusp arm versus 53 of 126 patients (42.1%) in the investigator's choice arm were alive and had a best response of PD by Day 100. In these patients, OS was superior for tebentafusp compared with investigator's choice (HR 0.43; 95% CI: 0.27, 0.68; Figure 31), even when considering key baseline covariates. These data provide a potential explanation for why tebentafusp can have a low RECIST-based response rate but dramatic OS benefit and suggest that radiographic-defined PD for tebentafusp may not always equate with lack of benefit or a reason for treatment.

The FDA's Assessment:

FDA does not consider post hoc analyses and does not agree with the Applicant that any conclusions can be made regarding efficacy in the subgroup of patients that were treated beyond progression. The lack of randomization is unable to account for potential differences in inherent patient characteristics that may influence the interpretation of this post hoc analysis. See FDA comment above.

8.1.3. Supportive Study 102

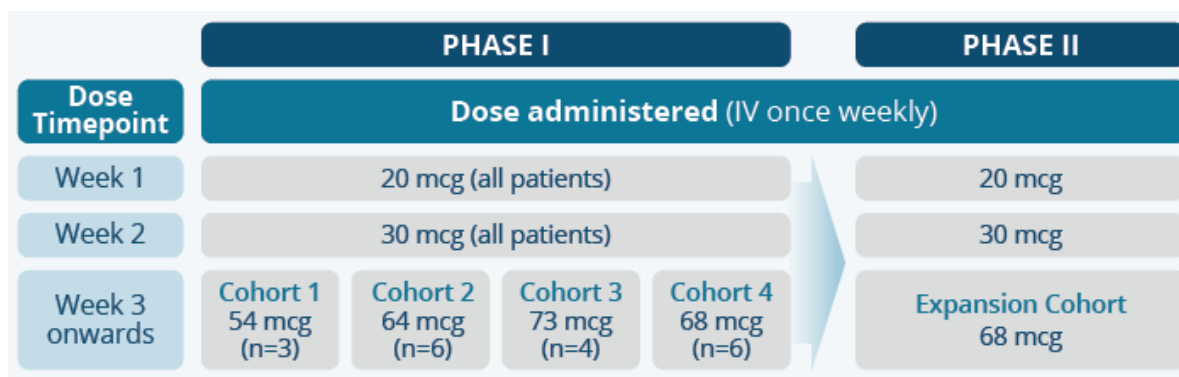
Trial Design

The Applicant's Description:

Overall design

This was a Phase 1/2 study of tebentafusp administered on a QW basis with an intra-patient escalation dosing regimen (Figure 33). The intra-patient escalation regimen consisted of fixed low doses of tebentafusp at C1D1 (20 mcg) and C1D8 (30 mcg), followed by an escalated cohort specified QW dose administered at C1D15 and beyond. According to this regimen, all patients in the study received 2 QW doses of tebentafusp at a dose level below the identified RP2D-QW (50 mcg; determined in Study IMCgp100-01), and then dose escalation commenced at the third QW dose at C1D15 with the goal to achieve a long-term dosing regimen at a dose higher than that identified for the straight QW dosing regimen (RP2D-QW). Doses between 54 and 73 mcg were evaluated in the Phase 1 dose escalation cohorts. Dose escalation identified the RP2D-IE; 68 mcg was selected for Phase 2 dose expansion.

Figure 33 Study 102 Design



IV = intravenous(ly).

The Phase 1 portion of the study had a standard 3 + 3 dose escalation design. After the dose escalation portion was complete and the MTD or the RP2D-IE was identified, two Phase 2 dose expansion cohorts in mUM were to be enrolled. The Phase 2 dose expansion Cohort A was to enroll patients with mUM in the second-line setting after disease progression following systemic treatment with a checkpoint inhibitor and to recruit approximately 20 patients. Phase 2 dose expansion Cohort B was to enroll patients with mUM in the second- or third-line settings with up to 1 prior line of LDT and to recruit approximately 130 patients. However, in practice, there was significant overlap between the Cohort A and Cohort B populations, and it was not clear that patients belonged distinctly in either cohort. Therefore, this report will present data for the single combined Phase 2 dose expansion cohort. This expansion cohort was designed to further characterize the safety, tolerability, and preliminary PK and antitumor activity of tebentafusp.

Eligibility criteria

Key inclusion criteria included:

- ≥ 18 years of age at the time of informed consent.
- Histologically or cytologically confirmed mUM.
- Cohort A: Disease progression on 1 systemic treatment regimen containing a checkpoint inhibitor. Any prior LDT was acceptable.¹
- Cohort B: Disease progression on 1 or 2 prior lines of therapy, including chemotherapy, immunotherapy, or targeted therapy. Prior LDT was counted as a line of therapy.¹
- HLA-A*02:01 positive by central assay.
- ECOG performance status score of 0 or 1.

Key exclusion criteria included:

- Systemic or untreated CNS metastases.

¹ In practice, there was significant overlap between Cohort A and Cohort B populations, and it was not clear that patients belonged distinctly in either cohort. Therefore, the data were presented for a single combined Phase 2 expansion cohort.

- History of severe hypersensitivity reactions to other iologic drugs or mAbs.
- Clinically significant cardiac or impaired cardiac function.
- Active infection that required systemic antibiotic therapy.
- Known HIV.
- Active hepatitis B virus or hepatitis C virus infection.
- Adrenal insufficiency.
- Treatment with systemic steroid therapy or any other immunosuppressive medication at any dose level.
- Radiotherapy within 2 weeks of first dose of study drug.
- Use of hematopoietic colony-stimulating growth factors.
- Systemic anticancer therapy within 2 weeks of the first dose of study drug.
- Requiring chronic, systemic corticosteroid therapy at any dose for longer than 2 weeks.

Dose selection

The selection of intra-patient dose escalation over the first 3 weeks was identified in FIH, Phase 1 Study 01. Several key observations in Study 01 led to recommending an intra-patient escalation regimen using fixed doses. First, in Study 01, patients with higher body weights who received higher absolute doses of tebentafusp experienced more severe treatment-related toxicity. Consequently, fixed doses, rather than weight-based doses, were incorporated during the study. Second, given no clinically meaningful differences in safety or efficacy were identified between the weekly and daily dosing regimens, and in light of the easier utility of a weekly regimen, subsequent evaluation focused on weekly dosing. Third, the emerging safety profile of tebentafusp suggested that CRS (and associated hypotension) was more likely to occur during the first 2 weeks, after which tachyphylaxis occurred. Therefore, as has been used for other T cell-engaging bispecifics, an intra-patient escalation regimen during Weeks 1 and 2 (ie, 20 and 30 mcg, respectively) prior to dosing 50 mcg was selected as the preferred regimen to evaluate further in Study 102.

Study Endpoints

The Applicant's Description:

Primary endpoints

The primary endpoints were:

- Phase 1 dose escalation: Incidence of DLT
- Phase 2 dose expansion: ORR by RECIST v1.1 assessed by ICR

Secondary endpoints

Secondary endpoints were:

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- ORR (Phase 1), PFS, DCR, DOR, TTR per RECIST v1.1²
- OS
- Tolerability (dose interruptions, reductions, and dose intensity)
- Serum PK parameters
- Anti-tebentafusp antibody formation
- Minor tumor responses (10% to 29% reduction in the sum of the longest diameters)

² For the Phase 2 dose expansion cohorts, primary assessment of tumor-based endpoints was provided by an ICR. Investigator assessment data were also collected for both Phase 1 dose escalation cohort (primary assessment) and Phase 2 dose expansion cohorts (secondary assessment).

Statistical Analysis Plan and Amendments

The Applicant's Description:

Analysis populations

Four analysis sets were used in this study, as defined in Table 24.

Table 24: Study 102: Analysis Populations

Analysis Set	Definition
All Patients Enrolled Set	The All Patients Enrolled Set comprised all patients who provided the main informed consent for this study. Patients who signed prescreening informed consent but not the main informed consent did not appear in this analysis set. The All Patients Enrolled Set was used to summarize patient disposition and the analysis sets. Any patients who signed the main informed consent, but never started the study drug for any reason were regarded as screen failures. For these patients, the eCRF data collected was not to be included in summary analyses but was to be reported in the clinical study report as part of the listings for patient disposition, treatment allocation and eligibility criteria.
Full Analysis Set	The FAS comprised all patients assigned to study drug and who received at least 1 full or partial dose of tebentafusp. The FAS was used for all demography, baseline characteristics, and efficacy data summaries and analyses.
Safety Analysis Set	The Safety Analysis Set included all patients who received at least 1 full or partial dose of tebentafusp. Patients were classified in this set according to initial treatment received. The Safety Analysis Set was used for the safety summary of the study.
Per-protocol Set	The PPS consisted of a subset of FAS patients in the Phase 2 dose expansion cohort who met the following criteria: • Presence of measurable disease at baseline according to Investigator assessment based on RECIST v1.1. • One or more postbaseline tumor assessment or discontinue prior to the first tumor assessment. • Received at least 1 full or partial dose of treatment. • No violation of key inclusion or exclusion criteria as described in the SAP. Patients in the PPS were classified according to planned treatment. The PPS defined the patients used in the sensitivity analysis of the primary efficacy endpoint (ie, ORR) and 1 of the secondary endpoints (DOR) for the Phase 2 dose expansion cohort only.

DOR = duration of response; FAS = Full Analysis Set; ORR = objective response rate; PPS = Per-protocol Set;
RECIST = Response Evaluation Criteria in Solid Tumors; SAP = statistical analysis plan.

SAP amendments

The first version of the SAP was released on 25 August 2016 and amended. The changes in each amendment are summarized in Table 25.

Table 25: Study 102: SAP Amendments Summary

SAP Version	Date	Major Changes
2	25 August 2016	Updated to align with Protocol Version 8 (Amendment 7), including major changes to the efficacy, safety, and exploratory sections
3	20 May 2020	Updates included but were not limited to: • Changes to exploratory efficacy • Additional subgroups in Section 7.5 • Further details on concomitant medications, AEsIs, exposure, vital signs, PK, immunogenicity, and patient-reported outcomes

AEsI = adverse event of special interest; PK = pharmacokinetics; SAP = statistical analysis plan.

Protocol Amendments

The Applicant's Description:

The original protocol was dated 06 October 2015. The global protocol was amended 7 times. Amendments 1 and 2 were instituted before the first patient was enrolled. The global protocol amendments are summarized in Table 26.

Table 26 : Study 102: Global Protocol Amendments Summary

Amendment Version and Date	Key Details of Amendment.	Rationale for Change
Amendment 1 dated 08 Dec 2015 was instituted prior to patient recruitment	Implemented dosing changes in the intra-patient dose escalation regimen with reduction of the starting dose on C1D1 to 20 mcg and C1D8 to 30 mcg.	To mitigate the potential for infusion toxicity associated with hypotension.
	Added large disease burden in the liver as an exclusion criterion in the dose escalation portion of the study (patients with replacement of >60% of the liver with disease were excluded).	Due to the possibility of hepatic toxicity.
Amendment 2 dated 12 Jan 2016 was instituted prior to patient recruitment	Implemented new monitoring strategy for occurrence of hypotension in the study. Mandatory hospitalization for the C1D8 dose was implemented. This hospitalization was in addition to the previous mandatory inpatient observations for the C1D1 and C1D15 doses.	These monitoring changes were in response to infusion-related toxicity with associated hypotension that has been observed in the ongoing FIH Phase 1 study of tebentafusp in metastatic melanoma (study number tebentafusp-01).
	Guidance for inpatient monitoring for the C1D22 dose was provided and based upon the individual patient's tolerability of the first 3 doses (C1D1, C1D8, and C1D15).	Inpatient observation for C1D22 was mandatory if the patient experienced infusion toxicity involving NCI CTCAE Grade 2 or greater hypotension requiring medical intervention at the previous dose on C1D15.

Table 26 : Study 102: Global Protocol Amendments Summary

Amendment Version and Date	Key Details of Amendment.	Rationale for Change
	Revised safety data for Study IMCgp100-01 study to the Investigator's Brochure (Edition 7, issued 17 Dec 2015).	To reflect the updated infusion-related toxicity events of Grade 2 or greater hypotension.
	Revised exclusion criteria.	To reflect the appropriate methods of highly effective contraception.
Amendment 3 dated 23 May 2016	Implemented new DLT criterion for transient Grade 3 ALT and/or AST elevations to be excluded from DLT provided these events were not associated with change in bilirubin and resolve to Grade 1 or lower within 72 hours.	To change the definition of DLT with respect to the observations of transient elevations of hepatic transaminases, ALT, and AST, in patients with UM in the 2 ongoing Phase 1 trials with tebentafusp, the FIH study.
	Changed exclusion criterion number 14 to exclude any patient with a history of adrenal insufficiency or any patient requiring long-term corticosteroid treatment.	Patients receiving chronic corticosteroid therapy for any reason were excluded due to the potential dysfunction of the hypothalamic-pituitary-adrenal axis in mediating response to stress.
Amendment 4 dated 07 Sep 2016	Given encouraging emerging clinical safety and efficacy data with tebentafusp in UM where a strong signal of disease stabilization has been observed in early dosing cohorts in this study, the sample size of the RP2D-IE expansion cohort was increased from 20 to 40 patients. Also, changed the inclusion criteria for the RP2D-IE expansion cohort to include approximately 40 patients treated in the second-line setting following disease progression with a checkpoint inhibitor.	To provide a larger safety dataset and more robust point estimate of overall survival in the selected patient population.
	Changed inclusion criterion #6 on HLA-A*02:01 allele expression.	To require central testing for the HLA-A*02:01 allele expression.
	Implemented new translational work in the Phase 2 RP2D-IE cohort.	To assess the predictive and pharmacodynamic impact of changes in circulating tumor DNA with UM mutations in GNAQ and GNA11.

Table 26 : Study 102: Global Protocol Amendments Summary

Amendment Version and Date	Key Details of Amendment.	Rationale for Change
Amendment 5 dated 11 Apr 2017	Updated the protocol-specified doses of tebentafusp throughout the protocol. This included updates to the 60, 70, 75, and 80 mcg dose. Updated AE management guidance was provided, including updated management of the events of cytokine release syndrome and hypotension.	To reflect the conduct of the dose escalation cohorts and updated protocol-specified dose levels.
Amendment 6 dated 15 Dec 2017	Increased the sample size of the Phase 2 dose expansion cohorts (from approximately 40 patients to approximately 150 patients) and added the primary endpoint of the single-arm Phase 2 dose expansion cohort of ORR assessed by independent central review based on RECIST v1.1. Two separate expansion cohorts were defined based on prior therapy. Given the formal efficacy measures implemented in this dose expansion cohort, the study was designated as a Phase 1/2 to reflect this new endpoint.	Based on the observation of durable partial responses and minor responses (defined as a tumor response where the SLD of target lesions is reduced by 10% to 29%) in the dose escalation cohorts of this study, and to provide a formal analysis of the antitumor efficacy in this patient population.
	Clarified the criteria for treatment beyond progression and treatment discontinuation in the circumstance of treatment beyond progression using modified irRECIST. The rationale for treatment beyond progression was provided.	To provide additional detail delineating criteria for treatment beyond progression.
	Clarified that an IDMC would review the safety data from the Phase 2 dose expansion cohorts on an ongoing basis and would also review both efficacy and safety after approximately 75 patients have been recruited to cohort.	To monitor the benefit-risk profile of tebentafusp.
	Added patient reported outcomes to screening assessments (EQ-5D,5L and EORTC QLQ-C30 questionnaires). Added additional guidance for the management of treatment-related toxicity including hypotension and cytokine release events (that were generally observed 2 to 24 hours after the dose of tebentafusp), rash, and pruritus. Clarified that antitumor response as assessed by irRECIST was an exploratory endpoint.	Clarification
Amendment 7 dated 26 Nov 2018	Revised language for allowed prior treatments.	To clarify the allowable and required prior therapies.
	Revised the hospitalization requirements indicate that “inpatient hospitalization” referred to a facility with fully functional resuscitation	Clarification

Table 26 : Study 102: Global Protocol Amendments Summary

Amendment Version and Date	Key Details of Amendment.	Rationale for Change
	facilities, 24-hour monitoring and physician availability.	
	Revised imaging assessments to allow either CT or MRI to be done for tumor assessment and no longer require both modalities.	Given the expansion of the study and to reduce the burden on patients.
	Addition of biochemical assessments (LDH and CRP) before and after the initial 3 doses.	To explore pharmacodynamic changes after tebentafusp administration and association with response.
	Optimized ctDNA collection timepoints and objectives.	To assess pharmacodynamic changes after treatment as well as to evaluate for predictors of resistance to treatment.
	Changed exclusion criterion #19 and added Section 6.6 on contraception requirements for women of childbearing potential.	To be consistent across tebentafusp clinical trials with Clinical Trial Facilitation Group recommendations
	Increased duration of safety follow-up period.	To provide further safety information and be consistent across tebentafusp clinical studies.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C#D# = Cycle# Day#; CRP = C-reactive protein; CT = computed tomography; ctDNA = Circulating tumor deoxyribonucleic acid; DLT = dose limiting toxicity; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer (EORTC) Quality of life Questionnaire-Core 30 (QLQ-C30); EQ 5D,5L = EuroQoL-5 Dimensions – 5-levels of disease severity scale; FIH = first in human; GNAQ = heterotrimeric G-protein alpha subunit q; GNA11 = heterotrimeric G-protein alpha subunit 11; HIV = human immunodeficiency virus; HLA A*02:01 = Human leukocyte antigen-A*02:01; IDMC = Independent data monitoring committee; irRECIST = Immune-related Response Criteria in Solid Tumors; LDH = Lactate dehydrogenase; MRI = Magnetic resonance imaging; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Event; ORR = objective response rate; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D-IE = Recommended Phase 2 dose — intra-patient escalation; SLD = sum of the longest diameters; UM = uveal melanoma.

The FDA’s Assessment:

FDA acknowledges and agrees with the Applicant’s summary of key elements and the trial design for Study 102.

The Applicant met with FDA on October 12, 2018, to discuss the proposed development plan and registrational strategy for tebentafusp. During this meeting, the Applicant proposed an accelerated approval pathway supported by ORR data (with a target lower 95% confidence limit of $\geq 5\%$ for confirmed ORR) submitted from Study 102 and supportive data from Study 202 available at the time of the planned interim analysis of Study 102.

FDA expressed uncertainty whether an ORR endpoint from a single-arm trial would be able to accurately and reliably predict clinical benefit in the intended patient population and whether the proposed target effect, that would exclude a lower 95% confidence limit of $\geq 5\%$ for

confirmed ORR, would demonstrate a clinically meaningful improvement in anti-tumor response or long-term disease benefit. At the time of this meeting tebentafusp had been observed to have a significant toxicity profile in the setting of a modest response rate further limiting the ability to conclude this product had a favorable risk:benefit profile based on ORR from a single-arm trial.

8.1.4. Study 102 Results

This section will focus mainly on the results from the Phase 2 expansion part of Study 102, which evaluated the proposed dosing regimen of tebentafusp.

Compliance with Good Clinical Practices

Data:

Not applicable.

The Applicant's Position:

The study was conducted in accordance with the protocol, the ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences ethical guidelines, applicable ICH GCP guidelines, and applicable laws and regulations, as described in the following sections of Protocol Version 8:

- Ethical consideration and administrative procedures: Protocol Section 11
- Data handling and management: Protocol Section 10
- Study drug compliance and accountability: Protocol Section 6.8.1

Immunocore Clinical Quality Assurance group or designee conducted audits at 2 study centers. No critical audit findings were observed. For all audit findings, appropriate corrective and preventive actions were undertaken.

Financial Disclosure

Data:

Not applicable.

The Applicant's Position:

Financial disclosures for Study 102 are addressed in Section 19.2 of this assessment aid.

Patient Disposition

Data:

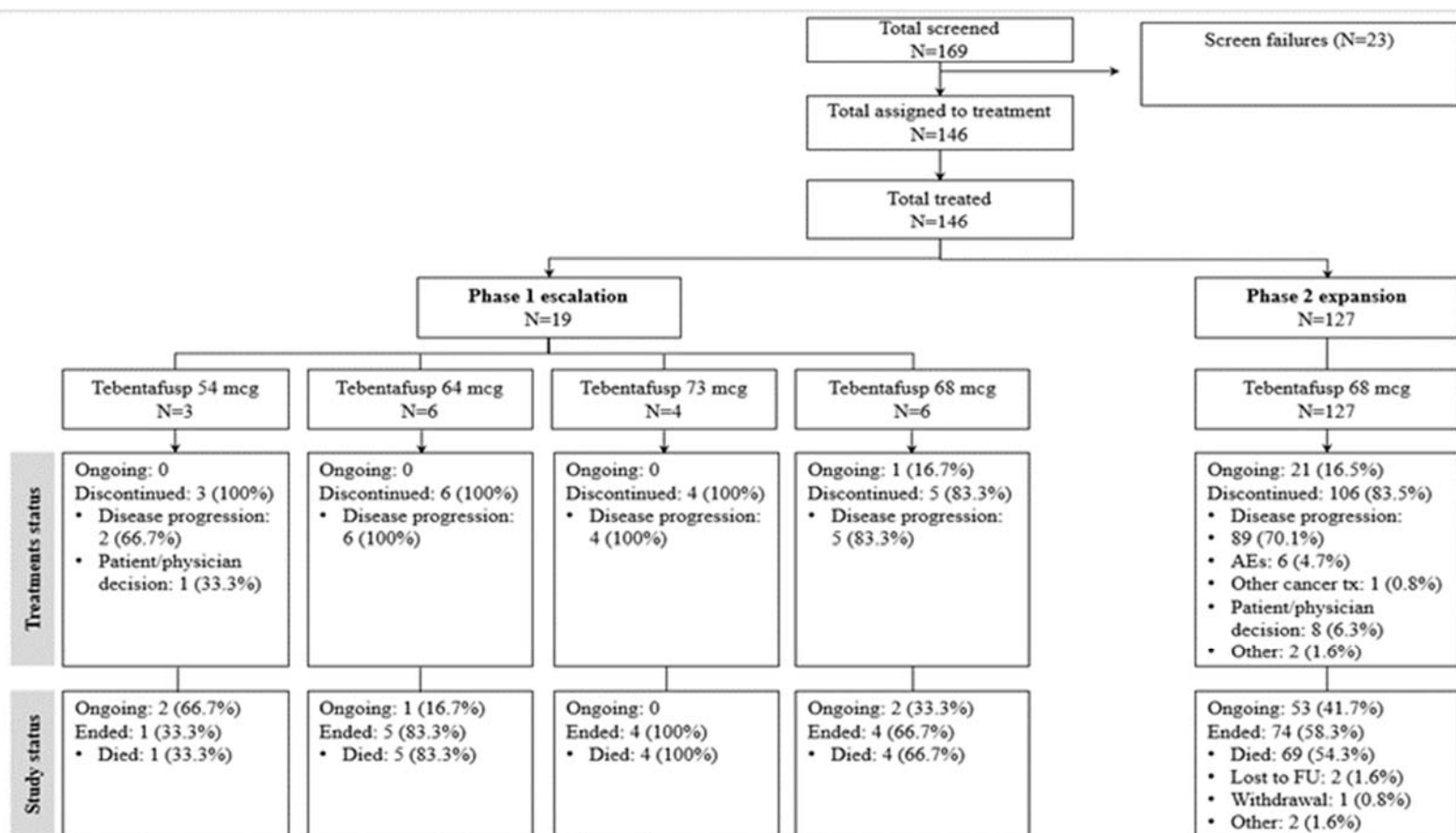
Patient disposition is summarized in Figure 34 for the Phase 1 dose escalation and Phase 2 dose expansion cohorts. The DCO date for this study was 20 March 2020.

Phase 1 dose escalation cohorts: Of the 21 patients screened, 19 patients were enrolled into 4 cohorts: 3 in Cohort 1 54 mcg, 6 in Cohort 2 64 mcg, 4 in Cohort 3 73 mcg, and 6 in Cohort 4 68 mcg. All 19 (100%) enrolled patients received study drug, of whom 18 (94.7%) patients discontinued study drug and 1 (5.3%) patient remained on treatment. At the DCO date, the duration of exposure for the patient who remains on treatment was 42.1 months. The primary reason for treatment discontinuation was disease progression (89.5%). At the data cut-off date, a total of 5 (26.3%) patients remained on study and 14 (73.7%) patients were reported to have ended the study (all due to death).

Phase 2 dose expansion cohort: Of the 148 patients screened, 127 patients were enrolled into the Phase 2 dose expansion part of the study. All 127 (100%) patients received study drug, of whom 106 (83.5%) patients discontinued study drug and 21 (16.5%) patients remained on treatment. The primary reason for treatment discontinuation was disease progression (70.1%). At the data cut-off date, 53 (41.7%) patients remained on study and 74 (58.3%) patients were reported to have ended the study. Death was the primary cause of study discontinuation (54.3%).

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Figure 34 Study 102: Patient Disposition for Dose Escalation and Phase 2 Dose Expansion Cohorts (All Patients Enrolled Set)



Source: Module 5.3.5.2, Study 102 CSR, Table 14.1.1 and Listing 16.2.4.1.

The Applicant's Position:

The causes of study treatment discontinuation were generally consistent with the disease under study.

Protocol Violations/Deviations

Data:

In the Phase 2 dose expansion cohort, the most common important protocol deviations were related to informed consent and trial procedures (7.9% each) (Table 27). These patients were re-consented using the incorrect version of the ICFs, re-consenting was not done in a timely manner, and fresh tumor biopsy samples were not collected in a timely manner.

One patient was excluded from the PPS as the patient did not complete post-treatment scans required per-protocol until PD. The patient refused to have post-treatment scans (but did not formally withdraw consent).

Table 27 : Study 102: Important Protocol Deviations for Phase 2 Dose Expansion Cohort and Overall Summary (Full Analysis Set)

Category	Phase 2 dose expansion (N=127)		Overall (N=146)	
	Number of deviations	Number of patients n (%)	Number of deviations	Number of patients n (%)
Number of patients with important protocol deviations		29 (22.8%)		33 (22.6%)
Total number of important protocol deviations	46		57	
Informed Consent / HIPAA	17	12 (9.4%)	26	15 (10.3%)
Inclusion / Exclusion Criteria	2	2 (1.6%)	2	2 (1.4%)
IP Intervention	8	5 (3.9%)	8	5 (3.4%)
Prohibited Medications	0	0	0	0
Safety Reporting	6	5 (3.9%)	6	5 (3.4%)
Trial Procedures	12	10 (7.9%)	13	11 (7.5%)
Discontinuation Criteria	0	0	0	0
Other	1	1 (0.8%)	2	2 (1.4%)

HIPAA = Health Insurance Portability and Accountability Act; N = Total number of patients; n = number of patients with an observation; IP = investigational product.

Cohort was re-named to reflect the actual dose rather than maximum theoretical dose, due to initial over-estimates in dose preparation.

The overall summary consists of data from both the Phase 1 dose escalation cohorts and Phase 2 dose expansion cohort.

Patients with multiple deviations in the same category are counted only once in that category. Patients with deviations in more than 1 category are counted once in each of those categories.

Percentages are based on the number of patients in the Full Analysis Set.

Source: Module 5.3.5.2, Study 102, Table 14.1.3.

The Applicant's Position:

Overall, the deviations identified as important are consistent with the execution of a Phase 1/2 clinical study with an intensive schedule of assessments, frequent dosing, and visits. Given the number of patients enrolled, and volume of data collected over the study duration, the deviations were determined to not impact the interpretation of the study results as they pertain to the study's relevant objectives and endpoints. Moreover, the COVID-19 pandemic had no substantial impact on the assessment of the study objectives.

Protocol deviations were managed according to the protocol deviation guidance provided by the Sponsor and were reviewed monthly by the Sponsor.

Table of Demographic Characteristics

Data:

In the Phase 2 dose expansion cohort, the majority of patients were White (99.3%) and approximately half were female (50.7%), with a mean age of 60.4 years (range, 25 to 88 years) (Table 28). There was a higher proportion of patients who were <65 years of age (63.0%) versus ≥65 years of age (37.0%). The majority of patients (70.1%) had an ECOG performance status score of 0 at baseline. A total of 58.3% of patients had baseline LDH >ULN, 80.3% of patients had baseline ALC $\geq 1.0 \times 10^9/L$, and 70.9% of patients had baseline ALP $\leq$ ULN.

Table 28 : Study 102: Demography for Phase 2 Dose Expansion Cohort and Overall Summary (Full Analysis Set)

Characteristic	Statistic	Phase 2 dose expansion (N=127)	Overall (N=146)
Age (years)	n	127	146
	Mean (Std)	61.0 (10.93)	60.4 (11.05)
	Median	61.0	60.5
	Min, Max	25, 88	25, 88
<65	n (%)	80 (63.0%)	92 (63.0%)
≥65	n (%)	47 (37.0%)	54 (37.0%)
Sex			
Male	n (%)	63 (49.6%)	72 (49.3%)
Female	n (%)	64 (50.4%)	74 (50.7%)
Race			
White	n (%)	126 (99.2%)	145 (99.3%)
Other	n (%)	1 (0.8%)	1 (0.7%)
Ethnicity			
Hispanic or Latino	n (%)	4 (3.1%)	5 (3.4%)
Not Hispanic or Latino	n (%)	123 (96.9%)	141 (96.6%)
Country			
Canada	n (%)	19 (15.0%)	19 (13.0%)

**Table 28 : Study 102: Demography for Phase 2 Dose Expansion Cohort and Overall Summary
(Full Analysis Set)**

Characteristic	Statistic	Phase 2 dose expansion (N=127)	Overall (N=146)
Germany	n (%)	10 (7.9%)	10 (6.8%)
Spain	n (%)	9 (7.1%)	9 (6.2%)
United Kingdom	n (%)	14 (11.0%)	17 (11.6%)
United States	n (%)	75 (59.1%)	91 (62.3%)
Region			
North America	n (%)	94 (74.0%)	110 (75.3%)
Europe	n (%)	33 (26.0%)	36 (24.7%)
ECOG performance status at baseline			
(0)	n (%)	89 (70.1%)	103 (70.5%)
(1)	n (%)	38 (29.9%)	43 (29.5%)
Baseline lactate dehydrogenase			
≤ULN	n (%)	53 (41.7%)	58 (39.7%)
>ULN	n (%)	74 (58.3%)	85 (58.2%)
Missing	n (%)	0	3 (2.1%)
Baseline absolute lymphocyte count			
<1.0 x 10 ⁹ /L	n (%)	25 (19.7%)	29 (19.9%)
≥1.0 x 10 ⁹ /L	n (%)	102 (80.3%)	117 (80.1%)
Baseline alkaline phosphatase			
≤ULN	n (%)	90 (70.9%)	99 (67.8%)
>ULN	n (%)	37 (29.1%)	47 (32.2%)
Smoking history/status			
Current cigarette smoker	n (%)	4 (3.1%)	7 (4.8%)
Former cigarette smoker	n (%)	47 (37.0%)	51 (34.9%)
Never smoked	n (%)	70 (55.1%)	80 (54.8%)
Unknown	n (%)	6 (4.7%)	8 (5.5%)
Pack years	n	46	53
	Mean (Std)	19.928 (21.2174)	19.187 (20.4041)
	Median	11.000	10.000
	Min, Max	0.00, 92.00	0.00, 92.00

BMI = body mass index, ECOG = Eastern Cooperative Oncology Performance; Min = minimum; Max = maximum; N = Total number of patients; n = number of patients with an observation; Std = standard deviation; 0 = fully active, 1 = restricted in physically strenuous activity.

The overall summary consists of data from both the Phase 1 dose escalation cohorts and Phase 2 dose expansion cohort.

Age was calculated relative to informed consent date. For patients from Germany in which only birth year was recorded, age was derived by imputing birth month and day as 15 June. For patients from Canada in which only birth month and year was recorded, age was derived by imputing birthday as 15.

Source: Module 5.3.5.2, Study 102 CSR, Table 14.1.4.

The Applicant's Position:

The demographic characteristics of the patients enrolled in Study 102 were generally consistent with the target mUM population.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Baseline disease characteristics

For most patients in the Phase 2 expansion cohort, the choroid was the initial UM site (75.7%) and metastasis was not observed at initial diagnosis (92.3%) (Table 29). Approximately one-third of patients had LDH > ULN 250 U/L (36.0%), a poor prognostic factor for advanced UM, and more than half of the patients' largest metastatic lesion recorded at baseline was ≤ 3 cm (55.3%). For the majority of patients (79.9%), the pre-randomization choice of therapy was pembrolizumab. Most patients did not receive prior surgery for metastatic disease (91.3%).

Table 29 : Study 102: Baseline Disease Characteristics for Phase 2 Dose Expansion Cohort and Overall Summary (Full Analysis Set)

Characteristic	Statistic	Phase 2 dose expansion (N=127)	Overall (N=146)
Stage at initial diagnosis			
Stage I	n (%)	11 (8.7%)	15 (10.3%)
Stage II	n (%)	41 (32.3%)	46 (31.5%)
Stage III	n (%)	28 (22.0%)	36 (24.7%)
Stage IV	n (%)	21 (16.5%)	22 (15.1%)
Missing	n (%)	26 (20.5%)	27 (18.5%)
Time since primary diagnosis (years)	n	127	146
	Mean (Std)	6.25 (5.454)	6.14 (5.467)
	Median	4.42	4.39
	Min, Max	0.6, 28.5	0.3, 28.5
Time from primary diagnosis to metastatic disease (years)	n	127	146
	Mean (Std)	4.80 (4.850)	4.66 (4.763)
	Median	2.96	2.96
	Min, Max	0.0, 28.1	0.0, 28.1
Time since first metastases (years)	n	127	146
	Mean (Std)	1.45 (1.727)	1.48 (1.737)
	Median	0.94	0.94
	Min, Max	0.1, 12.3	0.1, 12.3
Largest liver metastasis (Investigator assessment) ^[a]			
Diameter <3cm	n (%)	44 (34.6%)	55 (37.7%)
Diameter ≥3cm	n (%)	73 (57.5%)	79 (54.1%)
No liver metastases	n (%)	10 (7.9%)	12 (8.2%)
Largest liver metastasis (ICR) ^[b]			
Diameter <3cm	n (%)	43 (33.9%)	50 (34.2%)
Diameter ≥3cm	n (%)	69 (54.3%)	73 (50.0%)

Table 29 : Study 102: Baseline Disease Characteristics for Phase 2 Dose Expansion Cohort and Overall Summary (Full Analysis Set)

Characteristic	Statistic	Phase 2 dose expansion (N=127)	Overall (N=146)
No liver metastases	n (%)	15 (11.8%)	23 (15.8%)
Prior oncology treatments			
Oncology Chemotherapy and Medication	n (%)	90 (70.9%)	103 (70.5%)
Oncology Radiation Therapy	n (%)	88 (69.3%)	104 (71.2%)
Oncology Surgery and Procedures	n (%)	56 (44.1%)	66 (45.2%)
Other	n (%)	29 (22.8%)	38 (26.0%)

ICR = Independent Central Review; Min = minimum; Max = maximum; N = Total number of patients; n = number of patients with an observation; Std = standard deviation.

^[a] Liver metastases measurements based on Investigator assessment.

^[b] Liver metastases measurements based on ICR.

The overall summary consists of data from both the Phase 1 dose escalation cohorts and Phase 2 dose expansion cohort.

Time since primary diagnosis/first metastasis to start of study is calculated relative to treatment start date. Partial primary diagnosis dates are imputed using 15th day of month if only month/year present or 02 July if only year present.

Patients can be counted in more than one prior oncology treatment.

Source: Module 5.3.5.2, Study 102, Table 14.1.5.

Prior medications

All Phase 2 dose expansion patients received at least 1 prior anticancer therapy in the metastatic setting, two-thirds of patients received 1 line of prior anticancer therapy, and one-third of patients received at least 2 lines of prior anticancer therapy. The most commonly reported prior anticancer therapies were systemic therapies (83.5%, of which immunotherapy was reported in 73.2% of patients), radiotherapy (75.6%), LDT (44.9%), and surgery (40.9%). Forty-three (33.9%) patients received ≥ 2 lines of prior anticancer therapy. The most commonly reported prior anticancer therapy regimen was radiotherapy (77.2%).

The Applicant's Position:

The disease characteristics and prior therapies of the mUM population enrolled in Study 102 were generally consistent with the target mUM population of pretreated patients with poor prognostic indicators.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Data are presented below as part of the applicant's position.

The Applicant's Position:

Treatment compliance

In the Phase 2 expansion cohort, the median relative dose intensity was 100.0% (range, 62.6% to 100%) for tebentafusp.

Concomitant medications

The most commonly reported concomitant medications were paracetamol (89.0%) and IV sodium chloride (52.0%).

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Objective response rate (RECIST v1.1) assessed by ICR

Objective response rate per RECIST v1.1 according to ICR for the FAS is summarized in

Table 30. Of the 127 patients who received study drug, an OR of PR was observed in 6 (4.7%) patients (95% CI: 1.8%, 10.0%).

Table 30: Study 102: Best Overall Response - Objective Response Rate and Disease Control Rate (RECIST v1.1 by Independent Central Review) - Phase 2 Dose Expansion Cohort (Full Analysis Set)

	Statistic	Phase 2 dose expansion (N=127)
Best overall response		
Complete response (CR) ^[a]	n (%)	0
Partial response (PR) ^[a]	n (%)	6 (4.7%)
Stable disease ≥8 weeks (SD)	n (%)	57 (44.9%)
Minor response (MinR) ^[a]	n (%)	8 (6.3%)
Stable disease ≥16 weeks	n (%)	34 (26.8%)
Stable disease ≥24 weeks	n (%)	23 (18.1%)
Unconfirmed complete or partial response ^[b]	n (%)	1 (0.8%)
Cannot be confirmed with further follow-up ^[c]	n (%)	0
Progressive disease (PD)	n (%)	60 (47.2%)
Disease progression	n (%)	54 (42.5%)
Death in absence of disease progression	n (%)	6 (4.7%)

Table 30: Study 102: Best Overall Response - Objective Response Rate and Disease Control Rate (RECIST v1.1 by Independent Central Review) - Phase 2 Dose Expansion Cohort (Full Analysis Set)

	Statistic	Phase 2 dose expansion (N=127)
Not evaluable	n (%)	4 (3.1%)
Stable disease <8 weeks	n (%)	0
Incomplete postbaseline assessments ^[d]	n (%)	4 (3.1%)
Objective response rate (CR or PR)	n (%)	6 (4.7%)
	(95% CI) ^[e]	(1.8%, 10.0%)
Disease control rate (CR or PR or SD ≥16 weeks)	n (%)	40 (31.5%)
	(95% CI) ^[e]	(23.5%, 40.3%)
Disease control rate (CR or PR or SD ≥24 weeks)	n (%)	29 (22.8%)
	(95% CI) ^[e]	(15.9%, 31.1%)

CI = confidence interval; ICR = Independent Central Review; N = total number of patients.

^[a] Response confirmation at least 4 weeks later following initial evaluation.

^[b] PR or CR achieved but either no confirmation assessment performed, or a confirmation assessment performed but response not confirmed.

^[c] Patients with disease progression/death or completed End of Study eCRF page following unconfirmed complete or partial response.

^[d] Includes disease progression or death occurring >2 tumor assessment visits after last evaluable tumor assessment.

^[e] 95% CI are calculated for the rate using the exact Clopper-Pearson method.

A minor response was defined as a reduction from baseline in the sum of longest diameters or short axis of target lesions (mm) of 10% to 29%, where non-target lesion response was not unequivocal progression, and no new lesions were present. Confirmation is required after ≥4 weeks.

The sub-categories under stable disease were not mutually exclusive categories.

Percentages were based on the number of patients in the Full Analysis Set.

Tumor assessment was based on RECIST v1.1 by ICR.

Source: Module 5.3.5.2, Study 102, Table 14.2.1.1.1.

Sensitivity analysis

Objective response rate per RECIST v1.1 according to ICR for the PPS. Of the 126 patients who received the study drug, an OR of PR was observed in 6 (4.8%) patients (95% CI: 1.8%, 10.0%). These results were similar to those from the primary analysis of ORR for the FAS.

The Applicant's Position:

The primary endpoint of ORR per RECIST v1.1 according to ICR, as evaluated in the Phase 2 dose expansion cohort, was 4.7%. Results from the sensitivity analyses (4.8%) were similar to those from the primary analysis of ORR for the FAS.

Data Quality and Integrity

Data:

Not applicable.

The Applicant's Position:

No issues were identified that could potentially impact data integrity, prevent an adequate assessment of the data, and change the conclusions drawn.

Efficacy Results – Secondary and other relevant endpoints

Data:

Disease control rate

Of the 127 patients in the Phase 2 expansion cohort, 57 (44.9%) patients had SD at ≥ 8 weeks per RECIST v1.1 according to ICR (

Table 30). The DCR was 31.5% (40 patients; 95% CI: 23.5%, 40.3%) at ≥ 16 weeks and 22.8% (29 patients; 95% CI: 15.9%, 31.1%) at ≥ 24 weeks.

Duration of Response

Among patients with an objective response in the Phase 2 expansion cohort, the median duration of response was 8.7 months (95% CI: 5.6, 24.5) (Table 31). The estimated percentage of ongoing responders was 60.0% (95% CI: 12.6%, 88.2%) at 6 months and 20.0% (95% CI: 0.8%, 58.2%) at 12 months. Results were similar for the FAS and PPS.

Table 31: Study 102: Kaplan-Meier Estimates of Duration of Objective (Complete or Partial) Response (RECIST v1.1 by Independent Central Review) - Phase 2 Dose Expansion Cohort (Full Analysis Set)

	Phase 2 dose expansion (N=127)
Number of patients with an objective response	6
Total number of events [a]	5
Total censored for any reason	1
Kaplan-Meier analysis	
Median duration of objective response - months (95% CI)	8.706 (5.552, 24.542)
Estimated % of patients in response at [b]	
3 months (95% CI)	100.0% (NC, NC)
6 months (95% CI)	60.0% (12.6%, 88.2%)
9 months (95% CI)	40.0% (5.2%, 75.3%)
12 months (95% CI)	20.0% (0.8%, 58.2%)

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Kimmtrak (tebentafusp)

CI = confidence interval; ICR = Independent Central Review; N = total number of patients; NC = not calculable.

^[a] Events were patients with a date of disease progression or death in the absence of disease progression, following the first documented objective response (CR or PR). Patients without disease progression or death, were censored at the last evaluable tumor assessment. Response confirmation is required ≥ 4 weeks later following initial evaluation for complete and partial response.

^[b] Percentage of patients in response were estimated using the Kaplan-Meier method.

Only patients who had a confirmed objective response (complete response or partial response) were included.

Tumor assessment was based on RECIST v1.1 by ICR.

Source: Module 5.3.5.2, Study 102 CSR, Table 14.2.1.1.2.

Time to response

Among patients with an objective response in the Phase 2 expansion cohort, the mean (Std) time to response was 7.0 months (6.9), with response times ranging from 1.6 to 20.5 months.

Rate and duration of minor response

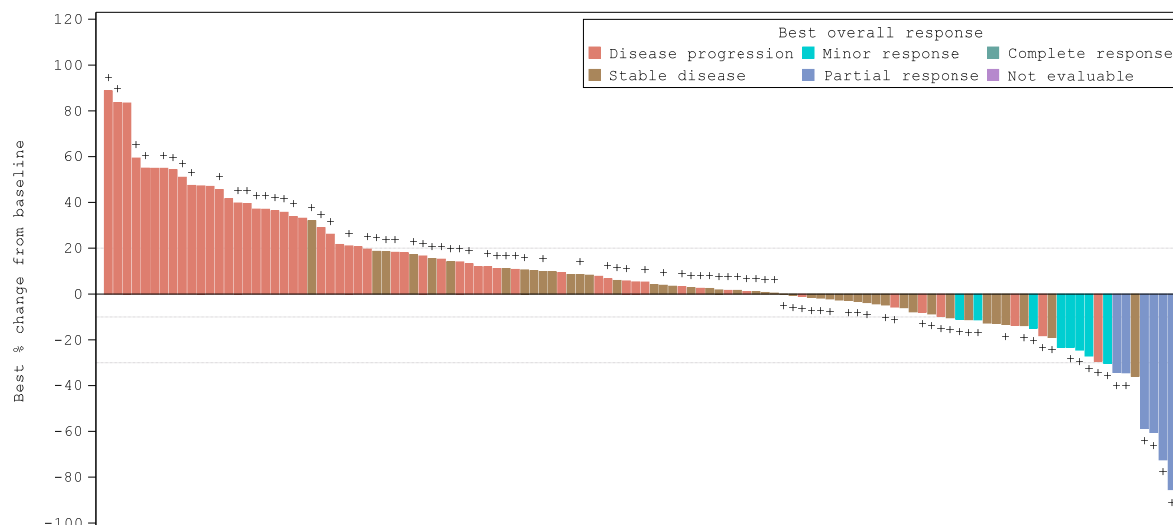
In the Phase 2 expansion cohort, the rate of MinR or better (CR, PR, or MinR) was 11.0% (14 of 127 patients; 95% CI: 6.2%, 17.8%). The median duration of MinR or better was 10.3 months (95% CI: 5.8, 23.2). The estimated percentage of responders (including those with a MinR) was 78.6% (95% CI: 47.2%, 92.5%) at 6 months and 33.3% (95% CI: 10.9%, 58.0%) at 12 months.

Evaluation of tumor size

Tumor size was presented graphically using a waterfall plot, to present each patient's best percent change from baseline in tumor size and BOR as assessed by RECIST v1.1 by ICR for the Phase 2 dose expansion cohort in Figure 35. Overall, the waterfall plots illustrate benefit beyond traditional PR defined by RECIST v1.1.

Figure 35 Study 102: Tumor Size – Best Percent Change from Baseline Waterfall Plot (RECIST v1.1 by Independent Central Review) - Phase 2 Dose Expansion

Treatment group: Phase 2 dose expansion cohort (N=127, n=119)



+ Patient received prior immunotherapy.

Tumor size was measured as the sum of longest diameters or short axis of the target lesions according to RECIST v1.1 by Independent Central Review.

Best percent change in target lesion size was the maximum percent reduction from baseline or the minimum percent increase from baseline (in the absence of a reduction), up until disease progression or starting subsequent alternative cancer therapy. Complete response, partial response or minor response required confirmation at least 4 weeks later.

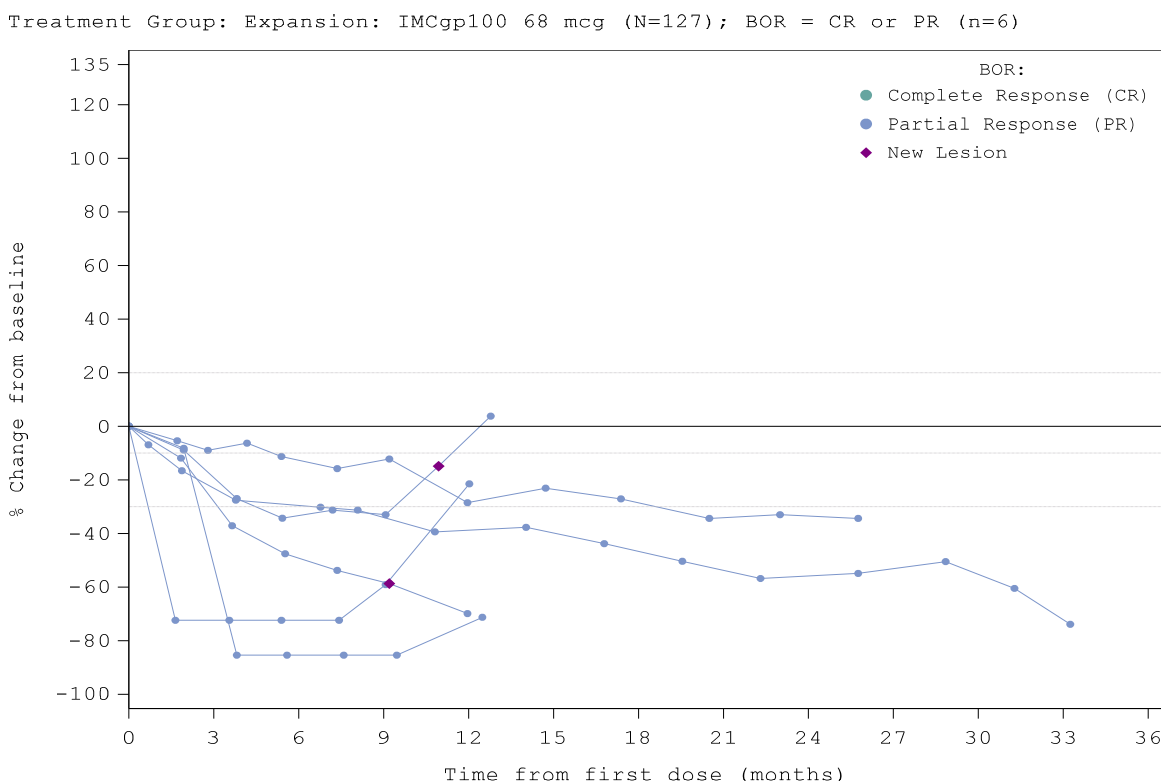
Reference lines at 20%, -10%, and -30% mark target lesion response criteria for disease progression, minor response, and partial response, respectively.

Only patients with at least one evaluable postbaseline target lesion scan were included. Eleven patients overall were not included due to non-measurable disease at baseline or no evaluable postbaseline target lesion scans. Evaluable postbaseline scans must be on or prior to disease progression or starting subsequent alternative cancer therapy to be considered.

Source: Module 5.3.5.2, Study 102 CSR, Figure 14.2.5.1.

In addition, a spider plot was produced to display the percent change from baseline in tumor size over time (Figure 36). Overall, the spider plots demonstrated unique patterns of radiographic changes. Notably, some patients exhibited rapid decreases in tumor burden at the first disease assessment at 6 weeks, whereas others had more gradual decreases. For the majority of responders, responses were durable.

Figure 36 Study 102: Tumor Size – Best Percent Change from Baseline Spider Plot (RECIST v1.1 by Independent Central Review) - Phase 2 Dose Expansion



BOR = Best Overall Response (RECIST v1.1); ICR = Independent Central Review; n = total number of patients per BOR category; m = total number of patients presented per page, if the number of patients within a response category continues onto multiple pages.

Tumor size was measured as the sum of longest diameters or short axis of the target lesions according to RECIST v1.1 by Independent Central Review (ICR).

Reference lines at 20%, -10%, and -30% mark target lesion response criteria for disease progression, minor response, and partial response, respectively.

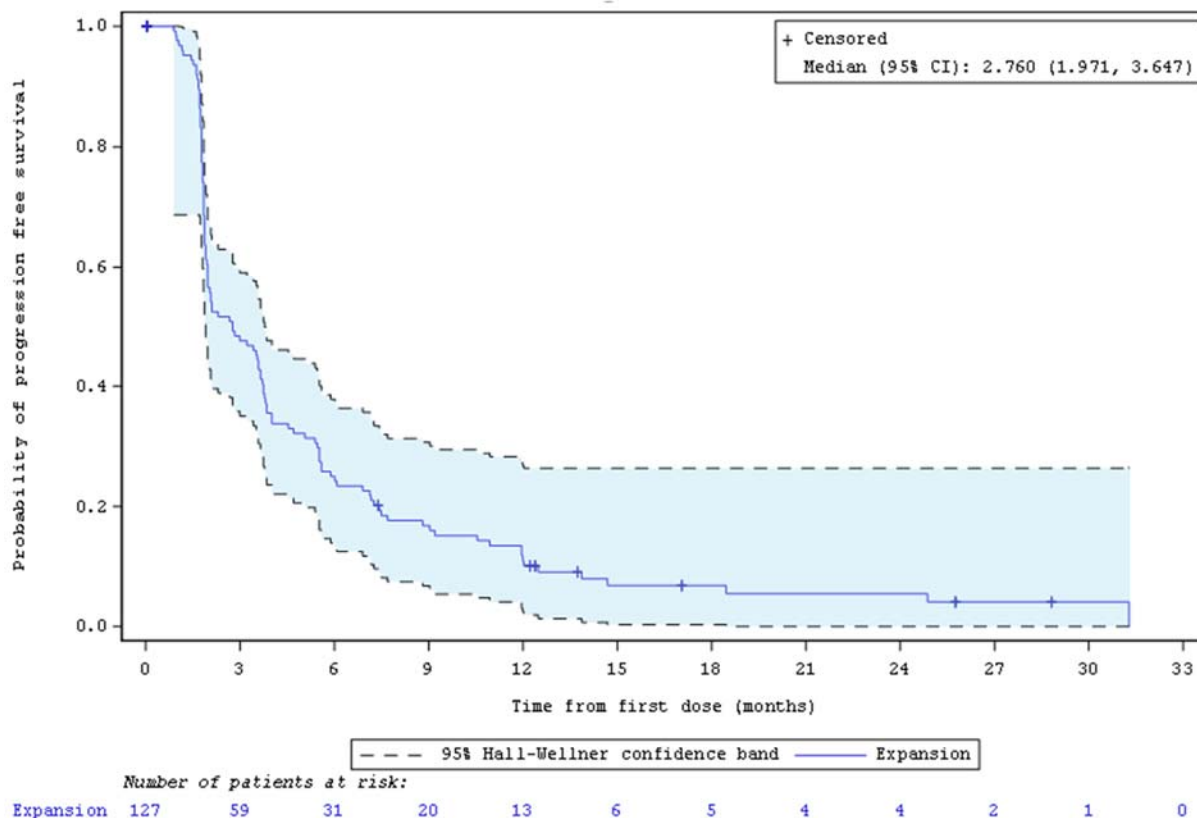
Only patients with at least one evaluable postbaseline target lesion scan are included. 10 patients overall in the Expansion cohort are not included due to non-measurable disease at baseline or no evaluable postbaseline target lesion scans.

Source: Module 5.3.5.2, Study 102 CSR, Figure 14.2.6.1.

Progression-free survival

In the Phase 2 expansion cohort, the median PFS was 2.8 months (95% CI: 2.0%, 3.7%) (Figure 37). Of the 127 patients in the Phase 2 dose expansion cohort, the estimated PFS rates were 25.0% (95% CI: 17.8%, 32.9%) at 6 months and 10.9% (95% CI: 6.2%, 17.2%) at 12 months. A total of 117 (92.1%) patients had the event of disease progression (106 [83.5%] patients) or death in the absence of disease progression (11 [8.7%] patients).

Figure 37 Study 102: Kaplan-Meier Plot of Progression-free Survival (RECIST v1.1 by Independent Central Review) - Phase 2 Dose Expansion



CI = confidence interval; ICR = Independent Central Review

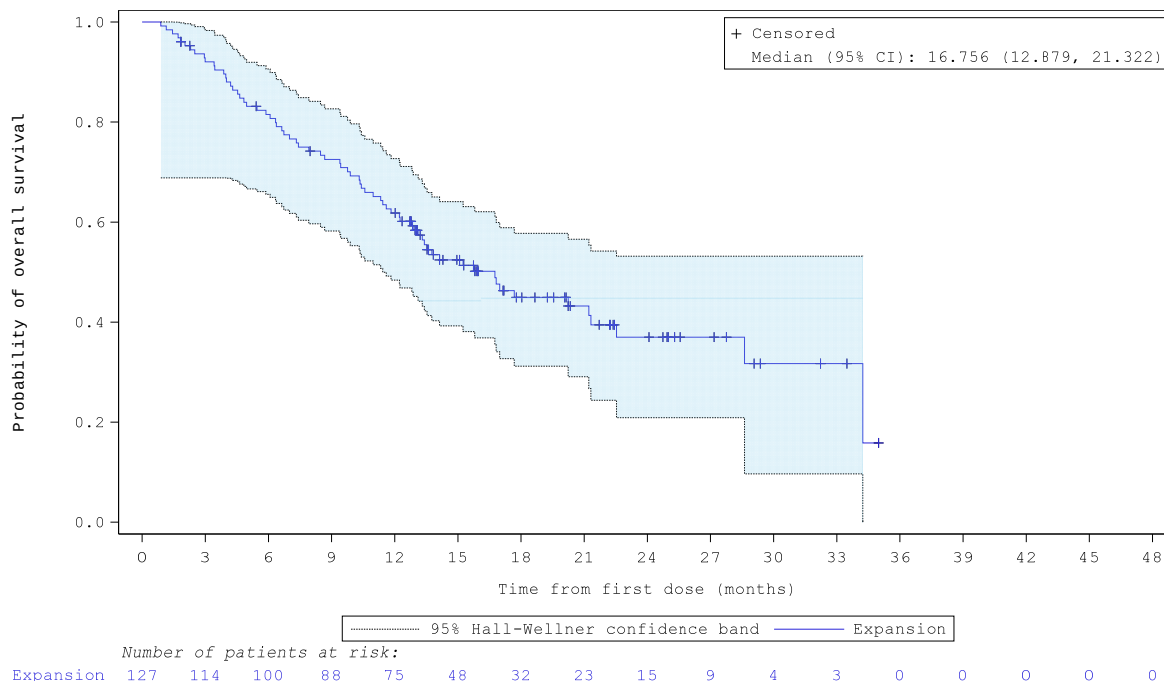
Events were either disease progression or death in the absence of disease progression, which occurred within 2 tumor assessment visits of the last evaluable assessment. Events that did not occur within 2 tumor assessment visits were censored. Tumor assessment was based on RECIST v1.1 by ICR.

Source: Module 5.3.5.2, Study 102 CSR, Figure 14.2.2.3.

Overall survival

In the Phase 2 expansion cohort, the median duration of follow-up was 19.6 months (95% CI: 16.0, 22.2). The median OS was 16.8 months (95% CI: 12.9, 21.3) (Figure 38). Sixty-nine patients died and 58 patients were censored for any reason. Of the 127 patients in the Phase 2 dose expansion cohort, the OS rates were 61.8% (95% CI: 52.6%, 69.8%) at 12 months and 37.0% (95% CI: 26.5%, 47.5%) at 24 months.

Figure 38 Study 102: Kaplan-Meier Plot of Overall Survival - Phase 2 Dose Expansion



CI = confidence interval.

Events were deaths due to any cause. Patients not known to have died at the time of analysis are censored.

Source: Module 5.3.5.2, Study 102 CSR, Figure 14.2.3.2.

The Applicant's Position:

Together, these findings indicate that responses were durable and patients derived benefit beyond the traditional PR defined by RECIST.

Tebentafusp demonstrated encouraging survival benefit. After a median follow-up of 19.6 months, the median OS was 16.8 months. Although this was a single-arm study, when compared with historical data (median OS < 12 months; Khoja, 2019), the OS results are promising in mUM patients, many of whom were heavily pretreated and had poor prognostic factors.

Dose/Dose Response

Data:

Not applicable.

The Applicant's Position:

Not applicable.

Durability of Response

Data:

Data are presented below as part of the applicant's response.

The Applicant's Position:

Among patients with an objective response in the Phase 2 expansion cohort, the median duration of response was 8.7 months (95% CI: 5.6, 24.5) (Table 31). The estimated percentage of ongoing responders was 60.0% (95% CI: 12.6%, 88.2%) at 6 months and 20.0% (95% CI: 0.8%, 58.2%) at 12 months.

Persistence of Effect

Data:

See Section 8.1.2.

The Applicant's Position:

See Section 8.1.2.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Health-related quality of life

Health-related quality-of-life data were collected using the EORTC QLQ-C30 and EQ-5D,5L PRO instruments.

EORTC-QLQ-C30

There was no deterioration (based on a threshold of 10 points) at Cycle 1, Cycle 5, or Cycle 9 across all dimensions: physical functioning, role functioning, cognitive functioning, and social functioning, nausea, vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties, and global health status/quality of life.

EQ-5D, 5L

The EQ-5D-5L questionnaire compliance results were 75.3% at baseline (expected, 93 according to protocol version 7 or later, of which 70 evaluable), 78.7% at C3D1, 80.4% at C5D1, and 82.1% on C9D1.

Mean EQ-5D index and EQ-VAS scores at baseline were 0.8109 and 77.2, respectively, and not significantly different to that of the general population norms (0.779 for index and 77.8 for EQ-VAS). There was no deterioration in either EQ-5D or EQ-VAS at Cycle 1, Cycle 5, or Cycle 9, or at the EOT (based on MID= 0.075 or 7.5, respectively) (Szende, 2014).

The Applicant's Position:

Health-related quality of life, as assessed by the EORTC-QLQ-C30 and EQ-5D,5L PRO instruments, showed no deterioration in patients treated with tebentafusp.

Additional Analyses Conducted on the Individual Trial

Data:

Not applicable

The Applicant's Position:

Not applicable

The FDA's Assessment:

FDA has reviewed the Applicant's description of the conduct of Study 102, including compliance with GCP, patient characteristics and disposition, treatment compliance and concomitant medications, data quality and integrity along with the Applicant's analyses of primary, secondary, and exploratory endpoints; however, as this is a supportive study, FDA did not verify the analyses and results are considered exploratory.

FDA considers the analysis of PFS and OS in Study 102 to be descriptive in nature, as results of

these endpoints in a single-arm study are uninterpretable. Similarly, FDA notes that no conclusions should be drawn from PRO analyses in a single arm study.

The observed response rate was 5% in Study 102, creating significant uncertainties with respect to risk-benefit based on the single arm trial. Accordingly, randomized Study 202 was necessary to assess whether tebentafusp provided benefit to patients, especially given the potential for life-threatening cytokine release syndrome.

8.1.5. Integrated Review of Effectiveness

The FDA's Assessment:

Study 202 is the primary study supporting the efficacy claim for this BLA. Study 102 was submitted as a supportive study. Study 202 and Study 102 were evaluated separately, and no integrated review of effectiveness was performed.

8.1.6. Assessment of Efficacy Across Trials

When comparing the efficacy results between Phase 3 Study 202 and the Study 102 Phase 2 expansion, key differences between the 2 studies, should be considered. Briefly, these include the following: (1) Study 202 enrolled patients who had not received prior systemic therapy in the metastatic setting (1L), whereas Study 102 Phase 2 expansion enrolled patients who were previously treated in the metastatic setting (2L+); (2) Study 202 included a control group (investigator's choice) whereas Study 102 was a single-arm study; and (3) the primary endpoint was OS in Study 202 and ORR in Study 102 Phase 2 expansion (ORR and OS were secondary endpoints in Study 202 and Study 102, respectively).

Primary Endpoints

Data:

Overall survival

Table 32 summarizes OS in Phase 3 Study 202 and Study 102 Phase 2 expansion.

In Study 202, based on a median follow-up duration of 14.1 months and 150 death events in the ITT Analysis Set, the primary endpoint of OS significantly favored tebentafusp with a HR of 0.51 (95% CI: 0.37, 0.71; $p < 0.0001$) (Table 20 and Figure 27 above). Although not yet mature, the Kaplan-Meier estimates suggest median OS was significantly prolonged in the tebentafusp arm compared with the investigator's choice arm (21.7 vs 16.0 months). Kaplan-Meier estimates of OS at 12 and 24 months were 73.2% and 44.8%, respectively, for tebentafusp, and 58.5% and 20.3%, respectively, for investigator's choice.

In Study 102 Phase 2 expansion, based on a median follow-up duration of 19.6 months and 69 death events in the FAS, the median OS was 16.8 months (Figure 38 above). Kaplan-Meier

estimates of OS at 12 and 24 months were 61.8% and 37.0%, respectively.

Table 32: Summary of Overall Survival in Study 202 (ITT Analysis Set) and Study 102 Phase 2 Expansion (FAS)

Parameter	Study 202 (1L)		Study 102 (2L+)
	Tebentafusp (N = 252)	Investigator's Choice (N = 126)	Tebentafusp (N = 127)
Patients with events, n (%)	87 (34.5)	63 (50.0)	69 (54.3)
Survival			
Median (95% CI), months	21.7 (18.6, 28.6)	16.0 (9.7, 18.4)	16.8 (12.9, 21.3)
Hazard ratio (95% CI) – stratified	0.51 (0.37, 0.71)	--	NA
p value	<0.0001	--	NA
Survival probability, % (95% CI)			
6 months	88.8 (84.1, 92.2)	78.1 (69.6, 84.6)	81.5 (73.5, 87.3)
9 months	81.1 (75.3, 85.7)	63.2 (53.4, 71.5)	72.5 (63.8, 79.5)
12 months	73.2 (66.4, 78.8)	58.5 (48.3, 67.3)	61.8 (52.6, 69.8)
18 months	61.5 (5.3, 68.7)	42.9 (31.5, 53.8)	44.9 (35.2, 54.2)
24 months	44.8 (34.9, 54.2)	20.3 (9.1, 34.7)	37.0 (26.5, 47.5)
30 months	33.6 (20.2, 47.6)	10.2 (1.1, 31.1)	31.7 (19.2, 45.0)
Median follow-up time, months (95% CI)	14.1 (12.5, 16.1)	14.3 (10.9, 17.0)	19.6 (16.0, 22.2)
Combined median follow-up time, months (95% CI)	14.1 (12.7, 15.6)		NA

1L = first line; 2L+ = second line and greater; CI = confidence interval; FAS = Full Analysis Set; ITT = Intent-to-treat; NA = not applicable.

Source: Module 2.7.3, Table 9.

The Applicant's Position:

Overall, tebentafusp demonstrated a statistically significant and clinically meaningful OS benefit compared with investigator's choice in HLAA*02:01-positive patients with mUM who had not received prior systemic therapy in the metastatic setting in Study 202, confirming the promising OS observed in Study 102 Phase 2 expansion in HLA-A*02:01-positive patients with previously treated mUM.

The FDA's Assessment:

FDA's assessment of efficacy is based primarily on Study 202. FDA considered Study 102 separately only as a supportive trial. Comparisons between the trials were not performed due to the limitations of cross trial comparisons. In addition, event endpoints like OS and PFS are uninterpretable in single arm trials.

Secondary and Other Endpoints

Data:

Progression-free survival

Table 33 summarizes PFS in Phase 3 Study 202 and Study 102 Phase 2 expansion.

In Study 202, based on a median follow-up duration of 11.4 months and 295 PD or death events, PFS favored tebentafusp and met statistical significance (HR 0.73; 95% CI: 0.58, 0.94; p = 0.0139) (Table 21 and Figure 28 above). Median PFS was 3.3 months in the tebentafusp arm and 2.9 months in the investigator's choice arm, and 6-month PFS rates were 30.9% and 18.9%, respectively.

In Study 102 Phase 2 expansion, based on a median follow-up duration of 25.8 months and 117 PD or death events, the median PFS was 2.8 months and 6-month PFS rate was 25.0% (Figure 37).

Table 33: Summary of Progression-free Survival in Study 202 (ITT Analysis Set) and Study 102 Phase 2 Expansion (FAS)

Parameter	Study 202 (1L)		Study 102 (2L+)
	Tebentafusp (N = 252)	Investigator's Choice (N = 126)	Tebentafusp (N = 127)
Patients with PFS events, n (%)	198 (78.6)	97 (77.0)	117 (92.1)
PFS			
Median (95% CI), months	3.3 (3.0, 5.0)	2.9 (2.8, 3.0)	2.8 (2.0, 3.7)
Hazard ratio (95% CI) – stratified	0.73 (0.58, 0.94)	--	NA
p value	0.0139	--	NA
PFS probability, % (95% CI)			
3 months	54.8 (48.3, 60.9)	42.3 (32.9, 51.3)	47.6 (38.6, 56.0)
6 months	30.9 (25.0, 37.0)	18.9 (12.0, 27.2)	25.0 (17.8, 32.9)
9 months	19.8 (1.7, 25.5)	11.7 (6.1, 19.2)	16.8 (10.8, 23.9)
12 months	14.1 (9.5, 19.5)	6.2 (2.3, 13.0)	10.9 (6.2, 17.2)
Median follow-up time, months (95% CI)	13.8 (10.9, 16.8)	11.3 (8.3, 16.9)	25.8 (12.4, NC)
Combined median follow-up time, months (95% CI)	11.4 (11.1, 1.6)		NA

1L = first line; 2L+ = second line and greater; CI = confidence interval; FAS = Full Analysis Set; ITT = Intent-to-treat; NA = not applicable; NC = not calculable; PFS = progression-free survival.

Source: Module 2.7.3, Table 10.

Tumor response

Table 34 summarizes tumor response in Phase 3 Study 202 and Study 102 Phase 2 expansion.

In Study 202, ORR (investigator-reported) was numerically higher with tebentafusp than investigator's choice (9.1% vs 4.8%) (Table 34). In the tebentafusp arm, BORs were 1 CR (0.4%), 22 PRs (8.7%), 92 SDs (36.5%), and 131 PDs (52.0%). In the investigator's choice arm, there were no CRs; 6 patients (4.8%) had PRs, 28 (22.2%) had SD, and 78 (61.9%) had PD. Disease control rate (defined as CR + PR + SD ≥ 12 weeks) favored tebentafusp compared with

investigator's choice, with rates of 45.6% and 27.0%, respectively. The median DOR was similar between the 2 treatment arms (9.9 vs 9.7 months).

In Study 102 Phase 2 expansion, the ORR (IRC-reported) was 4.7% (Table 34). There were no CRs; 6 patients (4.7%) had PRs, 57 (44.9%) had SD, and 60 (47.2%) had PD. Disease control rate (defined as CR + PR + SD $\geq$ 24 weeks) was 22.8%. The median DOR was 8.7 months.

Table 34: Summary of Tumor Response in Study 202 (ITT Analysis Set) and Study 102 Phase 2 Expansion (FAS)

Parameter	Study 202 (1L)		Study 102 (2L+)
	Tebentafusp (N = 252)	Investigator's Choice (N = 126)	Tebentafusp (N = 127)
Best overall response, n (%)			
Complete response	1 (0.4)	0	0
Partial response	22 (8.7)	6 (4.8)	6 (4.7)
Stable disease	92 (36.5)	28 (22.2)	57 (44.9)
Progressive disease	131 (52.0)	78 (61.9)	60 (47.2)
Not evaluable	6 (2.4)	14 (11.1)	4 (3.1)
Objective response rate (CR + PR)			
n (%)	23 (9.1)	6 (4.8)	6 (4.7)
95% CI ^a	5.9, 13.4	1.8, 10.1	1.8, 10.0
Disease control rate (CR + PR + SD) ^b			
n (%)	115 (45.6)	34 (27.0)	29 (22.8)
95% CI ^a	39.4, 52.0	19.5, 35.6	15.9, 31.1
Duration of response			
Median (95% CI), months	9.9 (5.4, --)	9.7 (2.7, --)	8.7 (5.6, 24.5)

-- = missing; 1L = first line; 2L+ = second line and greater; CI = confidence interval; CR = complete response; FAS = Full Analysis Set; ITT = Intent-to-treat; PR = partial response; SD = stable disease.

^a 95% CIs are calculated for the rate using the exact Clopper-Pearson method.

^b SD $\geq$ 12 weeks for Study 202 and $\geq$ 24 weeks for Study 102.

Source: Module 2.7.3, Table 11.

The Applicant's Position:

Tebentafusp demonstrated favorable PFS in both Study 202 and Study 102 Phase 2 expansion and rather with a statistically significant benefit over investigator's choice in patients with mUM who had not received prior systemic therapy in the metastatic setting in Study 202.

Tumor response rates were modest in both Study 202 and Study 102 Phase 2 expansion. However, the response rate was numerically higher for tebentafusp compared with investigator's choice in patients with mUM who had not received prior systemic therapy in the metastatic setting in Study 202. Across both studies, RECIST based endpoints consistently underestimated the OS benefit from tebentafusp.

The FDA's Assessment:

Comparisons between the trials were not performed due to the limitations of cross trial comparisons. In addition, event endpoints like OS and PFS are uninterpretable in single arm trials.

FDA agrees that ORR in Study 202 was not consistent with the observed OS and does not appear to be an appropriate endpoint to predict the OS benefit seen in the tebentafusp arm.

Subpopulations

Data:

Table 35 presents a side-by-side comparison of median OS and 1-year OS rates by comparable subgroups between Study 202 and Study 102 expansion. Forest plots for OS by subgroups are presented in Figure 39 for Study 202 and in Figure 40 for Study 102 Phase 2 expansion.

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Table 35: Overall Survival by Subgroups in Study 202 (ITT Analysis Set) and Study 102 Phase 2 Expansion (FAS)

Parameter	Study 202 (1L)						Study 102 (2L+)		
	Tebentafusp (N = 252)			Investigator's Choice (N = 126)			Tebentafusp (N = 127)		
	n	Median OS (95% CI), mo	1-yr OS %	n	Median OS (95% CI), mo	1-yr OS %	n	Median OS (95% CI), mo	1-yr OS %
Age									
< 65 years	130	23.4 (18.6, --)	77.9	61	15.7 (9.3, 18.4)	59.4	80	21.2 (14.1, 34.2)	67.8
≥ 65 years	122	19.1 (15.9, 27.4)	68.2	65	16.9 (8.3, 20.5)	57.4	47	12.8 (7.9, 16.8)	51.4
Gender									
Male	128	20.2 (14.7, --)	66.1	62	13.1 (7.7, 16.7)	52.6	63	13.5 (11.3, 17.7)	59.2
Female	124	22.2 (18.6, 32.3)	80.5	64	18.4 (9.7, 23.4)	64.2	64	21.3 (12.2, NC)	64.4
Region									
North America	86	32.3 (20.0, --)	77.7	52	18.5 (13.7, 21.4)	70.6	94	16.8 (12.8, 22.5)	61.8
Non-North America/Europe ^a	166	19.1 (17.5, 24.1)	70.9	74	12.9 (7.7, 17.2)	50.1	33	13.4 (7.4, 34.2)	62.2
Baseline ECOG performance status									
Grade 0	192	24.1 (20.2, 32.3)	79.9	85	16.9 (13.7, 19.3)	65.1	89	17.0 (12.9, 34.2)	65.5
Grade 1	49	17.4 (7.6, 19.5)	53.2	31	8.3 (4.7, 20.5)	40.7	38	13.4 (7.4, 22.5)	53.0
Baseline LDH									
≤ ULN	162	28.6 (22.2, --)	94.7	80	18.4 (16.0, 21.4)	77.9	53	28.6 (17.7, NC)	86.2
> ULN	90	9.1 (7.0, 11.7)	35.8	46	6.7 (3.6, 8.3)	26.4	74	11.0 (7.4, 13.1)	44.5
Baseline ALP									
≤ ULN	198	27.4 (21.6, --)	83.6	102	17.2 (13.7, 19.5)	65.6	90	21.3 (16.8, NC)	72.7
> ULN	53	7.0 (5.0, 14.1)	37.2	24	3.3 (2.5, 8.6)	28.1	37	8.5 (3.9, 12.2)	34.6

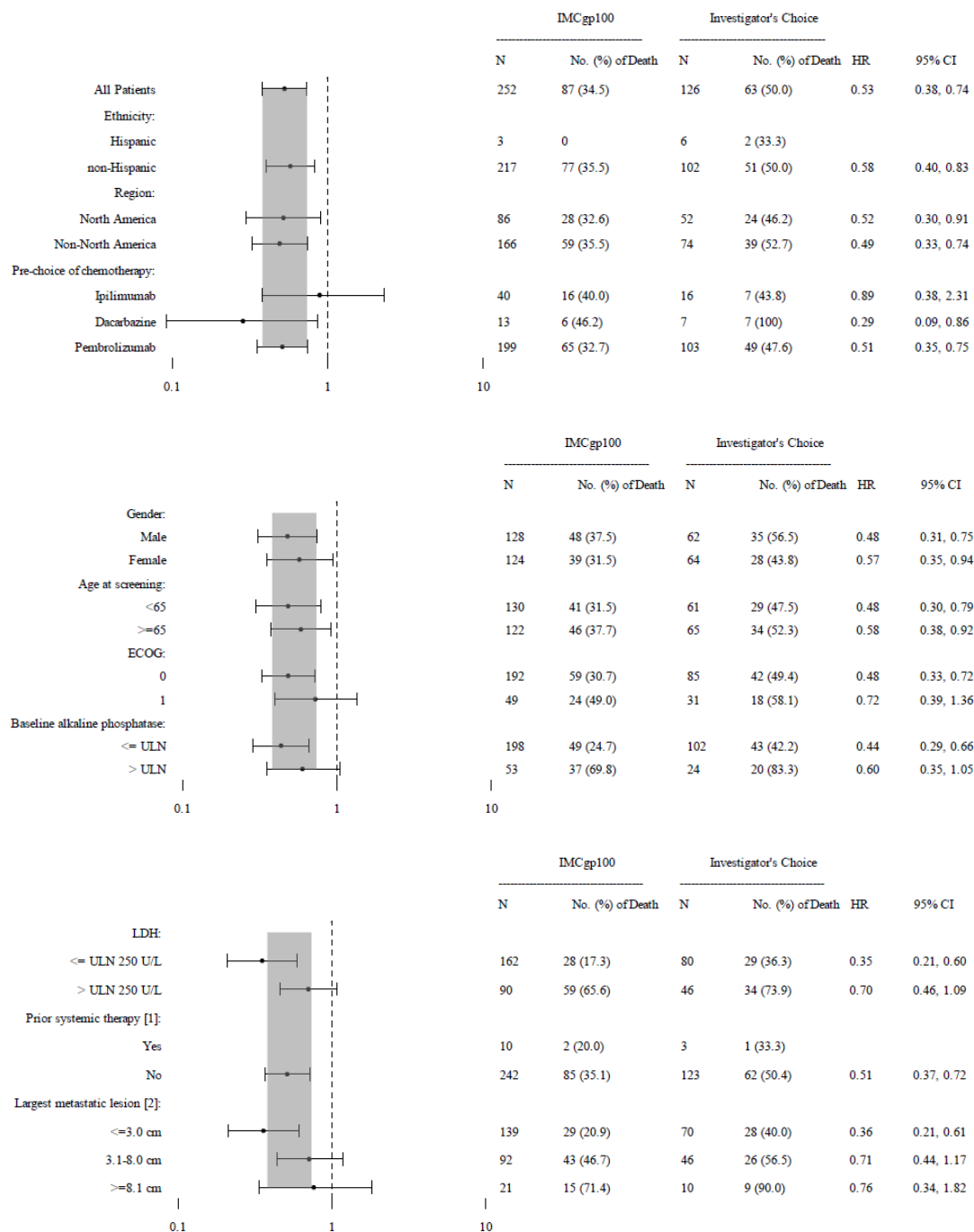
1L = first line; 2L+ = second line and beyond; ALP = alkaline phosphatase; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FAS = Full Analysis Set; ITT = Intent-to-treat; LDH = lactate dehydrogenase; mo = months; NC = not calculable; OS = overall survival; ULN = upper limit of normal; yr = year.

^a Non-North America for Study 202 and Europe for Study 102.

Source: Module 2.7.3, Table 12.

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Figure 39 Overall Survival by Subgroups in Study 202 (ITT Analysis Set)

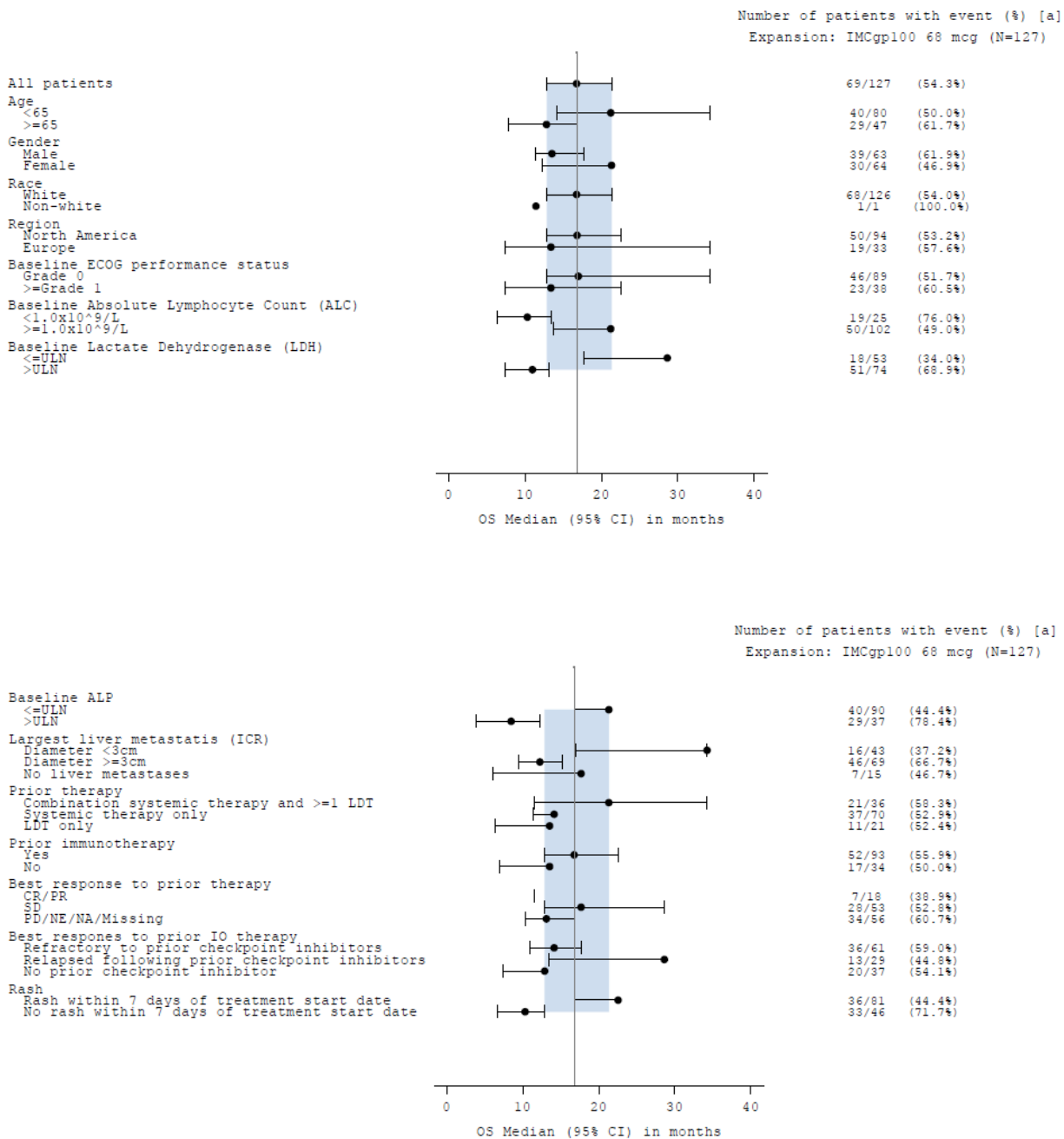


CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IMCgp100 = tebentafusp; ITT = Intent-to-treat; LDH = lactate dehydrogenase; ULN = upper limit of normal.

Source: Module 5.3.5.1, Study 202 CSR, Figure 14.2.6.1.

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Figure 40 Overall Survival by Subgroups in Study 102 Phase 2 Expansion (FAS)



CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FAS = Full Analysis Set; IMCgp100 = tebentafusp; LDH = lactate dehydrogenase; ULN = upper limit of normal.

^a Event = death due to any cause.

Source: Module 5.3.5.2, Study 102 CSR, Figure 14.2.9.5.4.

The Applicant's Position:

Overall, the OS benefit demonstrated with tebentafusp in Study 202 was generally observed across all prespecified major demographic and known prognostic subgroups. In Study 102 Phase 2 expansion, the trends in median OS and 1-year OS for each subgroup was generally similar to those observed in the tebentafusp arm of Study 202.

The FDA's Assessment:

While FDA does not object to the Applicant's presentation of the results of the OS analysis in Studies 202 and 102, FDA cautions against cross-study comparisons due to limitations inherent in such comparisons and the potential impact of differences between the studies.

FDA agrees with the Applicant's position that the OS benefit seen in Study 202 is consistent across the subgroups analyzed. The greatest difference in HR for OS is observed in subgroup analysis based on LDH, which was a stratification factor for Study 202. In Study 202, the HR for OS is 0.35 (95% CI: 0.21, 0.60) in patients with LDH $\leq$ 250 U/L and 0.70 (95% CI: 0.46, 1.09) in patients with LDH $>$ 250 U/L. However, FDA considers all subgroup analyses as exploratory only.

Additional Efficacy Considerations

The FDA's Assessment:

None

8.1.7. Integrated Assessment of Effectiveness

Data:

Data are presented below as part of the applicant's position.

The Applicant's Position:

The efficacy of tebentafusp is clearly established in mUM. In the pivotal Phase 3 Study 202 in HLA-A*02:01-positive patients with mUM who had not received prior systemic therapy in the metastatic setting, tebentafusp demonstrated a significant improvement in OS, reducing the relative risk of death by 49% compared with investigator's choice of either pembrolizumab, ipilimumab, or dacarbazine. The estimated 1-year OS rate was 73.2% for tebentafusp and 58.5% for investigator's choice. The superior tebentafusp OS benefit was generally observed across all subgroups analyzed, including patients with poor prognostic factors. These data confirm the promising OS observed in the supportive Study 102 Phase 2 expansion in HLA-A*02:01-positive patients with previously treated mUM.

Tebentafusp significantly improved PFS, reducing the relative risk of disease progression or death by 27%, compared with investigator's choice. Moreover, both DCR at 12 weeks (45.6% vs 27.0%) and the point estimate for ORR (9.1% vs 4.8%) were higher with tebentafusp than investigator's choice. As observed for other immunotherapies, RECIST response rate underestimated the OS benefit from tebentafusp.

While Study 202 was not designed to identify the contribution of treatment beyond initial progression, investigators were permitted by the protocol to allow for treatment beyond initial progression for tebentafusp and pembrolizumab. At the time of the DCO, just under half (43.3%) of patients in the tebentafusp arm were treated beyond initial progression; 21.5% of the total tebentafusp treatment administered during the study was delivered after the initial tumor progression. Based on a landmark OS analysis from Study 202 in patients with BOR of PD, tebentafusp provides a dramatic OS benefit, resulting in a 57% reduction in the relative risk of death over investigator's choice. These data suggest that a best response of PD is not a sign of lack of benefit and should not be the sole reason for discontinuation of tebentafusp treatment.

Together, tebentafusp showed a highly significant OS benefit versus investigator's choice in the Phase 3 Study 202 in HLA-A*02:01-positive patients with mUM who had not received prior systemic therapy in the metastatic setting. The control arm was generally consistent with historical reported trials confirming that tebentafusp provides substantial improvement over available therapies (Rantala, 2019; Pelster, 2021; Piulats, 2021). Tebentafusp is the first systemic treatment to demonstrate a statistically significant and clinically meaningful survival benefit in mUM, representing an essential treatment option for patients with this serious and life-threatening disease.

The FDA's Assessment:

The analysis of effectiveness of tebentafusp was based on data submitted from 378 patients enrolled to Study 202. FDA agrees that tebentafusp demonstrated a statistically significant and clinically meaningful improvement in OS over investigator choice for patients with HLA-A*02:01-positive metastatic uveal melanoma who had not received prior systemic therapy in the metastatic setting (HR of 0.51 [95% CI: 0.37, 0.71], $p < 0.0001$). The results of Study 202 support full approval for this indication.

FDA does not agree with the Applicant's analysis of treatment past progression, and no conclusions regarding benefit of continuing treatment with tebentafusp after evidence of progressive disease can be drawn.

8.2. Review of Safety

The Applicant's Position:

The clinical development program of tebentafusp in melanoma is comprised of 5 Immunocore sponsored clinical studies, including 2 completed studies (Phase 1, IMCgp100-01 [Study 01];

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Phase 2 rollover study IMCgp100401 [Study 401]) and 3 ongoing studies (Phase 1/2, IMCgp100-102 [Study 102]; Phase 1b/2, IMCgp100-201 [Study 201]; and Phase 3, IMCgp100-202 [Study 202]). Across these clinical studies, 587 patients with melanoma, including 410 patients with uveal melanoma (UM), have been exposed to tebentafusp monotherapy.

Table 36: Overview of the Tebentafusp Clinical Development Program

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, andomized, controlled, multi- center	HLAA*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+) HLAA*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 HLAA*02:01- positive advanced melanoma	Tebentafusp monotherapy	84 (n = 19 with mUM)	Final DBL date: 11Aug2017 Final CSR date: 09Feb2018 BLA DCO date: 11Aug2017
IMCgp100-401 (Study 401) Completed	Phase 2, open- label, multi- center, rollover	Previously treated HLAA*02:01- positive advanced melanoma	Tebentafusp monotherapy	3	Final DBL date: 14May2019 Final CSR date: 13Nov2019 BLA DCO date: 14May2019
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

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1L = first line; 2L+ = second line and greater; BLA = Biologics License Application; CM = cutaneous melanoma; CSR = clinical study report; DBL = database lock; DCO = data cutoff; FIH = first-in-human; HLA = human leukocyte antigen; mUM = metastatic uveal melanoma; UM = uveal melanoma.

*Patients randomized/treated.

The FDA's Assessment:

FDA agrees with the Applicant's summary of studies.

8.2.1. Safety Review Approach

The Applicant's Position:

Two pools of safety data will be considered: Pool 1 comprising UM patients (Uveal Melanoma Patients) and Pool 2 comprising all melanoma patients who received tebentafusp as monotherapy (All Melanoma Monotherapy Patients).

- **Pool 1 (Uveal Melanoma Patients):** Safety data will be reported side by side for UM patients from Study 01 (including rollover Study 401 data), Study 102 dose-escalation patients (Phase 1), Study 102 dose-expansion patients (Phase 2), Study 202 (tebentafusp arm only), pooled data for the tebentafusp arms of Study 102 (dose escalation and expansion) and Study 202, and pooled data for all studies. The uveal melanoma pool (n=410) provides primary evidence of safety and tolerability of tebentafusp monotherapy in the target metastatic uveal melanoma patient population regardless of line of therapy, where the randomized Study 202 (n=245) provides the majority of the safety data.
- **Pool 2 (All Melanoma Monotherapy Patients):** Safety data will be reported side by side for Study 01 (including rollover Study 401 data), Study 102 (combining dose escalation and expansion), Study 202 (tebentafusp arm only), monotherapy patients from Study 201, and pooled data for all studies. A supportive assessment of safety and tolerability of tebentafusp monotherapy is provided in the all melanoma pool (N=505). This safety dataset allows characterization of the safety profile of tebentafusp as a monotherapy, in patients across tumor types and regardless of line of therapy. The pool will be used to assess any difference in profile due to adding of cutaneous melanoma patients. Table 37 shows the number of patients from each study included in Pools 1 and 2.

Table 37: Pooled Safety Datasets

Study	Number of Patients (Specific Criteria)	
	Pool 1 (Uveal Melanoma Patients)	Pool 2 (All Melanoma Monotherapy Patients)
Study 202	245 (20/30/68 mcg ^a)	245 (20/30/68 mcg ^a)
Study 102	19 (Phase 1, all doses) 127 (Phase 2, 20/30/68 mcg ^a)	146 (Phases 1 and 2, all doses)
Study 01	19 (all doses)	81 (all doses)
Study 401	--	3 (all doses)
Study 201	--	30 (all monotherapy)
All Studies	410	505

^a20/30/68 mcg refers to the dosing regimen applied throughout the study. The proposed dosing regimen is 20 mcg at Cycle 1 Day 1, 30 mcg at Cycle 1 Day 8, and 68 mcg at Cycle 1 Day 15 and weekly thereafter.

When comparing the two pools of safety data, there is consistency of results between UM and all melanoma pool. Therefore, the primary presentation in this document will be done using the UM pool of patients.

Overall, tebentafusp has a well-established safety profile across the 5 Immunocore-sponsored clinical studies in 587 patients with melanoma, including 410 patients with UM, who were exposed to tebentafusp monotherapy. The randomized Study 202 provides the primary safety data and is proposed to be the basis for labeling presentation of Warning and Precautions and Adverse Events sections of the USPI. While the Study 102 safety data are consistent with Study 202 and supportive of the proposed indication and dosing regimen.

The FDA's Assessment:

The primary data used by FDA to assess and characterize the safety of tebentafusp at the proposed recommended dosage (20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter until disease progression, unacceptable toxicity, or death) is derived from the pivotal trial, Study 202, in which 245 patients received at least 1 dose of tebentafusp and 111 patients received at least 1 dose of investigator's choice agent.

Patients enrolled to Study 202 were required to be 18 years old or older. Key exclusion criteria for this study impacting interpretation of safety data include:

- Serum creatinine $> 1.5 \times \text{ULN}$ and/or creatinine clearance (calculating using Cockcroft-Gault formula, or measured) $< 50 \text{ mL/minute}$
- Total bilirubin $> 1.5 \times \text{ULN}$, except for patients with Gilbert's syndrome who are excluded if total bilirubin $> 3.0 \times \text{ULN}$ or direct bilirubin $> 1.5 \times \text{ULN}$
- Alanine aminotransferase $> 3 \times \text{ULN}$, Aspartate aminotransferase $> 3 \times \text{ULN}$
- Absolute neutrophil count $< 1.0 \times 10^9/\text{L}$, Absolute lymphocyte count $< 0.5 \times 10^9/\text{L}$
- Platelet count $< 75 \times 10^9/\text{L}$, Hemoglobin $< 8 \text{ g/dL}$
- Clinically significant cardiac disease or impaired cardiac function (NYHA Grade ≥ 2 , QTcF $> 470 \text{ msec}$, acute myocardial infarction or unstable angina pectoris < 6 months prior to screening.
- Known history of HIV infection
- Active HBV or HCV infection
- History of adrenal insufficiency, interstitial lung disease, pneumonitis that required corticosteroid treatment or current pneumonitis, history of colitis or inflammatory bowel disease

The protocol included dose modifications for tebentafusp for the following toxicities:

- Skin Toxicity Pruritis:
 - For Grade 3 events, hold tebentafusp until $\leq$ Grade 1
- Rash/Photosensitivity
 - For Grade 2 and 3 events, hold tebentafusp until $\leq$ Grade 1
 - For Grade 4 events, permanently discontinue tebentafusp
- Hypotension
 - For Grade 4 events, dose reduce or permanently discontinue tebentafusp

- Infusion-related Reactions/Anaphylaxis (occurring during infusion)
 - For Grade 3 events that do not improve by at least 1 grade within 6 hours with medical management or Grade 4 toxicity, permanently discontinue tebentafusp
- Infusion-related Reactions (occurring after infusion/Cytokine Release Syndrome (based on Lee 2014 grading criteria))
 - For Grade 3 events, hold tebentafusp until resolution of symptoms and restart after discussion and written approval of Sponsor's Medical Monitor
 - For Grade 4 events, permanently discontinue tebentafusp
- Hepatic Function Abnormalities
 - For Grade 3 or 4 events, hold tebentafusp until $\leq$ Grade 1
- Vomiting
 - For Grade 3 or 4 events, hold tebentafusp until $\leq$ Grade 1
- Other Adverse Events:
 - For Grade $\geq$ 3 events, hold study drug until Grade 1.

The protocol-specified dose reductions of tebentafusp for toxicity is as follows: from a starting tebentafusp dose of 68 mcg, the dose will be reduced to 54 mcg for any toxicity requiring dose reduction. The dose may be reduced further to 50 mcg for recurrent toxicity. Patients who require more than 2 dose reductions of tebentafusp should discontinue treatment.

To confirm the Applicant's safety signals identified in Study 202 and to identify any additional, rare, but potentially serious safety signals, FDA reviewed the Applicant's analyses for Pool 1 and separately analyzed Applicant Pool 2 which comprised 505 patients with uveal or cutaneous melanoma who received at least 1 dose of tebentafusp at any dose level. For FDA's analyses, Applicant Pool 2 is referred to as ISS_Pool. The analysis of the ISS_Pool is summarized in Section 8.2.11. In its safety analysis, FDA did not consider safety analyses of individual studies other than the pivotal trial Study 202.

FDA calculated the frequency of all treatment emergency adverse events (TEAEs) at the PT, HLT, HLGT, SOC MedDRA levels as well as using standard narrow, broad, and algorithmic SMQs, and FDA Office of Oncologic Disease (OOD) defined grouped terms (GT) for Study 202 and the ISS_Pool. The FDA defined group terms are a set of related preferred term and are defined in Appendix 19.3. Use of a grouped term is denoted by (GT) following the group name e.g., Fatigue (GT) comprises the preferred terms fatigue and asthenia. In its analysis of TEAEs, FDA considered all reported events regardless of investigator assessment of relatedness.

Analysis of the adverse reaction of cytokine release syndrome (CRS) is discussed in detail along with the other adverse events of special interest (AESIs), which include skin reaction/rash and hepatotoxicity, in Section 8.2.5.

For safety assessments based on laboratory and vital signs, FDA considered the objective data

rather than adverse event reporting. In general, FDA has not included TEAE reporting for laboratory investigations in TEAE frequency tables (i.e., in labeling).

8.2.2. Review of the Safety Database

Overall Exposure

Data:

The clinical development program of tebentafusp in melanoma is comprised of 5 Immunocore sponsored clinical studies, including 2 completed studies (Phase 1, IMCgp100-01 [Study 01]; Phase 2 rollover study IMCgp100401 [Study 401]) and 3 ongoing studies (Phase 1/2, IMCgp100-102 [Study 102]; Phase 1b/2, IMCgp100-201 [Study 201]; and Phase 3, IMCgp100-202 [Study 202]) (Table 38).

Table 38: Overview of the Tebentafusp Clinical Development Program

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					

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Study Number Study Status	Study Design	Patient Population	Treatment	Patient Sample Size	Analysis Cutoff Dates
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
IMCgp100-401 (Study 401) Completed	Phase 2, open- label, multi- center, rollover	Previously treated HLA-A*02:01- positive advanced melanoma	Tebentafusp monotherapy	3	Final DBL date: 14May2019 Final CSR date: 13Nov2019 BLA DCO date: 14May2019
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

1L = first line; 2L+ = second line and greater; BLA = Biologics License Application; CM = cutaneous melanoma; CSR = clinical study report; DBL = database lock; DCO = data cutoff; FIH = first-in-human; HLA = human leukocyte antigen; mUM = metastatic uveal melanoma; UM = uveal melanoma.

^a Patients randomized/treated.

The Applicant's Position:

Across the clinical studies presented in Table 38, 587 patients with melanoma, including 410 patients with uveal melanoma (UM), have been exposed to tebentafusp monotherapy. Study 202 contributes both primary efficacy and safety data for the proposed indication. Studies 102 and 01 contribute both supportive efficacy and safety data for the proposed indication. Studies 201 and 401 contribute safety data for the proposed indication.

The FDA's Assessment:

The Applicant's table, Table 38, summarizes the number of patients across the development program that have received tebentafusp. Table 39 summarizes the exposure for patients in the

safety analysis set for Study 202. At the time of the primary cut off for the CSR (4/21/2021) the median duration of exposure to study treatment was greater in the tebentafusp group compared to the Investigator Choice group.

Table 39: Summary of Treatment Exposure: Study 202 Safety Population

	Tebentafusp N = 245 N (%)	Investigator Choice N = 111 N (%)
Treatment Duration (days)		
Mean (SD)	220 (192)	119 (130)
Median (Min - Max)	163 (1 - 1016)	65 (1 - 658)
Cycles Started		
Mean (SD)	11 (9)	6 (6)
Median (Min - Max)	8 (1 - 44)	4 (1 - 32)
Cycles Completed		
Mean (SD)	9 (8)	6 (6)
Median (Min - Max)	7 (0 - 38)	4 (1 - 32)
Relative Dose Intensity (%)		
Mean (SD)	100 (0)	100 (0)
Median (Min - Max)	100 (95 - 100)	100 (100 - 100)

Source: ADSL (Subject-Level Analysis Dataset) - 2021-05-21, ADEXSUM (Study Drug Expo Summary Analysis Dataset) - 2021-04-21. Variables used: USUBJID, TRT01A, SAFFL, PARAM, AVAL

Relevant characteristics of the safety population:

Data:

Table 40 shows the demographic and baseline characteristics of UM Patients for individual studies and all studies combined.

Table 40: Uveal Melanoma Patients: Demographic and Baseline Characteristics (Safety Analysis Set)

Parameter	Study 01 All Doses (N = 19)	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 = 410)
Age, years					

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Parameter	Study 01 All Doses (N = 19)	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 = 410)
N	19	19	127	245	410
Mean (SD)	57.0 (11.73)	56.5 (11.37)	61.0 (10.93)	61.0 (11.89)	60.6 (11.59)
Median (min, max)	61.0 (31, 71)	55.0 (34, 73)	61.0 (25, 88)	63.0 (23, 91)	62.0 (23, 91)
18 - < 65, n (%)	13 (68.4%)	12 (63.2%)	80 (63.0%)	130 (53.1%)	235 (57.3%)
65 - < 75, n (%)	6 (31.6%)	7 (36.8%)	31 (24.4%)	93 (38.0%)	137 (33.4%)
≥ 65, n (%)	6 (31.6%)	7 (36.8%)	47 (37.0%)	115 (46.9%)	175 (42.7%)
≥ 75, n (%)	0	0	16 (12.6%)	22 (9.0%)	38 (9.3%)
Sex, n (%)					
Male	12 (63.2%)	9 (47.4%)	63 (49.6%)	125 (51.0%)	209 (51.0%)
Female	7 (36.8%)	10 (52.6%)	64 (50.4%)	120 (49.0%)	201 (49.0%)
Race, n (%)					
Asian	1 (5.3%)	0	0	0	1 (0.2%)
American Indian or Alaska Native	0	0	0	0	0
Black or African American	0	0	0	0	0
White	18 (94.7%)	19 (100.0%)	126 (99.2%)	216 (88.2%)	379 (92.4%)
Not reported	0	0	0	22 (9.0%)	22 (5.4%)
Not allowed as per local regulatory	0	0	0	5 (2.0%)	5 (1.2%)
Other	0	0	1 (0.8%)	1 (0.4%)	2 (0.5%)
Unknown	0	0	0	1 (0.4%)	1 (0.2%)
Region, n (%)					
North America	5 (26.3%)	16 (84.2%)	94 (74.0%)	85 (34.7%)	200 (48.8%)
Non-North America	14 (73.7%)	3 (15.8%)	33 (26.0%)	160 (65.3%)	210 (51.2%)
Country, n (%)					
Australia	0	0	0	9 (3.7%)	9 (2.2%)
Belgium	0	0	0	11 (4.5%)	11 (2.7%)
Canada	0	0	19 (15.0%)	14 (5.7%)	33 (8.0%)
France	0	0	0	23 (9.4%)	23 (5.6%)
Germany	0	0	10 (7.9%)	36 (14.7%)	46 (11.2%)
Italy	0	0	0	5 (2.0%)	5 (1.2%)

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Parameter	Study 01 All Doses (N = 19)	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 = 410)
Netherlands	0	0	0	3 (1.2%)	3 (0.7%)
Poland	0	0	0	14 (5.7%)	14 (3.4%)
Russia	0	0	0	8 (3.3%)	8 (2.0%)
Spain	0	0	9 (7.1%)	11 (4.5%)	20 (4.9%)
Switzerland	0	0	0	6 (2.4%)	6 (1.5%)
Ukraine	0	0	0	8 (3.3%)	8 (2.0%)
United Kingdom	14 (73.7%)	3 (15.8%)	14 (11.0%)	26 (10.6%)	57 (13.9%)
United States	5 (26.3%)	16 (84.2%)	75 (59.1%)	71 (29.0%)	167 (40.7%)
ECOG performance status, n (%)					
0: Fully active	15 (78.9%)	14 (73.7%)	89 (70.1%)	191 (78.0%)	309 (75.4%)
1+: Restricted in physically strenuous activity, or greater	4 (21.1%)	5 (26.3%)	38 (29.9%)	49 (20.0%)	96 (23.4%)
Missing/ not reported	0	0	0	5 (2.0%)	5 (1.2%)
Lactate dehydrogenase, n (%)					
≤ ULN	5 (26.3%)	5 (26.3%)	53 (41.7%)	158 (64.5%)	221 (53.9%)
> ULN	14 (73.7%)	11 (57.9%)	74 (58.3%)	87 (35.5%)	186 (45.4%)
Missing	0	3 (15.8%)	0	0	3 (0.7%)
Absolute lymphocyte count, n (%)					
< 1.0 x 10 ⁹ /L	4 (21.1%)	4 (21.1%)	25 (19.7%)	22 (9.0%)	55 (13.4%)
< 0.5 x 10 ⁹ /L	0	1 (5.3%)	1 (0.8%)	1 (0.4%)	3 (0.7%)
≥ 1.0 x 10 ⁹ /L	15 (78.9%)	15 (78.9%)	102 (80.3%)	223 (91.0%)	355 (86.6%)
Alkaline phosphatase, n (%)					
≤ ULN	15 (78.9%)	9 (47.4%)	90 (70.9%)	193 (78.8%)	307 (74.9%)
> ULN	4 (21.1%)	10 (52.6%)	37 (29.1%)	51 (20.8%)	102 (24.9%)
Missing	0	0	0	1 (0.4%)	1 (0.2%)
Renal function/ impairment group (eGFR), n (%)					
Normal (≥ 90 mL/min)	13 (68.4%)	13 (68.4%)	71 (55.9%)	146 (59.6%)	243 (59.3%)
Mild (60 - 89 mL/min)	6 (31.6%)	6 (31.6%)	46 (36.2%)	84 (34.3%)	142 (34.6%)
Moderate (30 - 59 mL/min)	0	0	7 (5.5%)	14 (5.7%)	21 (5.1%)
Severe (15 - 29 mL/min)	0	0	0	0	0

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Parameter	Study 01 All Doses (N = 19)	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 = 410)
Missing	0	0	3 (2.4%)	1 (0.4%)	4 (1.0%)
Melanoma type, n (%)					
Uveal melanoma	19 (100.0%)	19 (100.0%)	127 (100.0%)	245 (100.0%)	410 (100.0%)
Non-uveal melanoma	0	0	0	0	0
Stage at initial diagnosis, n (%)					
Stage I	3 (15.8%)	4 (21.1%)	11 (8.7%)	47 (19.2%)	65 (15.9%)
Stage II	1 (5.3%)	5 (26.3%)	42 (33.1%)	85 (34.7%)	133 (32.4%)
Stage III	2 (10.5%)	8 (42.1%)	31 (24.4%)	55 (22.4%)	96 (23.4%)
Stage IV	3 (15.8%)	1 (5.3%)	16 (12.6%)	23 (9.4%)	43 (10.5%)
Time from initial diagnosis to study treatment, years					
N	19	19	127	245	410
Mean (SD)	6.89 (6.26)	5.42 (5.65)	6.25 (5.45)	4.47 (4.56)	5.18 (5.05)
Median (min, max)	4.53 (1.2, 24.7)	3.63 (0.3, 26.2)	4.43 (0.6, 28.5)	2.98 (0.1, 25.1)	3.48 (0.1, 28.5)
Time from metastatic diagnosis to study treatment, years					
N	0	19	127	242	388
Mean (SD)	-	1.64 (1.84)	1.46 (1.73)	0.39 (0.61)	0.80 (1.28)
Median (min, max)	-	1.10 (0.2, 7.6)	0.94 (0.1, 12.3)	0.21 (0.0, 4.7)	0.32 (0.0, 12.3)
Largest liver lesion diameter (investigator assessment), n (%)					
0 - < 3 cm ^a	6 (31.6%)	13 (68.4%)	48 (37.8%)	132 (53.9%)	199 (48.5%)
≥ 3 cm	9 (47.4%)	6 (31.6%)	73 (57.5%)	104 (42.4%)	192 (46.8%)
No liver lesion	4 (21.1%)	0	6 (4.7%)	9 (3.7%)	19 (4.6%)

BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; ICR = independent central review; SD = standard deviation; ULN = upper limit of normal.

^a Non-target liver lesions are counted in the 0 - < 3 cm category.

Age is calculated relative to informed consent date. For patients from Germany in which only birth year is recorded, age is derived by imputing birth month and day as 2 July. For patients from Canada in which only birth month and year is recorded, age is derived by imputing birth day as 15.

Time since initial diagnosis/first metastasis to start of study (in years) is calculated relative to treatment start date, dividing the time in days by 365:25. Partial primary diagnosis dates are imputed using 15th day of month if only month/year present or July 02 if only year present.

Patients can be counted in more than one prior oncology treatment.

Source: Module 5.3.5.3, Table ISS 01.01.02.01; Module 5.3.5.3, Table ISS 01.01.03.01.

The Applicant's Position:

Demographics and baseline characteristics were generally similar across studies with some differences in baseline characteristics (i.e., elevated lactate dehydrogenase [LDH], largest liver lesion diameter, time from initial diagnosis to study treatment) related to first line (1L) vs. second line or greater (2L+) population.

Overall, approximately half of the patients were male (51%), with a median age of 62 years (range 23 to 91 years). More than half of the patients were between 18 and < 65 years (57.3%) and 42.7% of patients were ≥ 65 years of age. The majority of patients (75.4%) had an ECOG performance status score of 0 (fully active). Approximately one-third of patients had an initial diagnosis of stage II disease and nearly one-quarter of patients had a stage III diagnosis. The vast majority of patients (95.4%) had a liver lesion, 48.5% of which were < 3 cm and 46.8% of which were ≥ 3 cm.

The FDA's Assessment:

Table 41 summarizes the key demographic characteristics for the safety analysis set of Study 202. Overall, the two arms were well balanced with respect to gender, age, ECOG performance status, race, and ethnicity. FDA notes that although uveal melanoma occurs much less frequently in Black/African American, Asian, and American Indian/Alaskan Native patients, these populations appeared to be underrepresented in Study 202.

Table 41: Key Demographics: Study 202 Safety Population

	Tebentafusp N = 245 N (%)	Investigator Choice N = 111 N (%)
Gender		
M	125 (51)	55 (50)
F	120 (49)	56 (50)
Age (years)		
Mean (SD)	61 (12)	64 (11)
Median (Min - Max)	64 (23 - 92)	66 (25 - 88)
Age Group (years)		
< 65	126 (51)	50 (45)
≥ 65	119 (49)	61 (55)
ECOG Performance Status		
0	191 (78)	81 (73)
1	49 (20)	28 (25)

	Tebentafusp N = 245 N (%)	Investigator Choice N = 111 N (%)
2	0	1 (0.9)
Not Reported	5 (2.0)	1 (0.9)
Race		
WHITE	216 (88)	92 (83)
Not Available ¹	28 (11)	18 (16)
American Indian or Alaska Native	0	1 (0.9)
Ethnicity		
Not Hispanic or Latino	211 (86)	89 (80)
HISPANIC OR LATINO	3 (1.2)	4 (3.6)
Not Available ¹	31 (13)	2 (16)

Source: ADSL (Subject-Level Analysis Dataset) - 2021-04-21. Variables used: USUBJID, TRT01A, SAFFL, SEX, AGE, AGEGR1, ECOGBL, RACE, ETHNIC, COUNTRY

¹ includes not reported, not allowed per local regulations, or not known

Adequacy of the safety database:

The Applicant's Position:

Based on the incidence of metastatic uveal melanoma in the US and globally, a safety database of 410 uveal melanoma patients treated with tebentafusp is representative and considered adequate to determine the overall safety profile of tebentafusp. The integrated safety findings are consistent with the safety observed in the randomized Study IMCgp100-202, which is the study proposed as the primary basis for labeling of safety in the USPI.

The FDA's Assessment:

The size of the safety database is adequate to provide a reasonable estimate of adverse reactions that may be observed with tebentafusp at the proposed dosage; duration of the treatment is adequate to allow assessment of adverse reactions over time. The safety database represents the gender, age, and race consistent with that observed in the overall population of patients who are diagnosed with uveal melanoma. However, the lack of data for patients who identify as Black/African American, Asian and American Indian/Alaskan Native may limit the generalizability of conclusions to these populations.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

The rationale for integrating safety data was to provide an assessment of the overall safety profile of tebentafusp and to increase precision around the likely incidence of rare events. However, differences in study design, including eligibility criteria and dosing regimens, should be considered when interpreting the pooled safety data. Given the key design differences among the studies, integrated safety tables will present the individual study results as well as the pooled results. No tables will present pooled results only.

The FDA's Assessment:

FDA performed the following analyses to assess the quality and consistency of the safety data:

1. Comparison of coding: The FDA reviewer compared the coding of the actual reported term (AETERM) to the lowest level term in the MedDRA hierarchy (AELLT) for the 9448 treatment emergent adverse events (TEAEs) that were reported for patients enrolled on Study 202. Overall the coding was consistent and appropriate. The reporting of Cytokine Release Syndrome by investigators likely underrepresents the incidence. This is discussed further in Section 8.2.5. This does not represent an issue with data integrity or a coding error.
2. Comparison of treatment discontinuations due to adverse events as reported in the subject level ADSL, which includes patient disposition, and as reported in ADAE variable AECN (action taken) did not identify significant discrepancies.
3. Comparison of dose delays and modifications due to adverse events as reported in the exposure data file and as reported in adverse events did not identify significant discrepancies.
4. Comparison of assessment of relatedness to study treatment for fatalities and serious adverse events based on evaluation of narratives did not identify significant discrepancies.
5. FDA confirmed the safety results reported by the Applicant in this review and provided in the label.

Categorization of Adverse Event

Data:

Categorization of AEs are described below.

The Applicant's Position:

For the integrated analyses, AEs were coded using the Medical Dictionary for Regulatory

Activities (MedDRA) Version 23.1 or later and graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03. Data from studies originally reported in previous versions of MedDRA were recoded to the most current version for the integrated summary of safety (ISS) database.

For pooling of TEAE data, the incidence of each preferred term (PT) and system organ class (SOC) was pooled across the relevant studies based on the original individual study reporting and derivations using the Analysis Data Model datasets. A TEAE was defined as any AE that occurred on or after the date of initial receipt of study drug. The analysis of AEs (as describe in this SCS) was limited to TEAEs. Any AEs considered to be non-treatment emergent are presented in the individual CSRs only. All TEAEs were summarized descriptively by MedDRA SOC and PT count with (n) and percentage (%).

Based on data from ongoing and completed tebentafusp clinical studies, the following adverse events of special interest (AESI) have been specified: CRS, acute skin reactions, and LFT elevations. Other events of interest include cardiac and eye disorders were identified in Studies 202 and 102. These events are discussed further in Section 8.2.5.

The FDA's Assessment:
FDA agrees.

Routine Clinical Tests

The Applicant's Position:

The SeCore® HLA Sequencing System and uTYPE® Dx v1.0 HLA Sequence Analysis Software developed by Thermo Fisher Scientific have been used as a companion diagnostic (CDx) to identify HLA-A*02:01 positive patients for tebentafusp clinical studies.

The FDA's Assessment:

In Study 202, hematology and chemistry laboratory assessment values were graded for severity according to NCI-CTCAE 4.03. The schedule for vital sign and laboratory assessments depended on the treatment to be administered. For patients randomized to receive tebentafusp, vital signs were performed before and after dosing according to protocol and institutional standards (minimum every 4 hours for 16 hours C1D1, C1D8, C1D15). Laboratory assessments (hematology and chemistry panels) were assessed weekly prior to each dose. Patients were also evaluated for safety events with physical examination and adverse event monitoring.

8.2.4. Safety Results

Deaths

Data:

A summary of deaths is presented in Table 42 for UM Patients across individual studies and all studies combined.

Table 42: Uveal Melanoma Patients: Summary of Deaths by Cause and Timing (Safety Analysis Set)

Parameter	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Primary cause of death					
Any death ^a	5 (26.3%)	14 (73.7%)	70 (55.1%)	84 (34.3%)	173 (42.2%)
Disease progression	3 (15.8%)	14 (73.7%)	68 (53.5%)	80 (32.7%)	165 (40.2%)
Unknown	2 (10.5%)	0	0	0	2 (0.5%)
Adverse event	0	0	0	2 (0.8%)	2 (0.5%)
Adverse event leading to death related to tebentafusp ^{b, d}	0	0	0	0	0
Adverse event leading to death unrelated to tebentafusp ^{b, e}	0	0	0	2 (0.8%)	2 (0.5%)
Other	0	0	2 (1.6%)	2 (0.8%)	4 (1.0%)
Timing of death					
On-treatment up until ≤ 30 days after the last dose of tebentafusp	0	1 (5.3%)	7 (5.5%)	5 (2.0%)	13 (3.2%)
> 30 days after the last dose of tebentafusp ^c	5 (26.3%)	13 (68.4%)	63 (49.6%)	79 (32.2%)	160 (39.0%)

^a As recorded on death electronic case report form (eCRF) page or adverse event (AE)/serious adverse event (SAE) eCRF page.

^b As recorded on AE/SAE eCRF page.

^c This row may include deaths that are not treatment-emergent, i.e., with a death date greater than 90 days after last dose of study drug or start of alternative cancer therapy post treatment discontinuation (whichever occurs first).

^d Determined by the investigator to be possibly related, probably related, definitely related, or related to Tebentafusp

^e Includes fatal AEs that are not treatment emergent.

Percentages are based on the number of patients in the safety analysis set within each treatment group.

Source: Module 5.3.5.3, Table ISS 02.03.07.01.01.

The Applicant's Position:

Across the tebentafusp clinical development program, the vast majority of deaths were due to disease progression. None of the deaths were considered to be related to tebentafusp by the investigator.

Across all studies, a total 173 patients (42.2%) died. The most common cause of death was disease progression in 165 patients (40.2%); followed by deaths due to “other” reasons in 4 patients (1%); two patients (0.5%) who died due to “unknown” reasons; and two patients (0.5%) who died due to adverse events. None of these were considered related to tebentafusp.

Among the 4 deaths where the primary cause was due to “other” reasons, the free text descriptions in the CRF included the following: “fell downstairs and had stroke” 163 days after tebentafusp was discontinued due to disease progression [Study 102, Patient (b) (6)], “clinical disease progression” [Study 102, Patient (b) (6)] and “unknown” for two patients in Study 202 [Patient (b) (6) and Patient (b) (6)]. Patient (b) (6) died 235 days after tebentafusp was discontinued due to disease progression, while the death for Patient (b) (6) occurred 27 days after the last tebentafusp dose and was due to metastatic uveal melanoma and unrelated to tebentafusp per investigator.

The two deaths where the primary cause was due to “unknown” reasons occurred in Study 01 [Patient (b) (6) and Patient (b) (6)] 143 and 173 days, respectively, after treatment with tebentafusp was discontinued due to disease progression.

The two deaths where the primary cause was due to AEs occurred on Study 202 (pneumonia [Patient (b) (6)], pulmonary embolism [Patient (b) (6)]). None of these two deaths were considered related to study drug by the investigator.

All deaths in Studies 01, 102 and 202 were reviewed to ensure no casualty with tebentafusp; narratives were written on all of these patients and included in the relevant CSRs.

The FDA’s Assessment:

Table 43 summarizes deaths occurring in patients enrolled to Study 202 based on reporting in the ADSL. Of patients enrolled to the tebentafusp arm, 84 patients (34%) had died as of data cutoff. As noted by the Applicant, almost all patients died due to disease progression. In the tebentafusp arm, 2 patients (0.8%) died as a result of adverse event, only one of these occurred within 30 days of the last dose of tebentafusp.

Review of TEAE reporting (ADAE) identifies one Grade 5 event of pulmonary embolism (0.4%) in the tebentafusp arm and 2 Grade 5 events of pulmonary embolism and left ventricular dysfunction (1.8%) in the IC arm occurring within 30 days of the last dose of study drug.

Table 43: Summary of Deaths: Study 202 Safety Population

	Tebentafusp N = 245 n (%)	Investigator Choice N = 111 n (%)
Total Deaths	84 (34)	57 (51)
Disease Progression	80 (33)	52 (47)
Adverse Event	2 (0.8)	3 (2.7)
Other: Unknown	2 (0.8)	1 (0.9)
Other: Subdural Hematoma	0 (0)	1 (0.9)
Within 30 days after last dose	5 (2.0)	5 (4.5)
Disease Progression	3 (1.2)	3 (2.7)
Adverse Event	1 (0.4)	2 (1.8)
Other: Unknown	1 (0.4)	0
Beyond 30 days after last dose	79 (32)	52 (47)
Disease Progression	77 (31)	49 (44)
Adverse Event	1 (0.4)	1 (0.9)
Other: Unknown	1 (0.4)	1 (0.9)
Other: Subdural Hematoma	0	1 (0.9)

Source: Reviewer Table: Study 202 ADSL (Subject-Level Analysis Dataset) - 2021-04-21. Variables used: USUBJID, TRT01A, SAFFL, DTHCAUS, DTHDT, DTHFL, TRTEDT

Narratives for patients enrolled to the tebentafusp arm of Study 202 who died on study within 90 days of last dose of study drug, not including those who unequivocally died from progressive disease, are summarized in Table 43. There were no deaths occurring in patients enrolled in the tebentafusp arm considered by the reviewer to be related to study drug.

Table 44: Summary of Selected Narratives for Patients Enrolled to Tebentafusp Arm: Study 202

Patient ID; Cause of Death; Attribution	Brief Synopsis
(b) (6) Cause of Death: Pulmonary Emboli Investigator Assessment: Not related	57 year old gentleman with no medical history reported. Sites of disease at study entry included liver. Patient received 12 doses of tebentafusp before discontinuing due to disease progression. Target lesions exceeded 20 cm suggestive of marked progression. On the day of the last dose, during routine scans, patient was found to have pulmonary emboli. Patient was treated and

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Reviewer Assessment: PE unlikely to be related to study drug. More likely related to underlying disease.	discharged. Nineteen days after the last dose, the patient died. Cause of noted in the narrative as due to PE.
(b) (6) Death: Cause of Pneumonia Investigator Assessment: Not related Reviewer Assessment: Not related	69 year old woman with PMHx significant for antiphospholipid syndrome, TIA, GE reflux. Patient's ongoing medical conditions at study entry included hypercholesterolemia and hypertension. Reported site of disease at study entry included liver. Patient received 3 cycles of tebentafusp before discontinuing due to disease progression. Forty-one days after the last dose, the patient developed pneumonia. Nine days later, the patient died due to pneumonia.
(b) (6) Cause of Death: Progressive Disease Reviewer Assessment: Not related	72 year old gentleman. The patient's ongoing medical conditions at study entry included Vitamin D deficiencies. Reported site of disease at study entry included liver. Patient received a total of 6 doses of tebentafusp. The patient discontinued due to disease progression. At 35-36 days after the last dose, the patient experienced Grade 3 general health deterioration, asthenia, decreased appetite, Grade 4 AST increase, worsening (Grade 3) hyperbilirubinemia, and AST elevation. At 48 days after the last dose of study drug, the patient died due to disease progression.
(b) (6) Cause of Death: Progressive Disease Reviewer Assessment: Not related. There is no evidence that hepatic failure contributed to the patient's death.	56 year old gentleman with PMHx significant for epilepsy and hypertension. Reported site of disease at study entry included liver. Patient received a total of 3 doses of tebentafusp. Within 3-4 days of the first dose of tebentafusp, the patient experienced Grade 1 creatinine increased, Grade 3 hyperbilirubinemia, elevated AST and ALT. Cycle 1 Days 8 and 15 doses were omitted and the events of hyperbilirubinemia and creatinine increase resolved. Cycle 2 Day 1 dose was reduced to 20 mcg. Cycle 2 Day 2, the patient experienced Grade 4 hypotension, elevated creatinine, elevated LDH. Cycle 2 Day 8 dose was omitted. Within 3 days of Cycle 2 Day 15 dose, the patient experienced Grade 3 hepatic failure. Imaging around that time showed disease progression. 11 days after the last dose of study drug, the patient died due to progressive disease.

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(b) (6) Cause Death: Progressive Disease Investigator Assessment: Not related Reviewer Assessment: Not related	76 year old gentleman with PMHx significant for salivary gland neoplasm. Ongoing medical conditions at study entry included BPH and osteoarthritis. Sites of disease at study entry included lung, liver, left iliac wing, and subcutaneous fat nodules. The patient received a total of 12 doses of tebentafusp. The patient discontinued treatment due to progressive disease. 21 days after the last dose (and after initiating treatment with ipilimumab and nivolumab) the patient experienced Grade 3 pulmonary emboli. 63 days after last dose of study drug, the patient died due to progressive disease.
(b) (6) Cause of Death: Unknown Investigator Assessment: Not related. The Investigator assessed the cause of death as most likely due to disease progression as suggested by the patient's progressive asthenia, RUQ fullness, worsening liver enzymes, ascites, and increased edema of the lower extremities. Reviewer Assessment: Not related. Based on the AE reporting and the overall clinical picture, most likely cause of death is progressive disease.	64 year old gentleman with ongoing medical conditions at study entry including rheumatoid arthritis, AST increased, fatigue, and abdominal pain. Sites of disease at study entry included liver, lung, and lymph node. The patient received a total of 5 doses of tebentafusp. On Cycle 2 Day 12, treatment was discontinued due to patient decision. Prior to discontinuing treatment, the patient experienced Grade 3 AST and bilirubin elevation, Grade 3 tumor lysis syndrome. At the time of treatment discontinuation, the following non-serious AEs were ongoing: dizziness, nausea, constipation, ascites, abdominal distension, muscular weakness, AST increased, hyperbilirubinemia, peripheral edema. Approximately 3 weeks after discontinuing treatment, the patient withdrew consent for further study-related procedures and visits. No imaging to assess disease progression was performed. 27 days after the last dose of study drug, the patient died. Cause of death was reported as unknown.
Source: Reviewer summaries based on Narratives submitted with Study 202 CSR	

For the ISS_Pool dataset, 0.8% of patients (4/505) had fatal adverse events. These were intra-abdominal hemorrhage, malignant melanoma, pneumonia, and pulmonary embolism. The event of abdominal hemorrhage occurred in a 44 year old gentleman with a diagnosis of metastatic cutaneous melanoma. The patient received his first dose of tebentafusp at a dose of 0.0006 mg/kg. Six days later, the patient experienced fatal abdominal hemorrhage after presenting to the emergency department with right upper quadrant pain, dyspnea, hypoxia, and no palpable pulse. The patient died despite aggressive resuscitation. The cause of death was stated as abdominal hemorrhage, possibly related to liver biopsy performed before study treatment was given and repeated 2 days later. Both the Investigator and Sponsor assessed the

event as unrelated to administration of tebentafusp but possibly related to the study procedure. There is insufficient information to assess causality.

Reviewer Comment: Fatal adverse events within 90 days of the last dose of tebentafusp are rare. Across the development program in 505 patients who received at least one dose of tebentafusp monotherapy, there were no fatal adverse events that are assessed by this reviewer, based on the limited information contained in the narratives, as related to tebentafusp.

Serious Adverse Events

Data:

Table 45 presents SAEs regardless of causality in $\geq 1\%$ of UM patients for individual studies and all studies combined.

Table 45: Uveal Melanoma Patients: Serious Adverse Events Regardless of Causality Reported in $\geq 1\%$ of Patients by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Number of patients with any serious TEAE	6 (31.6%)	10 (52.6%)	43 (33.9%)	69 (28.2%)	128 (31.2%)
Blood and lymphatic disorders	1 (5.3%)	0	0	1 (0.4%)	2 (0.5%)
Anaemia	1 (5.3%)	0	0	1 (0.4%)	2 (0.5%)
Cardiac disorders	0	0	6 (4.7%)	0	6 (1.5%)
Atrial flutter	0	0	2 (1.6%)	0	2 (0.5%)
Sinus tachycardia	0	0	2 (1.6%)	0	2 (0.5%)
Gastrointestinal disorders	1 (5.3%)	1 (5.3%)	6 (4.7%)	7 (2.9%)	15 (3.7%)
Abdominal pain	1 (5.3%)	1 (5.3%)	2 (1.6%)	2 (0.8%)	6 (1.5%)
Nausea	0	0	2 (1.6%)	4 (1.6%)	6 (1.5%)
Diarrhoea	0	0	2 (1.6%)	0	2 (0.5%)
General disorders and administration site conditions	1 (5.3%)	1 (5.3%)	11 (8.7%)	7 (2.9%)	20 (4.9%)
Pyrexia	0	1 (5.3%)	9 (7.1%)	6 (2.4%)	16 (3.9%)
Adverse drug reaction	1 (5.3%)	0	0	0	1 (0.2%)
Hepatobiliary disorders	0	1 (5.3%)	4 (3.1%)	8 (3.3%)	13 (3.2%)
Hyperbilirubinaemia	0	1 (5.3%)	0	2 (0.8%)	3 (0.7%)

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System Organ Class Preferred Term	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Immune system disorders	1 (5.3%)	0	4 (3.1%)	25 (10.2%)	30 (7.3%)
Cytokine release syndrome	1 (5.3%)	0	4 (3.1%)	24 (9.8%)	29 (7.1%)
Infections and infestations	2 (10.5%)	0	6 (4.7%)	4 (1.6%)	12 (2.9%)
Sepsis	0	0	3 (2.4%)	0	3 (0.7%)
Biliary tract infection	1 (5.3%)	0	1 (0.8%)	0	2 (0.5%)
Lower respiratory tract infection	1 (5.3%)	0	0	0	1 (0.2%)
Injury, poisoning and procedural complications	0	1 (5.3%)	1 (0.8%)	1 (0.4%)	3 (0.7%)
Infusion related reaction	0	1 (5.3%)	0	0	1 (0.2%)
Investigations	2 (10.5%)	2 (10.5%)	4 (3.1%)	3 (1.2%)	11 (2.7%)
Alanine aminotransferase increased	0	1 (5.3%)	3 (2.4%)	1 (0.4%)	5 (1.2%)
Aspartate aminotransferase increased	0	2 (10.5%)	2 (1.6%)	1 (0.4%)	5 (1.2%)
Gamma-glutamyltransferase increased	0	0	2 (1.6%)	0	2 (0.5%)
Laboratory test abnormal	1 (5.3%)	0	0	0	1 (0.2%)
Liver function test increased	1 (5.3%)	0	0	0	1 (0.2%)
Metabolism and nutrition disorders	1 (5.3%)	1 (5.3%)	2 (1.6%)	1 (0.4%)	5 (1.2%)
Hypophosphataemia	1 (5.3%)	1 (5.3%)	2 (1.6%)	0	4 (1.0%)
Hypocalcaemia	1 (5.3%)	0	0	0	1 (0.2%)
Musculoskeletal and connective tissue	1 (5.3%)	2 (10.5%)	3 (2.4%)	0	6 (1.5%)
Back pain	1 (5.3%)	0	2 (1.6%)	0	3 (0.7%)
Bone pain	0	1 (5.3%)	0	0	1 (0.2%)
Pain in extremity	0	1 (5.3%)	0	0	1 (0.2%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (5.3%)	0	3 (2.4%)	3 (1.2%)	7 (1.7%)
Tumour pain	0	0	2 (1.6%)	2 (0.8%)	4 (1.0%)
Tumour haemorrhage	1 (5.3%)	0	0	0	1 (0.2%)
Nervous system disorders	0	1 (5.3%)	4 (3.1%)	5 (2.0%)	10 (2.4%)
Spinal cord compression	0	0	2 (1.6%)	1 (0.4%)	3 (0.7%)

System Organ Class Preferred Term	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Aphasia	0	1 (5.3%)	0	0	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	0	2 (10.5%)	4 (3.1%)	4 (1.6%)	10 (2.4%)
Pleural effusion	0	0	2 (1.6%)	0	2 (0.5%)
Pulmonary embolism	0	1 (5.3%)	0	1 (0.4%)	2 (0.5%)
Hypoxia	0	1 (5.3%)	0	0	1 (0.2%)
Skin and subcutaneous tissue disorders	0	0	4 (3.1%)	14 (5.7%)	18 (4.4%)
Rash	0	0	1 (0.8%)	6 (2.4%)	7 (1.7%)
Rash maculo-papular	0	0	3 (2.4%)	4 (1.6%)	7 (1.7%)
Vascular disorders	2 (10.5%)	1 (5.3%)	5 (3.9%)	5 (2.0%)	13 (3.2%)
Hypotension	2 (10.5%)	1 (5.3%)	3 (2.4%)	5 (2.0%)	11 (2.7%)

n = number of patients; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event. Patients with multiple TEAEs per SOC or PT are counted only once in each row.

Adverse events (AEs) are coded using MedDRA version 23.1.

TEAEs are defined as any AE with a start date from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.

Number (%) of patients are sorted alphabetically for SOC and by descending frequency overall for PT. A patient can have one or more PTs reported under a given SOC.

Serious adverse events (SAEs) include deaths reportable as SAEs and non-fatal SAEs.

Source: Module 5.3.5.3, Table ISS 02.03.03.01.01.

The Applicant's Position:

Across all studies, 128 patients (31.2%) experienced an SAE. The most common SAEs reported were CRS in 29 patients (7.1%), hypotension in 11 patients (2.7%), and pyrexia in 16 patients (3.9%).

The FDA's Assessment:

Table 46 shows the frequency of SAEs occurring in Study 202. Overall, the incidence of SAEs was slightly higher in the tebentafusp arm compared with the IC arm. The pattern of SAEs between the two arms differs. The most common SAEs reported in the tebentafusp arm are CRS, events associated with CRS including nausea, dyspnea, and hypotension, and skin disorders including rash, pruritis, urticaria, and skin reaction. These SAEs were rarely reported in patients receiving IC.

Table 46: Serious Adverse Events Occurring in ≥ 1 Patient in the Tebentafusp Arm: Study 202 Safety Population

	Tebentafusp N = 245 n (%)	Investigator Choice N = 111 n (%)
Patients with at least 1 SAE	69 (28)	26 (23)
Immune System Disorders		
Cytokine Release Syndrome	24 (10)	0
Anaphylactic Reaction	1 (0.4)	0
Skin And Subcutaneous Tissue Disorders		
Rash (GT) ¹	11 (4.5)	0
Pruritus	1 (0.4)	0
Skin Reaction	1 (0.4)	0
Urticaria	1 (0.4)	0
Gastrointestinal Disorders		
Abdominal Pain (GT) ¹	4 (1.6)	3 (2.7)
Nausea	4 (1.6)	1 (0.9)
Vomiting (GT) ¹	2 (0.8)	0
Diarrhea (GT) ¹	0 (0)	3 (2.7)
Gastritis	0 (0)	1 (0.9)
General Disorders And Administration Site Conditions		
Pyrexia (GT) ¹	6 (2.4)	2 (1.8)
Fatigue (GT) ¹	2 (0.8)	0
General Physical Health Deterioration	1 (0.4)	0
Oedema (GT) ¹	1 (0.4)	0
Hepatobiliary Disorders		
Hepatotoxicity	2 (0.8)	0
Hyperbilirubinemia	2 (0.8)	0
Biliary Obstruction	1 (0.4)	0
Hepatic Failure	1 (0.4)	0
Hepatic Necrosis	1 (0.4)	0
Hypertransaminasaemia	1 (0.4)	0
Nervous System Disorders		

	Tebentafusp N = 245 n (%)	Investigator Choice N = 111 n (%)
Brain Oedema	1 (0.4)	0
Dizziness (GT) ¹	1 (0.4)	0
Motor Dysfunction	1 (0.4)	0
Presyncope	1 (0.4)	0
Spinal Cord Compression	1 (0.4)	0
Vascular Disorders		
Hypotension (GT)	5 (2.0)	0
Infections And Infestations		
Appendicitis	1 (0.4)	0
Covid-19	1 (0.4)	0
Erysipelas	1 (0.4)	0
Salmonella Sepsis	1 (0.4)	0
Respiratory, Thoracic And Mediastinal Disorders		
Dyspnea (GT) ¹	2 (0.8)	0
Pulmonary Embolism	1 (0.4)	3 (2.7)
Pulmonary Oedema	1 (0.4)	0
Investigations		
Blood Creatinine Increased	2 (0.8)	0
Alanine Aminotransferase Increased	1 (0.4)	0
Amylase Increased	1 (0.4)	0
Aspartate Aminotransferase Increased	1 (0.4)	0
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)		
Tumor Pain	2 (0.8)	0
Meningioma	1 (0.4)	0
Renal And Urinary Disorders		
Acute Kidney Injury (GT) ¹	2 (0.8)	0
Blood And Lymphatic System Disorders		
Anemia	1 (0.4)	0
Eye Disorders		
Diplopia	1 (0.4)	0

	Tebentafusp N = 245 n (%)	Investigator Choice N = 111 n (%)
Injury, Poisoning And Procedural Complications		
Procedural Pain	1 (0.4)	1 (0.9)
Metabolism And Nutrition Disorders		
Tumor Lysis Syndrome	1 (0.4)	0
Psychiatric Disorders		
Mental Status Changes	1 (0.4)	0
Reproductive System And Breast Disorders		
Scrotal Inflammation	1 (0.4)	0

Source: Reviewer Table: Study 202 ADSL (Subject-Level Analysis Dataset) - 2021-04-21, ADAE (Adverse Events Analysis Dataset) - 2021-04-21. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEBODSYS, AESER

¹ Does not include investigator reported laboratory abnormalities.

² GT (Grouped Term) represents collection of related preferred terms. See Appendix 19.3.

In the ISS_Pool, 36% of patients (182/505) had at least one SAE. The most commonly reported event by PT occurring in $\geq 2\%$ of patients were CRS (6%), pyrexia (3.4%), and hypotension (2.8%). An additional SAE of note is multiple organ dysfunction syndrome (Grade 4) occurring in 2 patients (0.4%).

Multiple organ dysfunction syndrome occurred in 1 patient enrolled to the dose expansion phase of Study 102. Patient ^{(b) (6)} was a 53 year old woman with a diagnosis of uveal melanoma who developed Grade 3 CRS and Grade 4 hypotension after her first dose of tebentafusp. The patient was treated with fluid resuscitation, steroids, phenylephrine, vasopressor, and tocilizumab. The day after the infusion, the patient developed Grade 4 multiple organ dysfunction syndrome including acute kidney injury, respiratory failure, and shock liver. The patient was intubated. The patient was ultimately extubated and transitioned to hemodialysis. The event of CRS was reported as resolved; the event of multiple organ dysfunction was ongoing at the time the patient was discharged to hospice. The patient subsequently died of progressive disease 27 days after the patient's only dose of study drug. The SAE of multiple organ dysfunction syndrome was ongoing at the time of death.

Multiple organ dysfunction syndrome occurred in 1 patient, a 78 year old gentleman, enrolled to study 201. Narrative was not available.

Reviewer Comment: Across the development program, the most frequently observed SAEs are consistent with those observed in Study 202 and associated with CRS. The potentially fatal

event of multiple organ system dysfunction, which may be associated with CRS, was reported in 0.4% of patients.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 47 presents drug-related TEAEs resulting in study drug discontinuation and is presented by SOC and PT for UM patients for the individual studies and all studies combined. The choice to present a summary of study drug discontinuation due to drug-related TEAEs per Investigator, rather than TEAE regardless of causality, is because this is how the investigators made the decision to continue or discontinue study drug during the study. In general, drug-related TEAEs are more likely to exclude TEAE resulting from disease progression or underlying morbidity.

Table 47: Uveal Melanoma Patients: Drug Related Adverse Events Resulting in Study Drug Discontinuation Reported in Patients by System Organ Class and Preferred Term (Safety Analysis Set)

MedDRA System Organ Class Preferred Term	Study 01 All Doses (N = 19)	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 = 410)
Number of patients with any TEAE leading to permanent discontinuation of tebentafusp and causally related to tebentafusp ^a	0	0	3 (2.4%)	5 (2.0%)	8 (2.0%)
Cardiac disorders	0	0	2 (1.6%)	0	2 (0.5%)
Atrial fibrillation	0	0	1 (0.8%)	0	1 (0.2%)
Left ventricular dysfunction	0	0	1 (0.8%)	0	1 (0.2%)
General disorders and administration site conditions	0	0	1 (0.8%)	1 (0.4%)	2 (0.5%)
Fatigue	0	0	0	1 (0.4%)	1 (0.2%)
Multiple organ dysfunction syndrome	0	0	1 (0.8%)	0	1 (0.2%)
Hepatobiliary disorders	0	0	0	1 (0.4%)	1 (0.2%)
Hepatotoxicity	0	0	0	1 (0.4%)	1 (0.2%)
Immune system disorders	0	0	1 (0.8%)	2 (0.8%)	3 (0.7%)
Cytokine release syndrome	0	0	1 (0.8%)	1 (0.4%)	2 (0.5%)
Anaphylactic reaction	0	0	0	1 (0.4%)	1 (0.2%)
Vascular disorders	0	0	0	1 (0.4%)	1 (0.2%)
Hypotension	0	0	0	1 (0.4%)	1 (0.2%)

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n = number of patients; TEAE = treatment-emergent adverse event.

^a Determined by the investigator to be possibly related, probably related, definitely related, or related to tebentafusp.

Patients with multiple TEAEs per SOC or PT are counted only once in each row.

Adverse events (AEs) are coded using MedDRA version 23.1.

TEAEs are defined as any AE with a start date from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.

Number (%) of patients are sorted alphabetically for SOC and by descending frequency overall for PT. A patient can have one or more PTs reported under a given SOC.

Source: Module 5.3.5.3, Table ISS 02.03.04.02.01.

The Applicant's Position:

Across all studies, 15 patients (3.7%) experienced a TEAE that led to study drug discontinuation. The most common TEAE that led to study drug discontinuation regardless of causality was CRS in 2 patients (0.5%).

Across all studies, TEAEs that led to study drug discontinuation and considered to be drug related by the Investigator were reported in 8 patients (2.0%). The vast majority of these AEs appear to be cytokine mediated. No patients discontinued due to acute skin AEs.

The FDA's Assessment:

Table 48 summarizes the reasons for patient discontinuation from Study 202. As reported in the ADSL, 6 patients (2.4%) in the tebentafusp arm discontinued treatment due to AE. This was smaller but overall comparable to what was observed in the IC arm.

Table 48: Summary of Reasons for Patient Discontinuation: Study 202 Safety Population

	Tebentafusp N = 245 n (%)	Investigator Choice N = 111 n (%)
Patients discontinued from Treatment	172 (70)	100 (90)
Treatment discontinuation due to AEs	6 (2.4)	5 (4.5)
Treatment discontinuation due to "other"	166 (68)	95 (86)
Disease Progression	154 (63)	78 (70)
Patient Decision	7 (2.9)	3 (2.7)
Death	3 (1.2)	1 (0.9)
Initiation Of Alternative Anti-cancer Therapy	1 (0.4)	1 (0.9)
Investigator Decision	1 (0.4)	2 (1.8)

	Tebentafusp N = 245 n (%)	Investigator Choice N = 111 n (%)
Completion Of 4 Planned Doses Of Study Drug (ipilimumab Only)	0 (0)	10 (9)

Source: Reviewer Table: Study 202 ADSL (Subject-Level Analysis Dataset) - 2021-04-21. Variables used: USUBJID, TRT01A, SAFFL, DCTREAS

Based on adverse event reporting (dataset ADAE), 8 patients (3.3%) in the tebentafusp arm and 7 patients (6%) in the IC arm had at least one AE that led to treatment discontinuation. The following TEAEs resulted in permanent discontinuation in 1 patient (0.4%) in the tebentafusp arm in Study 202: anaphylactic reaction, brain edema, cytokine release syndrome, fatigue (GT), hepatotoxicity, hypotension (GT), nausea, spinal cord compression. No TEAE by PT led to discontinuation in the tebentafusp arm in more than 1 patient.

In the ISS_Pool, 5% of patients (27/505) had an adverse event leading to permanent discontinuation of tebentafusp. This is similar to that observed in Study 202. Evaluation of the specific AEs leading to discontinuation did not identify a safety signal not identified in Study 202.

Reviewer Comment: Tebentafusp rarely leads to treatment discontinuation.

Dose Interruption/Reduction Due to Adverse Effects

Data:

Table 49 presents drug-related TEAEs resulting in study drug interruptions by SOC and PT reported in UM Patients for the individual studies and all studies combined.

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Table 49: Uveal Melanoma Patients: Drug-related Adverse Events Resulting in Study Drug Interruptions Reported in Patients by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Study 01 All Doses (N = 19)	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 = 410)
Number of patients with any TEAE leading to drug interruption of tebentafusp and causally related to tebentafusp ^a	1 (5.3%)	5 (26.3%)	22 (17.3%)	44 (18.0%)	72 (17.6%)
Blood and lymphatic system disorders	0	2 (10.5%)	2 (1.6%)	1 (0.4%)	5 (1.2%)
Lymphopenia	0	2 (10.5%)	2 (1.6%)	0	4 (1.0%)
Neutropenia	0	0	0	1 (0.4%)	1 (0.2%)
Cardiac disorders	0	0	1 (0.8%)	0	1 (0.2%)
Sinus tachycardia	0	0	1 (0.8%)	0	1 (0.2%)
Eye disorders	0	1 (5.3%)	1 (0.8%)	1 (0.4%)	3 (0.7%)
Diplopia	0	0	0	1 (0.4%)	1 (0.2%)
Eye inflammation	0	1 (5.3%)	0	0	1 (0.2%)
Periorbital oedema	0	0	1 (0.8%)	0	1 (0.2%)
Gastrointestinal disorders	0	1 (5.3%)	6 (4.7%)	7 (2.9%)	14 (3.4%)
Nausea	0	0	3 (2.4%)	2 (0.8%)	5 (1.2%)
Vomiting	0	1 (5.3%)	2 (1.6%)	2 (0.8%)	5 (1.2%)
Abdominal pain	0	0	1 (0.8%)	3 (1.2%)	4 (1.0%)
Diarrhoea	0	0	3 (2.4%)	1 (0.4%)	4 (1.0%)
General disorders and administration site conditions	0	0	5 (3.9%)	12 (4.9%)	17 (4.1%)
Fatigue	0	0	1 (0.8%)	6 (2.4%)	7 (1.7%)
Pyrexia	0	0	3 (2.4%)	4 (1.6%)	7 (1.7%)

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System Organ Class Preferred Term	Study 01 All Doses (N = 19)	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 = 410)
Chills	0	0	1 (0.8%)	2 (0.8%)	3 (0.7%)
Asthenia	0	0	1 (0.8%)	0	1 (0.2%)
Inflammation	0	0	0	1 (0.4%)	1 (0.2%)
Oedema peripheral	0	0	0	1 (0.4%)	1 (0.2%)
Hepatobiliary disorders	0	1 (5.3%)	0	5 (2.0%)	6 (1.5%)
Hyperbilirubinaemia	0	1 (5.3%)	0	2 (0.8%)	3 (0.7%)
Hepatotoxicity	0	0	0	2 (0.8%)	2 (0.5%)
Hepatic necrosis	0	0	0	1 (0.4%)	1 (0.2%)
Hypertransaminasaemia	0	0	0	1 (0.4%)	1 (0.2%)
Immune system disorders	1 (5.3%)	0	1 (0.8%)	1 (0.4%)	3 (0.7%)
Cytokine release syndrome	1 (5.3%)	0	1 (0.8%)	1 (0.4%)	3 (0.7%)
Infections and infestations	0	0	0	1 (0.4%)	1 (0.2%)
Diverticulitis	0	0	0	1 (0.4%)	1 (0.2%)
Investigations	1 (5.3%)	1 (5.3%)	5 (3.9%)	15 (6.1%)	22 (5.4%)
Lipase increased	0	1 (5.3%)	0	7 (2.9%)	8 (2.0%)
Alanine aminotransferase increased	1 (5.3%)	0	1 (0.8%)	4 (1.6%)	6 (1.5%)
Amylase increased	0	0	2 (1.6%)	3 (1.2%)	5 (1.2%)
Aspartate aminotransferase increased	1 (5.3%)	0	1 (0.8%)	3 (1.2%)	5 (1.2%)
Blood alkaline phosphatase increased	0	0	1 (0.8%)	2 (0.8%)	3 (0.7%)
Transaminases increased	0	0	1 (0.8%)	2 (0.8%)	3 (0.7%)
Gamma-glutamyltransferase increased	0	0	1 (0.8%)	1 (0.4%)	2 (0.5%)
Blood lactate dehydrogenase increased	0	0	0	1 (0.4%)	1 (0.2%)

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System Organ Class Preferred Term	Study 01 All Doses (N = 19)	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 = 410)
Troponin I increased	0	0	1 (0.8%)	0	1 (0.2%)
Metabolism and nutrition disorders	0	0	2 (1.6%)	2 (0.8%)	4 (1.0%)
Decreased appetite	0	0	1 (0.8%)	0	1 (0.2%)
Dehydration	0	0	0	1 (0.4%)	1 (0.2%)
Hyperlipasaemia	0	0	0	1 (0.4%)	1 (0.2%)
Hypomagnesaemia	0	0	1 (0.8%)	0	1 (0.2%)
Musculoskeletal and connective tissue disorders	0	0	1 (0.8%)	0	1 (0.2%)
Arthralgia	0	0	1 (0.8%)	0	1 (0.2%)
Nervous system disorders	0	0	0	1 (0.4%)	1 (0.2%)
Dizziness	0	0	0	1 (0.4%)	1 (0.2%)
Psychiatric disorders	0	0	1 (0.8%)	1 (0.4%)	2 (0.5%)
Confusional state	0	0	1 (0.8%)	0	1 (0.2%)
Mental status changes	0	0	0	1 (0.4%)	1 (0.2%)
Renal and urinary disorders	0	0	1 (0.8%)	0	1 (0.2%)
Renal failure	0	0	1 (0.8%)	0	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	0	0	4 (3.1%)	1 (0.4%)	5 (1.2%)
Pleural effusion	0	0	1 (0.8%)	1 (0.4%)	2 (0.5%)
Asthma	0	0	1 (0.8%)	0	1 (0.2%)
Dyspnoea	0	0	1 (0.8%)	0	1 (0.2%)
Productive cough	0	0	1 (0.8%)	0	1 (0.2%)
Pulmonary oedema	0	0	0	1 (0.4%)	1 (0.2%)
Skin and subcutaneous tissue disorders	0	0	3 (2.4%)	4 (1.6%)	7 (1.7%)

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System Organ Class Preferred Term	Study 01 All Doses (N = 19)	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 = 410)
Rash	0	0	1 (0.8%)	3 (1.2%)	4 (1.0%)
Pruritus	0	0	2 (1.6%)	0	2 (0.5%)
Blister	0	0	0	1 (0.4%)	1 (0.2%)
Rash maculo-papular	0	0	1 (0.8%)	0	1 (0.2%)
Rash pruritic	0	0	0	1 (0.4%)	1 (0.2%)
Vascular disorders	0	0	2 (1.6%)	1 (0.4%)	3 (0.7%)
Hypotension	0	0	2 (1.6%)	1 (0.4%)	3 (0.7%)

n = number of patients; TEAE = treatment-emergent adverse event.

^a Determined by the investigator to be possibly related, probably related, definitely related, or related to

Patients with multiple TEAEs per SOC or PT are counted only once in each row.

Adverse events (AEs) are coded using MedDRA version 23.1.

TEAEs are defined as any AE with a start date from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.

Number (%) of patients are sorted alphabetically for SOC and by descending frequency overall for PT. A patient can have one or more PTs reported under a given SOC.

Source: Module 5.3.5.3, Table ISS 02.03.04.04.01.

The Applicant's Position:

Across all studies, 107 patients (26.1%) experienced TEAE that led to study drug discontinuation. The most common TEAEs that led to study discontinuation regardless of causality were pyrexia in 10 patients (2.9%), ALT increased in 10 patients (2.4%), and AST increased in 10 patients (2.4%).

Across all studies, TEAEs that led to study drug interruption and considered to be drug-related by the Investigator were reported in 72 patients (17.6%). This approach enables identification of AEs the Investigator deemed drug-related vs. interruptions that are more related to disease progression or other comorbidities.

The FDA's Assessment:

FDA did not consider investigator assigned causality in its safety analysis.

In Study 202, the percentage of patients who had at least one TEAE leading to treatment interruption is similar between the arms with 62 patients (25%) in the tebentafusp arm and 27 patients (24%) in the IC arm having at least one AE leading to interruption. Table 50 summarizes the TEAEs leading to treatment interruption in at least 2 patients in the tebentafusp arm.

In the ISS_Pool, 24% of patients (121/505) had at least one TEAE leading to treatment interruption. This is similar that observed in Study 202. The most common TEAE leading to discontinuation were consistent with those identified in Study 202, including CRS and AEs associated with CRS.

Table 50: Adverse Events Leading to Treatment Interruption in ≥ 2 patient in the Tebentafusp Arm: Study 202 Safety Population.

	Tebentafusp N = 245 N (%)	Investigator Choice N = 111 N (%)
Study treatment - drug interrupted - due to AEs	62 (25)	27 (24)
Fatigue (GT) ¹	10 (4.1)	0
Lipase Increased	7 (2.9)	4 (3.6)
Pyrexia (GT) ¹	6 (2.4)	0
Alanine Aminotransferase Increased	5 (2.0)	3 (2.7)
Aspartate Aminotransferase Increased	5 (2.0)	3 (2.7)

Source: Reviewer Table: Study 202 ADSL (Subject-Level Analysis Dataset) - 2021-04-21, ADAE (Adverse Events Analysis Dataset) - 2021-04-21. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEBODSYS, AESER

¹ GT (Grouped Term) represents collection of related preferred terms. See Appendix 19.3.

Significant Adverse Events

The Applicant's Position:

Table 51 presents SAEs regardless of causality in $\geq 1\%$ of UM patients for individual studies and all studies combined. Across all studies, 128 patients (31.2%) experienced an SAE. The most common SAEs reported were CRS in 29 patients (7.1%), hypotension in 11 patients (2.7%), and pyrexia in 16 patients (3.9%).

Table 51: Uveal Melanoma Patients: Serious Adverse Events Regardless of Causality Reported in $\geq 1\%$ of Patients by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Number of patients with any serious TEAE	6 (31.6%)	10 (52.6%)	43 (33.9%)	69 (28.2%)	128 (31.2%)
Blood and lymphatic disorders	1 (5.3%)	0	0	1 (0.4%)	2 (0.5%)
Anaemia	1 (5.3%)	0	0	1 (0.4%)	2 (0.5%)
Cardiac disorders	0	0	6 (4.7%)	0	6 (1.5%)
Atrial flutter	0	0	2 (1.6%)	0	2 (0.5%)
Sinus tachycardia	0	0	2 (1.6%)	0	2 (0.5%)
Gastrointestinal disorders	1 (5.3%)	1 (5.3%)	6 (4.7%)	7 (2.9%)	15 (3.7%)
Abdominal pain	1 (5.3%)	1 (5.3%)	2 (1.6%)	2 (0.8%)	6 (1.5%)
Nausea	0	0	2 (1.6%)	4 (1.6%)	6 (1.5%)
Diarrhoea	0	0	2 (1.6%)	0	2 (0.5%)
General disorders and administration site conditions	1 (5.3%)	1 (5.3%)	11 (8.7%)	7 (2.9%)	20 (4.9%)
Pyrexia	0	1 (5.3%)	9 (7.1%)	6 (2.4%)	16 (3.9%)
Adverse drug reaction	1 (5.3%)	0	0	0	1 (0.2%)
Hepatobiliary disorders	0	1 (5.3%)	4 (3.1%)	8 (3.3%)	13 (3.2%)
Hyperbilirubinaemia	0	1 (5.3%)	0	2 (0.8%)	3 (0.7%)
Immune system disorders	1 (5.3%)	0	4 (3.1%)	25 (10.2%)	30 (7.3%)
Cytokine release syndrome	1 (5.3%)	0	4 (3.1%)	24 (9.8%)	29 (7.1%)
Infections and infestations	2 (10.5%)	0	6 (4.7%)	4 (1.6%)	12 (2.9%)
Sepsis	0	0	3 (2.4%)	0	3 (0.7%)
Biliary tract infection	1 (5.3%)	0	1 (0.8%)	0	2 (0.5%)
Lower respiratory tract infection	1 (5.3%)	0	0	0	1 (0.2%)
Injury, poisoning and procedural complications	0	1 (5.3%)	1 (0.8%)	1 (0.4%)	3 (0.7%)
Infusion related reaction	0	1 (5.3%)	0	0	1 (0.2%)
Investigations	2 (10.5%)	2 (10.5%)	4 (3.1%)	3 (1.2%)	11 (2.7%)

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Alanine aminotransferase increased	0	1 (5.3%)	3 (2.4%)	1 (0.4%)	5 (1.2%)
Aspartate aminotransferase increased	0	2 (10.5%)	2 (1.6%)	1 (0.4%)	5 (1.2%)
Gamma-glutamyltransferase increased	0	0	2 (1.6%)	0	2 (0.5%)
Laboratory test abnormal	1 (5.3%)	0	0	0	1 (0.2%)
Liver function test increased	1 (5.3%)	0	0	0	1 (0.2%)
Metabolism and nutrition disorders	1 (5.3%)	1 (5.3%)	2 (1.6%)	1 (0.4%)	5 (1.2%)
Hypophosphataemia	1 (5.3%)	1 (5.3%)	2 (1.6%)	0	4 (1.0%)
Hypocalcaemia	1 (5.3%)	0	0	0	1 (0.2%)
Musculoskeletal and connective tissue	1 (5.3%)	2 (10.5%)	3 (2.4%)	0	6 (1.5%)
Back pain	1 (5.3%)	0	2 (1.6%)	0	3 (0.7%)
Bone pain	0	1 (5.3%)	0	0	1 (0.2%)
Pain in extremity	0	1 (5.3%)	0	0	1 (0.2%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (5.3%)	0	3 (2.4%)	3 (1.2%)	7 (1.7%)
Tumour pain	0	0	2 (1.6%)	2 (0.8%)	4 (1.0%)
Tumour haemorrhage	1 (5.3%)	0	0	0	1 (0.2%)
Nervous system disorders	0	1 (5.3%)	4 (3.1%)	5 (2.0%)	10 (2.4%)
Spinal cord compression	0	0	2 (1.6%)	1 (0.4%)	3 (0.7%)
Aphasia	0	1 (5.3%)	0	0	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	0	2 (10.5%)	4 (3.1%)	4 (1.6%)	10 (2.4%)
Pleural effusion	0	0	2 (1.6%)	0	2 (0.5%)
Pulmonary embolism	0	1 (5.3%)	0	1 (0.4%)	2 (0.5%)
Hypoxia	0	1 (5.3%)	0	0	1 (0.2%)
Skin and subcutaneous tissue disorders	0	0	4 (3.1%)	14 (5.7%)	18 (4.4%)
Rash	0	0	1 (0.8%)	6 (2.4%)	7 (1.7%)
Rash maculo-papular	0	0	3 (2.4%)	4 (1.6%)	7 (1.7%)
Vascular disorders	2 (10.5%)	1 (5.3%)	5 (3.9%)	5 (2.0%)	13 (3.2%)
Hypotension	2 (10.5%)	1 (5.3%)	3 (2.4%)	5 (2.0%)	11 (2.7%)

n = number of patients; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Patients with multiple TEAEs per SOC or PT are counted only once in each row.

Adverse events (AEs) are coded using MedDRA version 23.1.

TEAEs are defined as any AE with a start date from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.

Number (%) of patients are sorted alphabetically for SOC and by descending frequency overall for PT. A patient can have one or more PTs reported under a given SOC.

Serious adverse events (SAEs) include deaths reportable as SAEs and non-fatal SAEs.

Source: Module 5.3.5.3, Table ISS 02.03.03.01.01.

The FDA's Assessment:

SAEs are discussed earlier in Section 8.2.4.

Grade 3-4 TEAES

FDA considered Grade 3-4 TEAES as significant adverse events. Table 52 shows Grade 3-4 TEAES, not including investigator AE reported laboratory abnormalities, occurring in at least 2% of patients in the tebentafusp arm in Study 202. A higher percentage of patients in the tebentafusp arm (54%) had at least one Grade 3-4 TEAE compared to patients in the IC arm (34%). As seen in the analysis of SAEs, most Grade 3-4 TEAES in the tebentafusp arm were CSR, related to CSR, or related to skin toxicity. Overall, the Grade 3-4 analysis did not identify any new safety signal with the exception of hypertension. In patients who received tebentafusp, 9% had the adverse event of hypertension. As noted by the Applicant in Section 8.2.5, because of the risk of hypotension associated with tebentafusp related CRS, Studies 102 and 202 required patients with pre-existing hypertension to temporarily hold anti-hypertensive medications prior to the first few doses of tebentafusp. This may explain the higher frequency of hypertension seen in the tebentafusp arm compared to the IC arm.

Table 52: Grade 3-4 Adverse Events Occurring in at least 2% of patients in the Tebentafusp Arm: Study 202 Safety Population¹

	Tebentafusp N = 245 N (%)	Investigator Choice N = 111 N (%)
Patients with ≥ 1 Grade 3-4 TEAES	132 (54)	38 (34)
Skin And Subcutaneous Tissue Disorders		
Rash (GT) ²	45 (18)	0
Pruritus	11 (4.5)	0
Vascular Disorders		
Hypertension (GT) ²	21 (9)	3 (2.7)
Hypotension (GT) ²	9 (3.7)	0
General Disorders And Administration Site Conditions		
Fatigue (GT) ²	14 (6)	1 (0.9)
Pyrexia (GT) ²	9 (3.7)	1 (0.9)
Gastrointestinal Disorders		
Abdominal Pain (GT) ²	7 (2.9)	4 (3.6)
Nausea	5 (2.0)	1 (0.9)

Source: Reviewer Table: Study 202 ADSL (Subject-Level Analysis Dataset) - 2021-04-21, ADAE (Adverse Events Analysis Dataset) - 2021-04-21. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEBODSYS, AESER

¹ Does not include investigator reported laboratory abnormalities.

² GT (Grouped Term) represents collection of related preferred terms. See Appendix 19.3.

In the ISS_Pool, 60% of patients (304/505) had at least one Grade 3-4 TEAE. The most common

TEAEs occurring in $\geq 2\%$ of patients were consistent with those seen in Study 202 and included TEAEs associated with CRS.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 53 provides an overall summary of AEs for UM Patients across individual studies and all studies combined. Rates of common AEs (frequency $\geq 10\%$ in all studies) in UM Patients are presented for individual studies and all studies combined in Table 54.

Table 53: Uveal Melanoma Patients: Overall Summary of Adverse Events (Safety Analysis Set)

Patients with	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Any TEAE	19 (100.0%)	19 (100.0%)	127 (100.0%)	245 (100.0%)	410 (100.0%)
TEAE by highest CTCAE Grade					
1	3 (15.8%)	0	2 (1.6%)	14 (5.7%)	19 (4.6%)
2	2 (10.5%)	2 (10.5%)	50 (39.4%)	98 (40.0%)	152 (37.1%)
3	7 (36.8%)	15 (78.9%)	62 (48.8%)	117 (47.8%)	201 (49.0%)
4	7 (36.8%)	2 (10.5%)	13 (10.2%)	15 (6.1%)	37 (9.0%)
5	0	0	0	1 (0.4%)	1 (0.2%)
Any TEAE causally related tebentafusp ^a	19 (100.0%)	19 (100.0%)	127 (100.0%)	243 (99.2%)	408 (99.5%)
Any TEAE with maximum CTCAE of Grade 3 or 4	14 (73.7%)	17 (89.5%)	75 (59.1%)	133 (54.3%)	239 (58.3%)
Any TEAE with maximum CTCAE of Grade 4	7 (36.8%)	2 (10.5%)	13 (10.2%)	15 (6.1%)	37 (9.0%)
Any TEAE with maximum CTCAE of Grade 3 or 4 and causally related to tebentafusp ^a	12 (63.2%)	15 (78.9%)	59 (46.5%)	109 (44.5%)	195 (47.6%)
Any serious TEAE	6 (31.6%)	10 (52.6%)	43 (33.9%)	69 (28.2%)	128 (31.2%)

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Patients with	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Any serious TEAE causally related to tebentafusp ^a	3 (15.8%)	6 (31.6%)	27 (21.3%)	54 (22.0%)	90 (22.0%)
A TEAE leading to permanent discontinuation of tebentafusp	0	0	7 (5.5%)	8 (3.3%)	15 (3.7%)
A TEAE leading to permanent discontinuation of tebentafusp and causally related to tebentafusp ^a	0	0	3 (2.4%)	5 (2.0%)	8 (2.0%)
Any TEAE leading to drug interruptions of tebentafusp	3 (15.8%)	8 (42.1%)	34 (26.8%)	62 (25.3%)	107 (26.1%)
Any TEAE leading to drug interruptions of tebentafusp that were causally related to tebentafusp ^a	1 (5.3%)	5 (26.3%)	22 (17.3%)	44 (18.0%)	72 (17.6%)
Any TEAE leading to dose reductions of tebentafusp	0	4 (21.1%)	3 (2.4%)	13 (5.3%)	20 (4.9%)
Any TEAE leading to dose reductions of tebentafusp that were causally related to tebentafusp ^a	0	4 (21.1%)	3 (2.4%)	12 (4.9%)	19 (4.6%)
A TEAE leading to death	0	0	0	1 (0.4%)	1 (0.2%)
A TEAE leading to death and causally related to tebentafusp ^a	0	0	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events; n = number of patients; TEAE = treatment-emergent adverse event

^a Determined by the investigator to be possibly related, probably related, definitely related, or related to tebentafusp.

TEAEs are defined as any adverse event (AE) with a start date from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

Serious adverse events (SAEs) include deaths as an outcome of SAEs and non-fatal SAEs.

Patient IMCGP100-202- (b) (6) had a Grade 3 TEAE of “pulmonary embolism” which increased to Grade 5. This patient is counted under “Grade 5”, “maximum CTCAE Grade 3 or 4”, and “TEAE leading to death” in this table.

Source: Module 5.3.5.3, Table ISS 02.03.01.01.

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Table 54: Uveal Melanoma Patients: Adverse Events Reported in ≥ 10% of Patients in All Studies (Safety Analysis Set)

System Organ Class (SOC)/ Preferred Term (PT)	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Number of patients with any TEAE	19 (100.0%)	19 (100.0%)	127 (100.0%)	245 (100.0%)	410 (100.0%)
Blood and lymphatic system disorders	9 (47.4%)	9 (47.4%)	24 (18.9%)	63 (25.7%)	105 (25.6%)
Anaemia	6 (31.6%)	6 (31.6%)	17 (13.4%)	25 (10.2%)	54 (13.2%)
Cardiac disorders	5 (26.3%)	4 (21.1%)	37 (29.1%)	37 (15.1%)	83 (20.2%)
Tachycardia	2 (10.5%)	2 (10.5%)	15 (11.8%)	24 (9.8%)	43 (10.5%)
Eye disorders	11 (57.9%)	15 (78.9%)	68 (53.5%)	79 (32.2%)	173 (42.2%)
Periorbital oedema	8 (42.1%)	12 (63.2%)	34 (26.8%)	26 (10.6%)	80 (19.5%)
Gastrointestinal disorders	17 (89.5%)	19 (100.0%)	113 (89.0%)	194 (79.2%)	343 (83.7%)
Nausea	13 (68.4%)	16 (84.2%)	85 (66.9%)	120 (49.0%)	234 (57.1%)
Vomiting	12 (63.2%)	10 (52.6%)	53 (41.7%)	73 (29.8%)	148 (36.1%)
Abdominal pain	4 (21.1%)	11 (57.9%)	45 (35.4%)	60 (24.5%)	120 (29.3%)
Diarrhoea	5 (26.3%)	9 (47.4%)	34 (26.8%)	61 (24.9%)	109 (26.6%)
Constipation	5 (26.3%)	10 (52.6%)	32 (25.2%)	44 (18.0%)	91 (22.2%)
Abdominal pain upper	3 (15.8%)	5 (26.3%)	25 (19.7%)	50 (20.4%)	83 (20.2%)
Dyspepsia	3 (15.8%)	4 (21.1%)	15 (11.8%)	20 (8.2%)	42 (10.2%)
General disorders and administration site conditions	18 (94.7%)	19 (100.0%)	124 (97.6%)	231 (94.3%)	392 (95.6%)
Pyrexia	13 (68.4%)	18 (94.7%)	104 (81.9%)	187 (76.3%)	322 (78.5%)
Fatigue	13 (68.4%)	17 (89.5%)	78 (61.4%)	125 (51.0%)	233 (56.8%)
Chills	9 (47.4%)	14 (73.7%)	85 (66.9%)	117 (47.8%)	225 (54.9%)
Oedema peripheral	5 (26.3%)	16 (84.2%)	44 (34.6%)	66 (26.9%)	131 (32.0%)
Face oedema	6 (31.6%)	5 (26.3%)	15 (11.8%)	25 (10.2%)	51 (12.4%)
Influenza like illness	5 (26.3%)	5 (26.3%)	23 (18.1%)	18 (7.3%)	51 (12.4%)

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System Organ Class (SOC)/ Preferred Term (PT)	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Asthenia	0	0	9 (7.1%)	38 (15.5%)	47 (11.5%)
Hepatobiliary disorders	2 (10.5%)	6 (31.6%)	22 (17.3%)	51 (20.8%)	81 (19.8%)
Hyperbilirubinaemia	0	3 (15.8%)	10 (7.9%)	28 (11.4%)	41 (10.0%)
Immune system disorders	3 (15.8%)	2 (10.5%)	15 (11.8%)	55 (22.4%)	75 (18.3%)
Cytokine release syndrome	2 (10.5%)	0	10 (7.9%)	51 (20.8%)	63 (15.4%)
Investigations	7 (36.8%)	13 (68.4%)	66 (52.0%)	132 (53.9%)	218 (53.2%)
Aspartate aminotransferase increased	1 (5.3%)	5 (26.3%)	23 (18.1%)	56 (22.9%)	85 (20.7%)
Alanine aminotransferase increased	1 (5.3%)	5 (26.3%)	19 (15.0%)	51 (20.8%)	76 (18.5%)
Lipase increased	1 (5.3%)	2 (10.5%)	12 (9.4%)	35 (14.3%)	50 (12.2%)
Blood alkaline phosphatase increased	3 (15.8%)	5 (26.3%)	13 (10.2%)	23 (9.4%)	44 (10.7%)
Weight decreased	1 (5.3%)	4 (21.1%)	20 (15.7%)	16 (6.5%)	41 (10.0%)
Metabolism and nutrition disorders	7 (36.8%)	16 (84.2%)	70 (55.1%)	110 (44.9%)	203 (49.5%)
Decreased appetite	3 (15.8%)	7 (36.8%)	32 (25.2%)	45 (18.4%)	87 (21.2%)
Hypophosphataemia	3 (15.8%)	4 (21.1%)	15 (11.8%)	27 (11.0%)	49 (12.0%)
Musculoskeletal and connective tissue disorders	10 (52.6%)	18 (94.7%)	91 (71.7%)	116 (47.3%)	235 (57.3%)
Arthralgia	2 (10.5%)	10 (52.6%)	42 (33.1%)	53 (21.6%)	107 (26.1%)
Back pain	4 (21.1%)	13 (68.4%)	41 (32.3%)	45 (18.4%)	103 (25.1%)
Myalgia	5 (26.3%)	8 (42.1%)	23 (18.1%)	24 (9.8%)	60 (14.6%)
Pain in extremity	3 (15.8%)	10 (52.6%)	18 (14.2%)	24 (9.8%)	55 (13.4%)
Nervous system disorders	8 (42.1%)	17 (89.5%)	75 (59.1%)	127 (51.8%)	227 (55.4%)
Headache	7 (36.8%)	11 (57.9%)	42 (33.1%)	75 (30.6%)	135 (32.9%)
Dizziness	1 (5.3%)	8 (42.1%)	21 (16.5%)	27 (11.0%)	57 (13.9%)
Paraesthesia	3 (15.8%)	5 (26.3%)	10 (7.9%)	27 (11.0%)	45 (11.0%)
Psychiatric disorders	1 (5.3%)	10 (52.6%)	42 (33.1%)	45 (18.4%)	98 (23.9%)
Insomnia	0	7 (36.8%)	20 (15.7%)	22 (9.0%)	49 (12.0%)
Respiratory, thoracic and mediastinal disorders	10 (52.6%)	17 (89.5%)	69 (54.3%)	93 (38.0%)	189 (46.1%)
Cough	4 (21.1%)	8 (42.1%)	29 (22.8%)	44 (18.0%)	85 (20.7%)
Dyspnoea	2 (10.5%)	7 (36.8%)	24 (18.9%)	32 (13.1%)	65 (15.9%)

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System Organ Class (SOC)/ Preferred Term (PT)	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Skin and subcutaneous tissue disorders	18 (94.7%)	19 (100.0%)	122 (96.1%)	229 (93.5%)	388 (94.6%)
Pruritus	13 (68.4%)	17 (89.5%)	96 (75.6%)	169 (69.0%)	295 (72.0%)
Rash	12 (63.2%)	6 (31.6%)	56 (44.1%)	135 (55.1%)	209 (51.0%)
Dry skin	5 (26.3%)	12 (63.2%)	50 (39.4%)	77 (31.4%)	144 (35.1%)
Rash maculo-papular	7 (36.8%)	1 (5.3%)	51 (40.2%)	75 (30.6%)	134 (32.7%)
Erythema	4 (21.1%)	10 (52.6%)	36 (28.3%)	60 (24.5%)	110 (26.8%)
Hair colour changes	5 (26.3%)	8 (42.1%)	34 (26.8%)	48 (19.6%)	95 (23.2%)
Skin exfoliation	7 (36.8%)	1 (5.3%)	28 (22.0%)	51 (20.8%)	87 (21.2%)
Skin hypopigmentation	0	5 (26.3%)	24 (18.9%)	22 (9.0%)	51 (12.4%)
Vitiligo	1 (5.3%)	2 (10.5%)	8 (6.3%)	40 (16.3%)	51 (12.4%)
Skin hyperpigmentation	0	6 (31.6%)	21 (16.5%)	19 (7.8%)	46 (11.2%)
Vascular disorders	10 (52.6%)	17 (89.5%)	79 (62.2%)	131 (53.5%)	237 (57.8%)
Hypotension	8 (42.1%)	14 (73.7%)	53 (41.7%)	95 (38.8%)	170 (41.5%)
Hypertension	3 (15.8%)	2 (10.5%)	19 (15.0%)	38 (15.5%)	62 (15.1%)
Flushing	2 (10.5%)	1 (5.3%)	16 (2.6%)	25 (10.2%)	44 (10.7%)

n = number of patients; PT = preferred term, SOC = system organ class; TEAE = treatment-emergent adverse event

Patients with multiple TEAEs per SOC or PT are counted only once in each row.

Adverse events (AEs) are coded using MedDRA version 23.1.

TEAEs are defined as any AE with a start date from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.

Number (%) of patients are sorted alphabetically for SOC and by descending frequency overall for PT. A patient can have one or more PTs reported under a given SOC.

Source: Module 5.3.5.3, Table ISS 02.03.02.01.01.

The Applicant's Position:

For all studies combined, a total of 410 patients (100.0%) who received tebentafusp experienced any TEAE. System organ classes in which TEAEs were reported most frequently ($\geq 50\%$ of patients in tebentafusp arm) were general disorders and administration site conditions (95.6%), skin and subcutaneous tissue disorders (94.6%), gastrointestinal disorders (83.7%), vascular disorders (57.8%), musculoskeletal and connective tissue disorders (57.3%), nervous system disorders (55.4%), and investigations (53.2%).

TEAEs (PTs) with the highest incidence ($\geq 30\%$ of patients in tebentafusp arm) were pyrexia (78.5%), pruritus (72.0%), fatigue (56.8%), nausea (57.1%), chills (54.9%), rash (51.0%), hypotension (41.5%), vomiting (36.1%), dry skin (35.1%), headache (32.9%), rash maculopapular (32.7%), and oedema peripheral (32.0%).

These TEAEs are consistent with the mechanism of action of tebentafusp and can generally be divided into 2 major categories, skin and cytokine-mediated events. Tebentafusp redirects T cells to gp100+ melanocytes in the skin which leads to acute skin toxicities (rash, pruritis, erythema, and edema). Tebentafusp also activates T cells leading to cytokine release which results in cytokine mediated AEs including CRS (defined by pyrexia, hypotension, and hypoxia) as well as other AEs likely resulting from elevated cytokines (e.g., fatigue, nausea, chills, vomiting and headache). Other less frequent TEAEs included LFT, ocular events, and cardiac events.

Of the 410 patients who received tebentafusp, 408 (99.5%) reported TEAEs that were considered related to study drug by the investigator. A total of 195 patients (47.6%) had treatment-related TEAEs that were of Grade 3 or 4 severity. Serious TEAEs were reported in 128 patients (31.2%) and 90 (22.0%) reported serious TEAEs were considered related to study drug. Discontinuation of study drug due to TEAEs was uncommon and occurred in 15 patients (3.7%) with 8 (2.0%) patients experiencing events that were considered related to study drug. TEAEs resulting in death were reported in 1 patient (0.2%) in Study 202 (Patient (b) (6); pulmonary embolism) and was considered not related to study drug by the investigator.

The FDA's Assessment:

In the ISS_Pool, 100% of the 505 patients had at least 1 TEAE. Analysis of the TEAEs at all levels of the MedDRA hierarchy and using SMQ analysis did not identify any new or more severe safety signal beyond those identified in Study 202. No rare but potentially severe or life-threatening adverse reactions associated with tebentafusp was identified that was not already observed in Study 202.

Table 55 shows the most frequent TEAEs, occurring in $\geq 15\%$ of patients in the tebentafusp arm, for Study 202. While the percentage of patients experiencing at least 1 TEAE of any grade are similar between the tebentafusp and the IC arms, more patients in the tebentafusp arm had ≥ 1 Grade 3-4 TEAE compared to patients in the IC arm.

In the ISS_Pool, 100% of the 505 patients had at least 1 TEAE. Analysis of the TEAEs at all levels of the MedDRA hierarchy and using SMQ analysis did not identify any new or more severe safety signal beyond those identified in Study 202. No rare but potentially severe or life-threatening adverse reactions associated with tebentafusp was identified that was not already observed in Study 202.

Table 55: Adverse Events Occurring in ≥ 15 % of Patients in the Tebentafusp Arm: Study 202 Safety Population¹

	Tebentafusp N = 245		Investigator Choice N = 111	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Patients with ≥ 1 TEAEs	245 (100)	132 (54)	105 (95)	38 (34)
General Disorders And Administration Site Conditions				
Pyrexia (GT) ²	191 (78)	9 (3.7)	8 (7)	1 (0.9)
Fatigue (GT)	156 (64)	14 (6)	47 (42)	1 (0.9)
Chills	117 (48)	1 (0.4)	4 (3.6)	0
Oedema (GT)	98 (40)	0	8 (7)	0
Skin And Subcutaneous Tissue Disorders				
Rash (GT)	202 (82)	45 (18)	31 (28)	0
Pruritus	169 (69)	11 (4.5)	26 (23)	0
Dry Skin	77 (31)	0	4 (3.6)	0
Erythema	60 (24)	0	1 (0.9)	0
Hair Color Changes	48 (20)	1 (0.4)	0 (0.0)	0
Vitiligo	40 (16)	0	4 (3.6)	0
Gastrointestinal Disorders				
Nausea	120 (49)	5 (2.0)	29 (26)	1 (0.9)
Abdominal Pain (GT)	104 (42)	7 (2.9)	36 (32)	4 (3.6)
Vomiting (GT)	74 (30)	3 (1.2)	10 (9)	0
Diarrhea (GT)	61 (25)	3 (1.2)	22 (20)	5 (4.5)
Constipation	44 (18)	0	13 (12)	0
Vascular Disorders				
Hypotension (GT)	98 (40)	9 (3.7)	3 (2.7)	0
Hypertension (GT)	39 (16)	21 (9)	8 (7)	3 (2.7)
Nervous System Disorders				
Headache (GT)	78 (32)	1 (0.4)	11 (10)	1 (0.9)

	Tebentafusp N = 245		Investigator Choice N = 111	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Musculoskeletal And Connective Tissue Disorders				
Musculoskeletal Pain (GT)	105 (43)	3 (1.2)	34 (31)	1 (0.9)
Metabolism And Nutrition Disorders				
Decreased Appetite	45 (18)	2 (0.8)	15 (14)	0
Respiratory, Thoracic And Mediastinal Disorders				
Cough (GT)	47 (19)	1 (0.4)	12 (11)	1 (0.9)
Immune System Disorders				
Cytokine Release Syndrome	51 (21)	2 (0.8)	0	0

Source: Reviewer Table: Study 202 ADSL (Subject-Level Analysis Dataset) - 2021-04-21, ADAE (Adverse Events Analysis Dataset) - 2021-04-21. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEBODSYS, AESER

¹ Does not include investigator reported laboratory abnormalities.

² GT (Grouped Term) represents collection of related preferred terms. See Appendix 19.3.

Laboratory Findings

Data:

Selected clinically relevant laboratory abnormalities based on the frequency of $\geq$ Grade 3 events are included in Table 56.

Table 56: Selected Post-Baseline Laboratory Abnormalities Occurring in $\geq 20\%$ or Grade 3-4 ($\geq 5\%$) of Uveal Melanoma Patients Receiving Tebentafusp in Study 202

	Study 202			
	Tebentafusp (N=245)		Investigator Choice Therapy (N=111)	
Lab Parameter	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Hematology				
Lymphocyte count decreased	91	55.5	25	1.8
Chemistry				
Phosphate decreased	50	11	18	1.8
Lipase increased	37	14.3	26	5.4
Amylase increased	23	4.1	17	0.9
Liver Function Tests				
AST increased	54	12.2	38	1.8
ALT increased	51	9	29	1.8
Bilirubin increased	27	4.1	14	6.3

The Applicant's Position:

Clinically relevant laboratory abnormalities include lymphocyte count decreased, phosphate decreased, lipase increased, amylase increased, ALT/AST increased, and bilirubin increased. Other blood chemistry changes that occurred in $\geq 20\%$ patients receiving tebentafusp included hemoglobin decreased, creatinine increased, glucose increased, albumin decreased, calcium decreased, alkaline phosphatase increased, magnesium decreased, and sodium decreased. These laboratory findings were not considered clinically relevant and very few to none were $\geq$ Grade 3. Clinically relevant liver function tests for labelling included AST increase, ALT increase, and bilirubin increase.

Overall, the clinical chemistry and hematology changes observed during Study 202 were generally mild to moderate in severity and required no treatment or dose modification.

The FDA's Assessment:

Table 57 summarizes the incidence of laboratory abnormalities worsening from baseline for Study 202. The most common worsening laboratory abnormalities, occurring in $\geq 50\%$ of patients on the tebentafusp arm, were lymphocyte count decreased (91%), creatinine increased (87%), glucose increased (66%), AST increased (54%), ALT increased (52%), phosphate decreased (51%), and hemoglobin decreased (51%). Laboratory assessments worsening to Grade 3 in $\geq 5\%$ of patients in the tebentafusp arm occurred only for lymphocyte count decreased (41%), lipase increased (13%), AST increased (12%), phosphate decreased (12%), and ALT increased (8%). Laboratory assessments worsening to Grade 4 in $\geq 5\%$ of patients in the tebentafusp arm occurred only for lymphocyte count decreased (15%).

While laboratory abnormalities were common in patients who received tebentafusp, most were Grade 1 or 2. Many of the laboratory abnormalities were those associated with CRS.

Table 57: Laboratory Abnormalities ($\geq 10\%$ in Tebentafusp Arm) worsening from baseline: Study 202

	Tebentafusp N = 245			Investigator Choice N = 111		
	Grades 1-4 n/N ¹ (%)	Grade 3 n/N ¹ (%)	Grade 4 n/N ¹ (%)	Grades 1-4 n/N ¹ (%)	Grade 3 n/N ¹ (%)	Grade 4 n/N ¹ (%)
HEMATOLOGY						
Lymphocytes Count Decreased	222/245 (91)	100/245 (41)	36/245 (15)	28/109 (26)	1/109 (0.9)	0
Hemoglobin Decreased	124/245 (51)	2/245 (0.8)	0	22/109 (20)	1/109 (0.9)	0
Leukocyte Count Decreased	43/245 (18)	3/245 (1.2)	0	8/109 (7)	2/109 (1.8)	0
Platelet Count Decreased	38/245 (16)	0	0	16/109 (15)	1/109 (0.9)	0
Neutrophil Count Decreased	35/245 (14)	3/245 (1.2)	1/245 (0.4)	9/109 (8)	1/109 (0.9)	0
CHEMISTRY AND METABOLIC						
Creatinine Increased	213/245 (87)	1/245 (0.4)	0	79/109 (72)	0	0
Glucose Increased	161/244 (66)	8/244 (3.3)	0	42/108 (39)	5/108 (4.6)	0
AST Increased	132/243 (54)	29/243 (12)	1/243 (0.4)	42/108 (39)	2/108 (1.9)	0
ALT Increased	126/243 (52)	19/243 (8)	2/243 (0.8)	32/108 (30)	2/108 (1.9)	0
Phosphate Decreased	124/242 (51)	29/242 (12)	0	20/105 (19)	2/105 (1.9)	0
Albumin Decreased	114/244 (47)	5/244 (2.0)	0	14/108 (13)	1/108 (0.9)	0
Calcium Decreased	109/244 (45)	4/244 (1.6)	0	16/109 (15)	2/109 (1.8)	0
Lipase Increased	91/244 (37)	31/244 (13)	5/244 (2.0)	29/108 (27)	4/108 (3.7)	2/108 (1.9)
Magnesium Decreased	84/244 (34)	0	0	9/108 (8)	0	0
Alk Phos Increased	81/244 (33)	7/244 (2.9)	0	39/109 (36)	2/109 (1.8)	0
Potassium Increased	72/245 (29)	3/245 (1.2)	1/245 (0.4)	15/109 (14)	1/109 (0.9)	0
Sodium Decreased	72/245 (29)	7/245 (2.9)	(0)	15/109 (14)	1/109 (0.9)	0
Bilirubin Increased	64/245 (26)	10/245 (4.1)	0	16/109 (15)	7/109 (6)	0
Amylase Increased	56/243 (23)	9/243 (3.7)	1/243 (0.4)	19/107 (18)	1/107 (0.9)	0
Glucose Decreased	43/244 (18)	1/244 (0.4)	0	5/108 (4.6)	0	0
Potassium Decreased	43/245 (18)	2/245 (0.8)	0	9/109 (8)	1/109 (0.9)	0
Calcium Increased	32/244 (13)	0/244 (0.0)	0	4/109 (3.7)	0	0

Source: Reviewer Table: Study 202 ADSL (Subject-Level Analysis Dataset) - 2021-04-21, ADLB (Laboratory Test Results Analysis Dataset) - 2021-04-21. Variables used: USUBJID, TRT01A, SAFFL, PARAM, ABLFL, AVAL, ANRLO, ANRHI, TRTEDT, ADT, TRTSDT, ADY, ATOXGR2, ATOXGR1

Alk Phos = Alkaline Phosphatase; AST=aspartate aminotransferase; ALT=alanine aminotransferase

¹ The denominator, N, used to calculate the rate is based on the number of patients with a baseline value and at least one post-treatment value for the laboratory assessment.

Vital Signs

The Applicant's Position:

A decrease in SBP (from baseline to worst on-treatment/follow-up) of ≥ 35 mmHg was reported in 0 patients in the tebentafusp arm and 1 patient (0.9%) in the investigator's choice arm; the latter had Grade 3 hypertension at baseline (SBP ≥ 160 mmHg).

Based on reported body temperature measurements, 77 patients (31.4%) in the tebentafusp arm and 108 patients (97.3%) in the investigator's choice arm maintained normal body temperature, 106 (43.3%) and 1 (0.9%) patients, respectively, experienced Grade 1 fever, 56 (22.9%) and 1 (0.9%) patients, respectively, experienced Grade 2 fever, and 6 (2.4%) and 0 patients, respectively, experienced Grade 3 fever; no patient in either treatment arm had Grade 4 fever.

There were no notable changes between the tebentafusp and investigator's choice arms for shifts from baseline to worst on-treatment/follow-up for weight, pulse rate, and respiratory rate.

The FDA's Assessment:

FDA agrees. Transient changes in vital signs associated with CRS were frequently observed in patients receiving tebentafusp; however, analysis of vital signs did not identify changes in weight, pulse, or respiratory rate that persisted beyond resolution of CRS.

Electrocardiograms (ECGs)

Data:

Cardiac AEs related to ECG abnormalities included tachycardia in 2 (10.5%) patients and sinus tachycardia in 1 (5.6%) patient; these events were Grade 1 or 2 in severity, non-serious, and did not result in discontinuation of study drug.

The most commonly reported ($> 1\%$ of patients) cardiac AEs related to ECG abnormalities were tachycardia (11.8%), sinus tachycardia in (9.4%), sinus bradycardia (3.9%), atrial fibrillation (3.1%), and atrial flutter (2.4%), and supraventricular tachycardia (1.6%). No AEs of torsade's de pointes were reported. Cardiac AEs of Grade ≥ 3 severity were reported in 7 patients (5.5%); events related to ECG abnormalities (each in 1 patient, 0.8%) included Grade 3 and Grade 4 atrial fibrillation, atrial flutter, and tachycardia; all were considered treatment-related. Five patients experienced SAEs related to ECG abnormalities.

In Study 102 and Study 202, there were no clinically meaningful trends in ECG findings and associated cardiac AEs.

The Applicant's Position:

In Study 102 and Study 202, there were no clinically meaningful trends in ECG findings and associated cardiac AEs.

The FDA's Assessment:

For more comprehensive discussion of cardiac toxicity see Section 8.2.5.

Based on review of shifts for PR, QRS, and RR interval abnormalities provided in the CSR for Study 202, FDA agrees with the Applicant. There were no clinically meaningful trends in ECG findings.

QT

The Applicant's Position:

In Study 102 and Study 202, there were no clinically meaningful trends in ECG findings and associated cardiac AEs.

The FDA's Assessment:

Based on review of the analysis of ECGs provided in the CSR for Study 202, FDA does not find any evidence that tebentafusp is associated with meaningful or persistent QT prolongation. As stated in the CSR, a total of 4 patients (1.6%) in the tebentafusp arm and no patients in the IC arm had post baseline QTcF values > 500 msec. Of the 4 patients in the tebentafusp arm, 3 of them had baseline values ≤ 450 msec and 1 patient had a baseline between 450 and 480 msec. All 4 cases of prolonged QTcF were observed pre-dose (i.e., 1 week from the last dose of tebentafusp) were transient, and returned to < 450 msec at the next time point (i.e., 1 hour post-dose). In addition, 7 patients of patients in the tebentafusp arm (2.9%) and no patients who received IC had an increase from baseline in QTcF > 60 msec. The Applicant states that none of these QTcF changes were associated with clinically significant or reported cardiac disorders. Narratives for patients with post baseline QTcF values > 500 msec were reviewed.

Immunogenicity

The Applicant's Position:

Overall, there was no meaningful impact of ADA on either patient safety or efficacy, based on frequency or grade of hypersensitivity AEs before and after ADA onset. Treatment-emergent ADA were detected in 4% of patients in study IMCgp100-01 using a first-generation assay and limited sampling strategy. In later studies where a more robust assay and sampling strategy were employed, treatment-emergent ADA were detected in 33% and 29% of mUM patients in studies IMCgp100-102 and IMCgp100-202, respectively. In these studies, ADA had a median onset time of 6 (study IMCgp100-102) and 9 weeks (study IMCgp100-202) after the first dose of tebentafusp, and median titers of 8192 (study IMCgp100-102) and 2050 (study IMCgp100-202).

The majority of these ADA responses were *de novo* treatment-induced responses that persisted after onset. A small number of patients developed high titer ADA (≥ 8192) that resulted in increased tebentafusp clearance and reduced $C_{\max}$ exposure. However, there was no clinically relevant impact of ADA on either patient safety or efficacy, based on frequency or grade of hypersensitivity AEs before and after ADA onset, or changes in OS or tumor shrinkage by ADA status or titer, respectively. Thus, monitoring of ADA is not necessary.

The FDA's Assessment:

See Appendix 19.5. Key conclusions of FDA analysis are:

1. Immunogenicity positive subgroup did not show significant reduced efficacy compared with immunogenicity negative subgroup. However, the result should be considered with caution due to the limited number of patients (N=30) in ADA 8 weeks positive subgroup.
2. The high titer immunogenicity positive subgroup did not show significant reduced efficacy compared with the immunogenicity negative or low titer subgroup. However, the result should be considered with caution due to the limited number of patients (N=11) in high titer subgroup.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Cytokine Release Syndrome

Data:

To ensure consistency, this section summarizes programmatically derived CRS using the ASTCT 2019 consensus criteria rather than investigator-reported CRS.

In Study 202, which forms the largest dataset of programmatically derived CRS events, 89% of patients experienced any grade CRS. Most patients had Grade 1 (12%) or Grade 2 (76%) CRS. One patient (0.4%) in the tebentafusp treatment arm had an event of CRS that resulted in discontinuation of study drug. The incidence of Grade 3 CRS was 0.8% (2 patients). There was no Grade 4 CRS or death due to CRS. Common symptoms of CRS included pyrexia (64.9%), hypotension (24.9%) and infrequently hypoxia (0.4%). Other commonly associated symptoms included chills (29%), nausea (19.6%), vomiting (13.5%), fatigue (12.2%), and headache (10.6%).

Table 58 summarizes AESI of CRS programmatically identified as per ASTCT 2019 CRS consensus grading for tebentafusp in UM patients for Studies 102 and 202 and both studies combined. In Study 202, the maximum Grade 1 - 4 CRS were: 29 (11.84%), 186 (75.92%), 2 (0.82%), and 0 (0%), (respectively).

Table 58: Adjudicated CRS by Study and Maximum Grade (Safety Analysis Set)

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

Table 59 summarizes time to onset of AESI of CRS in UM Patients for individual studies and all studies combined.

Table 59: Time to Onset of First Adverse Event of Special Interest - CRS (Safety Analysis Set)

Parameter	Study 01 All Doses (N = 19)	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) ^a
Time to treatment emergent AESI (any grade), days					
n	NA	18	109	217	344
Mean (SD)	NA	1.6 (1.88)	6.0 (25.54)	3.0 (16.76)	3.9 (19.61)
Median (min, max)	NA	1.0 (1, 9)	1.0 (1, 218)	1.0 (1, 225)	1.0 (1, 225)
Time to treatment emergent AESI (grade ≥ 2), days					
n	NA	15	66	188	269
Mean (SD)	NA	3.9 (4.35)	14.9 (67.40)	2.1 (3.32)	5.4 (33.76)
Median (min, max)	NA	1.0 (1, 15)	1.0 (1, 505)	1.0 (1, 30)	1.0 (1, 505)
Time to treatment emergent AESI (grade ≥ 3), days					
n	NA	0	5	2	7
Mean (SD)	NA	-	3.8 (3.83)	11.5 (14.85)	6.0 (7.79)
Median (min, max)	NA	-	1.0 (1, 8)	11.5 (1, 22)	1.0 (1, 22)

AESI = adverse event of special interest; NA = not applicable; SD = standard deviation.

^a Includes only Studies 102 and 202.

Only those patients who have a treatment emergent AESI are included.

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Treatment-emergent adverse events are defined as any adverse event with a start date from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.

CRS is based on the adjudication of potential CRS episodes in Studies 102 and 202 only using the ASTCT consensus CRS grading criteria.

All other AESIs are graded according to CTCAE (version 4.03).

Source: Module 5.3.5.3, Table ISS 02.03.08.04.01.

The Applicant's Position:

CRS is an important identified risk based on the mechanism of action of tebentafusp. CRS was graded based on the ASTCT consensus grading for CRS (Lee, 2019).

Most cases of CRS occurred approximately within 1 day of tebentafusp infusion and mostly after the first initial doses of tebentafusp. There were too few patients with Grade ≥ 3 CRS to reliably interpret a median time to onset or resolution. The incidence and severity decreased with repeated dosing. In the vast majority of cases, CRS started the day of infusion. Pyrexia was noted in nearly all cases of CRS, and in these patients, an increase in body temperature generally occurred within the first 8 to 10 hours after tebentafusp infusion. CRS rarely (1.2%) led to treatment discontinuation. Most cases of CRS of any grade or Grade ≥ 2 severity, resolved by the day after most recent tebentafusp infusion.

The FDA's Assessment:

Cytokine release syndrome (CRS) is an expected class safety issue for biological products that engage T-cells. Drug-induced CRS is a clinical diagnosis based on fever $\geq 38^{\circ}\text{C}$ 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 (Shimabukuro-Vorhagen, 2018). CRS can start within minutes or hours of the first dose and up to 14 days after infusion, depending on the specific drug 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 multiple system organ dysfunction.

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

There are multiple grading systems for CRS in use. Initially, in Study 102 and Study 202, reporting of CRS was based on NCI CTCAE 4.03 criteria, shown in Table 60. In October 2017, the Lee CRS grading criteria (Lee, 2014), shown in Table 61, was incorporated into both studies.

Table 60: CTCAE 4.03 Cytokine Release Syndrome Grading Criteria

Grade	Symptoms
1	Mild reaction; infusion interruption not indicated intervention not indicated
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.
3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)
4	Life-threatening consequences; pressor or ventilatory support indicated
5	Death

Table 61: Lee Cytokine Release Syndrome Grading Criteria¹

Grade	Symptoms
1	Symptoms are not life-threatening and require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, and malaise)
2	Symptoms require and response to moderate intervention: • Oxygen requirement < 40% • Hypotension responsive to fluids or 1 low-dose vasopressor • Grade 2 organ toxicity
3	Symptoms require and response to aggressive intervention: • Oxygen requirement > 40% • Hypotension requiring high-dose or multiple vasopressors • Grade 3 organ toxicity • Grade 4 transaminitis
4	Life-threatening symptoms • Requirement for ventilator support • Grade 4 organ toxicity (excluding transaminitis)
5	Death

¹ Lee et. al, 2014

In Study 202, based on investigator assessed TEAE reporting, 51 patients (21%) had at least one event of CRS, with 20 patients (8%) having a maximum Grade 1 event, 29 patients (12%) having a maximum Grade 2 event, and 2 patients (0.8%) having a maximum Grade 3 event. There were no investigator-reported Grade 4 or 5 CRS events. There were no investigator-reported cases of

infusion-related reactions. One patient had an event of CRS that resulted in discontinuation of study drug.

To support a more complete analysis of CRS associated with tebentafusp, the Applicant performed a retrospective analysis based on ASTCT 2019 CRS grading criteria, shown in Table 62. For the analysis, the Application utilized investigator TEAE reporting, vital signs, concomitant medications, and laboratory assessments to identify potential cases of CRS. To identify potential cases of CRS, the Applicant considered the following for each patient infusion:

- Investigator report of a SAE of any of the following preferred terms on the day of the infusion and up to 2 days afterwards: cytokine release syndrome, cytokine storm, infusion related reaction, pulmonary edema, adverse drug reaction, hypersensitivity reaction, drug hypersensitivity, systemic inflammatory response syndrome, acute distress syndrome event.
- Fever: considered positive if patient had an investigator report of “pyrexia” or “tachycardia” on the day of the infusion or up to 2 days afterwards OR patient received an antipyretic as recorded in the concomitant medications on the day of the infusion and up to 3 days afterwards OR patient had record of maximum temperature $\geq 38^{\circ}$ C as recorded in the vital signs on the day of or within 2 days of the infusion.
- Hypotension: considered positive if the patient had an investigator report of “hypotension” or “diastolic hypotension” OR systolic blood pressure < 90 mm/Hg as recorded in the vital signs on the day of or within 2 days of the infusion.
- Hypoxia: considered positive if the patient had an investigator report of “hypoxia”, “acute respiratory syndrome”, or “dyspnea” on the day of or within 2 days of the infusion OR the patient received oxygen as reported in the concomitant medications on the day of or within 3 days of the infusion.
- Vasopressor use: considered positive if the patient received norepinephrine, epinephrine, dopamine, dobutamine, vasopressin, or phenylephrine as reported in the concomitant medications on the day of or within 3 days of the infusion.
- Steroid use: considered positive if the patient received a corticosteroid for systemic use as reported in the concomitant medications on the day of or within 3 days of the infusion.
- IV Fluid use: considered positive if the patient received fluids via IV as reported in the concomitant medications on the day of or within 3 days of the infusion.

A spreadsheet of these events was then evaluated by a panel of oncologists experienced with CRS which graded each potential case based on the information provided. Additional information for pre and post vital signs was available. Out of the initial 1127 records of potential cases of CRS in the tebentafusp arm, the panel assessed 805 events occurring in 217 patients as being $\geq$ Grade 1. The remaining records did not meet ASCTC criteria for CRS. Thus, 89% of patients (217/245) in the tebentafusp arm had at least 1 episode of CRS based on an algorithmic adjudication process using ASCTC consensus criteria. The cases comprised 29 patients (12%) with maximum Grade 1 CRS, 186 patients (76%) with maximum Grade 2 CRS, and 2 patients (0.8%) with maximum Grade 3 CRS. There were no Grade $\geq$ 4 events.

Table 62: ASCTC 2019 Cytokine Release Syndrome Consensus Grading Criteria¹

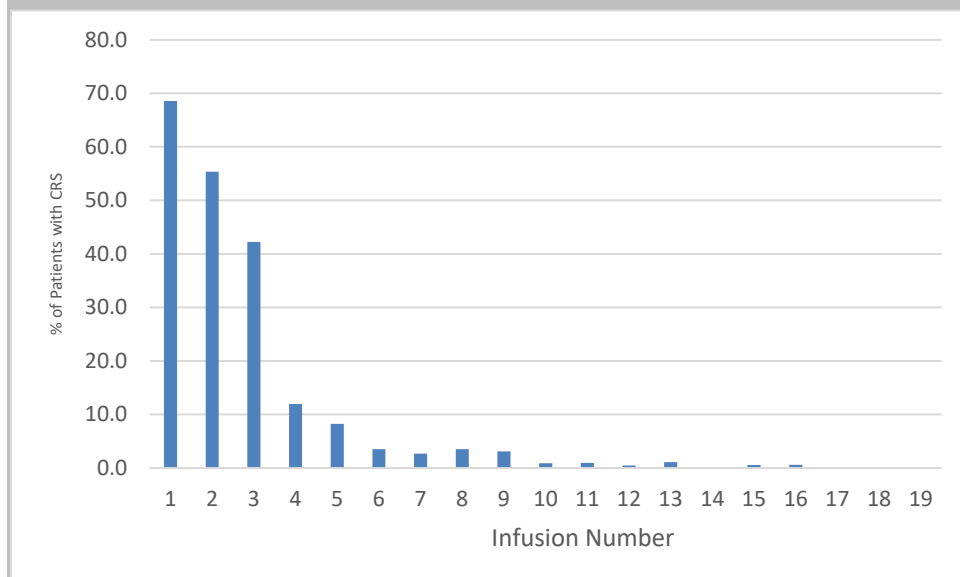
Grade	Symptoms
1	• Temperature $\geq 38^{\circ}$ C (not attributable to other cause) with • No hypotension, hypoxia
2	• Temperature $\geq 38^{\circ}$ C (not attributable to other cause) with • Hypotension not requiring vasopressors and/or • hypoxia requiring low-flow nasal canula or blow-by
3	• Temperature $\geq 38^{\circ}$ C (not attributable to other cause) with • Hypotension requiring a vasopressor with or without vasopressin and/or • hypoxia requiring high-flow nasal canula, facemask, nonrebreather mask, or venturi mask
4	• Temperature $\geq 38^{\circ}$ C (not attributable to other cause) with • Hypotension requiring multiple vasopressors (excluding vasopressin) and/or • hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation).

¹ Lee et. al., 2019a

An analysis of CRS events by infusion number (week number) shows that the percentage of patients experiencing Grade $\geq$ 2 CRS (out of the total number of patients receiving tebentafusp that week) is highest during the first 3 infusions with the frequency dropping off drastically after infusion 3 (Cycle 1 Day 15). This is shown in Figure 41 below.

A patient could have more than one CRS event. Considering only Grade $\geq$ 2 events, the median number of CRS events for an individual patient was 2 with a range of 1 to 12 events.]

Figure 41: Percentage of Patients Receiving Tebentafusp By Week With Grade 2-4 Cytokine Release Syndrome: Study 202¹



Source: Reviewer Figure: Study 202 ADCRS, ADEX - 2021-04-21

¹ Percentage calculated as number of patients with CRS events at time point/ total number of patients receiving tebentafusp infusion at time point.

The primary interventions used for CRS are oxygen, IV fluids, steroids, and vasopressor(s). The percentage of patients requiring these interventions for CRS related to at least 1 infusion is shown in Table 63. The most commonly administered intervention was IV fluids with 40% of patients receiving IV fluids for at least one infusion. Twenty-four percent (24%) of patients on the tebentafusp arm received steroids for CRS related to at least 1 infusion. Use of oxygen and vasopressor(s) were rare.

Table 63: Percentage of Patients Requiring Interventions for CRS: Study 202 Tebentafusp Arm

Intervention	Tebentafusp N = 245 n (%)
Oxygen	20 (8)
IV Fluids	98 (40)
Steroids	60 (24)
Vasopressor	3 (1.2)

Source: Reviewer Figure: Study 202 ADCRS - 2021-04-21

Table 64 summarizes narratives for the 4 patients who received tebentafusp on Study 202 who had a Grade 3 event of CRS either by investigator reporting (2 patients) or Applicant-adjudicated identification using ASCTC criteria (2 patients).

Table 64: Narratives for Grade 3 Cytokine Release Syndrome Study 202 Tebentafusp Arm

Patient ID	Narrative Summary
(b) (6) Source: Investigator Reporting (Lee's Criteria)	66 year old woman who received 1 dose of tebentafusp. Following the dose, the patient experienced an SAE of Grade 3 CRS. Signs and symptoms included pyrexia, hypotension, and dyspnea. The patient was treated with IV fluids, hydrocortisone, oxygen (< 6 L/min), and acetaminophen. No use of vasopressors was reported. The patient also experienced transient Grade 3 transaminase increase, Grade 3 atelectasis, and Grade 3 metabolic acidosis. The event of CRS resolved 5 days after onset.
(b) (6) Source: Investigator Reporting (Lee's Criteria)	The patient experienced an SAE of Grade 3 CRS after the first dose of tebentafusp. Signs and symptoms included pyrexia, hypotension, shaking, and vomiting. The patient was treated with methylprednisolone and IV fluids. No use of vasopressors was reported. The event of CRS resolved 2 days after onset. The patient received a total of 16 doses of tebentafusp and discontinued due to disease progression.
(b) (6) Source: Applicant-adjudicated (ASCTC criteria)	68 year old gentleman who experienced Grade 3 CRS following C2D1 dosing of tebentafusp. Signs and symptoms included pyrexia and hypotension. The patient was treated with IV fluids, acetaminophen, and oxygen (94%-98% fraction of inspired oxygen). The event of CRS resolved the next day. The patient received a total of 20 doses of tebentafusp and discontinued due to disease progression.
(b) (6) Source: Applicant-adjudicated (ASCTC criteria)	58 year old woman who experienced Grade 3 CRS following the first dose of tebentafusp. Signs and symptoms included pyrexia, hypotension, and dyspnea. The patient was treated with IV fluids and dopamine. Hypotension resolved the following day. The patient received a total of 14 doses of tebentafusp and discontinued due to progressive disease.
Source: Reviewer summaries based on Narratives submitted with Study 202 CSR and Clinical Summary of Safety	

Reviewer Comment: The actual frequency of CRS in patients receiving tebentafusp is not known. The investigator reporting of 21% of patients with at least one CRS event likely underestimates the frequency, while the ASCTC based Applicant adjudicated calculation of 89% of patients having at least one CRS event likely overestimates the frequency. The true frequency may be closer to the 77% calculation which considers only Grade ≥ 2 ASCTC Applicant

adjudicated CRS. Analysis of only Grade ≥ 2 events is reasonable as patients with Grade 1 CRS do not require intervention beyond possible administration of antipyretic.

While CRS is common in patients receiving tebentafusp, Grade 3 events were rare, and across Studies 202 and 102, there was only 1 case of Grade 4 CRS in which a patient developed multi-organ system failure. While the CRS resolved, the multi-organ system failure persisted and was ongoing at the time the patient died from progressive disease.

While use of IV fluids on Study 202 was common and may have reflected protocol guidelines which specified IV fluids for Grade 1 hypotension and allowed administration of IV fluids prior to tebentafusp administration, use of oxygen and vasopressor(s) were rare.

Because CRS has the potential to be a serious and fatal condition, CRS has been included in Section 5 (Warnings and Precautions) and in a Black Box warning in the USPI to inform prescribers of the association between tebentafusp and CRS. The labeling provides information with respect to monitoring and treatment of CRS. Immunocore has also voluntarily developed a communication plan to inform clinicians who will prescribe tebentafusp regarding the risk of CRS.

8.2.5.2 Acute Skin Reactions

Data:

Table 65 provides an overall summary of AESI of acute skin reactions for UM Patients across individual studies and all studies combined.

Table 65: Uveal Melanoma Patients: Overall Summary of Adverse Events of Special Interest - Acute Skin Reactions (Safety Analysis Set)

Patients with	Study 01 All Doses (N = 19)	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 = 410)
Any TEAE	18 (94.7%)	17 (89.5%)	120 (94.5%)	224 (91.4%)	379 (92.4%)
TEAE by highest CTCAE Grade					
1	4 (21.1%)	1 (5.3%)	43 (33.9%)	68 (27.8%)	116 (28.3%)
2	7 (36.8%)	10 (52.6%)	53 (41.7%)	107 (43.7%)	177 (43.2%)
3	7 (36.8%)	6 (31.6%)	24 (18.9%)	49 (20.0%)	86 (21.0%)
4	0	0	0	0	0
5	0	0	0	0	0
Any TEAE causally related tebentafusp ^a	17 (89.5%)	17 (89.5%)	119 (93.7%)	224 (91.4%)	377 (92.0%)

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Patients with	Study 01 All Doses (N = 19)	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 = 410)
Any TEAE with maximum CTCAE of Grade 3 or 4	7 (36.8%)	6 (31.6%)	24 (18.9%)	49 (20.0%)	86 (21.0%)
Any TEAE with maximum CTCAE of Grade 4	0	0	0	0	0
Any TEAE with maximum CTCAE of Grade 3 or 4 and causally related to tebentafusp ^a	7 (36.8%)	6 (31.6%)	24 (18.9%)	49 (20.0%)	86 (21.0%)
Any serious TEAE	0	0	4 (3.1%)	14 (5.7%)	18 (4.4%)
Any serious TEAE causally related to tebentafusp ^a	0	0	4 (3.1%)	14 (5.7%)	18 (4.4%)
A TEAE leading to permanent discontinuation of tebentafusp	0	0	0	0	0
A TEAE leading to permanent discontinuation of tebentafusp and causally related to tebentafusp ^a	0	0	0	0	0
Any TEAE leading to drug interruptions of tebentafusp	0	1 (5.3%)	3 (2.4%)	5 (2.0%)	9 (2.2%)
Any TEAE leading to drug interruptions of tebentafusp that were causally related to tebentafusp ^a	0	1 (5.3%)	3 (2.4%)	4 (1.6%)	8 (2.0%)
Any TEAE leading to dose reductions of tebentafusp	0	0	0	5 (2.0%)	5 (1.2%)
Any TEAE leading to dose reductions of tebentafusp that were causally related to tebentafusp ^a	0	0	0	5 (2.0%)	5 (1.2%)
A TEAE leading to death	0	0	0	0	0
A TEAE leading to death and causally related to tebentafusp ^a	0	0	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events (version 4.03); TEAE = treatment-emergent adverse event.

^a Determined by the investigator to be possibly related, probably related, definitely related, or related to tebentafusp.

TEAEs are defined as any AE with a start date from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.

Acute skin reactions are specified by a sponsor-provided list of preferred terms.

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Patients with	Study 01 All Doses (N = 19)	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 = 410)

Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

Serious adverse events (SAEs) include deaths as an outcome of SAEs and non-fatal SAEs.

All other AESIs are graded according to CTCAE (version 4.03).

Source: Module 5.3.5.3, Table ISS 02.03.08.01.01.

Table 66 summarizes AESI of acute skin reactions considered to be related to study drug in $\geq 10\%$ of UM Patients for individual studies and all studies combined.

Table 66: Uveal Melanoma Patients: Drug-related Adverse Events of Special Interest Reported in ≥ 10% of Patients in Any Study – Acute Skin Reactions (Safety Analysis Set)

TEAE of Special Interest Category Sub-category Preferred Term	Study 01 All Doses (N = 19)	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 = 410)
Acute skin toxicities TEAE of special interest causally related to tebentafusp^a	17 (89.5%)	17 (89.5%)	119 (93.7%)	224 (91.4%)	377 (92.0%)
Rash	16 (84.2%)	15 (78.9%)	112 (88.2%)	203 (82.9%)	346 (84.4%)
Rash	12 (63.2%)	5 (26.3%)	54 (42.5%)	135 (55.1%)	206 (50.2%)
Rash maculo-papular	6 (31.6%)	1 (5.3%)	50 (39.4%)	74 (30.2%)	131 (32.0%)
Skin exfoliation	7 (36.8%)	1 (5.3%)	28 (22.0%)	50 (20.4%)	86 (21.0%)
Rash erythematous	6 (31.6%)	2 (10.5%)	5 (3.9%)	12 (4.9%)	25 (6.1%)
Rash pruritic	1 (5.3%)	4 (21.1%)	5 (3.9%)	15 (6.1%)	25 (6.1%)
Rash macular	0	8 (42.1%)	0	7 (2.9%)	15 (3.7%)
Dermatitis acneiform	0	2 (10.5%)	8 (6.3%)	1 (0.4%)	11 (2.7%)
Rash papular	0	3 (15.8%)	2 (1.6%)	5 (2.0%)	10 (2.4%)
Blister	0	2 (10.5%)	2 (1.6%)	5 (2.0%)	9 (2.2%)
Dermatitis bullous	0	4 (21.1%)	1 (0.8%)	4 (1.6%)	9 (2.2%)
Pruritis	12 (63.2%)	17 (89.5%)	94 (74.0%)	169 (69.0%)	292 (71.2%)
Pruritis	12 (63.2%)	17 (89.5%)	94 (74.0%)	169 (69.0%)	292 (71.2%)
Erythema	4 (21.1%)	11 (57.9%)	36 (28.3%)	66 (26.9%)	117 (28.5%)
Erythema	4 (21.1%)	10 (52.6%)	35 (27.6%)	56 (22.9%)	105 (25.6%)
Photosensitivity reaction	0	3 (15.8%)	2 (1.6%)	7 (2.9%)	12 (2.9%)
Oedema	8 (42.1%)	12 (63.2%)	39 (30.7%)	45 (18.4%)	104 (25.4%)
Periorbital oedema	8 (42.1%)	12 (63.2%)	34 (26.8%)	26 (10.6%)	80 (19.5%)

n = number of patients; TEAE = treatment-emergent adverse event.

^a Determined by the investigator to be possibly related, probably related, definitely related, or related to tebentafusp.

Patients with multiple TEAEs of special interest per category or PT are counted only once in each row.

AEs are coded using MedDRA version 23.1.

TEAEs are defined as any AE with a start date from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.

Number (%) of patients are sorted by sponsor-provided order for category and by descending frequency overall for PT. A patient can have one or more PTs reported under a given category.

Acute skin toxicities are specified by a sponsor-provided list of preferred terms.

Source: Module 5.3.5.3, Table ISS 02.03.08.03.01.

The Applicant's Position:

Acute skin reactions have been reported with tebentafusp infusion, likely based on its mechanism of action and gp100 expression in normal melanocytes in the skin.

For all studies combined, 379 patients (92.4%) experienced an event of acute skin reaction. Of the 379 patients, 377 patients (92.0%) reported an acute skin reaction that was considered related to study drug. CTCAE Grade 3 acute skin reaction events considered related to study drug were reported in 86 patients (21.0%). Serious TEAEs of acute skin reactions considered drug related were reported in 18 patients (4.4%). No patients experienced a TEAE of acute skin reaction that led to discontinuation or death. TEAEs (PTs) of acute skin reaction with the highest incidence ($\geq 10\%$ of patients in tebentafusp arm) were pruritus (71.2%), rash (50.2%), rash maculo-papular (32.0%), erythema (25.6%), skin exfoliation (21.0%), and periorbital oedema (19.5%).

Acute skin reactions typically occurred following each of the first three infusions, with decreasing severity and frequency. The median time to onset of acute skin reactions was 1 day in the tebentafusp treated patients and median time to improvement to $\leq$ Grade 1 was 6 days. There were no discontinuations of tebentafusp due to acute skin reactions. Majority of symptoms resolved without any systemic corticosteroid or any long term sequelae. No cases of Stevens-Johnson syndrome or toxic epidermal necrolysis were reported.

Acute skin reactions were managed with antihistamine and topical corticosteroids. Systemic steroids were used for persistent or severe symptoms.

The FDA's Assessment:

Acute skin reactions associated with tebentafusp include the subcategories of rash, pruritis, pigment change, erythema, edema, dry skin, and other changes.

The list of PTs for the composite term rash used by the Applicant Study 202 included blister, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, dermatosis, drug eruption, eczema, eczema eyelids, erythema multiforme, excoriation, exfoliative rash, interstitial granulomatous dermatitis, lichenification, lichenoid keratosis, palmar-plantar erythrodysesthesia syndrome, papule, prurigo, psoriasis, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, seborrhoea, seborrheic dermatitis, skin abrasion, skin erosion, skin exfoliation, skin irritation, skin plaque, solar dermatitis, toxic skin eruption, and urticaria.

FDA agrees with the composition of the Applicant's group term rash. FDA validated the frequency for the AESI skin toxicity and the individual component PTs for Study 202 without regard to investigator assigned causality. Table 67 summarizes the frequency of rash (composite term) by grade for Study 202. There were no Grade ≥ 4 events. In the tebentafusp arm, 12 patients (4.9%) had AESI of rash that were considered SAEs, 4 patients (1.6%) had AESI

of rash that resulted in study drug being held, while no patient discontinued study treatment due to AESI of rash.

Table 67: Frequency of Rash by Grade: Study 202

Arm	Any Grade n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)
Tebentafusp (N=245)	203 (83)	66 (27)	92 (38)	45 (18)
IC (N=111)	31 (28)	24 (22)	7 (6)	0

To provide more meaningful information to clinicians and patients, FDA reanalyzed the group term hypo/hyper pigmentation as follows:

- Skin hypopigmentation comprising the PTs skin depigmentation, skin hypopigmentation, vitiligo, pigmentation disorder (for the PT pigmentation disorder, the AE was determined to be hypo or hyper based on actual term reported by the investigator)
 - o 68 patients (28%) in the tebentafusp arm on study 202 had skin hypopigmentation compared to 6 patients (5%) in the IC arm.
- Skin hyperpigmentation comprising the PTs ephelides, lentigo, skin hyperpigmentation, solar lentigo, and pigmentation disorder (for pigmentation disorder, the AE was determined to be hypo or hyper based on actual term reported by the investigator)
 - o 29 (12%) of patients in the tebentafusp arm had skin hyperpigmentation compared to 2 patients (1.8%) in the IC arm.
- Hair color changes comprising the PTs: eyelash discolouration and hair colour change.
 - o 49 patients (20%) in the tebentafusp arm had hair color changes compared to no patients in the IC arm.

These grouped terms were incorporated into the USPI.

Reviewer Comment: FDA agrees with the Applicant's assessment of skin toxicity. Although common, skin toxicity did not result in treatment discontinuation or fatalities. While 3 patients (1.2%) had TEAEs of erythema multiforme, 2 were Grade 1 and 1 was Grade 2. There were no cases of Stevens-Johnson Syndrome or Drug Rash with Eosinophilia and Systemic Symptoms (DRESS). Due to the frequency of events, Skin Reactions were included in Section 5 (Warnings and Precautions) of the USPI.

8.2.5.3 Liver Function Test Evaluations

The Applicant's Position:

LFT elevations are not uncommon in mUM since the liver is the predominant site of hematogenous spread from uveal melanoma. Tumor progression within the liver can result in liver injury with a rise in LFTs (Diener-West 2004, Eskelin 1999).

Hepatocytes do not express gp100 and tebentafusp did not redirect T cells against normal hepatocytes in nonclinical in vitro studies. However, treatment with tebentafusp may result in transient secondary effects from tebentafusp-induced inflammation in mUM liver lesions, including either activated immune cells (e.g., T cells) or cytokines.

Due to the number of patients enrolled, optimal schedule of laboratory collection and comparative AE and laboratory data, Study 202 provides the best reference for characterization of changes of laboratory values over time and reporting of adverse events.

In Study 202, based on investigator reported target and non-target lesions, greater than 95% of patients had baseline liver metastases and nearly two thirds of tebentafusp treated patients (158/245; 64.5%) and approximately half of investigator choice treated patients (53/111; 47.7%) had an increase in post-baseline grade of ALT/AST. Although numerically higher, the majority of ALT/AST elevations in the tebentafusp treatment arm were mild, occurred early, and did not result in treatment discontinuation. Since most patients had pre-existing liver metastases, LFT elevations may be secondary to T cell redirection into liver metastases.

No deaths due to ALT/AST elevations were observed and more than 90% of patients were able to continue treatment beyond worst grade ALT/AST elevation. Most patients experiencing Grade 3 or 4 ALT/AST elevations had improvement to $\leq$ Grade 1 within 7 days. Elevations in bilirubin have been reported in 27% of patients and these were primarily associated with increase in size of liver metastasis.

Across all studies, patients with largest liver lesion $\geq$ 3 cm or values $>$ upper limit of normal (ULN) for LDH and alkaline phosphatase (ALP) at baseline were at higher risk of developing elevated LFTs during treatment. However, this may have been due to the poor prognostic nature of these baseline variables and that these patients are more likely to have disease progression of their liver lesions as a likely cause of the on-treatment LFT increase.

The FDA's Assessment:

The Applicant identified cases of hepatotoxicity using the Standardized MedDRA Query (SMQ, Broad and narrow) Drug related hepatic disorders. Table 68 summarizes drug related hepatic disorders by grade for Study 202. In the tebentafusp arm, 11 patients (4.4%) had hepatotoxicity AESIs, as identified by SMQ, that were SAEs. In the tebentafusp arm, hepatotoxicity AESIs, as identified by SMQ, resulted in withholding of study drug in 13 (5%) of patients and permanent discontinuation of study treatment in 1 patient (0.4%).

Worsening laboratory assessments from baseline are presented in Table 57. While the majority of patients on the tebentafusp arm had a worsening of AST and/or ALT, only 12% and 8% respectively worsened to Grade 3, and only 0.4% and 0.8% of patients respectively had maximum toxicity Grade 4.

Table 68: Drug related hepatic disorders (SMQ) by grade: Study 202

Arm	Any Grade n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Tebentafusp (N=245)	99 (40)	43 (18)	27 (11)	28 (11)	1 (0.4)
IC (N=111)	32 (29)	11 (10)	14 (13)	7 (6)	0

Reviewer Comment: Abnormalities in liver tests were common in patients receiving tebentafusp. This may have been due to CRS or underlying liver metastases. Overall, however, the abnormalities were mild and did not require discontinuation of study treatment. However, due to the frequency of events and the potential for serious outcomes Elevated Liver Enzymes were included in Section 5 (Warnings and Precautions) of the USPI.

8.2.5.4 Eye Disorders

Data:

Patients with UM have baseline recurrent or persistent local ocular events relating to their primary treatment (e.g., enucleation, complication of RT, intravitreal anti-VEGF therapy). In addition, eye disorders were initially identified as a risk since gp100 positive intra-ocular melanocytes could serve as a target for tebentafusp which in theory may lead to uveitis or vision changes. As a result, detailed baseline and on-study ophthalmologic exams were incorporated into Study 01.

No concerning or related intra-ocular clinical findings or overt vision changes were identified per detailed ophthalmologic exams. Most reported eye AEs were extra-ocular and due to inflammation or peri-orbital skin AEs, including periorbital oedema (41 patients, 48.8%), eye pain (3 patients, 3.6%), and eye pruritus (3 patients, 3.6%). All reported ophthalmologic AEs were of CTCAE Grade 1 or 2. The periorbital AEs are consistent with tebentafusp redirecting T cells to gp100-positive melanocytes in the skin, do not impact vision, are reversible and have been observed in tebentafusp treated patients in all studies.

In Study 202, a total of 79 patients (32.2%) in the tebentafusp arm and 15 patients (13.5%) in the investigator's choice arm had events in the SOC of eye disorders. Events with the highest incidence ($\geq 3\%$ of patients in either the tebentafusp or investigator's choice arms) were periorbital edema (10.6% vs 0.9%) and lacrimation increased (3.3% vs 1.8%). Grade ≥ 3 events were reported in 3 patients (1.2%) in the tebentafusp arm and 2 patients (1.8%) in the investigator's choice arm and included cataract, eye pain, glaucoma (0.4% vs 0% each), retinal

detachment and uveitis (0% vs 0.9% each). Events were considered treatment-related by the investigator in 60 patients (24.5%) in the tebentafusp arm and 6 patients (5.4%) in the investigator's choice arm. Treatment-related events of Grade ≥ 3 severity were reported in 2 patients (0.8%) and 1 patient (0.9%), respectively; these events were cataract and eye pain in the tebentafusp arm and uveitis in the investigator's choice arm.

The Applicant's Position:

Serious eye disorders were reported in 2 patients (0.8%) in the tebentafusp arm and 1 patient (0.9%) in the investigator's choice arm who received pembrolizumab. The SAEs were diplopia (Patient (b) (6)) and periorbital edema (Patient (b) (6)) in the tebentafusp arm and uveitis (Patient (b) (6)) in the investigator's choice arm. All SAEs were considered treatment-related and the events of periorbital edema and uveitis resolved. None of the events in the eye disorders SOC resulted in study drug discontinuation.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of eye disorders.

8.2.5.5 Cardiac Disorders

Data:

In Study 102 in the Phase 1 dose escalation cohorts, cardiac disorders (regardless of causality) were reported in 4 (21.1%) patients. Cardiac AEs related to ECG abnormalities included tachycardia in 2 (10.5%) patients and sinus tachycardia in 1 (5.6%) patient; these events were Grade 1 or 2 in severity, non-serious, and did not result in discontinuation of study drug.

In Study 102 in the Phase 2 dose expansion cohort, cardiac disorders (regardless of causality) were reported in 38 (29.9%) patients. The most commonly reported ($> 1\%$ of patients) cardiac AEs related to ECG abnormalities were tachycardia (11.8%), sinus tachycardia in (9.4%), sinus bradycardia (3.9%), atrial fibrillation (3.1%), and atrial flutter (2.4%), and supraventricular tachycardia (1.6%). No AEs of torsades de pointes were reported. Cardiac AEs of Grade ≥ 3 severity were reported in 7 patients (5.5%); events related to ECG abnormalities (each in 1 patient, 0.8%) included Grade 3 and Grade 4 atrial fibrillation, atrial flutter, and tachycardia; all were considered treatment-related. Two patients experienced cardiac AEs that led to treatment discontinuation: one patient with grade 4 atrial fibrillation after day 1 of study treatment [Patient (b) (6)] and a second patient with grade 3 left ventricular dysfunction after day 8 of study treatment [Patient (b) (6)]. Both of these cardiac AEs occurred in the setting of sponsor assessed Grade 3 CRS and were considered related to tebentafusp treatment by the investigator. No events of Grade 5 severity were reported. Five patients experienced SAEs related to ECG abnormalities.

In Study 202, a total of 37 patients (15.1%) in the tebentafusp arm and 8 patients (7.2%) in the

investigator's choice arm had events in the SOC of cardiac disorders. The event with the highest incidence ($\geq 3\%$ of patients in either the tebentafusp or investigator's choice arms) was tachycardia (9.8% vs 2.7%). Events were considered treatment-related by the investigator in 27 patients (11.0%) in the tebentafusp arm and 3 patients (2.7%) in the investigator's choice arm. All treatment-related events were Grade 1 or 2 in severity and included tachycardia (9.0% vs 0%), sinus tachycardia (2.4% vs 0.9%), atrioventricular block, bradycardia (0.4% vs 0% each), and palpitations (0% vs 1.8%). There were no clinically meaningful trends in ECG findings and associated cardiac AEs in either treatment arm.

The Applicant's Position:

During the pre-BLA administrative meeting, the US FDA requested that along with QT assessment, narratives for patients with arrhythmias, syncope, or with QTcF values > 500 msec should be provided with the BLA submission.

Given tebentafusp induces mild to moderate CRS, not surprisingly, the most frequent cardiac AEs were pyrexia, hypotension and tachycardia. Due to the anticipated risk of hypotension, Studies 102 and 202 required patients with pre-existing hypertension to temporarily suspend anti-hypertensive medications prior to the first few doses. Therefore, hypertension resulting from interruption of daily anti-hypertensives was occasionally observed during the first few weeks of treatment and reported as an AE. This hypertension is considered an iatrogenic AE and distinct from the mechanism of action of tebentafusp.

Serious cardiac disorders were reported in 0 patients in the tebentafusp arm and 1 patient (0.9%) in the investigator's choice arm. The patient in the investigator's choice arm who received dacarbazine (Patient (b) (6)) had a serious event of left ventricular dysfunction that resulted in study drug discontinuation and death; the event was considered as not related to study drug. Besides the event of left ventricular dysfunction on the investigator choice arm, none of the other events in the cardiac disorders SOC resulted in study drug discontinuation.

In Study 102 and Study 202, there were no clinically meaningful trends in ECG findings and associated cardiac AEs.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of cardiac toxicity.

8.2.5.6 Neurotoxicity

The FDA's Assessment

Neurotoxicity, including potentially life-threatening or fatal events, is an identified complication associated with T-cell engager therapies, including anti-CD19 CAR-T cells, bi-specific T cell engagers (Zheng et. al., 2019). Although neurotoxicity was not considered an AESI for Study 202

based on prior clinical experience, based on mechanism of action, FDA performed a separate assessment of the risks of neurotoxicity for Study 202.

The table below shows the frequency of neurotoxicities, which includes all PTs in the SOC “Nervous System Disorders”, with the exclusion of terms clearly related to structural pathology e.g, carpal tunnel syndrome, cerebral cyst, CSR fluid circulation disorder, intracranial aneurysm, intracranial mass, perineurial cyst, sciatica, spinal cord compression.

Neurotoxicities were frequent on Study 202. A higher percentage of patients in the tebentafusp arm (51%) had at least one neurotoxicity TEAE, any grade, compared to 24% in the IC arm; however, Grade 3-4 events were rare on either arm with only 2.4% of patients in the tebentafusp arm having at least one Grade 3 or 4 event. There were no fatal neurotoxicity TEAEs on either arm. In the tebentafusp arm, 4 patients (1.6%) had a neurotoxicity SAE while in the IC arm, 1 patient (0.9%) had a neurotoxicity SAE in the ICC arm. The SAEs in the tebentafusp arm were motor dysfunction, dizziness, brain edema, and presyncope.

The table below shows the most common neurotoxicity TEAEs. With the exception of headache and paraesthesia, the frequencies for these TEAEs is similar between arms.

Most Frequent ($\geq 1\%$ of patients in tebentafusp arm) Neurotoxicities¹ Observed on Study 202

PT	Tebentafusp N=245		IC N=111	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Any TEAE	124 (51)	6 (2.4)	28 (25)	4 (3.6)
Headache	74 (30)	1 (0.4)	11 (10)	1 (0.9)
Dizziness	27 (11)	0	9 (8)	1 (0.9)
Paraesthesia	27 (11)	0	1 (0.9)	0
Dysgeusia	12 (4.9)	0	3 (2.7)	0
Memory impairment	7 (2.9)	0	0	0
Presyncope	5 (2.0)	1 (0.4)	1 (0.9)	0
Tremor	5 (2.0)	0	2 (1.8)	0
Neuropathy peripheral	4 (1.6)	0	1 (0.9)	1 (0.9)
Hypoaesthesia	3 (1.2)	0	1 (0.9)	0
Lethargy	3 (1.2)	0	2 (1.8)	0
Peripheral sensory neuropathy	3 (1.2)	0	1 (0.9)	0

Source: Reviewer Table: Study 202 ADSL (Subject-Level Analysis Dataset) - 2021-04-21, ADAE (Adverse Events Analysis Dataset) - 2021-04-21. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEBODSYS

¹ Includes Preferred Terms in the SOC Nervous System Disorders not including PTs related to structural pathology e.g, carpal tunnel syndrome, cerebral cyst, CSR fluid circulation disorder, intracranial aneurysm, intracranial mass, perineurial cyst, sciatica, spinal cord compression.

Reviewer Comment: While TEAEs classified as neurotoxic AEs were very common in patients who received tebentafusp (51%), they were rarely (2.4%) $\geq$ Grade 2 and were never fatal. Neurotoxicity does not warrant additional labeling outside of reporting with other TEAEs in Section 6 of the USPI.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:

Not applicable

The Applicant's Position:

Not applicable

The FDA's Assessment:

FDA agrees.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

Across all studies, there were no clinically meaningful differences in the safety profile of tebentafusp vs investigator's choice with respect to age, sex, race, and ECOG performance status. No overall differences in safety were observed between patients ≥ 65 years of age compared to younger adult patients. The onset of the first AESI was not notably different among the subgroups.

The FDA's Assessment:

TEAEs by Sex

Table 69 summarizes AEs for the tebentafusp arm of Study 202 by sex. There are no significant differences between males and female with regards to occurrence of TEAEs. Analysis comparing the frequency of individual TEAEs by age in the tebentafusp arm identified the following differences:

- The following TEAEs were observed more frequently in females than males ($\geq 15\%$ difference): rash (64% versus 46%), alopecia (18% versus 0), vomiting (38% versus 22%).
- No TEAEs were observed more frequently in males than females ($\geq 15\%$ difference):

Some differences are to be expected due to chance alone and given the limited number of patients in each group, a true interaction between sex and these differences cannot be concluded. Thus, no sex specific labeling is indicated.

Table 69: Overall Summary of Adverse Events in Tebentafusp Arm by Sex Study 202

	Female 120 n (%)	Male 125 n (%)
Any TEAE	120 (100)	125 (100)
Fatal TEAE	0	1 (0.8)
Serious Adverse Event	32 (27)	37 (30)
Grade 3-4 TEAE	65 (54)	68 (54)
TEAE leading to discontinuation	3 (2.5)	5 (4)
TEAE leading to interruption	29 (24)	33 (26)

TEAEs by Age

Table 70 summarizes AEs for the tebentafusp arm of Study 202 by age. Patients were categorized as < 65 years or ≥ 65 years of age. There are no significant differences between patients < 65 years and ≥ 65 years of age with regards to occurrence of TEAEs. Analysis comparing the frequency of individual AEs between age group identified no differences (≥ 15%). Thus, no age specific labeling is indicated.

Table 70: Overall Summary of Adverse Events in Tebentafusp Arm by Age Study 202

	< 65 years N= 126 n (%)	≥ 65 years N= 119 n (%)
Any TEAE	126 (100)	119 (100)
Fatal TEAE	1 (0.7)	0
Serious Adverse Event	37 (29)	32 (27)
Grade 3-4 TEAE	70 (56)	63 (53)
TEAE leading to discontinuation	4 (3.2)	4 (3.4)
TEAE leading to interruption	33 (26)	29 (24)

8.2.8. Specific Safety Studies/Clinical Trials

Data:

Study 401 was a Phase 2, open-label, multi-center rollover study conducted to provide continued access to tebentafusp treatment for patients enrolled in a completed clinical study (Study 01) of tebentafusp. A total of 3 patients, all from the Study 01 parent study, were enrolled in this rollover study. All 3 patients were white, 2 were male and 1 was female, and their age ranged from 49 to 71 years. All patients had advanced melanoma with stage IV disease. Patients received 2, 18, and 26 cycles of tebentafusp with treatment durations of 43, 505, and 728 days. In

total, treatment durations from the first dose in the parent study were 423, 960, and 1156 days. No unexpected safety findings were observed in the 3 treated patients despite the additional exposure.

The Applicant's Position:

Following long-term exposure, the safety profile of tebentafusp was tolerable, manageable, and consistent with observations from other tebentafusp studies.

The FDA's Assessment:

Study 401 was not evaluated as part of FDA's assessment of safety as there were too few patients to provide meaningful additional safety information.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Not applicable

The FDA's Assessment:

Carcinogenicity studies were not indicated and have not been conducted with tebentafusp.

Human Reproduction and Pregnancy

Data:

See Reproductive and Developmental Toxicology

The Applicant's Position:

Due to the specificity for human targets, embryo-fetal development (EFD) studies cannot be conducted in nonclinical species. Therefore, a weight of evidence assessment was conducted to evaluate the risk of tebentafusp administration on pregnancy and embryo-fetal development. A literature search revealed that gp100 is expressed embryonically in melanocytes found in the skin, inner ear, and eyes by 7 weeks of gestation, and MHC Class I classical proteins (including HLA-A*02:01) and transporter-associated-with-antigen-processing (TAP) proteins required for presentation of antigen on the cell surface are expressed very early in embryonic development. In addition, CD3-positive T cells begin to populate the periphery and are capable of being activated by around 12 weeks of gestation.

However, tebentafusp's ability to directly affect embryo-fetal development requires that tebentafusp crosses the placenta and gains access to the fetus. The molecular weight of tebentafusp is 77 kDa, therefore, it is much too large to cross the placenta by diffusion. It also does not contain an Fc domain and, therefore, cannot bind to the neonatal Fc receptor (FcRn), which facilitates transfer of IgG molecules across the placenta, nor does it have domains that

could bind to other placental transporters. Thus, tebentafusp would not be able to gain access to or elicit pharmacologic activity directly in the embryo/fetus. There is also no evidence that tebentafusp could interfere with implantation or the maintenance of pregnancy through its mechanism of action.

Based on the results of this weight of evidence assessment, tebentafusp would not be expected to adversely affect embryo-fetal development or the maintenance of pregnancy when administered during pregnancy.

The FDA's Assessment:

FDA does not agree. There is data that biologics with a similar mechanism of action and molecular weight cross the placenta. See Section 5.1 of this review. The labeling was therefore amended to include in Warnings and Precautions (new Section 5.4 of KIMMTRAK Prescribing Information) information that there is a risk that tebentafusp may cause harm when administered to a pregnant woman. See Section 11.

Pediatrics and Assessment of Effects on Growth

Data:

Not applicable.

The Applicant's Position:

Safety and efficacy of tebentafusp have not been established in pediatric patients. Tebentafusp has received FDA agreement for the initial pediatric study plan for tebentafusp on 23 March 2021. The Sponsor has submitted a request for full pediatric waiver for tebentafusp to the BLA based on nonrelevance of gp100 as a molecular target for any pediatric cancers.

The FDA's Assessment:

The Applicant did not submit any data regarding safety in pediatric population.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

There has been no experience of overdosage with tebentafusp or evidence of drug abuse with tebentafusp from clinical studies.

The Applicant's Position:

There is no specific treatment for tebentafusp overdose and symptoms of overdose have not been established. Tebentafusp is unlikely to be abused due to its mode of action, physiological and pharmacological activity, lack of stimulant properties, and clinical setting of use. Because tebentafusp has no known potential for dependence, withdrawal or rebound events are not

relevant to tebentafusp dosing.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

Not applicable

The Applicant's Position:

Not applicable – Tebentafusp has not been marketed in any country to date.

The FDA's Assessment:

FDA agrees.

Expectations on Safety in the Postmarket Setting

Data:

Not applicable

The Applicant's Position:

In the pre-BLA meeting minutes from the meeting with FDA on March 12, 2021 the minutes noted -A preliminary discussion on the need for a REMS was held. It was concluded that a REMS will not be required for filing of the BLA based on the available data. A final decision will be made during the review of the application.

The FDA's Assessment:

Potential safety concerns beyond the risks observed in clinical trials and conveyed in the proposed labeling are not expected. Routine pharmacovigilance will be conducted to monitor for unexpected adverse events.

Given the risk of serious and potentially life threatening CRS, FDA amended the proposed label to include a black box warning for CRS. See Section 11.

8.2.11. Integrated Assessment of Safety

Data:

See the below section for the integrated assessment of safety summary.

The Applicant's Position:

Overall, tebentafusp has a well-established safety profile across the 5 Immunocore-sponsored clinical studies in 587 patients with melanoma, including 410 patients with UM, who were exposed to tebentafusp monotherapy. The randomized Study 202 provides the primary safety data and is proposed to be the basis for labeling presentation of Warning and Precautions and Adverse Events sections of the USPI. While the Study 102 safety data are consistent with Study 202 and supportive of the proposed indication and dosing regimen.

The safety profile of tebentafusp in mUM in Study 202 and Study 102 Phase 2 expansion was consistent with that observed in the pooled UM and CM populations, and no new safety signals were identified. The rate of permanent study drug discontinuation due to tebentafusp-related AEs was low in both studies (2.0% and 2.4%, respectively), and there were no treatment-related deaths among the 372 patients treated with tebentafusp in these two studies.

Overall, the most frequent TEAEs were associated with the mechanism of action of tebentafusp. These included skin AEs (e.g., rash, pruritus, and erythema), presumably resulting from T cells redirected to gp100+ melanocytes in the skin, and cytokine-mediated AEs, due to T cell activation. The most clinically relevant cytokine mediated AE is CRS, which is summarized using the most recent, and widely used, ASTCT 2019 consensus grading criteria. The proposed management algorithm for acute skin reactions and for CRS were based on those used in Study 102 and Study 202.

Most CRS events were mild to moderate with a low frequency of severe events, despite no requirement for primary prophylaxis with corticosteroid, antihistamine, or acetaminophen. The monitoring and management algorithm for rash and CRS used in the Phase 2 and 3 programs were successful based on low rate of drug related discontinuation, no drug related deaths and striking overall survival (OS) benefit. The majority of these AEs had onset within 1 day after the first 3 doses of tebentafusp when the patient was undergoing extended monitoring for at least 16 hours. As has been observed for other T cell engaging bispecifics, the CRS underwent tachyphylaxis with repeated dosing.

In first line mUM patients in Study 202, tebentafusp significantly improved OS compared to investigator's choice in the ITT analysis. The strong association between rash in Week 1 and OS benefit from tebentafusp suggests that rash may be a marker that the immune system can be mobilized by tebentafusp to target gp100+ cells. However, rash should not be used for clinical management since most patients develop a rash, rash was not independent of baseline prognostic features, and patients without a rash may still have better OS than similar patients in the control arm.

The other notable TEAE was LFT elevations, which were observed in both arms of Study 202 although with higher incidence in the tebentafusp arm (i.e., nearly two-thirds of patients). Liver function test elevation is a common feature of mUM since > 95% of patients had pre-existing liver metastases. The higher incidence of LFTs following tebentafusp, which occurred in a similar time frame to both cytokine increase and T cell trafficking to the liver tumors, may be due to spill over cellular inflammation from the UM lesions in the liver and injury to adjacent

hepatocytes or due to elevated cytokines. Elevations in LFTs typically occurred after the first few doses of tebentafusp and generally were transient and manageable with treatment interruption alone. No safety signal was observed in cardiac or eye disorders that would require specific labeling.

In a subset analysis, a trend for a higher risk of elevated LFTs was observed where patients with largest liver lesion >3 cm, elevated LDH, or elevated ALP at baseline. However, this may have that these patients are more likely to have disease progression of their liver lesions as a likely cause of the on-treatment LFT increase. In addition, these baseline factors are also known poor prognostic features in mUM.

mUM is a life-threatening disease with a dismal prognosis. There are currently no effective treatments for mUM that extend survival, and no standard of care exists. Tebentafusp is a first-in-class bispecific gp100-targeted TCR fusion protein that can redirect polyclonal T cells to target gp100+ tumor cells leading to T cell activation and release of inflammatory mediators. Tebentafusp monotherapy provides a dramatic OS benefit in HLA-A*02:01-positive patients with mUM. The safety profile of tebentafusp administered at the proposed dosing regimen is acceptable, with a very low rate of treatment-related discontinuations and no treatment-related deaths. AEs are consistent with mechanism of action of tebentafusp, predictable, generally reversible, and clinically manageable with appropriate surveillance and intervention. The totality of the data supports a positive benefit-risk profile of tebentafusp as a novel treatment option for HLA-A*02:01-positive adult patients with unresectable or mUM.

The FDA's Assessment:

The evaluation of the safety of tebentafusp at the proposed dosage in patients with metastatic uveal melanoma was based primarily on 356 patients randomized in Study 202 who received at least one dose of study drug (tebentafusp: 245 patients; IC: 111 patients). The Applicant included in their portion of the safety review analysis of data from 2 supportive trials (Study 01, Study 102 Phase 1 cohorts, Study 102 Phase 2 cohorts) and a pooled analysis (N= 410) comprised of all patients from these studies and the 245 patients who received at least one dose of tebentafusp on Study 202. FDA's assessment of safety included an analysis using a pooled set of 505 patients with cutaneous or uveal melanoma who received at least 1 dose of tebentafusp monotherapy on a clinical study (Study 01: 84 patients; Study 102: N= 146; Study 201: N=30; Study 202: N=245).

Study 202 excluded patients < 18 years of age, with a serum creatinine > 1.5 X ULN and/or creatinine clearance (calculating using Cockcroft-Gault formula, or measured) < 50 mL/minute, clinically significant cardiac disease or impaired cardiac function, history of HIV infection, active HBV or HCV infection, or history of adrenal insufficiency, interstitial lung disease, pneumonitis that required corticosteroid treatment or current pneumonitis, history of colitis of inflammatory bowel disease.

In Study 202, the median exposure was 163 days (range 1 day to 1016 days) in the tebentafusp

arm compared to 65 days (range 1 day to 658 days) in the IC arm. Table 71 summarizes the overall safety profile of tebentafusp at the proposed dosage as observed on Study 202.

Overall, tebentafusp was well tolerated with a very low rate of fatal TEAEs in Study 202 and across the development program, with no deaths identified as likely related to study drug based on review of available narratives and available data. The percentage of patients receiving tebentafusp on Study 202 who had at least one SAE was high but comparable to that observed with the IC. Over 50% of patients receiving tebentafusp on Study 202 had at least one Grade 3-4 TEAE. This was higher than observed in the IC arm. While SAEs and Grade 3-5 TEAEs were common in patients in the tebentafusp arm in Study 202, they rarely lead to permanent discontinuation, which was infrequent at 3.3%. A significant percentage of patients receiving tebentafusp had at least TEAE that lead to treatment interruption; however, this was comparable to that observed on the IC arm.

TEAE analysis of the ISS_Pool yielded similar results to what was seen in the tebentafusp arm for Study 202 with the exception of SAEs which was 8% higher in the ISS_Pool. The lower rate in Study 202 may represent improved management guidelines for CRS provided in Study 202.

Table 71: Summary of Treatment Emergent Adverse Events Study 202 and ISS_Pool

	Study 202		ISS_Pool N=505 n(%)
	Tebentafusp N=245 n(%)	IC N=111 n(%)	
Any TEAE	245 (100)	105 (95)	505 (100)
Fatal TEAE	1 (0.4)	2 (1.8)	4 (0.8)
SAE	69 (28)	26 (23)	182 (36)
Grade 3-4 TEAE	132 (54)	38 (34)	304 (60)
TEAE leading to discontinuation	8 (3.3)	7 (6)	27 (5)
TEAE leading to interruption	62 (25)	27 (24)	121 (24)
Grade $\geq$ 2 CRS ¹	188 (77)	0	N/A ²

¹ ASCTC Criteria Applicant Adjudicated

² Applicant Adjudication applied only to Studies 202 and 102

Adverse reactions associated with tebentafusp are primarily those associated with CRS including pyrexia, chills, nausea, vomiting, abdominal pain, hypotension, and those associated with skin reactions considered related to tebentafusp's mechanism of action. These skin reactions include rash, dry skin, and pruritis. Worsening laboratory abnormalities, including both hematologic, metabolic, and chemistry assessments were common and associated with CRS. They were usually transient. Only for lymphocyte count decreased was the percentage of patients with Grade 4 laboratory abnormality $\geq$ 5%.

The most important adverse reaction associated with tebentafusp is CRS. While there were no fatalities identified across the development program considered related to CRS, there were 2 cases of Grade 4 CRS associated events (0.8%) in the ISS_Pool, both being cases of multiple system organ dysfunction. In Study 202, the most commonly administered management interventions for CRS were IV fluids and steroids. Vasopressor(s) were rarely required.

Other than the rare and life-threatening CSR related event of multiple system organ dysfunction noted above, analysis of the ISS_Pool dataset did not identify any new or more serious safety already identified in Study 202.

The safety profile of tebentafusp at the proposed dosage in patient with advanced or metastatic uveal melanoma who have not received prior systemic therapy in the metastatic setting is acceptable with most adverse reactions being Grade 1 or 2 and higher grade toxicities adequately managed through temporary medical intervention or treatment interruption.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

No major statistical issues were identified while reviewing the data and results submitted in this application. Note that despite the statistically significant results observed for PFS, FDA considers the difference in PFS observed between the treatment arms was not clinically meaningful. ORR analysis was not formally tested at this interim look.

8.4. Conclusions and Recommendations

The FDA's Assessment:

FDA concludes that the results of Study 202 demonstrate that tebentafusp provides a statistically significant and clinically meaningful improvement in overall survival in patients who were randomized to receive tebentafusp compared to patients randomized to receive Investigator's Choice therapy. Overall survival is considered by FDA to be an acceptable endpoint to demonstrate the effectiveness of new therapeutics across oncology indications. Study 202 provides the evidence that supports the effectiveness of tebentafusp in patients with metastatic uveal melanoma who have not received prior systemic therapy in the metastatic setting. The safety profile of tebentafusp at the proposed recommended dosage of 20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter is acceptable in the context of patients with a serious and life-threatening condition and limited treatment options and is manageable with guidelines provided in product labeling. Overall, the review team deems the benefit: risk assessment of tebentafusp in the indicated population to be favorable and recommends regular approval for the following indication:

*KIMMTRACK is a bispecific peptide-HLA-directed CD3 T cell engager indicated for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.*

X

X

Primary Statistical Reviewer

Statistical Team Leader

X

X

Primary Clinical Reviewer

Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

No major review issues were identified during the review of this application, and thus, the review team did not seek input from external consultants or refer the application to the Oncologic Drug Advisory Committee.

10 Pediatrics

The Applicant's Position:

Tebentafusp has received FDA agreement for the initial pediatric study plan for tebentafusp on 23 March 2021. The Sponsor has submitted a request for full pediatric waiver for tebentafusp to the BLA based on nonrelevance of gp100 as a molecular target for any pediatric cancers.

The FDA's Assessment:

FDA concurs.

11 Labeling Recommendations

The Applicant's Position:

Not applicable – initial application.

The FDA's Assessment:

The proposed labeling submitted by the Applicant required extensive revision by FDA. The proposed labeling was edited with regards to format, language, and content to be consistent with current OOD practices. The table below summarizes key changes.

(b) (4)

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The risks of tebentafusp are acceptable in the indicated patient population with a serious and life-threatening condition; the safe use of tebentafusp can be adequately implemented in the post-marketing setting through product labeling that includes a black box warning for the risk of CRS. FDA requested the Applicant provide a plan to further communicate the risk of CRS to health care providers beyond product labeling through the distribution of a Dear Health Care Provider Letter. The Applicant agreed with this request and has provided the letter and a plan to distribute the letter to all health care providers expected to prescribe and manage treatment of tebentafusp outside the clinical trial setting.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The review team recommends issuing the following postmarketing requirement (PRMs) and postmarketing commitments (PMCs)

Clinical Pharmacology PMC:

1. Conduct an assessment to determine the presence of neutralizing anti-drug antibodies against tebentafusp-tebn in all patient samples that tested positive for binding anti-drug antibodies in studies IMCgp100-202 and IMCgp100-102 by using the validated neutralizing anti-drug antibody assay. Include an assessment of the clinical impact of the neutralizing anti-drug antibodies on pharmacokinetics, efficacy and safety of tebentafusp-tebn in the study report.

Clinical PMC:

1. Conduct an assay validation study to demonstrate that the assay can accurately differentiate HLA-A*02:01 from other HLA A alleles for identification of patients with uveal melanoma who may benefit from treatment with Kimmtrak (tebentafusp-tebn) and use the data to support an FDA approved companion diagnostic HLA typing assay patient selection test.

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

I agree with the clinical, statistical, non-clinical, pharmacology, and CMC recommendations with respect to the approvability of BLA 761228 as well as for the demonstrated favorable risk-benefit assessment for tebentafusp-tebn.

Tebentafusp-tebn (referred to as tebentafusp) is a bispecific biological product designed to bind to gp100 peptide presented by human leukocyte antigen-A*02:01 (HLA-A*02:01) on the cell surface of uveal melanoma tumor cells. Tebentafusp exerts its anti-tumor effect by redirecting T cells to attack the gp100-expressing tumor cells. The applicant for this BLA (Immunocore) seeks marketing authorization for tebentafusp for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. The proposed dosing regimen is 20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter, via intravenous infusion over 15-20 minutes.

The epidemiology of uveal melanoma is described above in this review. Briefly, Immunocore submitted data from one randomized clinical trial, Study 202, to support the approval of tebentafusp. Study 202 demonstrated a clinically meaningful and statistically significant improvement in overall survival (OS) in patients who received tebentafusp compared to those who received investigator's choice of therapy which included dacarbazine, pembrolizumab, or ipilimumab [HR of 0.51 (95% CI: 0.37, 0.71), $p < 0.0001$; with a median OS of 21.7 (18.6, 28.6) months in the tebentafusp arm versus 16.0 (9.7, 18.4) months in the control arm]. The results were robust (e.g., p value less than 0.01) and clinically significant and therefore consistent with FDA's requirement to demonstrate substantial evidence of effectiveness. Furthermore, I believe it would not be feasible or ethical to require a second randomized clinical trial, in this very rare malignancy without effective available therapies, prior to approval.

The adverse event profile of tebentafusp is extensively described above in this review. CRS, dermatological, and hepatic toxicities are important adverse reactions related to tebentafusp. Although important and potentially life threatening, the effect observed on overall survival supports a favorable risk-benefit assessment for the overall population of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

Tebentafusp will be prescribed by oncologists who are trained in the monitoring and management of drugs known to cause life threatening toxicities (including CRS). Risk minimization strategies include a Black Box Warning for CRS, specific instructions in labeling for monitoring and management, and a Medication Guide. In addition, health care providers that will be responsible for prescribing or managing patients receiving tebentafusp will receive a "Dear Health Care Provider" letter to increase awareness of the risk of CRS. The OMEPRM review provides an extensive discussion of REMS considerations; differences between

tebentafusp and blinatumomab (which has a REMS); and that a REMS was not considered necessary to ensure the benefits of tebentafusp outweigh its risks.

Finally, although tebentafusp will be indicated for HLA-A*02:01-positive adult patients, at the time of approval, there will not be an FDA approved/cleared in vitro companion diagnostic device to select patients for treatment. Although not available, HLA typing has been conducted for years in clinical practice (with accurate results necessary for allogeneic stem cell transplants and certain solid organ transplants). Nevertheless, Immunocore has committed, via a PMC, to conduct an assay validation study to demonstrate that the assay can accurately differentiate HLA-A*02:01 from other HLA A alleles. This PMC is intended to support the availability of an in vitro companion diagnostic device. Importantly, the final PMC report is expected in June of 2022. Although contemporaneous approval of a companion diagnostic device is preferable, given the circumstances of this application (including rare disease, high mortality, and observed clinical effects), I do not believe that approval of tebentafusp should be delayed for about 6 (or more) months while waiting for the approval of the device.

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19 Appendices

19.1. References

The Applicant's References:

Carvajal RD, Sosman JA, Quevedo JF, et al. Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial. JAMA. 2014;311:2397-405.

Carvajal RD, Schwartz GK, Tezel T, et al. Metastatic disease from uveal melanoma: treatment options and future prospects. Br J Ophthalmol. 2017;201:38-44

Chapman et al., Platelets Present Antigen in the Context of MHC Class I; J Immunol. 2012;189(2):916-23

Diener-West M, Reynolds SM, Agugliaro DJ, et al. Screening for metastasis from choroidal melanoma: the Collaborative Ocular Melanoma Study Group Report 23. J Clin Oncol. 2004;22(12):2438-44. doi: 10.1200/JCO.2004.08.194. PMID: 15197206

Eskelin S, Pyrhönen S, Summanen P, et al. Screening for metastatic malignant melanoma of the uvea revisited. Cancer. 1999;85(5):1151-9. PMID: 10091801

Hodi FS, Hwu WJ, Kefford R, et al. Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. J Clin Oncol. 2016;34(13):1510-7.

Jager MJ, Shields CL, Cebulla CM, et al. Uveal melanoma. Nat Rev Dis Primers. 2020;6:24

Khoja L, Atenafu EG, Joshua AM, et al. Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an international rare cancers initiative (IRCI) ocular melanoma study. Ann Oncol. 2019;30(8):1370-80

Lan KK, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70(3):659-63

Lee JS, Ruppin E. Multiomics prediction of response rates to therapies to inhibit programmed cell death 1 and programmed cell death 1 ligand 1. JAMA Oncol. 2019

Maio M, Danielli R, Chiarion-Sileni V, et al. Efficacy and safety of ipilimumab in patients with pre-treated, uveal melanoma. Ann Oncol. 2013;24:2911-2915

McLaughlin CC, Wu XC, Jemal A, et al. Incidence of noncutaneous melanomas in the U.S. Cancer. 2005;103:1000-7

Middleton MR, McAlpine C, Woodcock VK, et al. Tebentafusp, A TCR/Anti-CD3 biospecific fusion protein targeting gp100, potentially activated antitumor immune responses in patients with metastatic melanoma. Clin Cancer Res. 2020, Nov 15, 26(22): 5869-5878

- Nathan P, Cohen V, Coupland S, et al. Uveal melanoma UK national guidelines. *Eur J Cancer*. 2015;51(16):2404-12
- O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979;35(3):549-56
- Patel M, Smyth E, Chapman PB, et al. Therapeutic implications of the emerging molecular biology of uveal melanoma. *Clin Cancer Res*. 2011;17:2087-2100
- Pelster MS, Gruschkus SK, Bassett R, et al. Nivolumab and ipilimumab in metastatic uveal melanoma: results from a single-arm Phase II study. *J Clin Oncol*. 2020;39:599-607
- Piulats JM, Espinosa E, de la Cruz Merino L, et al. Nivolumab plus ipilimumab for treatment-naive metastatic uveal melanoma: an open-label, multicenter, Phase II trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402). *J Clin Oncol*. 2021;39:586-98
- Rantala ES, Hernberg M, Kivela TT. Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis. *Melanoma Res*. 2019;29:561-568
- Rothermel LD, Sabesan AC, Stephens DJ, et al. Identification of an immunogenic subset of metastatic uveal melanoma. *Clin Cancer Res*. 2016;22:2237-49
- Rowley et al., Genome-wide RNA-seq analysis of human and mouse platelet transcriptomes; *Blood*. 2011;118(14):e101-11
- Shoushtari AN, Carvajal RD. GNAQ and GNA11 mutations in uveal melanoma. *Melanoma Res*. 2014;24(6):525-34
- Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. *Ophthalmology*. 2011;118:1881-1885.
- Violanti SS, Bononi I, Gallenga CE, et al. New insights into molecular oncogenesis and therapy of uveal melanoma. *Cancers (Basel)*. 2019;11:694
- Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15(23):7412-20.
- Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. *N Engl J Med*. 2017;377(25):2500-1

The FDA's References:

- Kaliki, S., Shields, C. Uveal melanoma: relatively rare but deadly cancer. *Eye* **31**, 241–257 (2017). <https://doi.org/10.1038/eye.2016.275>
- Lee DW, Gardner R, Porter, DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124:188–95

Lee DW, Santomasso BD, Locke FL, et al, ASCTC consensus grading for cytokine release syndrome and neurological toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019; 25(4): 625-638. [Lee et.al., 2019a]

National Cancer Institute Common terminology criteria for adverse events (CTCAE).Version 4.03 available at https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

National Comprehensive Cancer Network. Uveal Melanoma (Version 2.2021).
https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf. Accessed January 20, 2022.

Rantala ES, Hernberg M, Kivela TT. Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis. *Melanoma Res*. 2019;29:561-568

Sayan M, Mamidanna S, Oncel D, et al. Clinical management of uveal melanoma: a comprehensive review with a treatment algorithm. *Radiat Oncol J*. 2020;38(3):162-169. doi:10.3857/roj.2020.00318

Shimabukuro-Vornhagen A, et al., Cytokine release syndrome. *J Immunother Cancer* 2018; 6:56.

Zheng PP, Kros JM, Wang G. Elusive Neurotoxicity in T Cell-Boosting Anticancer Therapies. *Trends Immunol*. 2019 Apr;40(4):274-278. doi: 10.1016/j.it.2019.02.005. Epub 2019 Mar 12. PMID: 30876815.

19.2. Financial Disclosure

The Applicant's Position:

Studies IMCgp100-102 and IMCgp100-202 are the two covered clinical studies. There is nothing to declare for financial interest by any investigator. At the time of conduct, data collection and analysis of these studies Immunocore was not public; therefore, there is no conflict to disclose. All financial support for the covered studies were for cost to conduct the studies and tracked by Immunocore's financial function.

The FDA's Assessment:

FDA notes there may be conflict of interest outside of public trading; however, given that all financial support was for cost to conduct the studies, FDA agrees there was no reportable conflicts of interest in the conduct of the two studies.

FDA has split the form filled out by the applicant into separate forms, one for each covered study.

Covered Clinical Study (Name and/or Number): Study IMCgp100-202

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>Study IMCgp100-202 – 63 PIs and 483 Subinvest</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details	Yes ☒	No ☐ (Request details from

of the disclosable financial interests/arrangements:		Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number):* Study IMCgp100-102

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>Study IMCgp100-102 – 24 PIs and 231 Subinvest</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		

Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

19.3. OOD Adverse Event Analysis Grouped Terms

Group Term (GT)	Constituent Preferred Terms (PT)
Abdominal Pain	Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Epigastric discomfort, Gastrointestinal pain, Hepatic pain
Acute Kidney Injury	Acute kidney injury, Anuria, Azotaemia, Creatinine renal clearance decreased, Glomerular filtration rate decreased, Nephropathy toxic, Oliguria Renal disorder, Renal failure, Renal impairment, Renal injury, Renal tubular acidosis, Renal tubular atrophy, Renal tubular disorder, Renal tubular dysfunction, Renal tubular injury, Renal tubular necrosis
Arrhythmia	Accelerated idioventricular rhythm, Accessory cardiac pathway, Adams-Stokes syndrome, Agonal rhythm, Arrhythmia, Arrhythmia supraventricular, Atrial conduction time prolongation, Atrial fibrillation, Atrial flutter, Atrial parasystole, Atrial tachycardia, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Atrioventricular conduction time shortened, Atrioventricular dissociation, Atrioventricular node dysfunction, BRASH syndrome, Bifascicular block, Bradyarrhythmia, Brugada syndrome, Bundle branch block, Bundle branch block bilateral, Bundle branch block left, Bundle branch block right, Cardiac fibrillation, Conduction disorder, Congenital supraventricular tachycardia, Defect conduction intraventricular, Electrocardiogram PR prolongation, Electrocardiogram PR shortened, Electrocardiogram QRS complex prolonged, Electrocardiogram QT prolonged, Electrocardiogram delta waves abnormal, Electrocardiogram repolarisation abnormality, Frederick's syndrome, Heart alternation, Heart rate irregular, Holiday heart syndrome, Junctional ectopic tachycardia, Lenegre's disease, Long QT syndrome, Nodal arrhythmia, Nodal rhythm, Pacemaker generated arrhythmia, Pacemaker syndrome, Parasystole, Paroxysmal arrhythmia, Paroxysmal atrioventricular block, Pulseless electrical activity, Reperfusion arrhythmia, Rhythm idioventricular, Sinoatrial block, Sinus arrest, Sinus arrhythmia, Sinus bradycardia, Sinus node dysfunction, Sinus tachycardia, Supraventricular extrasystoles, Supraventricular tachyarrhythmia, Supraventricular tachycardia, Torsade de pointes, Trifascicular block, Ventricular arrhythmia, Ventricular asystole, Ventricular dyssynchrony, Ventricular extrasystoles, Ventricular fibrillation, Ventricular flutter, Ventricular parasystole, Ventricular pre-excitation, Ventricular tachyarrhythmia, Ventricular tachycardia, Wandering pacemaker, Withdrawal arrhythmia, Wolff-Parkinson-White syndrome

Cough	Allergic cough, Atopic cough, Cough, Productive cough, Upper-airway cough syndrome
Diarrhea	Autoimmune colitis, Colitis, Colitis microscopic, Diarrhoea, Diarrhoea haemorrhagic, Enteritis, Enterocolitis, Frequent bowel movements
Dizziness	Cervicogenic vertigo, Dizziness, Dizziness exertional, Dizziness postural, Vertigo, Vertigo CNS origin, Vertigo labyrinthine, Vertigo positional
Dysgeusia	Ageusia, Anosmia, Dysgeusia, Hypergeusia, Hypogeusia, Product taste abnormal
Dyspnea	Dyspnoea, Dyspnoea at rest, Dyspnoea exertional
Fatigue	Asthenia, Fatigue
Hemorrhage	Abdominal wall haemorrhage, Acute haemorrhagic conjunctivitis, Adenoviral haemorrhagic cystitis, Administration site haemorrhage, Adrenal haemorrhage, Anal fissure haemorrhage, Anal haemorrhage, Anal ulcer haemorrhage, Anastomotic haemorrhage, Anastomotic ulcer haemorrhage, Anorectal varices haemorrhage, Application site haemorrhage, Arterial haemorrhage, Arteriovenous fistula site haemorrhage, Arteriovenous graft site haemorrhage, Basal ganglia haemorrhage, Brain stem haemorrhage, Brain stem microhaemorrhage, Breast haemorrhage, Bronchial haemorrhage, Bronchial varices haemorrhage, Catheter site haemorrhage, Central nervous system haemorrhage, Cerebellar haemorrhage, Cerebellar microhaemorrhage, Cerebral arteriovenous malformation haemorrhagic, Cerebral cyst haemorrhage, Cerebral haemorrhage, Cerebral microhaemorrhage, Cervix haemorrhage uterine, Choroidal haemorrhage, Chronic gastrointestinal bleeding, Ciliary body haemorrhage, Coital bleeding, Conjunctival haemorrhage, Corneal bleeding, Cystitis haemorrhagic, Diverticulitis intestinal haemorrhagic, Diverticulum intestinal haemorrhagic, Duodenal ulcer haemorrhage, Duodenitis haemorrhagic, Dysfunctional uterine bleeding, Ear haemorrhage, Encephalitis haemorrhagic, Enterocolitis haemorrhagic, Epidural haemorrhage, Epistaxis, Extra-axial haemorrhage, Eye haemorrhage, Eyelid bleeding, Gastric haemorrhage, Gastric ulcer haemorrhage, Gastric ulcer haemorrhage, obstructive, Gastric varices haemorrhage, Gastritis alcoholic haemorrhagic, Gastritis haemorrhagic, Gastroduodenal haemorrhage, Gastrointestinal haemorrhage, Gastrointestinal polyp haemorrhage, Gastrointestinal ulcer haemorrhage, Gastrointestinal vascular malformation haemorrhagic, Genital haemorrhage, Gingival bleeding, Graft haemorrhage, Haematuria, Haemoptysis, Haemorrhage, Haemorrhage coronary artery, Haemorrhage intracranial, Haemorrhage subcutaneous, Haemorrhage subepidermal, Haemorrhage urinary tract, Haemorrhagic adrenal infarction, Haemorrhagic arteriovenous malformation, Haemorrhagic ascites, Haemorrhagic breast cyst, Haemorrhagic cerebral infarction, Haemorrhagic cholecystitis, Haemorrhagic cyst, Haemorrhagic diathesis, Haemorrhagic disorder, Haemorrhagic erosive gastritis, Haemorrhagic hepatic cyst, Haemorrhagic infarction, Haemorrhagic necrotic pancreatitis, Haemorrhagic ovarian cyst, Haemorrhagic stroke, Haemorrhagic thyroid cyst, Haemorrhagic transformation stroke, Haemorrhagic tumour necrosis, Haemorrhagic urticaria, Haemorrhagic vasculitis, Haemorrhoidal haemorrhage, Hepatic haemorrhage, Implant site haemorrhage, Incision site haemorrhage, Infusion site haemorrhage, Injection site

	haemorrhage, Instillation site haemorrhage, Internal haemorrhage, Intestinal varices haemorrhage, Intra-abdominal haemorrhage, Intracranial tumour haemorrhage, Intraventricular haemorrhage, Iris haemorrhage, Joint microhaemorrhage, Lacrimal haemorrhage, Large intestinal haemorrhage, Large intestinal ulcer haemorrhage, Laryngeal haemorrhage, Lip haemorrhage, Lower gastrointestinal haemorrhage, Lymph node haemorrhage, Mediastinal haemorrhage, Medical device site haemorrhage, Mesenteric haemorrhage, Mouth haemorrhage, Mucocutaneous haemorrhage, Mucosal haemorrhage, Muscle haemorrhage, Myocardial haemorrhage, Naevus haemorrhage, Nail bed bleeding, Nephritis haemorrhagic, Ocular retrobulbar haemorrhage, Oesophageal haemorrhage, Oesophageal ulcer haemorrhage, Oesophageal varices haemorrhage, Oesophagitis haemorrhagic, Optic disc haemorrhage, Optic nerve sheath haemorrhage, Ovarian haemorrhage, Pancreatic haemorrhage, Pancreatitis haemorrhagic, Papillary muscle haemorrhage, Paranasal sinus haemorrhage, Parathyroid haemorrhage, Parotid gland haemorrhage, Pelvic haemorrhage, Penile haemorrhage, Peptic ulcer haemorrhage, Pericardial haemorrhage, Periorbital haemorrhage, Pharyngeal haemorrhage, Pituitary haemorrhage, Post procedural haemorrhage, Post-traumatic punctate intraepidermal haemorrhage, Postmenopausal haemorrhage, Procedural haemorrhage, Proctitis haemorrhagic, Pulmonary alveolar haemorrhage, Pulmonary haemorrhage, Puncture site haemorrhage, Putamen haemorrhage, Radiation associated haemorrhage, Rectal haemorrhage, Rectal ulcer haemorrhage, Renal cyst haemorrhage, Renal haemorrhage, Respiratory tract haemorrhage, Retinal haemorrhage, Retinopathy haemorrhagic, Retroperitoneal haemorrhage, Scleral haemorrhage, Shock haemorrhagic, Skin haemorrhage, Skin neoplasm bleeding, Skin ulcer haemorrhage, Small intestinal haemorrhage, Small intestinal ulcer haemorrhage, Soft tissue haemorrhage, Spermatic cord haemorrhage, Spinal cord haemorrhage, Spinal epidural haemorrhage, Spinal subarachnoid haemorrhage, Spinal subdural haemorrhage, Splenic haemorrhage, Splenic varices haemorrhage, Splinter haemorrhages, Spontaneous haemorrhage, Stoma site haemorrhage, Stomatitis haemorrhagic, Subarachnoid haemorrhage, Subchorionic haemorrhage, Subdural haemorrhage, Subendocardial haemorrhage, Subgaleal haemorrhage, Testicular haemorrhage, Thalamus haemorrhage, Thoracic haemorrhage, Thyroid haemorrhage, Tongue haemorrhage, Tonsillar haemorrhage, Tooth pulp haemorrhage, Tooth socket haemorrhage, Tracheal haemorrhage, Traumatic haemorrhage, Traumatic intracranial haemorrhage, Tumour haemorrhage, Ulcer haemorrhage, Umbilical haemorrhage, Upper gastrointestinal haemorrhage, Ureteric haemorrhage, Urethral haemorrhage, Urinary bladder haemorrhage, Urogenital haemorrhage, Uterine haemorrhage, Vaccination site haemorrhage, Vaginal haemorrhage, Vascular access site haemorrhage, Vascular graft haemorrhage, Venous haemorrhage, Vessel puncture site haemorrhage, Vitreous haemorrhage, Vulval haemorrhage, Wound haemorrhage
Headache	Basilar migraine, Cervicogenic headache, Chronic paroxysmal hemicrania, Cluster headache, Cold-stimulus headache, Craniocervical syndrome, Drug

	withdrawal headache, Exertional headache, External compression headache, Headache, Hemiplegic migraine, Medication overuse headache, Migraine, Migraine postdrome, Migraine with aura, Migraine without aura, New daily persistent headache, Occipital neuralgia, Ophthalmoplegic migraine, Post-traumatic headache, Postictal headache, Primary cough headache, Primary headache associated with sexual activity, Retinal migraine, SUNCT syndrome, Sinus headache, Status migrainosus, Tension headache, Thunderclap headache, Typical aura without headache, Vascular headache, Vestibular migraine
Hypertension	Blood pressure ambulatory increased, Blood pressure diastolic increased, Blood pressure increased, Blood pressure orthostatic increased, Blood pressure systolic increased, Diastolic hypertension, Hypertension, Hypertensive crisis, Labile hypertension, Malignant hypertension, Orthostatic hypertension, Secondary hypertension, Supine hypertension, Systolic hypertension, Withdrawal hypertension
Hypotension	Blood pressure decreased, Diastolic hypotension, Hypotension, Orthostatic hypotension
Hypothyroidism	Autoimmune hypothyroidism, Blood thyroid stimulating hormone increased, Hypothyroidic goitre, Hypothyroidism, Primary hypothyroidism, Secondary hypothyroidism, Tertiary hypothyroidism
Musculoskeletal Pain	Arthralgia, Arthritis, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Neck pain, Non-cardiac chest pain, Pain in extremity, Spinal pain
Neuropathy Peripheral	Autoimmune neuropathy, Dysaesthesia, Hyperaesthesia, Hypoaesthesia, Immune-mediated neuropathy, Neuralgia, Neuropathy peripheral, Paraesthesia, Peripheral motor neuropathy, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Polyneuropathy
Edema	Eye oedema, Eyelid oedema, Face oedema, Generalised oedema, Gravitational oedema, Lip oedema, Localised oedema, Oedema, Oedema genital, Oedema peripheral, Penile oedema, Periorbital oedema, Scrotal oedema, Skin oedema, Swelling, Testicular oedema, Vulval oedema
Pneumonia	Atypical mycobacterial lower respiratory tract infection, Atypical mycobacterial pneumonia, Atypical pneumonia, Candida pneumonia, Embolic pneumonia, Enterobacter pneumonia, Eosinophilic pneumonia, Eosinophilic pneumonia acute, Eosinophilic pneumonia chronic, Haemorrhagic pneumonia, Herpes simplex pneumonia, Idiopathic interstitial pneumonia, Idiopathic pneumonia syndrome, Lower respiratory tract herpes infection, Lower respiratory tract infection, Lower respiratory tract infection bacterial, Lower respiratory tract infection fungal, Lower respiratory tract infection viral, Lung abscess, Miliary pneumonia, Neonatal pneumonia, Paraneoplastic pneumonia, Parasitic pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia Acinetobacter, Pneumonia adenoviral, Pneumonia anthrax, Pneumonia aspiration, Pneumonia bacterial, Pneumonia Blastomyces, Pneumonia Bordetella, Pneumonia chlamydial, Pneumonia cryptococcal, Pneumonia cytomegaloviral, Pneumonia Escherichia, Pneumonia fungal, Pneumonia haemophilus, Pneumonia helminthic, Pneumonia herpes viral, Pneumonia

	influenzal, Pneumonia klebsiella, Pneumonia legionella, Pneumonia lipoid, Pneumonia measles, Pneumonia Moraxella, Pneumonia mycoplasmal, Pneumonia necrotizing, Pneumonia parainfluenzae viral, Pneumonia pneumococcal, Pneumonia proteus, Pneumonia pseudomonal, Pneumonia respiratory syncytial viral, Pneumonia salmonella, Pneumonia serratia, Pneumonia staphylococcal, Pneumonia streptococcal, Pneumonia toxoplasmal, Pneumonia tularaemia, Pneumonia viral, Post procedural pneumonia, Varicella zoster pneumonia
Pneumonitis	Acute interstitial pneumonitis, Immune-mediated pneumonitis, Interstitial lung disease, Organising pneumonia, Pneumonitis
Pyrexia	Body temperature increased, Hyperpyrexia, Hyperthermia, Pyrexia
Rash	Autoimmune dermatitis, Dermatitis, Dermatitis acneiform, Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalized, Drug eruption, Drug reaction with eosinophilia and systemic symptoms, Dyshidrotic eczema, Eczema, Eczema asteatotic, Erythema multiforme, Exfoliative rash, Eyelid rash, Genital rash, Immune-mediated dermatitis, Lichen planus, Mucocutaneous rash, Nodular rash, Palmar-plantar erythrodysesthesia syndrome, Pemphigoid, Penile rash, Perineal rash, Perivascular dermatitis, Rash, Rash erythematous, Rash follicular, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash morbilliform, Rash popular, Rash papulosquamous, Rash pruritic, Rash pustular, Rash vesicular, Scrotal dermatitis, Skin exfoliation, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, Urticarial dermatitis, Vasculitic rash, Vulvovaginal rash
Stomatitis	Aphthous ulcer, Cheilitis, Gingival erosion, Gingival ulceration, Glossitis, Mouth ulceration, Mucosal hyperaemia, Mucosal inflammation, Oral mucosal blistering, Oral mucosal erythema, Pharyngeal inflammation, Stomatitis, Tongue ulceration
Urinary Tract Infection	Bacterial pyelonephritis, Cystitis, Cytomegalovirus urinary tract infection, Emphysematous pyelonephritis, Escherichia pyelonephritis, Escherichia urinary tract infection, Pyelonephritis acute, Pyelonephritis chronic, Pyelonephritis fungal, Pyelonephritis mycoplasmal, Pyelonephritis viral, Streptococcal urinary tract infection, Urinary tract infection, Urinary tract infection bacterial, Urinary tract infection enterococcal, Urinary tract infection fungal, Urinary tract infection pseudomonal, Urinary tract infection staphylococcal, Urinary tract infection viral
Vomiting	Discoloured vomit, Faecal vomiting, Haematemesis, Retching, Vomiting

19.4. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

Tebentafusp can only recognize human HLA; therefore, all nonclinical toxicology studies were conducted in vitro. Human tissue and cell-based in vitro approaches were taken to understand potential organ-specific toxicities that may arise in the clinical setting with tebentafusp. These

approaches considered the on-target/off-tumor potential effects, as well as the off-target/off-tumor effects (cross-reactivity) of tebentafusp.

Tebentafusp was also investigated in toxicology studies to assess its cross-reactivity with normal tissues in a GLP-compliant tissue cross-reactivity study. The ability of tebentafusp to bind to a panel of 35 normal human tissues from 3 healthy donors was assessed using immunohistochemistry (IHC). Staining with tebentafusp was observed in the membrane and cytoplasm of lymphocytes throughout the human tissue panel examined. Similar staining was observed with the individual anti-CD3 component of tebentafusp, while no staining was observed with the individual TCR component, indicating that this staining was attributable to the binding of tebentafusp to CD3. As CD3 is a T lymphocyte marker, this staining was expected. No other staining was observed across the panel of tissues tested, indicating no unexpected cross-reactivity. It should be noted that the TCR targeting domain of tebentafusp recognizes very low target pHLA complexes (>5 pHLA complexes per cell), which are expected to be outside the normal range of sensitivity of the IHC method and would therefore inform on cross-reactivity above the threshold of detection of IHC only. Overall, the results of this study are consistent with published reports of gp100 being specific to melanocytes and melanoma cells, and not in other.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. See FDA's Assessment in Section 5.5.1.

19.5. OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

Basic characteristics of immunogenicity:

- Anti-drug antibodies (ADA) positive rate is 28.6% (63/225 patients) in study IMCgp100-202 and 33.3% (48/144) in study IMCgp100-102.
- Median ADA onset time was 8 weeks (range: around 1 -30 weeks).
- ADA positive rate was 14.4% (30/208 patients) at the week 8 landmark in study IMCgp100-202.
- Median ADA titer was 8192. There were about 12.6% of patients who developed an ADA titer ≥ 8192 .

Impact of immunogenicity on PK:

- Clearance increases by 32.9-fold in patients with high titer ADA (defined as titer > 8192). As a consequence, terminal half-life reduced from 6-7 hours to 10-14 minutes in this subgroup of patients. Relevant labeling of the basic characteristics of ADA and impact of immunogenicity on clearance was updated in section 6.2 and section 12.3 of the tebentafusp USPI.

Impact of immunogenicity on efficacy:

- An exploratory analysis of effect of ADA on outcomes of tebentafusp was conducted. For overall survival (OS), hazard ratio for the ADA 8 weeks' positive subgroup is 0.65 (95% CI: 0.36- 1.16) and hazard ratio for ADA 8 the weeks' negative subgroup is 0.44 (95% CI: 0.3, 0.64). The immunogenicity positive subgroup did not show significant reduced efficacy compared with the immunogenicity negative subgroup. However, the result needs to be interpreted with caution due to the limited number of patients (N=30) in the ADA 8 weeks' positive subgroup.
- An exploratory analysis of effect of high titer ADA on treatment effect of tebentafusp was also conducted. For overall survival (OS), hazard ratio for the high titer ADA 8 weeks' positive subgroup (titer ≥ 128) is 0.41 (95% CI: 0.35- 1.13) and hazard ratio for the ADA 8 weeks' low titer or negative subgroup is 0.48 (95% CI: 0.33, 0.69). The high titer ADA positive subgroup did not show significant reduced efficacy compared with the ADA negative or low titer subgroup. However, the result needs to be interpreted with caution due to the limited number of patients (N=11) in the high titer subgroup.

Please refer to section 19.5.4 for more details.

19.5.1. Population PK Analysis

19.5.1.1. The Applicant's Position:

Population Pharmacokinetic (PK) analysis was conducted across studies IMC-gp100-01, IMCgp100-102 and IMCgp100-202 to (1) characterize the PK properties of tebentafusp after IV infusion in melanoma patients and (2) to evaluate potential impact of patient demographics and clinical covariates on the PK exposure of tebentafusp. A two-compartment model with first-order elimination from the central compartment developed in patients with UM and non-UM was used to describe the PK profile. Tebentafusp C_{max} was achieved immediately after the end of intravenous (IV) infusion (median 0.5 hours), with a geometric mean C_{max} of 4063 pg/mL for Cycle 1 Day 1 (C1D1) (20 mcg dose) and 13040 pg/mL for C1D15 (68 mcg dose). The increase in geometric mean PK exposure (C_{max}) of tebentafusp was approximately dose proportional between the 20 mcg dose administered on C1D1 and the 68 mcg dose administered on C1D15. Subsequent weekly doses of 68 mcg from Cycle 2 and beyond indicated no further accumulation of Tebentafusp. From the dose escalation data, the observed t_{1/2} was 6.8 to 7.5 hours.

Estimated glomerular filtration rate (eGFR) and high-titer anti-drug antibodies (ADA) were identified as statistically meaningful covariates of Tebentafusp clearance (CL). In the final population PK model, estimated tebentafusp CL slightly decreased in patients with moderate renal impairment (creatinine clearance [CrCL] ranging 30 to 59 mL/min). However, high interpatient variability (78%) was observed and CL values in renally impaired patients were essentially within the range observed in patients with normal renal function. No impact on safety or efficacy parameters was identified in patients with mild to moderate renal impairment and no dose adjustments are recommended. There is no information available in patients with severe renal impairment. Estimated CL considerably increased when patient's generated ADA titers greater than 1:8192. However, neither ADA onset or titer magnitude were associated with safety or efficacy and thus, monitoring of ADA is not necessary.

19.5.1.2. Population PK Summary Table

Table 72: Population PK Summary Table

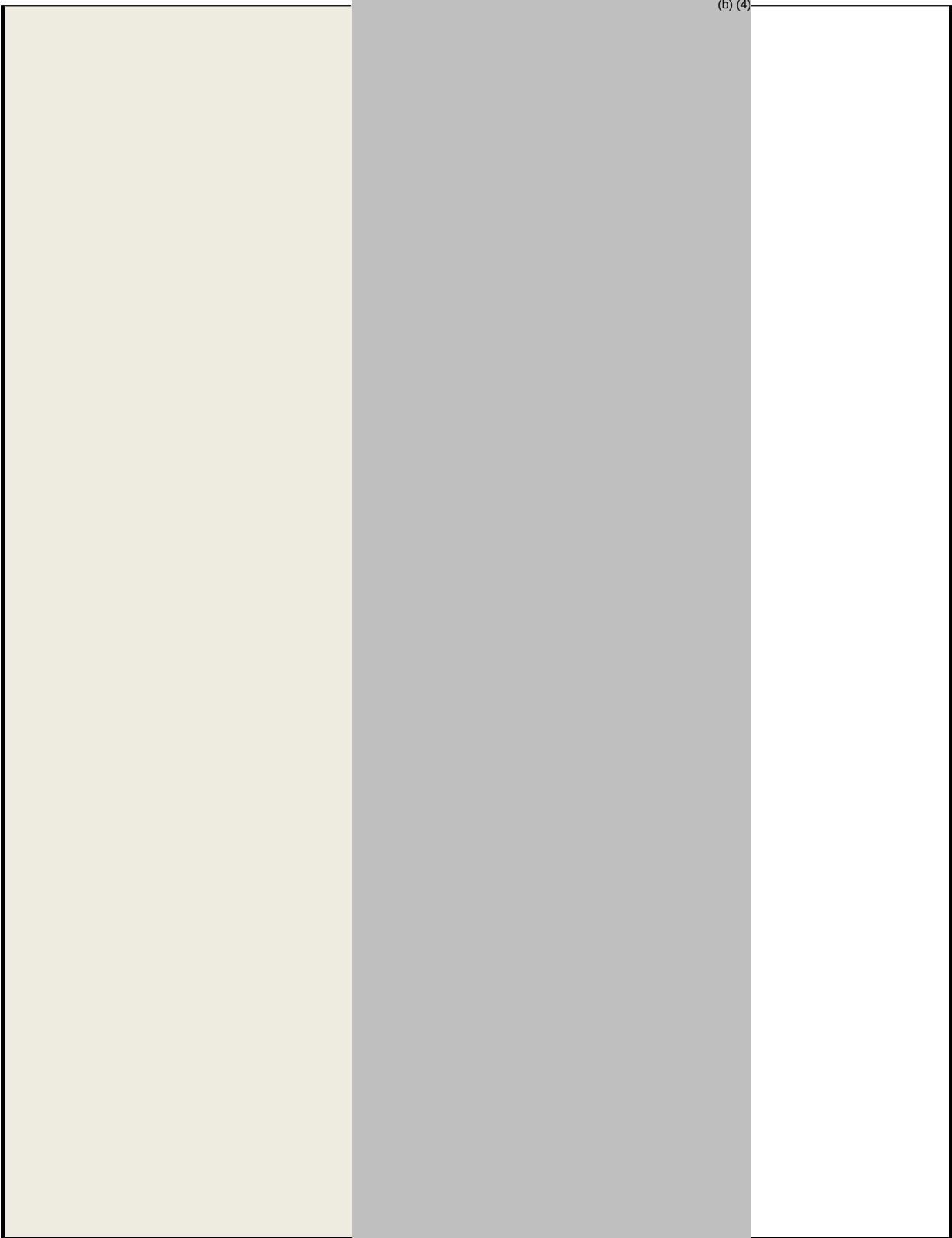
General Information	
Objectives of PPK Analysis	- To characterize the PK properties of tebentafusp in HLA A*02-positive melanoma patients - To evaluate the potential impact of demographic and clinical covariates on the PK exposure of tebentafusp - To evaluate the exposure-response relationship of clinical primary endpoints (eg, overall survival, tumor response) - To evaluate the exposure-response relationship of adverse events (eg, skin toxicity, hepatic toxicity, and Cytokine Release Syndrome [CRS]) and IL-6 levels - To evaluate the exposure-response of exploratory adverse events (eg, rash, hypo/hyper-pigmentation)
Study Included	<u>IMCgp100-01</u> - a Phase 1/2, open-label, dose finding study to assess the safety, tolerability, and efficacy of IMCgp100 in patients with advanced malignant melanoma. <u>IMCgp100-102</u> - a Phase 1/2, open-label, multi-center study of the safety and efficacy of IMCgp100 using the intra-patient escalation dosing regimen in patients with advanced uveal melanoma. <u>IMCgp100-202</u> - a Phase 3 randomized, open-label, multi-center study of the safety and efficacy of IMCgp100 compared with Investigator's choice in HLA-A*0201 positive patients with previously untreated advanced uveal melanoma.
Dose(s) Included	<u>IMCgp100-01</u> Arm 1: 5 ng/kg, 15 ng/kg, 45 ng/kg, 135 ng/kg, 270 ng/kg, 405 ng/kg, 600 ng/kg, 900 ng/kg. Arm 1 (flat dose): 20 mcg inpatient dose escalation, 30 mcg inpatient dose escalation, 50 mcg. Arm 2 (daily dosing): 10 mcg, 20 mcg, 30 mcg, 40 mcg, 50 mcg. <u>IMCgp100-102</u>: Day 1 – 20 mcg, Day 8 – 30 mcg, Day 15 and beyond – weekly 54 mcg, 63 mcg, 68 mcg, 73 mcg <u>IMCgp100-202</u>: Day 1 – 20 mcg, Day 8 – 30 mcg, Day 15 and beyond – weekly 68 mcg
Population Included	Patients with advanced malignant melanoma Patients with advanced metastatic uveal melanoma (ITT)

Population Characteristics	General	Age: median 62 yr (range 23-91 yr) Weight: median 78.6 kg (range 43-163.1 kg) Race White – 533 (90.8%) Black/African American – 1 (0.2%) Asian – 1 (0.2%) American Indian/Alaskan Native – 1 (0.2%) Other – 5 (0.9%) Not Reported – 36 (6.1%) Not Allowed – 8 (1.4%)
	Organ Impairment	Hepatic (Child-Pugh, NCI, etc): 0 (0%) Renal (CrCL, etc): Normal renal function 353 (60.2%) Mild impairment 201 (34.3%) Moderate impairment 25 (4.3%) Unknown 7 (1.2%)
	Pediatrics (if any)	Not Applicable
No. of Patients, PK Samples, and BLQ		3592 (38.9%) of pre-/post-dose BLQ (12.1% of all BLQ samples [435 BLQ out of 3592 BLQ total] were sampled at baseline [TIME=0])
Sampling Schedule	Rich Sampling	<u>IMCgp100-01:</u> Arm 1 Schedule 1: C1D1 Pre-dose, 0.5 h, 1 h, 2 h, 4 h, 10 h, 24 h, 48 h; C1D8 Pre-dose, D30. Arm 1 Schedule 2: C1D1 Pre-dose, 0.5 h, 1 h, 2 h, 4 h, 10 h, 24 h, 48 h; C1D8 Pre-dose, EOI; C1D9, C1D15 Pre-dose, EOI; C1D22 Pre-dose, EOI; C1D29 Pre-dose, EOI; C1D36 Pre-dose, EOI; C1D66. Arm 1 Flat Dosing: C1D1 Pre-dose, 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 24 h; C1D8 Pre-dose, EOI; C1D9, C1D15 Pre-dose, EOI; C1D22 Pre-dose, EOI; C1D29 Pre-dose, EOI; C1D36 Pre-dose, EOI; C1D43 Pre-dose, EOI; C1D50 Pre-dose, EOI; C1D51. Arm 1 Daily Dosing: C1D1 Pre-dose, 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h; C1D2 Pre-dose, EOI; C1D3 Pre-dose, EOI; C1D4 Pre-dose, EOI, 2h; C1D5; C1D25 2h <u>IMCgp100-102:</u> C1D1 Pre-dose, EOI, 4 h, 8 h, 12-24 h; C1D8 Pre-dose, EOI; C1D15 Pre-dose, EOI, 12-24 h; C1D22 Pre-dose, EOI

		<u>IMCgp100-202:</u> C1D1 Pre-dose, EOI, 12-24 h; C1D8 Pre-dose, EOI; C1D15 Pre-dose, EOI, 12-24 h	
	In ITT Population	<u>IMCgp100-202:</u> C1D1 Pre-dose, EOI, 12-24 h; C1D8 Pre-dose, EOI; C1D15	
Covariates Evaluated	Static	ADA status, weight	
	Time-varying	Renal function	
Final Model		Summary	Acceptability [FDA's comments]
Software and Version		NONMEM (version 7.3, ICON, Hanover, MD, USA) gfortran64 R (version 3.5.1; Platform: x86_64-w64-mingw32/x64, 64-bit) for graphical purposes. Xpose 4.4.0 - diagnosis plotting and VPC Perl-speaks-NONMEM (PsN Version 3.4.2) - diagnosis plotting and VPC	Although FDA's position is that BLQ not be deleted, sensitivity analysis with BLQ imputed as lower limit of quantitation (LLOQ) made no significant difference. Please refer to section 19.5.1.3 for more comments.
Model Structure		Tebentafusp concentrations were log-transformed for all modeling. Base model: 2-compartment model using ADVAN3 TRANS4 with linear elimination from central compartment with all CWRES >4 outliers excluded was selected as the base population pharmacokinetic model (Run # 507) Final model: 2-compartment model with first-order elimination from central compartment. Renal function and an ADA titer ≥ 8192 are covariates affecting CL	
Model Parameter Estimates		Table 74. Parameter Estimates and SE from Final Population PK Model (also included in Section 6, Table 3, pg. 28)	

Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	High interpatient variability was observed (78 %CV) and CL values in renal impaired patients were within range observed in patients with normal renal function	
BLQ for Parameter Accuracy	BLQ set to missing	
GOF, VPC	Figure 42. Goodness-of-fit Plots for the Final Population PK Model (OBS-PRED/IPRED, CWRES-TIME/PRED). (also included in Section 6, Figure 16) Figure 43. Composite Visual Predictive Check of Population PK Model (Log Scale [Run # 515]) Figure 44. VPC of Final Population PK Model, Stratified by Dose Level	
Significant Covariates and Clinical Relevance	Figure 45. Correlation Matrix of Baseline Covariate Assessment-Continuous Covariates Figure 46. Correlation Matrix of Baseline Covariate Assessment-Categorical Covariates Figure 47. Impact of Renal Clearance by Renal Functional Status on Exposure After First or Third Dose Figure 48. Impact of ADA Titer ≥ 8192 on Exposure.	
Labeling Language	Description	
12.3 PK	(b) (4)	Acceptability [FDA's comments] Please refer to section 19.5.1.3

(b) (4)



		(b) (4)

Table 73: Summary of Demographic Data by Study

	Study IMCgp100-01 (N = 84)	Study IMCgp100-102 (N = 146)	Study IMCgp100-202 (N = 357)	Overall (N = 587)
Sex, n (%)				
Male	54 (64.3)	72 (49.3)	180 (50.4)	306 (52.1)
Female	30 (35.7)	74 (50.7)	177 (49.6)	281 (47.9)
Race, n (%)				
American Indian/Alaskan Native	0 (0)	0 (0)	1 (0.3)	1 (0.2)
Asian	1 (1.2)	0 (0)	0 (0)	1 (0.2)
Black/African American	1 (1.2)	0 (0)	0 (0)	1 (0.2)
White	79 (94)	145 (99.3)	309 (86.6)	533 (90.8)
Other	3 (3.6)	1 (0.7)	1 (0.3)	5 (0.9)
Not Reported	0 (0)	0 (0)	36 (10.1)	36 (6.1)
Not Allowed	0 (0)	0 (0)	8 (2.2)	8 (1.4)
Anti-drug Antibody, n (%)				
Positive	3 (3.6)	58 (39.7)	77 (21.6)	138 (23.5)
Negative	81 (96.4)	88 (60.3)	279 (78.2)	448 (76.3)
Age (years) Mean (SD)	58.7 (11.5)	60.4 (11.1)	61.9 (11.5)	61.1 (11.4)
Body Weight (kg) mean (SD)	83.1 (19)	77.4 (18.6)	78.9 (17.9)	79.1 (18.3)
BMI (kg/m²) mean (SD)	27.7 (5.2)	26.7 (5.2)	27.2 (5.2)	27.2 (5.2)
eGFR (mL/min/1.73m²) mean (SD)	107.6 (23.9)	95 (22.1)	94.1 (21.4)	96.3 (22.4)

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BMI = body mass index; eGFR = estimated glomerular filtration rate; n (N) = number; SD = standard deviation

Source: Module 2.7.2, Table 3

Table 74. Parameter Estimates and SE from Final Population PK Model

Parameter	Units	Estimate	Standard Error
CL	L/day	4.33	2.8
V ₁	L	5.25	0.5
Q	L/day	11.4	3.1
V ₂	L	470	79.9
eGFR ~ CL	mL/min/1.73m ²	3.32	1.4
ADA Titer ≥ 8192 ~ CL	-	46.2	8.5
Interindividual Variability			
CL	CV%	78.5	46.9
V ₁		32.5	10.1
Q		40.9	7.3
V ₂		174.2	13.5
Residual Error			
Additive	ng/mL	0.24	0.081

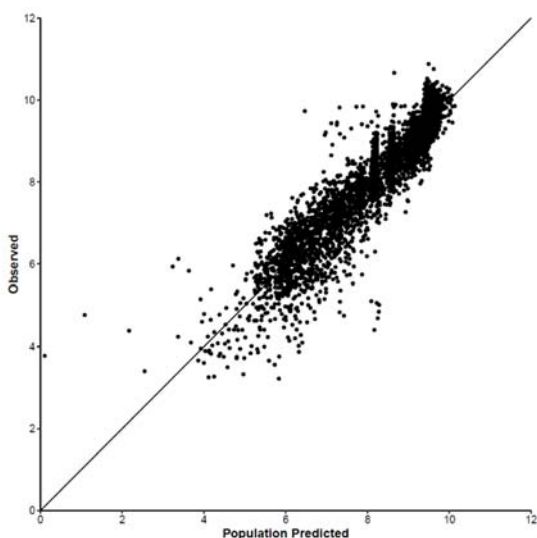
ADA = antidrug antibody; CL = clearance; CV = coefficient of variation; eGFR = estimated glomerular filtration rate; Q = intercompartment clearance between compartments 1 and 2; V₁ = central volume of distribution; V₂ = peripheral volume of distribution

Clearance is estimated by the following equation: $CL = 4.33 * (eGFR/120)^{3.32} * 46.2^{ADA}$

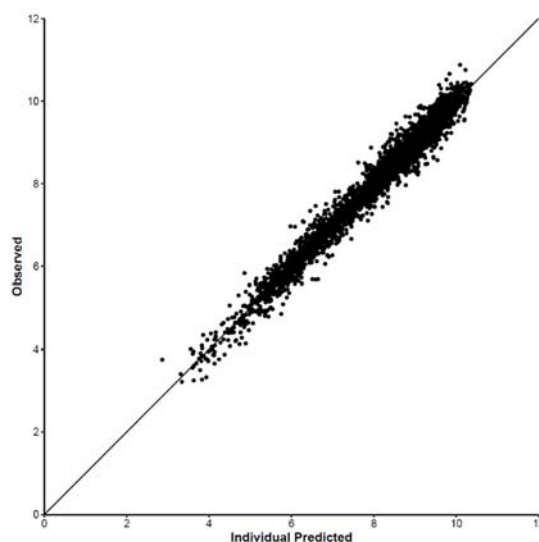
Source: Module 2.7.2, Table 4

Figure 42. Goodness-of-fit Plots for the Final Population PK Model (OBS-PRED/IPRED, CWRES-TIME/PRED).

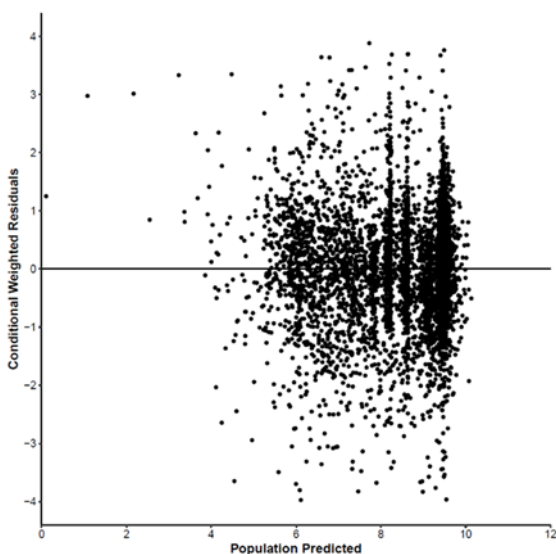
Population Predicted v Observed
Concentration



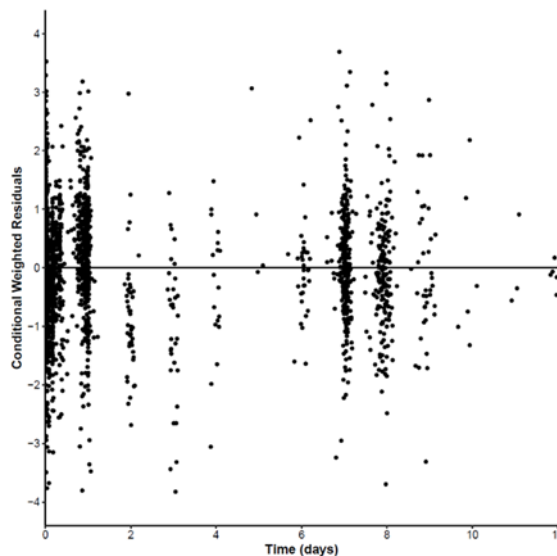
Individual Predicted v Observed
Concentration



Conditional Weighted Residual v Population
Predicted Concentration



Conditional Weighted Residual v Time



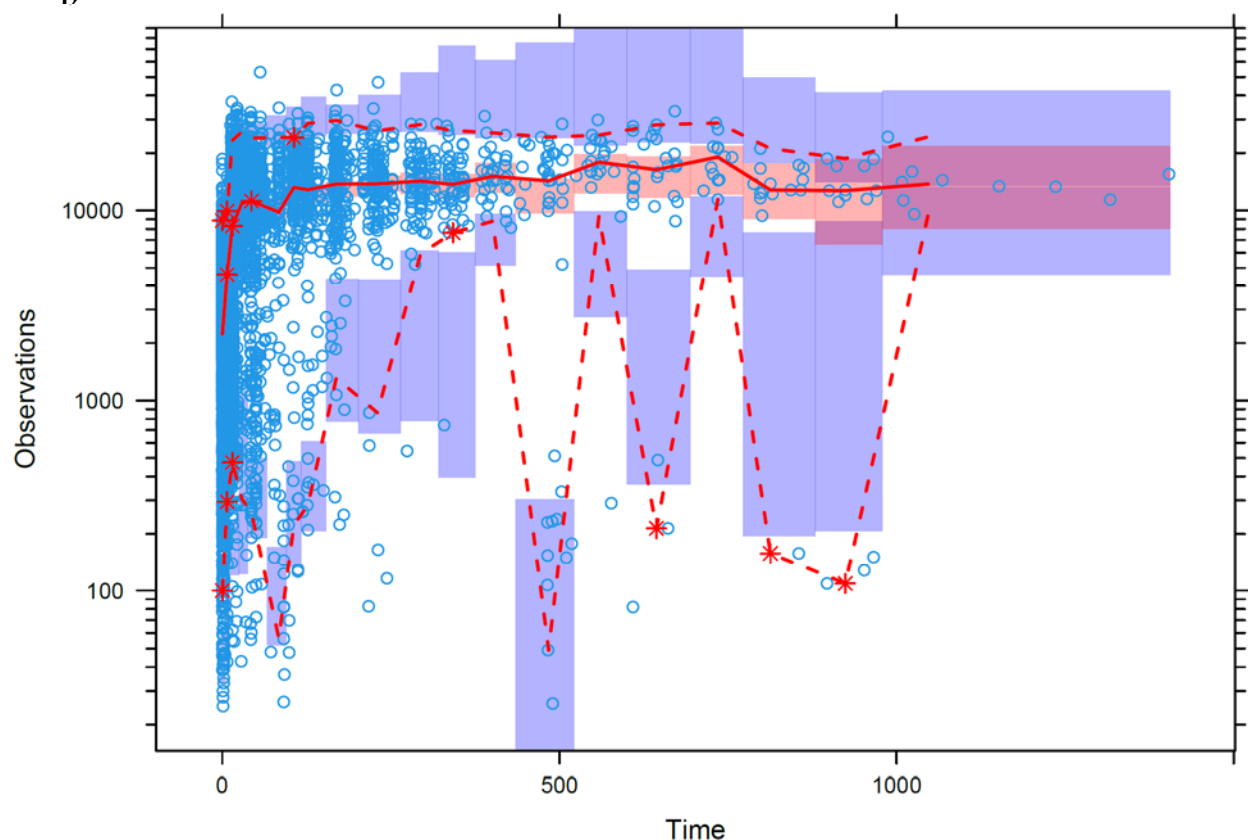
Top Left Panel: Population prediction of tebentafusp serum concentrations versus observed tebentafusp serum concentrations; Top Right Panel: Individual prediction of tebentafusp serum concentrations versus observed tebentafusp serum concentrations; Bottom Left Panel: Population prediction of tebentafusp serum concentrations versus conditional weighted residuals; Bottom Right Panel: Time versus conditional weighted residuals.

Note: Observed and Predicted concentration values are presented as log transformed values.

Source: Module 2.7.2, Figure 16.

The final PK model was evaluated using prediction corrected VPC (Bergstrand et al, 2011) to simulate 1000 replicated VPC datasets. The 95th percentile intervals across replicates were compared to corresponding summary statistics derived from observed data for composite VPC (Figure 43) and stratified by dose (Figure 44). The model predicted distribution overlap with the observed concentration well, indicating that the final PK model characterized the observed PK adequately.

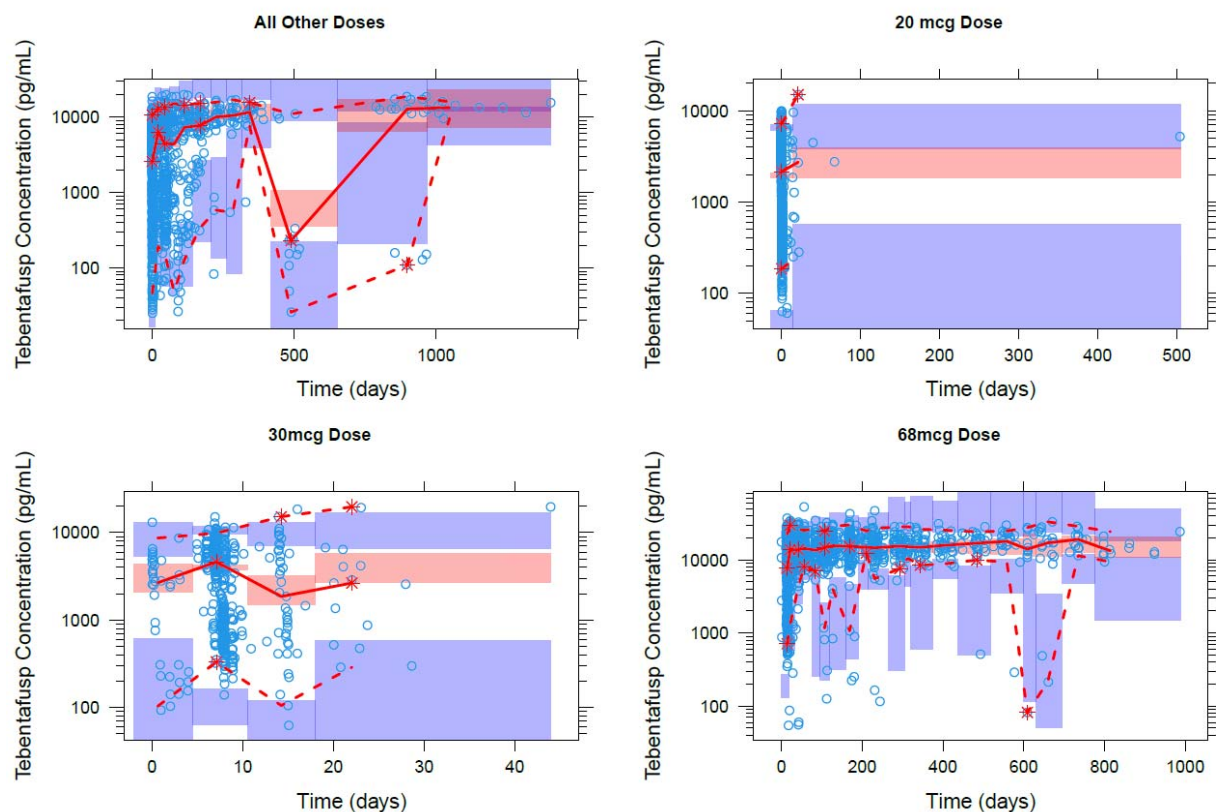
Figure 43. Composite Visual Predictive Check of Population PK Model (Log Scale [Run # 515])



The blue circle represents the observed concentration. The solid and dashed lines represent the median and 2.5th and 97.5th percentiles of the observations. The shaded red and blue areas represent the 95% CI of the median and 2.5th and 97.5th percentiles predicted by the model, respectively.

Source: Population Pharmacokinetic Modeling Report and Exposure-Response Analysis for Tebentafusp, Figure 4

Figure 44. VPC of Final Population PK Model, Stratified by Dose Level

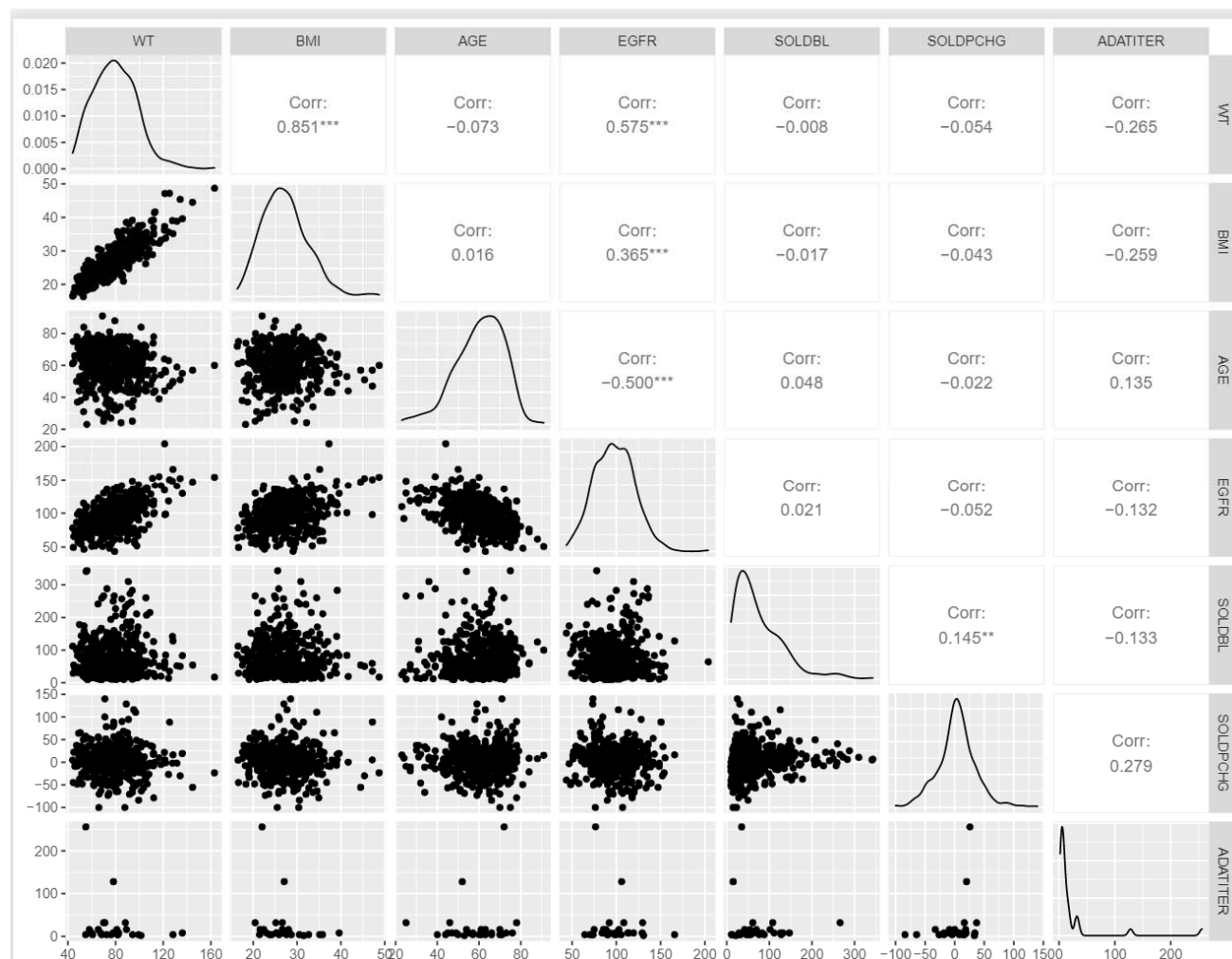


Blue circles represent observed concentrations. Solid and dashed lines represent the median and 2.5th and 97.5th percentiles of the observations, respectively. Shaded red and blue areas represent the 95% CI of median and 2.5th and 97.5th percentiles predicted by model, respectively.

Source: VPCs generated using final model code (5151.ctl)

The final model was developed by incorporating the effect of relevant covariates on key structural model parameters of the base model. Covariates were selected based on clinical judgment, mechanistic plausibility, and prior knowledge. PK parameter–covariate relationships were initially examined graphically. The model with a discrete covariate ADA effect (ADA titer ≥ 8192) on CL and a continuous covariate of eGFR on CL were concluded to be the final covariate model (Run # 515).

Figure 45. Correlation Matrix of Baseline Covariate Assessment-Continuous Covariates



Source: Population Pharmacokinetic Modeling Report and Exposure Response Analysis for Tebentafusp, Appendix Figure 5

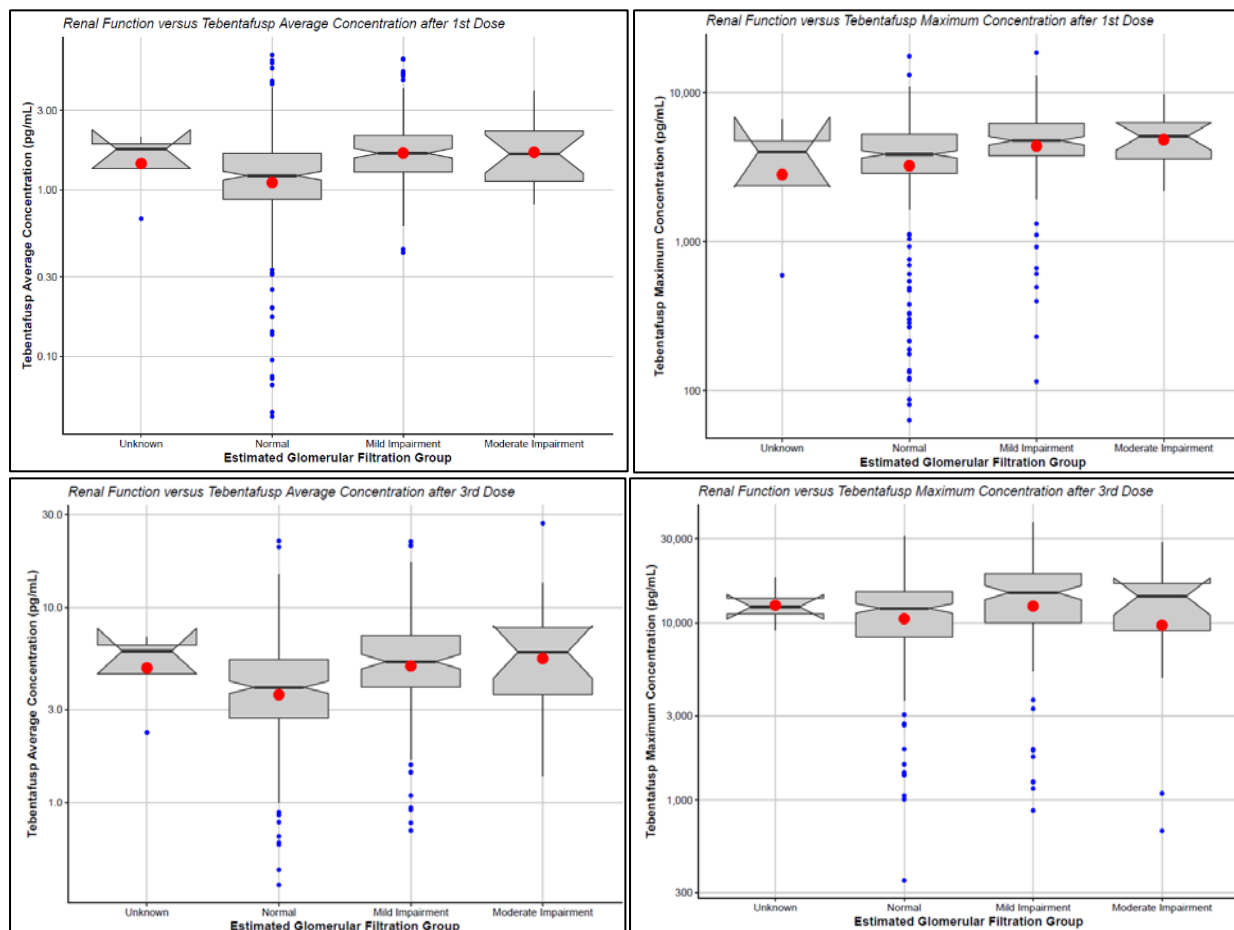
Figure 46. Correlation Matrix of Baseline Covariate Assessment-Categorical Covariates



Source: Population Pharmacokinetic Modeling Report and Exposure Response Analysis for Tebentafusp, Appendix Figure 6

Demographic covariates did not influence the inter-individual variability of the model based on graphical exploration. Therefore, clinical and physiologic covariates of interest, including renal function were added to the model in a stepwise fashion. Due to the molecular weight of tebentafusp, the effect of estimated glomerular filtration (eGFR) was investigated as a continuous covariate on CL. In the forwards addition of covariates, renal function exhibited the largest decrease in OFV and AIC.

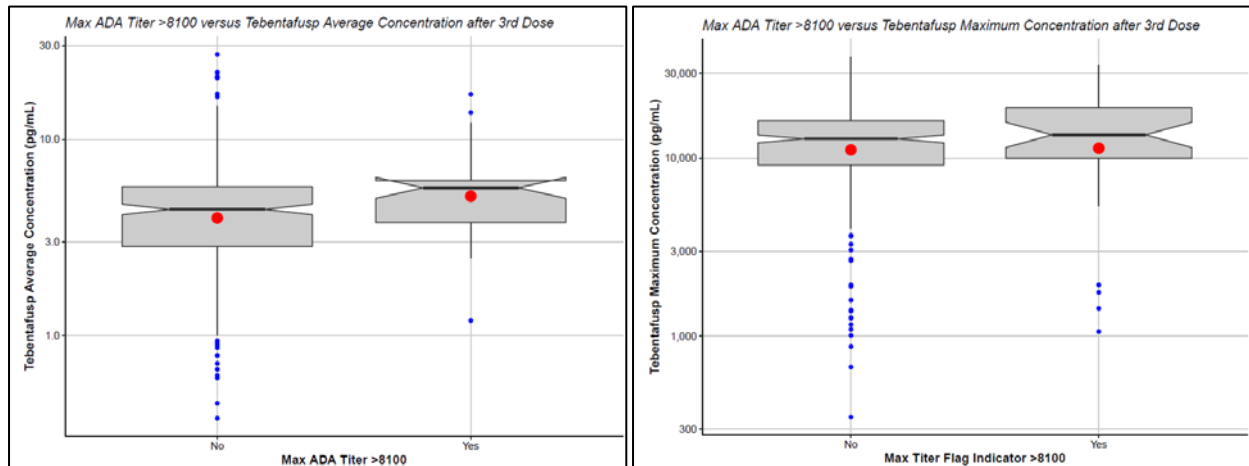
Figure 47. Impact of Renal Clearance by Renal Functional Status on Exposure After First or Third Dose



Source: Analysis based on data “sdtab515”

The final model predicted a trend for faster tebentafusp clearance in ADA-positive patients than that of ADA-negative patients, but the distributions of IIV of CL overlapped between the 2 groups. The ADA effect on PK was further evaluated by stratification of patients with maximum ADA titers greater than or equal to the median titer of 1:8192. In this analysis, tebentafusp exposure was predicted to decrease in the presence of high ADA titers (≥ 8192) beyond the third dose.

Figure 48. Impact of ADA Titer ≥ 8192 on Exposure.



Source: Analysis based on data "sdtab515"

19.5.1.3. The FDA's Assessment:

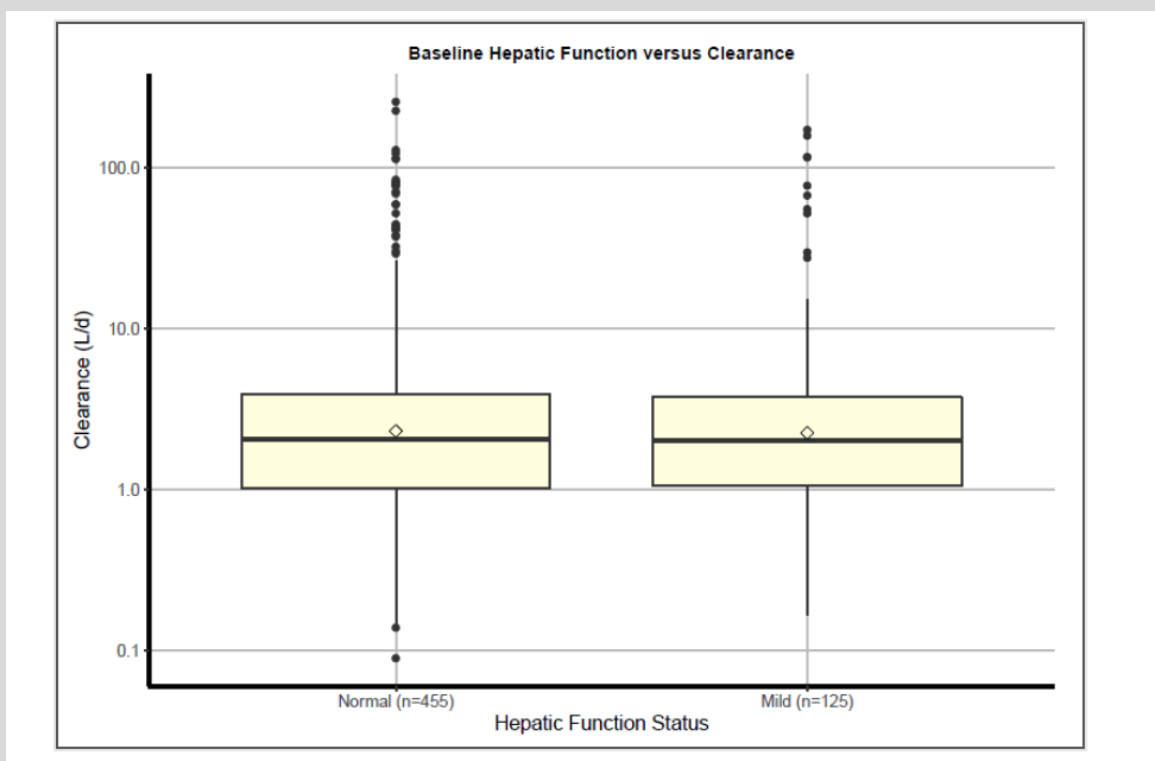
The Applicant's population PK (PPK) model is generally acceptable with minor changes of the definition of immunogenicity. FDA's position is that ADA status should be treated as time-varying covariates. Please refer to section 19.5.4 for detail. Impact of ADA Titer ≥ 8192 on exposure was re-estimated and the USPI was updated in section 12.3. The figures (Figure 15, Figure 48) visualizing the ADA effect on PK provided by the applicant treated ADA status or titer as a fixed factor; therefore, FDA does not agree with the presentation of the data.

Exposure comparison between hepatic impairment patients was requested by IR:

Exposure has been compared in patients with normal hepatic function (n=455) and patients with mild hepatic impairment (n=125) as measured by total bilirubin (TB) and aspartate aminotransferase (AST) (TB $\leq$ upper limit of normal (ULN) and AST $>$ ULN or TB $>$ 1 to 1.5x ULN and any AST). No clinically significant difference in the pharmacokinetics of tebentafusp were identified based on mild hepatic impairment (Figure 49).

Tebentafusp has not been studied in patients with moderate (TB $>$ 1.5 to 3x ULN, any AST) to severe (TB $>$ 3 to 10x ULN, any AST) hepatic impairment.

Figure 49: Comparison of Clearance between Normal and Mild Hepatic Impairment Patients



Source: Response to FDA request for information received on 2021.12.08.

19.5.2. Exposure-Response Analysis for Efficacy

19.5.2.1. The Applicant's Position:

Exposure-response analysis revealed no trends between tebentafusp exposure and key efficacy endpoints over the dose range investigated (weekly intravenous [IV] infusion of 5 ng/kg to 68 mcg of tebentafusp). There was no clinically significant trend between PK exposure and overall survival (OS) or maximal change in tumor size from baseline, a surrogate of OS identified in Phase 2. There was no trend or association between ADA status and OS.

19.5.2.2. ER Efficacy Summary Table

Table 75: ER Efficacy Summary Table

General Information		
Goal of ER analysis		To evaluate the exposure-response relationship of clinical primary endpoints
Study Included		Due to small number of patients in several dosing cohorts and limited PK sampling beyond cycle 1, PK results from studies IMCgp100-01, IMCgp100-102 and IMCgp100-202 were combined into an integrated analysis to investigate effect of PK on efficacy.
Endpoint		Overall survival, tumor percent change from baseline
No. of Patients (total, and with individual PK)		Total: 587, PK 476
Population Characteristics	General	Age median 62 yr (range 23-91 yr) Weight median 78.6 kg (range 43-163.1 kg) Race White – 533 (90.8%) Black/African American – 1 (0.2%) Asian – 1 (0.2%) American Indian/Alaskan Native – 1 (0.2%) Other – 5 (0.9%) Not Reported – 36 (6.1%) Not Allowed – 8 (1.4%)
	Pediatrics (if any)	Not Applicable
Dose(s) Included		<u>IMCgp100-01</u> : Arm 1: 5 ng/kg, 15 ng/kg, 45 ng/kg, 135 ng/kg, 270 ng/kg, 405 ng/kg, 600 ng/kg, 900 ng/kg. Arm 1 (flat dose): 20 mcg inpatient dose escalation, 30 mcg inpatient dose escalation, 50 mcg. Arm 2 (daily dosing): 10 mcg, 20 mcg, 30 mcg, 40 mcg, 50 mcg.

	<u>IMCgp100-102</u>: Day 1 – 20 mcg, Day 8 – 30 mcg, Day 15 and beyond – weekly 54 mcg, 63 mcg, 68 mcg, 73 mcg <u>IMCgp100-202</u>: Day 1 – 20 mcg, Day 8 – 30 mcg, Day 15 and beyond – weekly 68 mcg	
Exposure Metrics Explored (range)	C_{max} and C_{avg}	
Covariates Evaluated	Not applicable	
Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	Empirical assessment of overall survival, tumor percent change from baseline vs C_{max} and C_{avg}	The Applicant's analysis appears reasonable; however exposure response relationships for biologic products should be interpreted cautiously due to the potential for post-hoc confounding effects. Please refer to section 19.5.4 for more details.
Model Parameter Estimates	Not applicable, empirical assessment of endpoints vs PK exposure analyzed.	
Covariates and Clinical Relevance	Responder status, ADA status	
Visualization of E-R relationships	Figure 50. Overall Survival by Quartiles of Average Tebentafusp Concentrations Figure 51. Kaplan Meier Curve of Quartiles of Tebentafusp C_{avg} and Overall Survival Figure 52. Relationship Between Tebentafusp Concentration (C_{avg} or C_{max}) and Percent Change on Tumor Size by ADA Status	
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	(b) (4)	The applicant's description appeared reasonable.

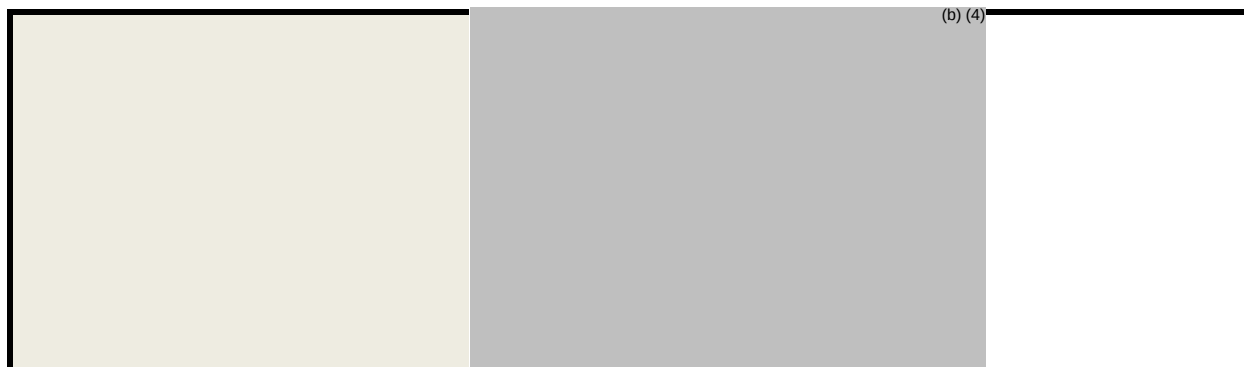


Table 76. Summary of Baseline Characteristics and Laboratory Values in the Dataset.

Descriptive Statistics of Baseline Categorical and Continuous Covariates ^a (Intent to Treat Population)

	Study IMCgp100-01	Study IMCgp100- 102	Study IMCgp100- 202	Total
Sex, n (%)				
Male	54 (64.3)	72 (49.3)	180 (50.4)	306 (52.1)
Female	30 (35.7)	74 (50.7)	177 (49.6)	281 (47.9)
Race, n (%)				
White	79 (94)	145 (99.3)	309 (86.6)	533 (90.8)
Black/African American	1 (1.2)	0 (0)	0 (0)	1 (0.2)
Asian	1 (1.2)	0 (0)	0 (0)	1 (0.2)
American Indian/Alaskan Native	0 (0)	0 (0)	1 (0.3)	1 (0.2)
Other	3 (3.6)	1 (0.7)	1 (0.3)	5 (0.9)
Not Reported	0 (0)	0 (0)	36 (10.1)	36 (6.1)
Not Allowed	0 (0)	0 (0)	8 (2.2)	8 (1.4)
Unknown	0 (0)	0 (0)	2 (0.6)	2 (0.3)
Anti-drug Antibody				
Positive	3 (3.6)	58 (39.7)	77 (21.6)	138 (23.5)
Negative	81 (96.4)	88 (60.3)	279 (78.2)	448 (76.3)
Baseline Anti-drug Antibody				
Baseline Positive	0 (0)	18 (12.3)	16 (4.5)	34 (5.8)
Baseline Negative	84 (100)	128 (87.7)	340 (95.2)	552 (94)
Best Overall Response				

Descriptive Statistics of Baseline Categorical and Continuous Covariates ^a (Intent to Treat Population)

	Study IMCgp100-01	Study IMCgp100- 102	Study IMCgp100- 202	Total
Complete Response	1 (1.2)	0 (0)	1 (0.3)	2 (0.3)
Partial Response	7 (8.3)	12 (8.2)	28 (7.8)	47 (8)
Stable Disease	50 (59.5)	61 (41.8)	120 (33.6)	231 (39.4)
Progressive Disease	28 (33.3)	70 (47.9)	201 (56.3)	299 (50.9)
Minor Response	1 (1.2)	3 (2.1)	7 (2)	11 (1.9)
Target Liver Lesion Diameter				
No target liver lesion	1 (1.2)	1 (0.7)	1 (0.3)	1 (0.2)
Diameter 0 to <3cm	16 (19)	62 (42.5)	192 (53.8)	268 (45.7)
Diameter ≥3cm	19 (22.6)	80 (54.8)	150 (42)	247 (42.1)
Melanoma Type				
Uveal	19 (22.6)	146 (100)	357 (100)	522 (88.9)
Non-Uveal	65 (77.4)	0 (0)	0 (0)	65 (11.1)
Melanoma Stage				
Stage I	12 (14.3)	16 (11)	60 (16.8)	86 (14.7)
Stage II	24 (28.6)	48 (32.9)	126 (35.3)	196 (33.4)
Stage III	20 (23.8)	40 (27.4)	87 (24.4)	145 (24.7)
Stage IV	16 (19)	18 (12.3)	30 (8.4)	62 (10.6)
CRS				
CRS Negative	84 (100)	6 (4.1)	100 (28)	190 (32.4)
CRS Positive	0 (0)	140 (95.9)	257 (72)	397 (67.6)
Maximum CRS Grade (medical adjudication using 2019 ASTCT criteria grading for CRS)				
CRS Grade 0	1 (1.2)	14 (9.6)	38 (10.6)	51 (8.7)
CRS Grade 1	1 (1.2)	47 (32.2)	33 (9.2)	79 (13.5)
CRS Grade 2	1 (1.2)	77 (52.7)	187 (52.4)	263 (44.8)
CRS Grade 3	1 (1.2)	5 (3.4)	3 (0.8)	7 (1.2)
CRS Grade 4	1 (1.2)	2 (1.4)	1 (0.3)	2 (0.3)
Fever				
Fever Negative	84 (100)	21 (14.4)	152 (42.6)	257 (43.8)

Descriptive Statistics of Baseline Categorical and Continuous Covariates ^a (Intent to Treat Population)

	Study IMCgp100-01	Study IMCgp100- 102	Study IMCgp100- 202	Total
Fever Positive	0 (0)	125 (85.6)	205 (57.4)	330 (56.2)
Hypotension				
Hypotensive Negative	84 (100)	77 (52.7)	255 (71.4)	416 (70.9)
Hypotensive Positive	0 (0)	69 (47.3)	102 (28.6)	171 (29.1)
Skin Toxicity				
Skin Toxicity Negative	5 (6)	9 (6.2)	79 (22.1)	93 (15.8)
Skin Toxicity Positive	79 (94)	137 (93.8)	278 (77.9)	494 (84.2)
Maximum Skin Tox Grade				
Skin Toxicity Grade 1	23 (27.4)	44 (30.1)	106 (29.7)	171 (29.1)
Skin Toxicity Grade 2	36 (42.9)	65 (44.5)	125 (35)	224 (38.2)
Skin Toxicity Grade 3	23 (27.4)	31 (21.2)	50 (14)	102 (17.4)
Hepatic Toxicity				
Hepatic Toxicity Negative	68 (81)	86 (58.9)	219 (61.3)	373 (63.5)
Hepatic Toxicity Positive	16 (19)	60 (41.1)	138 (38.7)	214 (36.5)
Maximum Hepatic Tox Grade				
Hepatic Toxicity Grade 1	8 (9.5)	27 (18.5)	57 (16)	90 (15.3)
Hepatic Toxicity Grade 2	5 (6)	12 (8.2)	44 (12.3)	59 (10.1)
Hepatic Toxicity Grade 3	5 (6)	16 (11)	36 (10.1)	55 (9.4)
Hepatic Toxicity Grade 4	2 (2.4)	9 (6.2)	5 (1.4)	14 (2.4)
Age (years)				
Mean	58.7	60.4	61.9	61.1
Standard Deviation	11.5	11.1	11.5	11.4
Minimum	25	25	23	23
Median	60	60.5	64	62
Maximum	78	88	91	91
Weight (kg)				
Mean	83.1	77.4	78.9	79.1
Standard Deviation	19	18.6	17.9	18.3
Minimum	47.3	44	43	43

Descriptive Statistics of Baseline Categorical and Continuous Covariates ^a (Intent to Treat Population)

	Study IMCgp100-01	Study IMCgp100-102	Study IMCgp100-202	Total
Median	84.1	76.5	79	78.6
Maximum	134.2	144.7	163.1	163.1
BMI (kg/m²)				
Mean	27.7	26.7	27.2	27.2
Standard Deviation	5.2	5.2	5.2	5.2
Minimum	17.9	16.6	16.4	16.4
Median	28	25.8	26.7	26.7
Maximum	45.4	44.5	48.7	48.7
Estimated Glomerular Filtration Rate (mL/min/1.73m²)				
Mean	107.6	95	94.1	96.3
Standard Deviation	23.9	22.1	21.4	22.4
Minimum	64.1	43.6	44.6	43.6
Median	102.8	97.8	92.8	94.9
Maximum	203.9	165.8	156.4	203.9
Baseline Sum of Diameter Target Lesions				
Mean	89	88.1	65.5	74.5
Standard Deviation	64.7	61.6	51	56.9
Minimum	10	10	10	10
Median	74	71	47	57.2
Maximum	288	343	310	343
Best Change from Baseline Sum of Diameter Target Lesions				
Mean	4.6	4.3	8.9	7.1
Standard Deviation	22.8	23.1	26.7	25.4
Minimum	-47	-66	-84	-84
Median	0	3	4	3
Maximum	106	102.4	145.5	145.5

Descriptive Statistics of Baseline Categorical and Continuous Covariates ^a (Intent to Treat Population)

	Study IMCgp100-01	Study IMCgp100-102	Study IMCgp100-202	Total
Best Percent Change from Baseline Sum of Diameter Target Lesions				
Mean	0.3	2.8	12	8
Standard Deviation	25.9	29.1	43.9	38.7
Minimum	-78.6	-84	-100	-100
Median	0	3.9	9	5.1
Maximum	78.5	110.3	220.7	220.7
Maximum Titer				
Mean	NA	427042.8	38363.6	220165.2
Standard Deviation	NA	2268487	137349.4	1559689.9
Minimum	NA	4	2	2
Median	NA	384	192	256
Maximum	NA	16777216	1048576	16777216

CR: complete response; CRS: cytokine release syndrome; MR: minor response; n: number; NA: not applicable; PD: progressive disease; PR: partial response; SD: stable disease.

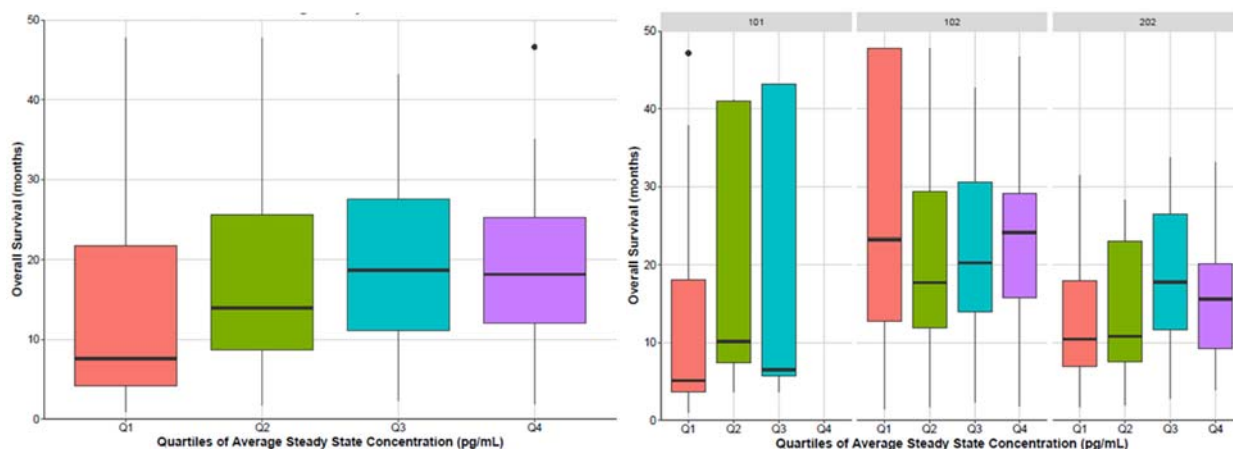
^a Categorical demographic data is presented as count (% population)

MR was treated as SD in exposure-response analysis. CRS Grade was based on a medical adjudication using 2019 ASCTC criteria for grading CRS. The incidence and severity of CRS was determined based on AE, concomitant medication, and vital signs data. Therefore, the incidence of CRS (based on adjudication by the Sponsor) as an AESI was higher than the incidence of the AE term CRS (per investigator).

Source: Population Pharmacokinetic Modeling Report and Exposure-Response Analysis for Tebentafusp, Table 6

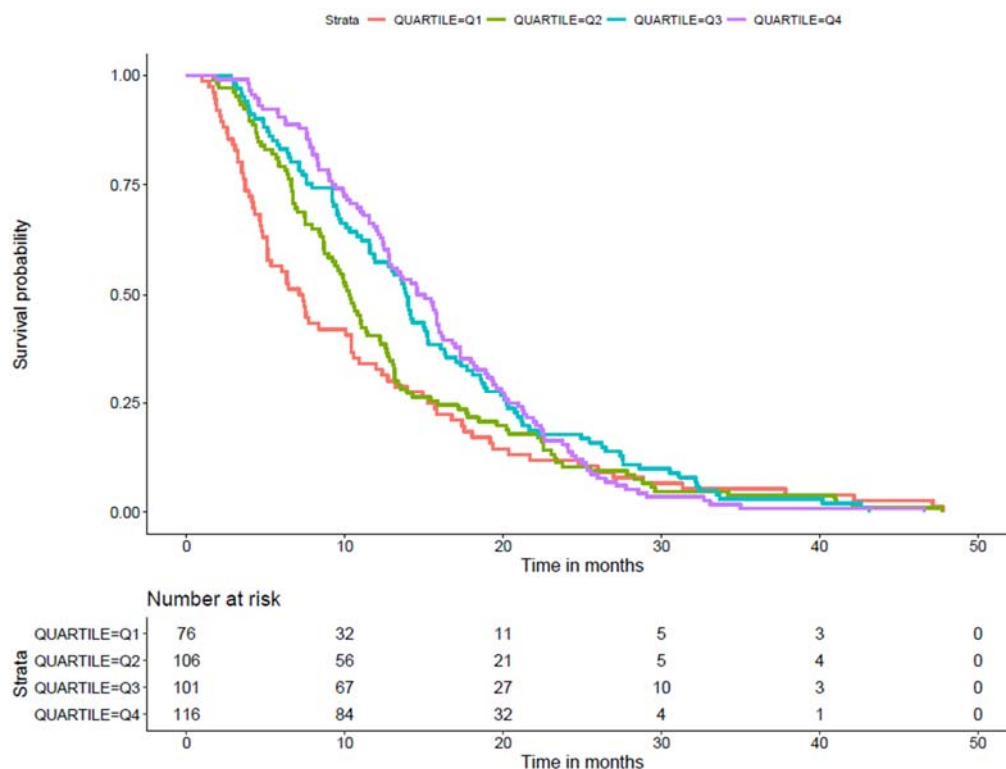
Overall, there were no clinically significant trends or associations exhibited between exposure and OS. While a slight trend for lower OS in the lowest C_{avg} quartile was noted in the integrated analysis across studies, there was also substantial overlap in OS among the quartiles. The apparent trend can be explained by the fact that the lowest C_{avg} quartile is predominantly composed of patients dosed with lower concentrations of tebentafusp from study IMCgp100-01. Therefore, monitoring of tebentafusp exposure and dose adjustments are not necessary.

Figure 50. Overall Survival by Quartiles of Average Tebentafusp Concentrations



Left Panel: Integrated summary across studies IMCgp100-01, IMCgp100-102 and IMCgp100-202. Right Panel: Analysis by individual study. For boxplots, bottom and top halves of each box correspond to first and third quartiles, respectively (inter quartile IQR), line inside box is median of the distribution. Upper and lower whiskers extend from the hinge to values $\leq 1.5 \cdot \text{IQR}$ from hinge. Outlier data beyond whiskers plotted individually as solid circles. Quartile 1 (orange)= 0 to 2592.6 pg/mL, Quartile 2 (green) = 2592.6 to 4217.5 pg/mL, Quartile 3 (blue) = 4217.5 to 5710.4 pg/mL, Quartile 4 (purple) = 5710.4 to 27005.0 pg/mL. Source: Module 2.7.2, Figure 17

Figure 51. Kaplan Meier Curve of Quartiles of Tebentafusp C_{avg} and Overall Survival

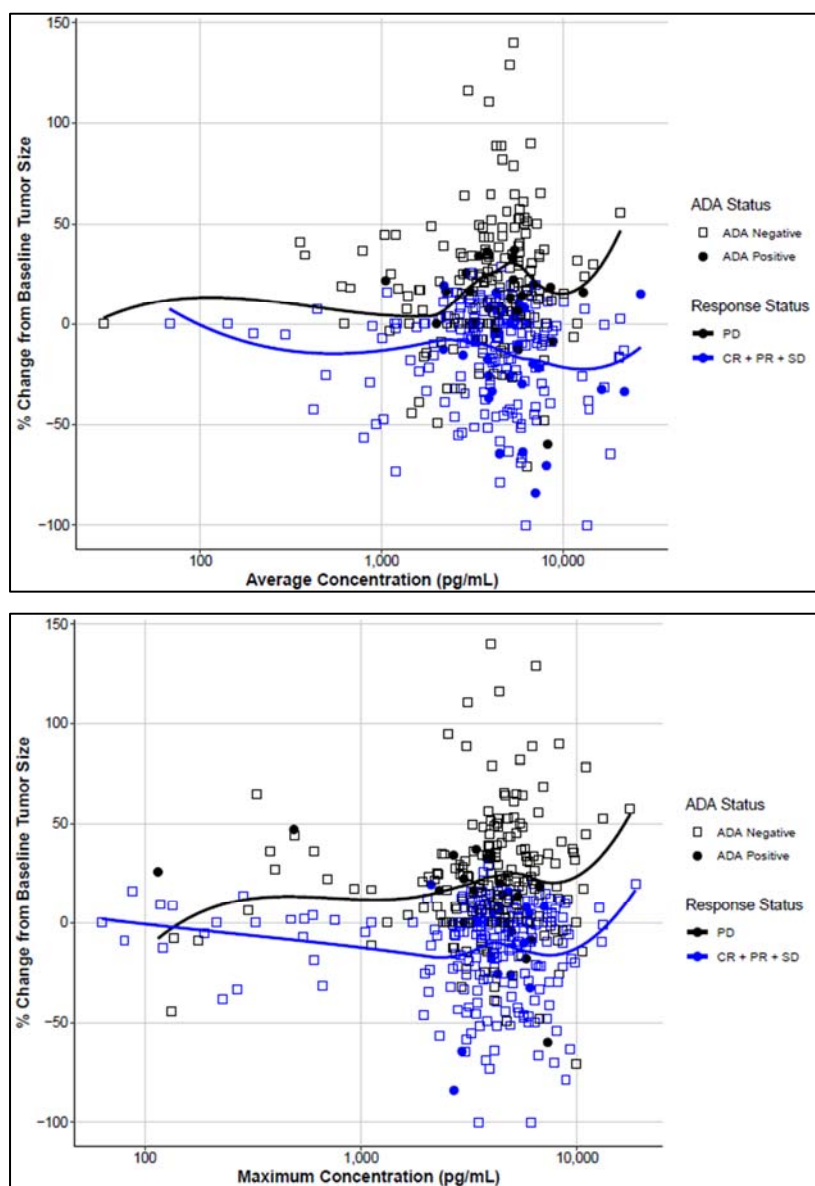


Quartiles represent the quartile of average concentration with 68 mcg dose. Quartile 1 = 0 to 2592.6 pg/mL, Quartile 2 = 2592.6 to 4217.5 pg/mL, Quartile 3 = 4217.5 to 5710.4 pg/mL, Quartile 4 = 5710.4 to 27005.0 pg/mL. Numbers at risk represent number of individual patients within each quartile of C_{avg} .

Source: Module 2.7.2, Figure 18

There was no trend for association between percent change from baseline in tumor size and C_{avg} or C_{max} of tebentafusp when stratified by ADA and RECIST v1.1 response status.

Figure 52. Relationship Between Tebentafusp Concentration (C_{avg} or C_{max}) and Percent Change on Tumor Size by ADA Status



ADA = anti-drug antibody; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

Solid lines represent loess line by responder status. Open squares represent ADA negative patients, solid dots represent ADA positive patients. Black dots/squares and loess line represent patients with PD. Blue dots/squares and loess line represent responders (patients with PR, SD, or CR).

Source: Module 2.7.2, Figure 20 (C_{avg}), Figure 21 (C_{max})

19.5.2.3. **The FDA's Assessment:**

The Applicant's analysis is reasonable; however, exposure-response relationships for biologic products should be interpreted with caution due to the potential for post-hoc confounding effects.

19.5.3. **Exposure-Response Analysis for Safety**

19.5.3.1. **The Applicant's Position:**

Exposure-response analysis revealed no trends between tebentafusp exposure and key safety endpoints over the dose range investigated (weekly intravenous [IV] infusion of 5 ng/kg to 68 mcg of tebentafusp). There was no association between PK exposure and acute skin reaction, rash, hypo/hyper-pigmentation, or hepatotoxicity. Cytokine release syndrome (CRS) is known to be dose dependent, and there was a trend for lower PK exposure in patients with no CRS. There was no trend between PK exposure and interleukin (IL) 6 concentration or either baseline or on-treatment lymphocyte counts.

19.5.3.2. **ER Safety Summary Table [Do not modify the grey cells.]**

Table 77: ER Safety Summary Table

General Information		
Goal of ER analysis		• To evaluate exposure-response relationship of adverse events (eg, skin toxicity, hepatic toxicity, and Cytokine Release Syndrome [CRS]) • To evaluate exposure-response of exploratory adverse events (eg, rash, hypo/hyper-pigmentation)
Study Included		Due to small number of patients in several dosing cohorts and the limited PK sampling beyond cycle 1, the PK from studies IMCgp100-01, IMCgp100-102 and IMCgp100-202 were combined as an integrated analysis to investigate effect of PK on safety.
Population Included		Patients with advanced malignant melanoma Patients with advanced metastatic uveal melanoma
Endpoint		Skin toxicity, hepatic toxicity, Cytokine Release Syndrome [CRS], rash, hypo/hyper-pigmentation, IL6, and absolute lymphocyte count
No. of Patients (total, and with individual PK)		Total: 587, PK 476
Population Characteristics	General	Age median 62 yr (range 23-91 yr) Weight median 78.6 kg (range 43-163.1 kg)

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		306 (52.1%) male Race White – 533 (90.8%) Black/African American – 1 (0.2%) Asian – 1 (0.2%) American Indian/Alaskan Native – 1 (0.2%) Other – 5 (0.9%) Not Reported – 36 (6.1%) Not Allowed – 8 (1.4%)
	Organ impairment	Hepatic (Child-Pugh, NCI, etc): 0 (0%) Renal (CrCL, etc): Normal renal function 353 (60.2%) Mild impairment 201 (34.3%) Moderate impairment 25 (4.3%) Unknown 7 (1.2%)
	Pediatrics (if any)	Not Applicable
	Geriatrics (if any)	Of the 410 patients with metastatic uveal melanoma treated, 175 (43%) were 65 years of age and older and 38 (9%) were 75 years of age and older. 306 (52.1%) male
Dose(s) Included		<u>IMCgp100-01</u> : Arm 1: 5 ng/kg, 15 ng/kg, 45 ng/kg, 135 ng/kg, 270 ng/kg, 405 ng/kg, 600 ng/kg, 900 ng/kg. Arm 1 (flat dose): 20 mcg inpatient dose escalation, 30 mcg inpatient dose escalation, 50 mcg. Arm 2 (daily dosing): 10 mcg, 20 mcg, 30 mcg, 40 mcg, 50 mcg. <u>IMCgp100-102</u> : Day 1 – 20 mcg, Day 8 – 30 mcg, Day 15 and beyond – weekly 54 mcg, 63 mcg, 68 mcg, 73 mcg <u>IMCgp100-202</u> : Day 1 – 20 mcg, Day 8 – 30 mcg, Day 15 and beyond – weekly 68 mcg
Exposure Metrics Explored (range)		Skin toxicity, rash, hypo/hyper-pigmentation or hepatotoxicity, Cytokine release syndrome (CRS), IL6 and absolute lymphocyte count (ALC)
Covariates Evaluated		Responder status, ADA status
Final Model Parameters		Summary
Model Structure		Empirical assessment of skin toxicity, rash, hypo/hyper-pigmentation or hepatotoxicity, Cytokine release syndrome (CRS), IL-6 and ALC vs C _{max} and C _{avg}
		Acceptability [FDA's comments]
		The Applicant's analyses appear reasonable; however exposure response

Model Parameter Estimates	Not applicable, empirical assessment of endpoints vs PK exposure analyzed.	relationships for biologic products should be interpreted with caution due to the potential for post-hoc confounding effects. Please refer to section 19.4.3.3 for more details.
Covariates and Clinical Relevance	Responder status, ADA status	
Visualization of E-R relationships	Figure 53. Relationship Between Average Tebentafusp Concentration and Acute Skin Reaction Figure 54. Relationship Between Maximum Tebentafusp Concentration and Acute Skin Reaction Figure 55. Relationship Between Average Tebentafusp Concentration and Rash by Responder Status Figure 56. Relationship Between Maximum Tebentafusp Concentration and Rash Figure 57. Relationship Between Average Tebentafusp Concentration and Hypo/Hyper-pigmentation Change Figure 58. Relationship Between Maximum Tebentafusp Concentration and Hypo/hyper-Pigment Change Figure 59. Relationship between Tebentafusp C_{avg} and Hepatic Toxicity by Responder Status	

	Figure 60. Relationship Between Maximum Tebentafusp Concentration and Hepatic Toxicity Figure 61. Relationship Between Average Tebentafusp Concentration and CRS Figure 62. Relationship Between Maximum Tebentafusp Concentration and CRS Figure 63. Plasma IL-6 Levels Versus Patient Status Figure 64. Relationship Between Average and Maximum Tebentafusp Concentration and IL-6 Release Over Time Figure 65. Relationship Between Average Tebentafusp Concentration and Lymphocyte Count Figure 66. Relationship Between Maximum Tebentafusp Concentration and Lymphocyte Count Figure 67. Box Plots of Tebentafusp C_{avg} and Baseline Lymphocyte Count by Responder Status	

Overall Clinical Relevance for ER	There was no clinically significant trend between PK exposure and overall survival (OS) or maximal change in tumor size from baseline, a surrogate of OS identified in Phase 2. Overall, there was no clinically significant trend or association between ADA status and key efficacy endpoints. There was no association between PK exposure and key on-treatment toxicities including: acute skin reactions, rash, hypo/hyper-pigmentation or hepatotoxicity. CRS is known to be dose dependent, and there was a trend for lower PK exposure in patients with no CRS.	
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	(b) (4)	The proposed description appears reasonable.

Table 78. Descriptive Statistics of Baseline Categorical and Continuous Covariates ^a (Intent to Treat Population)

	Study IMCgp100- 01	Study IMCgp100- 102	Study IMCgp100- 202	Total
Sex, n (%)				
Male	54 (64.3)	72 (49.3)	180 (50.4)	306 (52.1)
Female	30 (35.7)	74 (50.7)	177 (49.6)	281 (47.9)
Race, n (%)				
White	79 (94)	145 (99.3)	309 (86.6)	533 (90.8)
Black/African American	1 (1.2)	0 (0)	0 (0)	1 (0.2)
Asian	1 (1.2)	0 (0)	0 (0)	1 (0.2)
American Indian/Alaskan Native	0 (0)	0 (0)	1 (0.3)	1 (0.2)
Other	3 (3.6)	1 (0.7)	1 (0.3)	5 (0.9)
Not Reported	0 (0)	0 (0)	36 (10.1)	36 (6.1)
Not Allowed	0 (0)	0 (0)	8 (2.2)	8 (1.4)
Unknown	0 (0)	0 (0)	2 (0.6)	2 (0.3)
Anti-drug Antibody				
Positive	3 (3.6)	58 (39.7)	77 (21.6)	138 (23.5)
Negative	81 (96.4)	88 (60.3)	279 (78.2)	448 (76.3)
Baseline Anti-drug Antibody				
Baseline Positive	0 (0)	18 (12.3)	16 (4.5)	34 (5.8)
Baseline Negative	84 (100)	128 (87.7)	340 (95.2)	552 (94)
Best Overall Response				
Complete Response	1 (1.2)	0 (0)	1 (0.3)	2 (0.3)
Partial Response	7 (8.3)	12 (8.2)	28 (7.8)	47 (8)
Stable Disease	50 (59.5)	61 (41.8)	120 (33.6)	231 (39.4)
Progressive Disease	28 (33.3)	70 (47.9)	201 (56.3)	299 (50.9)
Minor Response	1 (1.2)	3 (2.1)	7 (2)	11 (1.9)
Target Liver Lesion Diameter				
No target liver lesion	1 (1.2)	1 (0.7)	1 (0.3)	1 (0.2)
Diameter 0 to <3cm	16 (19)	62 (42.5)	192 (53.8)	268 (45.7)

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	Study IMCgp100- 01	Study IMCgp100- 102	Study IMCgp100- 202	Total
Diameter≥3cm	19 (22.6)	80 (54.8)	150 (42)	247 (42.1)
Melanoma Type				
Uveal	19 (22.6)	146 (100)	357 (100)	522 (88.9)
Non-Uveal	65 (77.4)	0 (0)	0 (0)	65 (11.1)
Melanoma Stage				
Stage I	12 (14.3)	16 (11)	60 (16.8)	86 (14.7)
Stage II	24 (28.6)	48 (32.9)	126 (35.3)	196 (33.4)
Stage III	20 (23.8)	40 (27.4)	87 (24.4)	145 (24.7)
Stage IV	16 (19)	18 (12.3)	30 (8.4)	62 (10.6)
CRS				
CRS Negative	84 (100)	6 (4.1)	100 (28)	190 (32.4)
CRS Positive	0 (0)	140 (95.9)	257 (72)	397 (67.6)
Maximum CRS Grade (medical adjudication using 2019 ASTCT criteria grading for CRS)				
CRS Grade 0	1 (1.2)	14 (9.6)	38 (10.6)	51 (8.7)
CRS Grade 1	1 (1.2)	47 (32.2)	33 (9.2)	79 (13.5)
CRS Grade 2	1 (1.2)	77 (52.7)	187 (52.4)	263 (44.8)
CRS Grade 3	1 (1.2)	5 (3.4)	3 (0.8)	7 (1.2)
CRS Grade 4	1 (1.2)	2 (1.4)	1 (0.3)	2 (0.3)
Fever				
Fever Negative	84 (100)	21 (14.4)	152 (42.6)	257 (43.8)
Fever Positive	0 (0)	125 (85.6)	205 (57.4)	330 (56.2)
Hypotension				
Hypotensive Negative	84 (100)	77 (52.7)	255 (71.4)	416 (70.9)
Hypotensive Positive	0 (0)	69 (47.3)	102 (28.6)	171 (29.1)
Skin Toxicity				
Skin Toxicity Negative	5 (6)	9 (6.2)	79 (22.1)	93 (15.8)
Skin Toxicity Positive	79 (94)	137 (93.8)	278 (77.9)	494 (84.2)
Maximum Skin Tox Grade				

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	Study IMCgp100- 01	Study IMCgp100- 102	Study IMCgp100- 202	Total
Skin Toxicity Grade 1	23 (27.4)	44 (30.1)	106 (29.7)	171 (29.1)
Skin Toxicity Grade 2	36 (42.9)	65 (44.5)	125 (35)	224 (38.2)
Skin Toxicity Grade 3	23 (27.4)	31 (21.2)	50 (14)	102 (17.4)
Hepatic Toxicity				
Hepatic Toxicity Negative	68 (81)	86 (58.9)	219 (61.3)	373 (63.5)
Hepatic Toxicity Positive	16 (19)	60 (41.1)	138 (38.7)	214 (36.5)
Maximum Hepatic Tox Grade				
Hepatic Toxicity Grade 1	8 (9.5)	27 (18.5)	57 (16)	90 (15.3)
Hepatic Toxicity Grade 2	5 (6)	12 (8.2)	44 (12.3)	59 (10.1)
Hepatic Toxicity Grade 3	5 (6)	16 (11)	36 (10.1)	55 (9.4)
Hepatic Toxicity Grade 4	2 (2.4)	9 (6.2)	5 (1.4)	14 (2.4)
Age (years)				
Mean	58.7	60.4	61.9	61.1
Standard Deviation	11.5	11.1	11.5	11.4
Minimum	25	25	23	23
Median	60	60.5	64	62
Maximum	78	88	91	91
Weight (kg)				
Mean	83.1	77.4	78.9	79.1
Standard Deviation	19	18.6	17.9	18.3
Minimum	47.3	44	43	43
Median	84.1	76.5	79	78.6
Maximum	134.2	144.7	163.1	163.1
BMI (kg/m^2)				
Mean	27.7	26.7	27.2	27.2
Standard Deviation	5.2	5.2	5.2	5.2
Minimum	17.9	16.6	16.4	16.4
Median	28	25.8	26.7	26.7
Maximum	45.4	44.5	48.7	48.7

	Study IMCgp100- 01	Study IMCgp100- 102	Study IMCgp100- 202	Total
Estimated Glomerular Filtration Rate (mL/min/1.73m²)				
Mean	107.6	95	94.1	96.3
Standard Deviation	23.9	22.1	21.4	22.4
Minimum	64.1	43.6	44.6	43.6
Median	102.8	97.8	92.8	94.9
Maximum	203.9	165.8	156.4	203.9
Baseline Sum of Diameter Target Lesions				
Mean	89	88.1	65.5	74.5
Standard Deviation	64.7	61.6	51	56.9
Minimum	10	10	10	10
Median	74	71	47	57.2
Maximum	288	343	310	343
Best Change from Baseline Sum of Diameter Target Lesions				
Mean	4.6	4.3	8.9	7.1
Standard Deviation	22.8	23.1	26.7	25.4
Minimum	-47	-66	-84	-84
Median	0	3	4	3
Maximum	106	102.4	145.5	145.5
Best Percent Change from Baseline Sum of Diameter Target Lesions				
Mean	0.3	2.8	12	8
Standard Deviation	25.9	29.1	43.9	38.7
Minimum	-78.6	-84	-100	-100
Median	0	3.9	9	5.1
Maximum	78.5	110.3	220.7	220.7
Maximum Titer				
Mean	NA	427042.8	38363.6	220165.2

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	Study IMCgp100- 01	Study IMCgp100- 102	Study IMCgp100- 202	Total
Standard Deviation	NA	2268487	137349.4	1559689.9
Minimum	NA	4	2	2
Median	NA	384	192	256
Maximum	NA	16777216	1048576	16777216

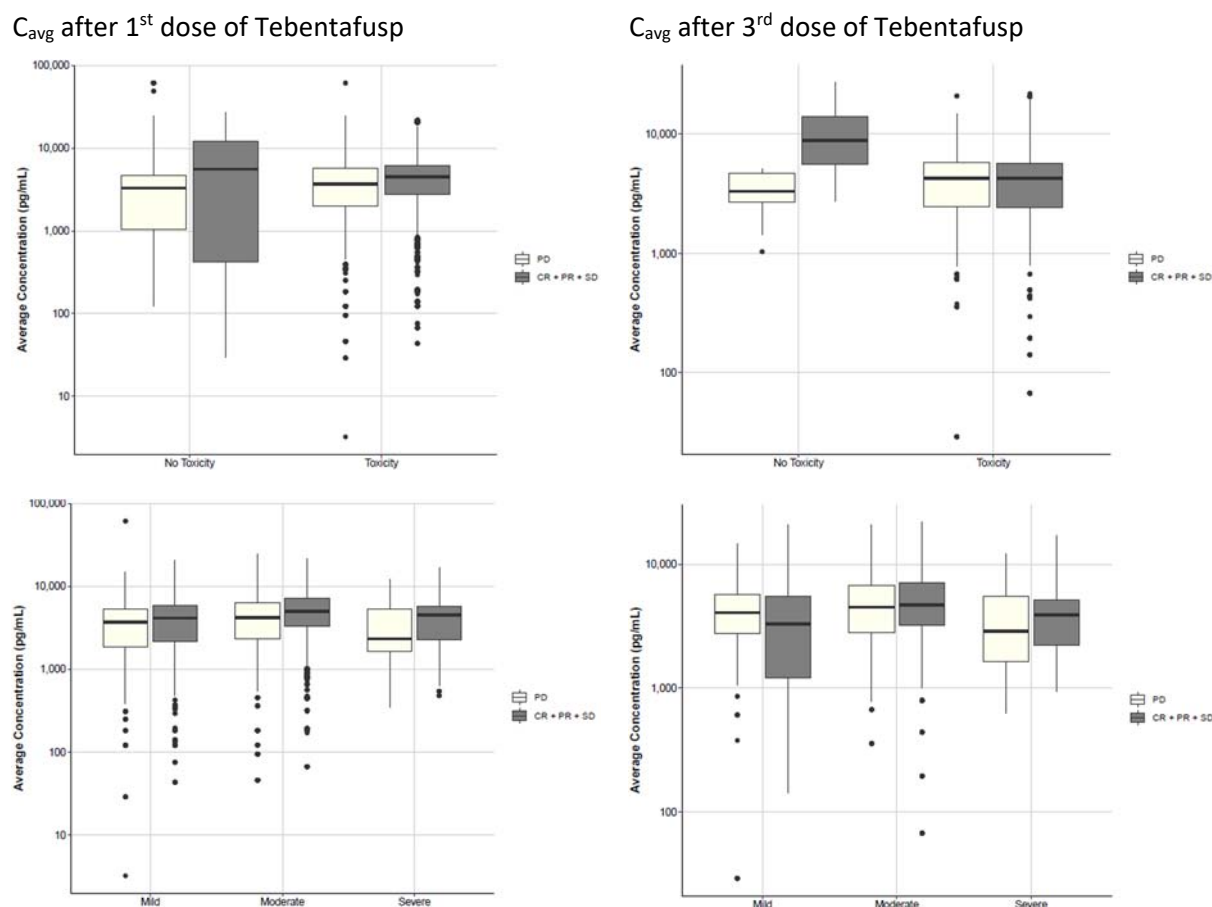
CR: complete response; CRS: cytokine release syndrome; MR: minor response; n: number; NA: not applicable; PD: progressive disease; PR: partial response; SD: stable disease.

a Categorical demographic data is presented as count (% population)

MR was treated as SD in exposure-response analysis. CRS Grade was based on a medical adjudication using 2019 ASCTC criteria for grading CRS. The incidence and severity of CRS was determined based on AE, concomitant medication, and vital signs data. Therefore, the incidence of CRS (based on adjudication by the Sponsor) as an AESI was higher than the incidence of the AE term CRS (per investigator).

Source: Population Pharmacokinetic Modeling Report and Exposure-Response Analysis for Tebentafusp, Table 6

Figure 53. Relationship Between Average Tebentafusp Concentration and Acute Skin Reaction



C_{avg} = average serum concentration; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

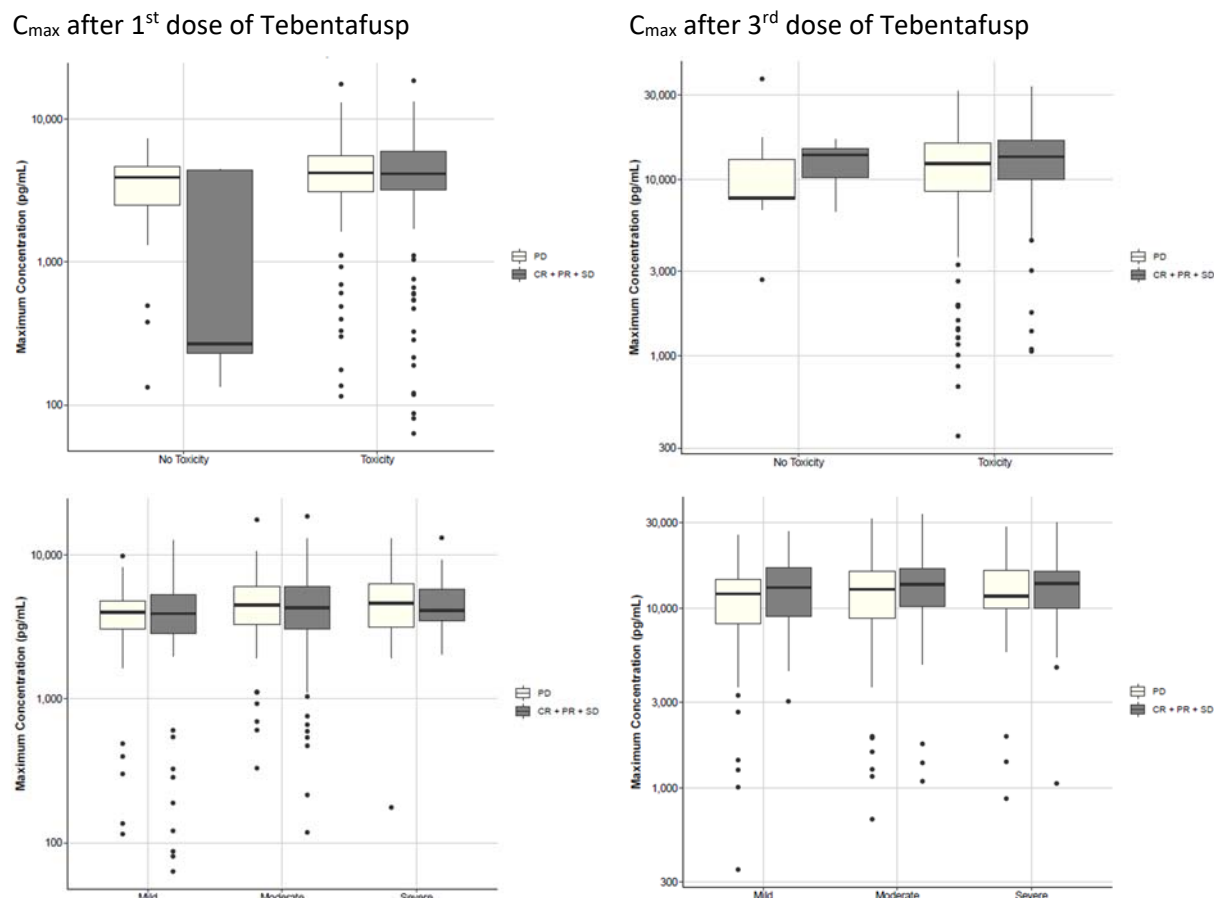
Top Left Panel: Integrated results of effect of average tebentafusp concentration on skin reaction after first dose (20 mcg). Bottom Left Panel: Integrated results of effect of average tebentafusp concentration on skin reaction after first dose stratified by toxicity grade. Top Right Panel: Integrated results of effect of average tebentafusp concentration on skin reaction after third dose (68 mcg). Bottom Right Panel: Integrated results of effect of average tebentafusp concentration on skin reaction after third dose (68 mcg) stratified by toxicity grade. Toxicity severity was based on CTCAE v4.03 criteria.

For boxplots, the bottom and top half of box correspond to the first and third quartiles, respectively (inter quartile IQR), while line inside box is median of the distribution. Upper and lower whiskers extend from hinge to values $\leq 1.5 \cdot \text{IQR}$ from the hinge. Outlier data beyond whiskers are plotted individually as solid circles.

White boxes represent patients with PD; Grey boxes represent patients with PR, SD, or CR.

Source: Module 2.7.2, Figure 22

Figure 54. Relationship Between Maximum Tebentafusp Concentration and Acute Skin Reaction



C_{max} = maximum serum concentration; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

Top Left Panel: Integrated results of effect of maximum tebentafusp concentration on skin reaction after first dose (20 mcg). Bottom Left Panel: Integrated results of effect of maximum tebentafusp concentration on skin reaction after first dose stratified by toxicity grade. Top Right Panel: Integrated results of effect of maximum tebentafusp concentration on skin reaction after third dose (68 mcg). Bottom Right Panel: Integrated results of effect of maximum tebentafusp concentration on skin reaction after third dose (68 mcg) stratified by toxicity grade.

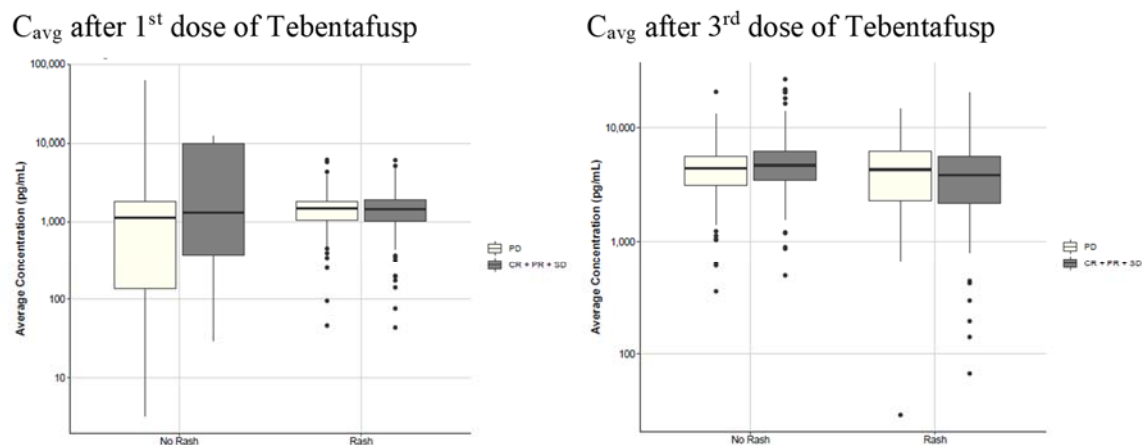
Notes: Skin reaction included subjects with pigment change, rash, and vitiligo. Toxicity severity is based on CTCAE v4.03 criteria.

For boxplots, bottom and top half of box correspond to the first and third quartiles, respectively (inter quartile IQR), while line inside box is the median of the distribution. Upper and lower whiskers extend from hinge to values $\leq 1.5 \cdot \text{IQR}$ from hinge. Outlier data beyond whiskers are plotted individually as solid circles.

White boxes represent patients with PD; Grey boxes represent patients with PR, SD, or CR.

Source: Module 2.7.2, Figure 23

Figure 55. Relationship Between Average Tebentafusp Concentration and Rash by Responder Status

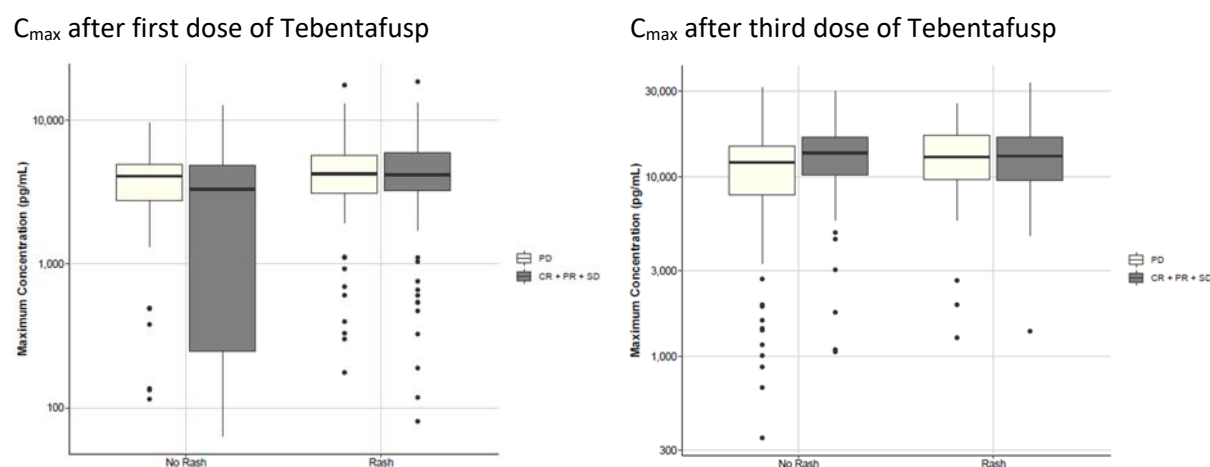


C_{avg} = average serum concentration; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

Left Panel: Average concentration of tebentafusp versus rash after first tebentafusp dose (20 mcg); Right Panel: Average concentration of tebentafusp versus rash after third tebentafusp dose (target 68 mcg).

Source: Module 2.7.2, Figure 24

Figure 56. Relationship Between Maximum Tebentafusp Concentration and Rash

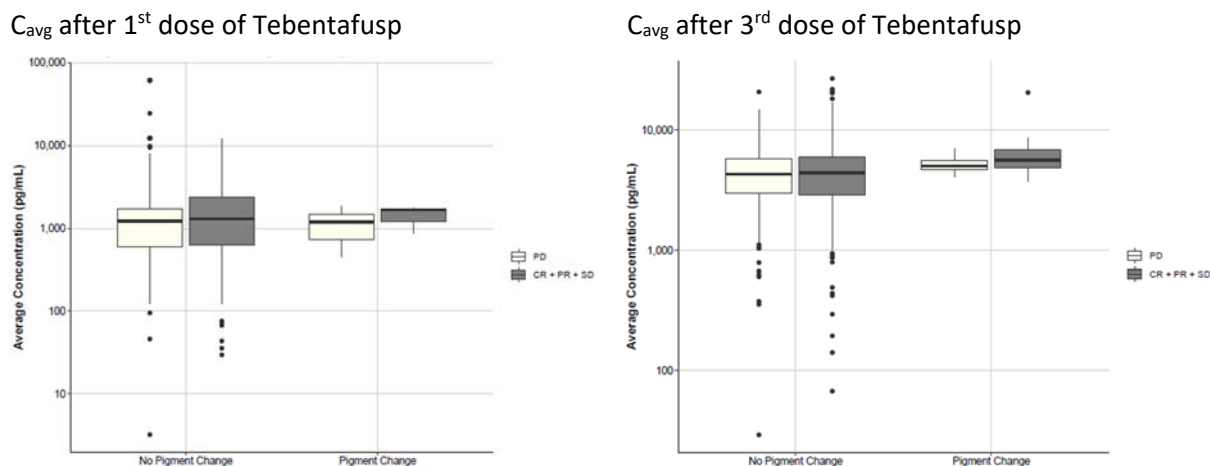


C_{max} = maximum serum concentration; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

Left Panel: Maximum concentration of tebentafusp versus rash after first tebentafusp dose; Right Panel: Maximum concentration of tebentafusp versus rash after third tebentafusp dose (target 68 mcg).

Source: Module 2.7.2, Figure 25

Figure 57. Relationship Between Average Tebentafusp Concentration and Hypo/Hyper-pigmentation Change



C_{avg} = average serum concentration; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

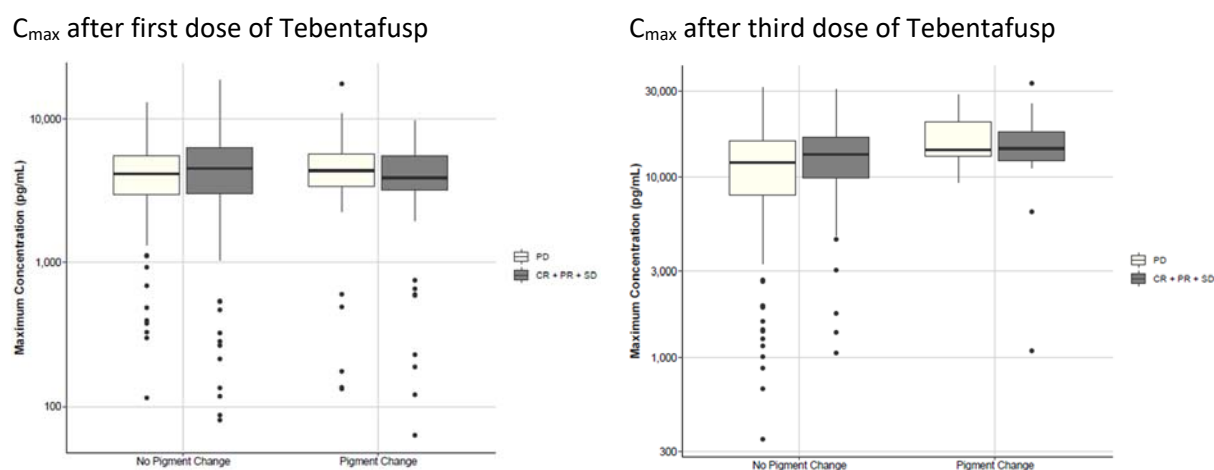
Left Panel: Average serum concentration of tebentafusp versus pigment change after first tebentafusp dose (20 mcg); Right Panel: Average serum concentration of tebentafusp versus pigment change after third tebentafusp dose (target 68 mcg).

For boxplots, the bottom and top half of the box correspond to the first and third quartiles, respectively (inter quartile IQR), while line inside box is the median of the distribution. The upper and lower whiskers extend from hinge to values $\leq 1.5 \cdot \text{IQR}$ from the hinge. Outlier data beyond whiskers are plotted individually as solid circles.

White boxes represent patients with PD; Grey boxes represent patients with PR, SD, or CR.

Source: Module 2.7.2, Figure 26

Figure 58. Relationship Between Maximum Tebentafusp Concentration and Hypo/hyper-Pigment Change

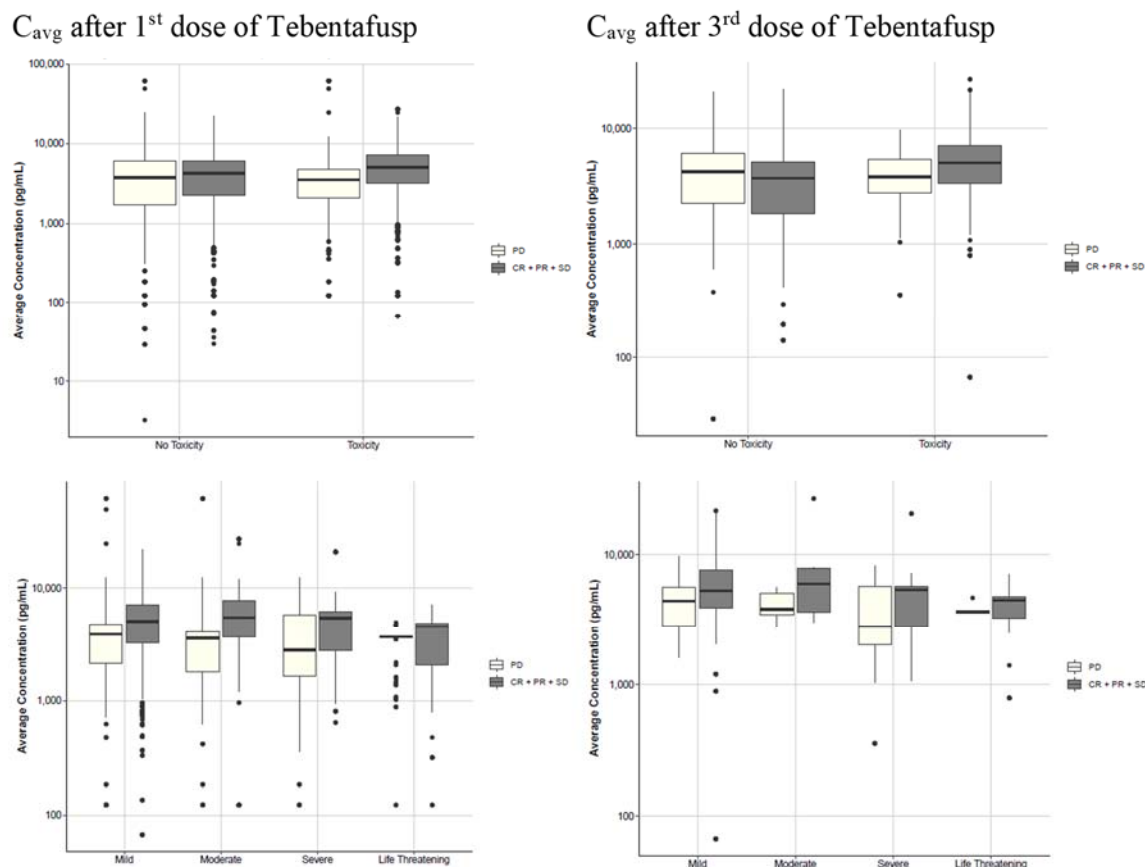


C_{max} = maximum serum concentration; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

Left Panel: Maximum concentration of tebentafusp versus pigment change after first tebentafusp dose; Right Panel: Maximum concentration of tebentafusp versus pigment change after third tebentafusp dose (target 68 mcg).

Source: Module 2.7.2, Figure 27

Figure 59. Relationship between Tebentafusp C_{avg} and Hepatic Toxicity by Responder Status



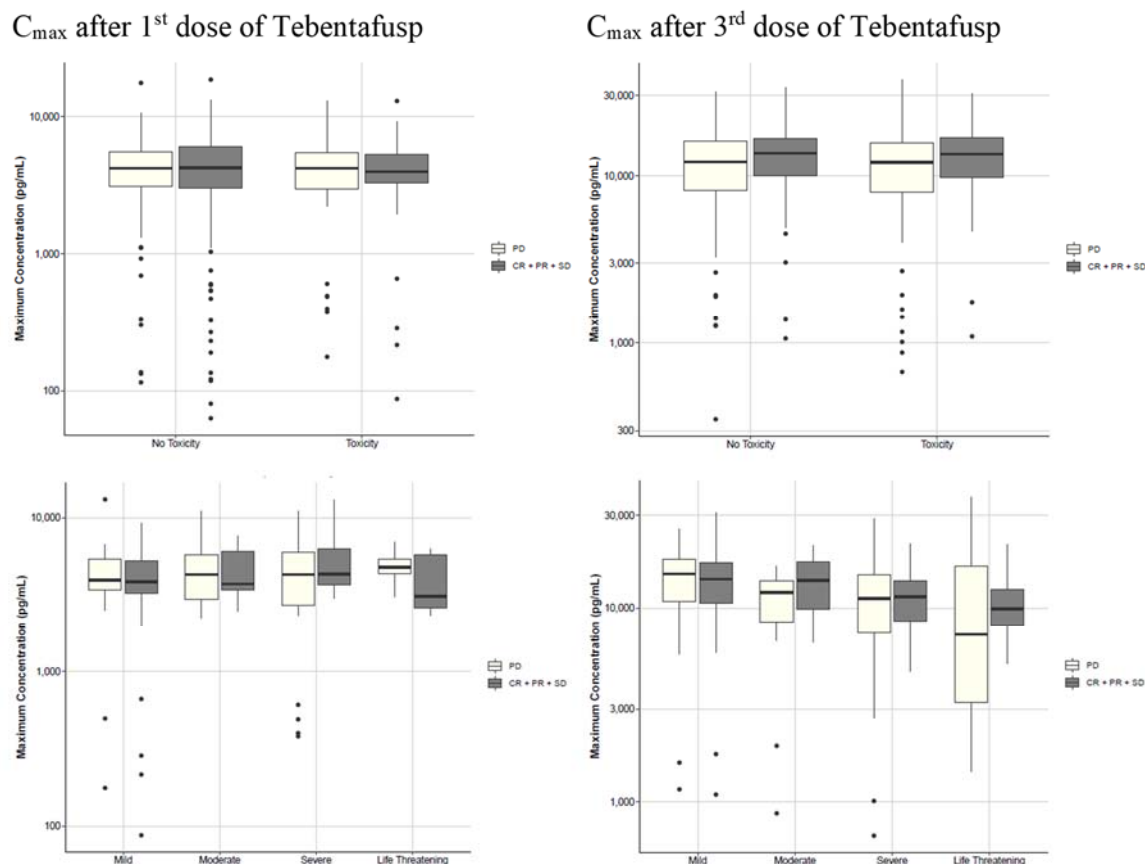
C_{avg} = average serum concentration; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

Top Left Panel: Integrated results of the effect of average tebentafusp concentration on liver function tests after the first dose (20 mcg). Bottom Left Panel: Integrated results of the effect of average tebentafusp concentration on liver function tests after the first dose stratified by toxicity grade. Top Right Panel: Integrated results of the effect of average tebentafusp concentration on liver function tests after the third dose (68 mcg). Bottom Right Panel: Integrated results of the effect of average tebentafusp concentration on liver function tests after the third dose (68 mcg) stratified by toxicity grade.

Note: Patient hepatic toxicity severity was classified based on CTCAE v4.03 criteria.

Source: Module 2.7.2, Figure 28

Figure 60. Relationship Between Maximum Tebentafusp Concentration and Hepatic Toxicity



C_{max} = maximum serum concentration; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

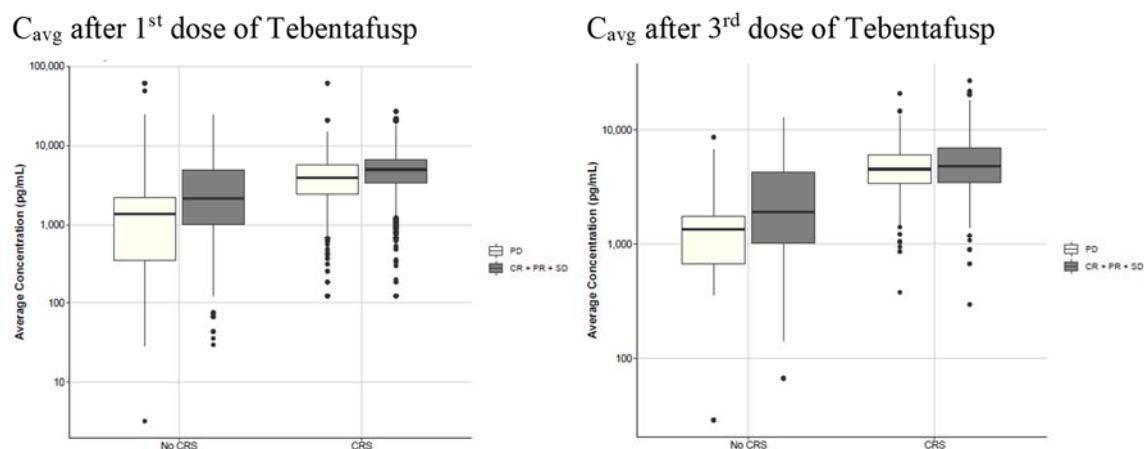
Top Left Panel: Integrated results of the effect of maximum tebentafusp concentration on liver function tests after the first dose (20 mcg). Bottom Left Panel: Integrated results of the effect of maximum tebentafusp concentration on liver function tests after the first dose stratified by toxicity grade. Top Right Panel: Integrated results of the effect of maximum tebentafusp concentration on liver function tests after the third dose (68 mcg). Bottom Right Panel: Integrated results of the effect of maximum tebentafusp concentration on liver function tests after the third dose (68 mcg) stratified by toxicity grade.

Note: Patient hepatic toxicity severity was classified based on CTCAE v4.03 criteria.

Source: Module 2.7.2, Figure 29

Patients were classified for CRS based on adjudicated American Society for Transplantation and Cellular Therapy (ASTCT) 2019 consensus grading for CRS. A trend was observed for lower C_{avg} after both the first and third dose, and lower C_{max} after the third dose in patients who did not experience CRS, independent of response status.

Figure 61. Relationship Between Average Tebentafusp Concentration and CRS



C_{avg} = average serum concentration; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

Left Panel: Integrated results of the effect of average tebentafusp concentration on CRS after the first dose (20 mcg).

Right Panel: Integrated results of the effect of average tebentafusp concentration on CRS after the third dose (68 mcg).

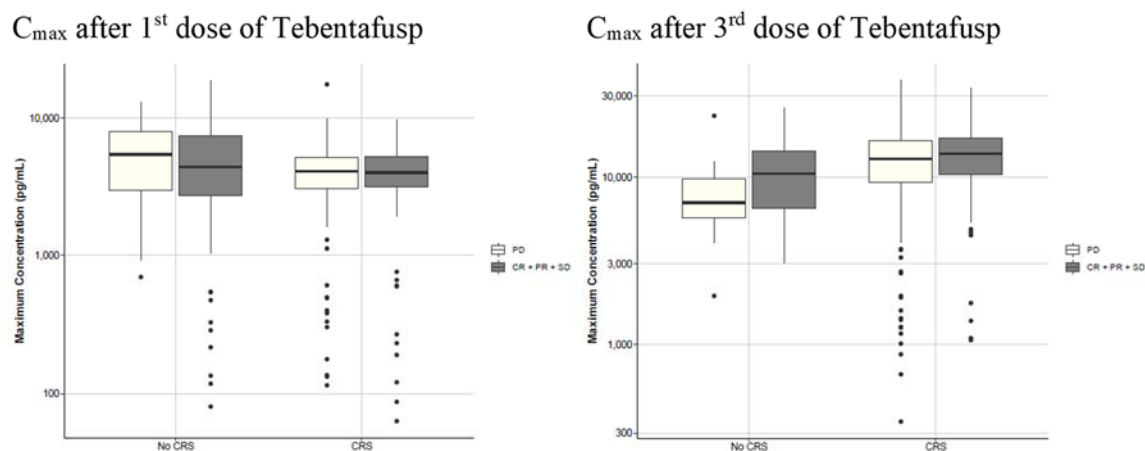
For the boxplots, the bottom and top half of the box correspond to the first and third quartiles, respectively (inter quartile IQR), while the line inside in the box is the median of the distribution. The upper and lower whiskers extend from the hinge to the values no further than $1.5 \cdot IQR$ from the hinge. Outlier data beyond whiskers are plotted individually as solid circles.

White boxes represent patients with PD; Grey boxes represent patients with PR, SD, or CR.

CRS Grade was based on a medical adjudication using 2019 ASCTC criteria for grading CRS. The incidence and severity of CRS was determined based on AE, concomitant medication, and vital signs data. Therefore, the incidence of CRS (based on adjudication by the Sponsor) as an AESI was higher than the incidence of the AE term CRS (per investigator).

Source: Module 2.7.2, Figure 30

Figure 62. Relationship Between Maximum Tebentafusp Concentration and CRS



C_{max} = maximum serum concentration; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

Left Panel: Integrated results of the effect of maximum tebentafusp concentration on CRS after the first dose (20 mcg). Right Panel: Integrated results of the effect of maximum tebentafusp concentration on CRS after the third dose (68 mcg).

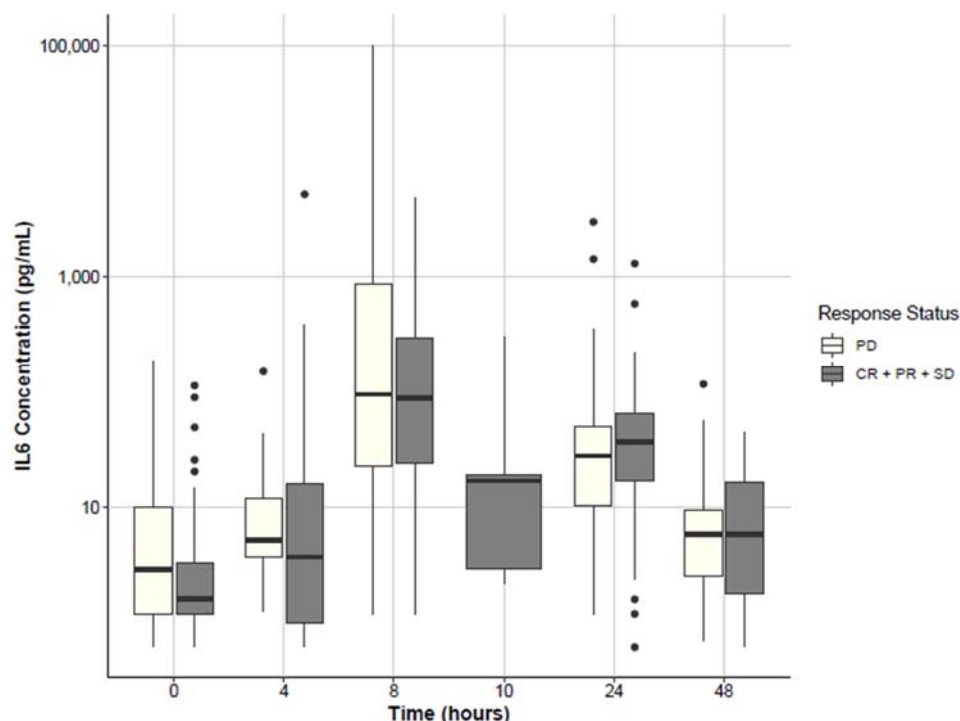
For the boxplots, the bottom and top half of the box correspond to the first and third quartiles, respectively (inter quartile IQR), while the line inside in the box is the median of the distribution. The upper and lower whiskers extend from the hinge to the values $\leq 1.5 \cdot \text{IQR}$ from the hinge. Outlier data beyond whiskers are plotted individually as solid circles.

White boxes represent patients with PD; Grey boxes represent patients with PR, SD, or CR.

Source: Module 2.7.2, Figure 31

The effect of tebentafusp PK exposure on IL-6 secretion was evaluated by plotting IL-6 concentrations over the first 48 hours after administration by response status or against the C_{max} and C_{avg} values following the first dose (20 mcg). IL-6 levels increased 8 hours post dose, then decreased approximately 12 - 24 hours post dose in patients independent of disease status (progressive disease, partial response, or stable disease).

Figure 63. Plasma IL-6 Levels Versus Patient Status



CR = complete response; IL-6 = interleukin-6; PD = progressive disease; PR = partial response; SD = stable disease
For the boxplots, the bottom and top half of the box correspond to the first and third quartiles, respectively (inter quartile IQR), while the line inside in the box is the median of the distribution. The upper and lower whiskers extend from the hinge to the values $\leq 1.5 \cdot \text{IQR}$ from the hinge. Outlier data beyond whiskers are plotted individually as solid circles.

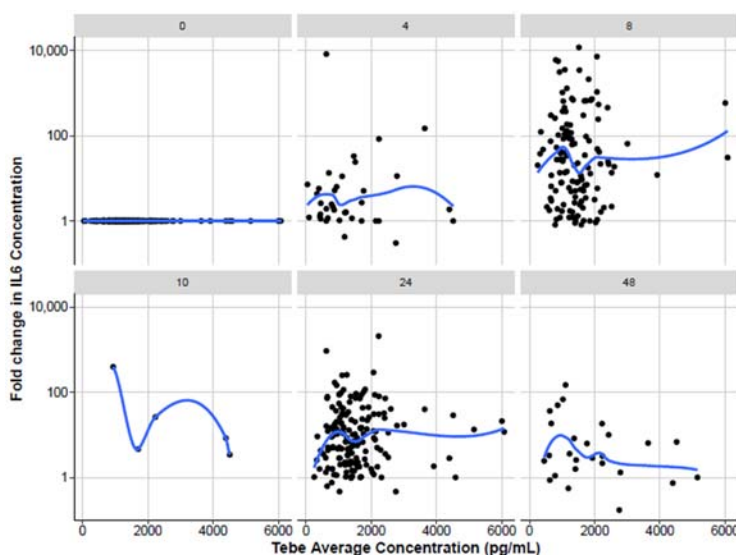
White boxes represent patients with PD; Grey boxes represent patients with PR, SD, or CR.

Source: Module 2.7.2, Figure 32

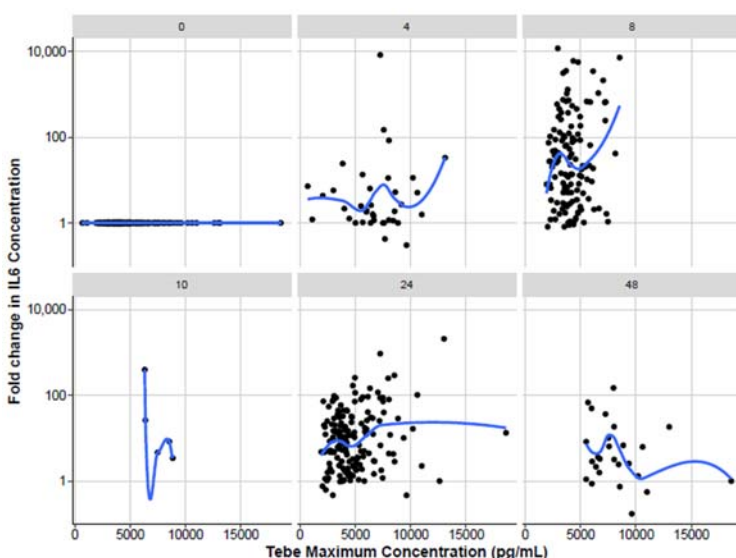
The effect of tebentafusp PK exposure on IL-6 secretion was evaluated by plotting IL-6 concentrations over the first 48 hours after administration by response status or against the C_{max} and C_{avg} values following the first dose (20 mcg). Overall, there were no trends of tebentafusp PK exposure (C_{max} or C_{avg}) on fold-change of IL-6 from baseline.

Figure 64. Relationship Between Average and Maximum Tebentafusp Concentration and IL-6 Release Over Time

C_{avg} after 1st dose of Tebentafusp



C_{max} after 1st dose of Tebentafusp



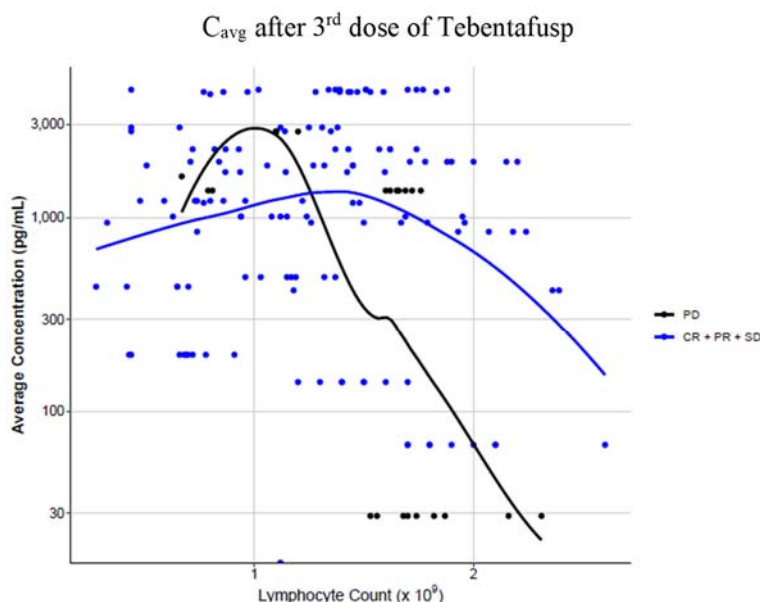
C_{max} = maximum serum concentration; IL-6 = interleukin 6

Solid blue lines represent the loess lines, black dots represent individual observations. Top panel: Average tebentafusp concentration versus IL-6 concentration after first tebentafusp dose (20 mcg); Bottom panel: Maximum tebentafusp concentration versus IL-6 concentration after first tebentafusp dose (20 mcg)

Source: Module 2.7.2, Figure 33

The effect of tebentafusp PK exposure on ALC and whether there were differences due to low baseline ALC levels ($< 10^9$) were evaluated. There was no trend for tebentafusp PK exposure (C_{avg}) on ALC after the third dose.

Figure 65. Relationship Between Average Tebentafusp Concentration and Lymphocyte Count



C_{avg} = average serum concentration; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

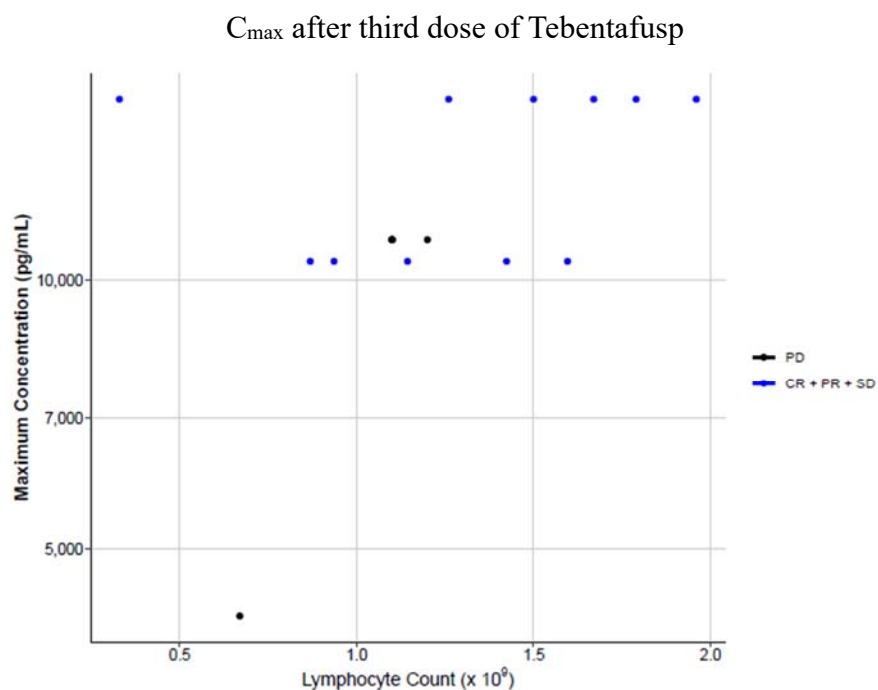
Solid lines represent the loess line by responder status; Black dots and loess line represent nonresponders (patients with PD). Blue dots and loess line represent responders (patients with PR, SD, or CR). Lymphocyte count presented as continuous count.

Average tebentafusp concentration versus lymphocyte count after third tebentafusp dose (68 mcg)

Source: Module 2.7.2, Figure 34

The effect of tebentafusp PK exposure on ALC and potential impact of low baseline ALC levels ($< 10^9$) were evaluated. There was no trend for tebentafusp PK exposure (C_{max}) on ALC after the third dose.

Figure 66. Relationship Between Maximum Tebentafusp Concentration and Lymphocyte Count



Cavg = average serum concentration; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

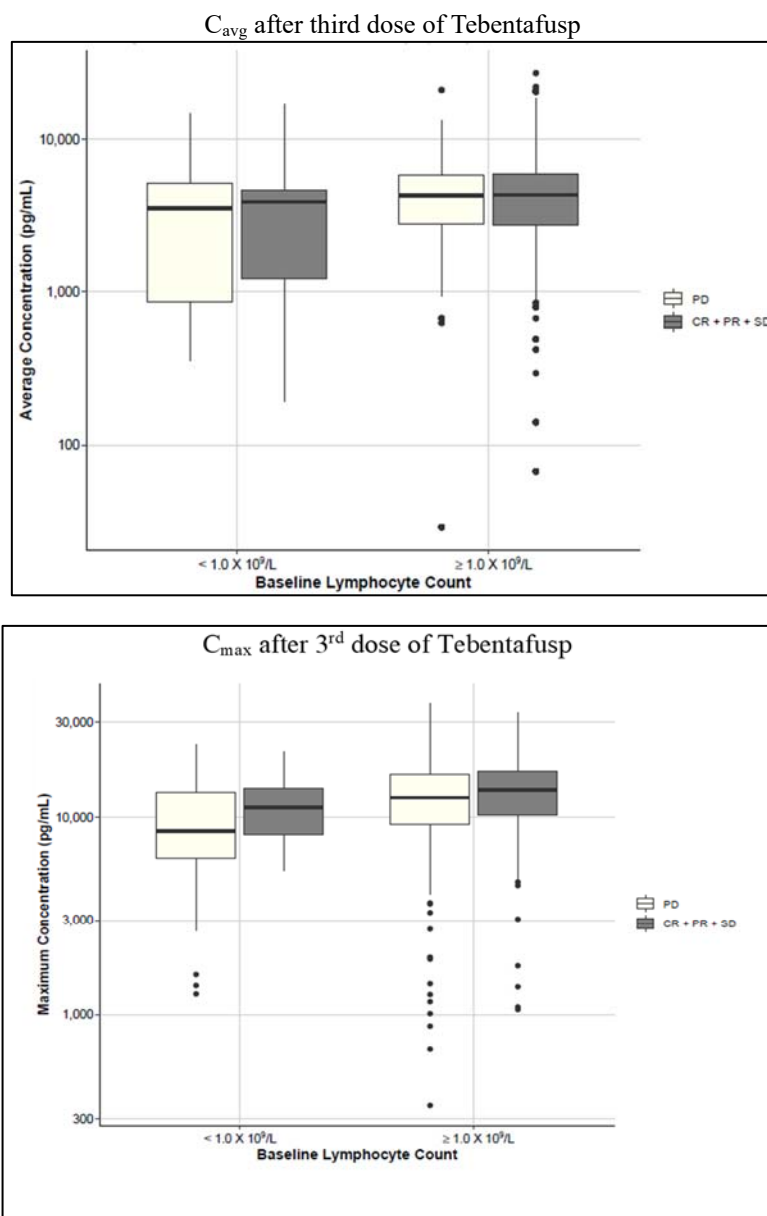
Solid lines represent the loess line by responder status; Black dots and loess line represent nonresponders (patients with PD). Blue dots and loess line represent responders (patients with PR, SD, or CR). Lymphocyte count presented as continuous count.

Average tebentafusp concentration versus lymphocyte count after third tebentafusp dose (68 mcg)

Source: Module 2.7.2, Figure 35

The effect of tebentafusp PK exposure on ALC and whether there were differences due to low baseline ALC levels ($< 10^9$) were evaluated. There was no trend for tebentafusp PK exposure (C_{avg} or C_{max}) by baseline ALC stratification ($1.0 \times 10^9/L$).

Figure 67. Box Plots of Tebentafusp C_{avg} and Baseline Lymphocyte Count by Responder Status



CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

For the boxplots, the bottom and top half of the box correspond to the first and third quartiles, respectively (inter quartile IQR), while the line inside in the box is the median of the distribution. The upper and lower whiskers extend from the hinge to the values no further than $1.5 \cdot IQR$ from the hinge. Outlier data beyond whiskers are plotted individually as solid circles.

White boxes represent non-responders (patients with PD); Grey boxes represent responders (patients with PR, SD, or CR). Source: Module 2.7.2, Figure 36 (C_{avg}), Figure 37 (C_{max})

19.5.3.3. The FDA's Assessment:

The Applicant's analyses were reasonable; however, exposure-response relationships for biologic products should be interpreted with caution due to the potential for post-hoc confounding effects.

19.5.4. FDA's Overall Independent Assessment

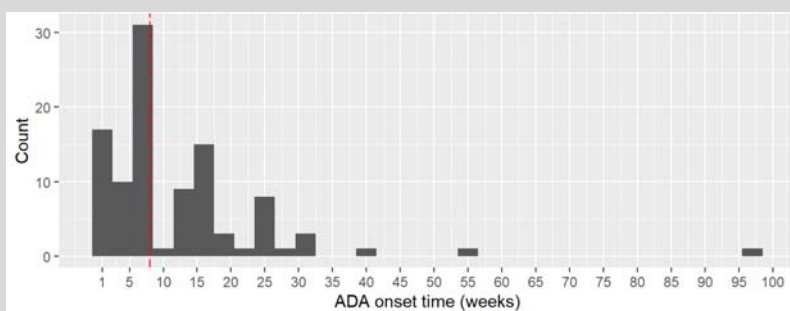
Key Review Questions:

1. What are the basic characteristics of tebentafusp immunogenicity?

The ADA positive rate was 28.6% (63/225 patients) in pivotal study IMCgp100-202 and 33.3% (48/144) in study IMCgp100-102. The ADA positive rate was 4% (3/78) in early-stage trial IMCgp100-01.

The time to median ADA onset was 8 weeks with a range from 1 -30 weeks (Figure 68).

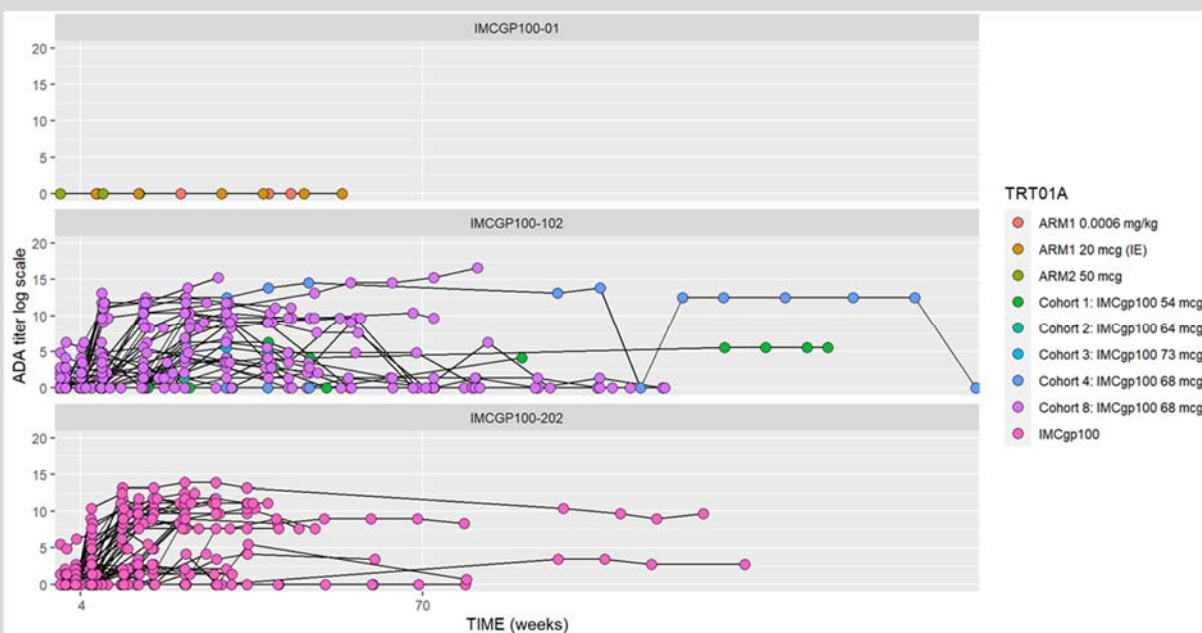
Figure 68: Histogram of anti-drug antibody onset time (weeks)



Source: Reviewer's independent analysis. Red line is the median onset time (8 weeks)

Tebentafusp ADA titer time course was shown in Figure 69 stratified by study and different dose levels.

Figure 69: Tebentafusp Anti-Drug Antibody Titer Time Course Stratified by Studies



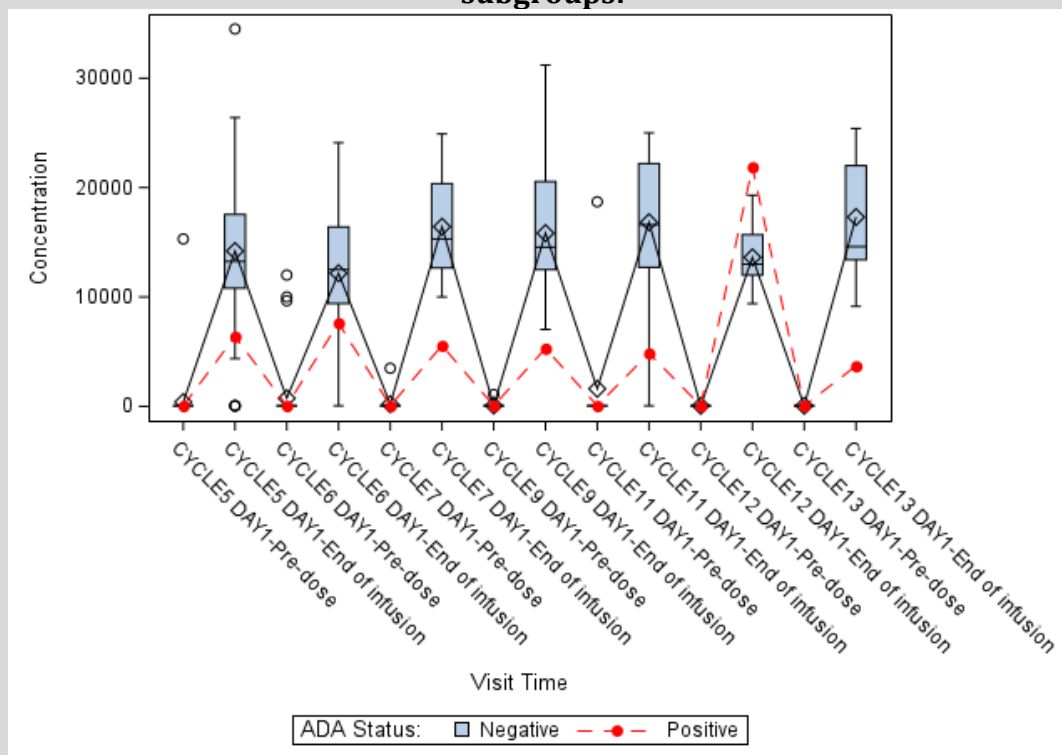
Source: Reviewer's independent analysis. ADA titer was in natural logarithm scale.

2. What is the impact of tebentafusp immunogenicity on tebentafusp pharmacokinetics?

Comparison of PK time course in ADA positive and ADA negative subgroups:

Tebentafusp drug concentrations over time were compared in the ADA positive subgroup (represented by red dots and dashed line) with the ADA negative subgroup (represented by blue solid box and solid line) in Figure 70. A difference could be visualized in C_{max} of each infusion cycle as there was no concentration detectable at the end of each infusion cycle.

Figure 70: Comparison of PK time course in ADA positive and ADA negative subgroups:



Source: Clinical Pharm Team Reviewer's Independent Analysis.

Population PK Analysis:

Since ADA titer is a time-varying covariate, FDA requested the applicant to re-define MAXTITFL as follows:

- When "ADATITER" ≥ 8129 , "MAXTITFL" was defined as 1.
- Otherwise "MAXTITFL" was defined as "."

With the new dataset "nonmen200.csv" and the final structure model (run 515), the newly estimated high titer ADA (>8192) increased tebentafusp clearance 32.9-fold. And this value was updated in section 12.3 of the tebentafusp USPI.

3. What is the impact of tebentafusp immunogenicity on efficacy?

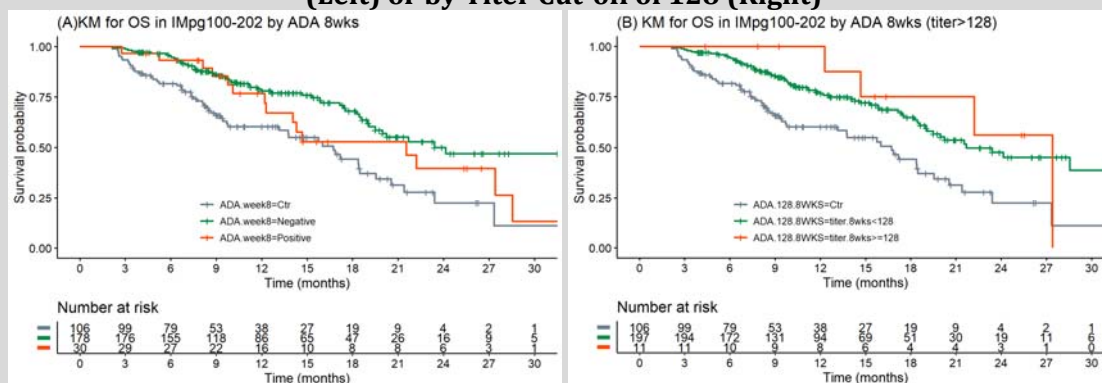
An exploratory analysis of the effect of ADA on treatment outcomes of tebentafusp was conducted (Figure 71: left). Patients in both the tebentafusp arm and the control arm who had an event or were censored less than 8 weeks were removed. The new ADA status grouped based on ADA status at 8 weeks were listed as follows:

ADA 8 weeks status	N (%)
ADA+ 8 weeks	30/208 (14.4%)
ADA- 8 weeks	178/208 (85.6%)

Based on cox regression analysis, for overall survival (OS), the hazard ratio for the ADA 8 weeks' positive subgroup is 0.65 (95% CI: 0.36- 1.16) and hazard ratio for the ADA 8 weeks' negative subgroup is 0.44 (95% CI: 0.3, 0.64) (Table 79). The ADA positive subgroup did not show significant reduced efficacy compared with the ADA negative subgroup. However, these results need to be interpreted with caution due to the limited number of patients (N=30) in the ADA 8 weeks' positive subgroup.

To explore the impact of high titer ADA on efficacy, an exploratory analysis of the effect of high titer ADA on treatment outcomes of tebentafusp was conducted (Figure 71, right). Based on cox regression model, for overall survival (OS), the hazard ratio for high titer ADA 8 weeks' positive subgroup (titer $\geq$ 128) is 0.41 (95% CI: 0.35- 1.13) and hazard ratio for ADA 8 weeks' low titer or negative subgroup is 0.48 (95% CI: 0.33, 0.69) (Table 79). The cut-off of titer 128 was the median ADA titer at week 8. The high titer ADA positive subgroup did not show significant reduced efficacy compared with the ADA negative or low titer subgroup. However, these results need to be interpreted with caution due to the limited number of patients (N=11) in the high titer subgroup.

Figure 71: KM for OS in Study IMpg100-202 by ADA Status at 8 Weeks in Overall Population (Left) or by Titer Cut-off of 128 (Right)



Source: FDA's Analysis. Red line represents ADA 8 weeks positive patient subgroup (overall positive in the left figure and titer $\geq$ 128 in the right figure). Green line represents ADA 8 weeks negative patients (overall negative in the left figure and titer <128 in the right figure). Gray line represents control group.

Table 79: Overall Survival Hazard Ratio in Study IMpg100-202 by ADA Status at 8 Weeks in Overall Population or by Titer Cut-off of 128

	ADA 8 weeks Positive	ADA 8 weeks Negative	Control
ADA Titer Cut-off: 1	0.65 (0.36 -1.16) N= 30	0.44 (0.3 – 0.64) N=178	- N=106
ADA Titer Cut-off: 128	0.41 (0.15 -1.13) N=11	0.48 (0.33 – 0.69) N=197	- N=106

Source: FDA's Analysis.

19.5.5. Summary of Bioanalytical Method

The Meso Scale Discovery (MSD) method was used to determine tebentafusp in human serum using HLA-A2 antigen capture in Study IMCgp100-01, Study IMCgp100-102 and IMCgp100-202. This method employs an indirect sandwich immunoassay format, with biotinylated HLA-A2 gp100 antigen used to capture the tebentafusp monoclonal TCR. After incubation with analyte, a rabbit anti-gp100 TCR antibody step is used followed by detection with a SULFO-TAG conjugated goat anti-rabbit antibody. The lower limit of quantification (LLOQ) of the method is 25 pg/mL and the upper limit of quantification (ULOQ) is 5,000 pg/mL. This method was developed and validated at (b) (4).

Analytical Method (b) (4)/007/V10 was validated over the concentration range 25 to 5,000 pg/mL in undiluted serum samples. The concentration levels of tebentafusp (Lot 00644, 0.5 mg/mL concentration) were as follows: 25 (LLOQ), 125 (Low), 600 (Medium), 3,200 (High), 5,000 (ULOQ) and 50,000 (dilution) pg/mL. The dilution quality control was diluted 100-fold with control human serum prior to analysis and the data confirmed linearity of dilution into the working range of the assay with up to 100-fold dilution in serum.

The intra-batch precision was less than or equal to 14.0% and the intra-run bias was between -13.6% and 3.0%. The inter-batch precision was less than or equal to 13.7% and the inter-batch bias was between -9.4% and 5.6%. The total error of the method was less than, or equal to 21.1% for the intra-batch data and less than or equal to 21.3% for the inter-batch data. The target LLOQ in this validation was 25 pg/mL; precision and bias at this level were found to be acceptable.

The long-term stability of tebentafusp (Lot 00644, 0.5 mg/mL concentration) when spiked into human serum and stored at -80°C was successfully assessed and established using the analytical method previously validated at YBS. Stability was assessed after approximately 6, 12, and 24 months. In addition, the stability of tebentafusp in working solution (assay buffer) when stored at -80°C was investigated after approximately 6 and 12 months of storage in polypropylene containers. Tebentafusp was found to be stable in human serum stored at -80°C for up to 24 months and in working solution when stored at -80°C for up to 373 days.

19.6. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

N/A

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Elizabeth Spehalski, PhD	CDER/OOD/DHOT	Section: 5	Select one: ☒ Authored ☒ Approved
Signature: Elizabeth I. Spehalski -S Digitally signed by Elizabeth I. Spehalski -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0012272551, cn=Elizabeth I. Spehalski -S Date: 2021.12.13 10:31:24 -05'00'				
Nonclinical Supervisor	Matthew Thompson, PhD, MPH	CDER/OOD/DHOT	Section: 5	Select one: ☐ Authored ☒ Approved
Signature: Matthew D. Thompson -S Digitally signed by Matthew D. Thompson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001270689, cn=Matthew D. Thompson -S Date: 2021.12.10 14:06:06 -05'00'				
Clinical Pharmacology Reviewer;	Huiming Xia, PhD	CDER/OTS/OCP	Sections: 6, 19.5	Select one: ☒ Authored ☐ Approved
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Clinical Pharmacology Team Leader	Hong Zhao, PhD	CDER/OTS/OCP	Sections:6, 19.5	Select one: ☒ Authored ☒ Approved
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Clinical Pharmacology Division Director	Rahman, Nam Atiqur, PhD	CDER/OTS/OCP	Sections: 6, 19.5	Select one: ☐ Authored ☒ Approved
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Pharmacometrics Reviewer	Yuan Xu, PhD	CDER/OTS/OCP	Sections: 6, 19.5	Select one: ☒ Authored ☐ Approved
Signature: Yuan Xu -S Digitally signed by Yuan Xu -S Date: 2021.12.13 10:10:29 -05'00'				

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Pharmacometrics Team Leader	Jiang Liu, Ph.D.	CDER/OTS/OCF	Sections: 6, 19.5	Select one: ☒ Authored ☒ Approved
Signature: Jiang Liu -S Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2021.12.13 10:18:09 -05'00'				
Clinical Reviewer	Margaret Thompson, MD	CDER/ODD/DO3	Sections: 2, 3, 4, 7, 8, 9, 10, 11, 12, 13	Select one: ☒ Authored ☐ Approved
Signature: Margaret Thompson -S Digitally signed by Margaret Thompson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001774060, cn=Margaret Thompson -S Date: 2021.12.18 12:56:06 -05'00'				
Clinical Team Leader	Jamie Brewer, MD	CDER/ODD/DO3	Sections: All	Select one: ☐ Authored ☒ Approved
Signature:				
Statistical Reviewer	Sirisha Mushti, MD	CDER/OTS/ OB/DBV	Sections: 1, 7, 8.1, 8.3 and 8.4	Select one: ☒ Authored ☒ Approved
Signature: Sirisha Mushti -S Digitally signed by Sirisha Mushti -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sirisha Mushti -S, 0.9.2342.19200300.100.1.1=2001315241 Date: 2021.12.13 11:44:14 -05'00'				
Statistical Team Leader	Joyce Cheng, PhD	CDER/OTS/ OB/DBV	Sections: 1, 7, 8.1, 8.3 and 8.4	Select one: ☐ Authored ☒ Approved
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Division Director (OB)	Shenghui Tang, PhD	CDER/OTS/OB/DBV	Sections: 1, 7, 8.1, 8.3 and 8.4	Select one: ☐ Authored ☒ Approved
Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shenghui Tang -S, 0.9.2342.19200300.100.1.1=1300224175 Date: 2021.12.09 07:39:46 -05'00'				
Associate Director for Labeling (ADL)	Bill Pierce, Pharm D, MPH	CDER/ODD	Sections: Section 11, Prescribing Information, Patient Information	Select one: ☒ Authored ☒ Approved
Signature: William F. Pierce -S Digitally signed by William F. Pierce -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235575, cn=William F. Pierce -S Date: 2021.12.14 13:23:48 -05'00'				

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Division Director	John Leighton, PhD	CDER/OOD/DHOT	Section: 5	Select one: ☐ Authored ☒ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Cross-Disciplinary Team Leader (CDTL)	Jamie Brewer, MD	CDER/OOD/DO3	Sections: All	Select one: ____ Authored _x_ Approved
	Signature:			
Division Director (Clinical)	Steven Lemery, MD	CDER/OOD/DO3	Sections: All	Select one: ____ Authored _x_ Approved
	Signature:			

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/s/

NATALIYA N FESENKO
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STEVEN J LEMERY
01/21/2022 03:51:25 PM

MARC R THEORET
01/21/2022 04:10:06 PM

My signature indicates that I have considered the FDA assessments and recommendations included in this Review in determining the regulatory action.