

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761228Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



IND 114314

MEETING MINUTES

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

Dear Dr. Thakur:¹

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tebentafusp (IMCgp100).

We also refer to the teleconference between representatives of your firm and the FDA on March 12, 2021. The purpose of the meeting was to meeting to discuss the RTOR submission plan for the tebentafusp BLA and gain feedback on the timing of PAI inspections, planned ISS/post-submission data update content and cut offs, and proposed regulatory plans for an HLA genotype assay submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:

- Meeting Minutes

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

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B

Meeting Category: Pre-BLA

Meeting Date and Time: March 12, 2021, 12:00-1:00 PM EST

Meeting Location: Teleconference

Application Number: IND 114314

Product Name: Tebentafusp (IMCgp100)

Indication: Treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma

Sponsor Name: Immunocore Ltd

Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Steven Lemery, M.D., M.H.S.

Meeting Recorder: Nataliya Fesenko, Pharm.D.

FDA ATTENDEES

Steven Lemery, M.D., M.H.S., Director (acting), DO3/OOD
Preeti Narayan, M.D., Clinical Team Lead, DO3/OOD
Margaret Thompson, M.D., Clinical Reviewer, DO3/OOD
Sirisha Mushti, Ph.D., Statistical Reviewer, OB/DBV
Joyce Cheng, Ph.D., Statistical Team Lead, OB/DBV
Krithika Arun Shetty, Ph.D., Clinical Pharmacology Reviewer, OCP/DCPI
Jeanne Fourie Zirkelbach, Ph.D., Clinical Pharmacology Team Lead, OCP/DCPI
Elizabeth Spehalski, Ph.D., Nonclinical Reviewer, DHOT/OOD
Matthew Thompson, Ph.D., M.P.H., Nonclinical Team Lead, DHOT/OOD
Samuel Mindaye, Ph.D., Product Quality Reviewer, OPQ/OBP/DBRRII
Yanming An, Ph.D., Product Quality Team Lead, OPQ/OBP/DBRRII
Zhao Wang, Ph.D., Product Quality Reviewer, CDER/OPQ/OPMA
Candace Gomez-Broughton, Ph.D., Microbiology Reviewer, CDER/OPQ/OPMA/DBM
Meihong Liu, Reviewer, CBER/OBRR/DBCD/DRB

SPONSOR ATTENDEES

Shaad Abdullah, Clinical Program Lead, tebentafusp
Mohammed Dar, Head of Clinical Development & CMO
Sheetal Thakur, Associate Director RA, Regulatory Lead, tebentafusp
Mark Moyer, Sr. VP. Regulatory Affairs, Project Lead tebentafusp
Chris Holland, Executive Director, Head of Biometrics
Erin Mill, Sr. Project Manager
Koustubh Ranade, Head of Translational Medicine David Berman, Head of Research & Development
Jay Wustner, Head of Bioanalytical Sciences

BACKGROUND

Key Regulatory History

- January 9, 2012, FDA received initial IND submission for IMCgp100-01
- February 8, 2012, FDA issued Study May Proceed letter
- October 14, 2015, Study IMCgp100-102 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”
- 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
- An amended iPSP requesting full waiver for all ages is under review.

Registration Plans

Immunocore plans to submit a BLA for potential approval in the first half of 2021 and plans to request priority review. The proposed indication for tebentafusp is for the treatment of HLA-A*01:02 positive adult patients with unresectable or metastatic uveal melanoma (mUM). The primary evidence supporting the BLA will be based on the prespecified interim analysis of overall survival (OS) in the randomized study IMCgp100-202. The primary analysis from the single arm study IMCgp100-102 will provide supportive information.

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Immunocore has begun submitting documents based on an agreed upon rolling submission. Immunocore submitted Module 4 (Nonclinical) and corresponding Module 2 documents for review on December 18, 2020. Immunocore plans to submit a complete Module 3 (CMC) and corresponding Module 2 documents by March 31, 2021. The remainder of the BLA submission, including all clinical components of the application, will be provided under the Real Time Oncology Review (RTOR) pathway to support an expedited approval. Immunocore proposes to submit the final component of the BLA (approximately) by June 28, 2021.

Immunocore proposes the following RTOR submission plan:

- Submission 1: **Submission Date February 26, 2021 (received)**
 - Module 1:
 - Administrative documents (financial disclosure, list of clinical sites)
 - Module 2 and 4: Nonclinical overview addendum, nonclinical literature references
 - Module 5:
 - Study 01 (Abbreviated CSR, no datasets or CRFs)
 - Study 102: CSR with appendices, CRFs, Datasets/CRT package, TLFs output, SAS programs
 - Bioanalytical Reports
- Submission 2: **Planned Submission Date March 15, 2021**
 - Module 2: Summary of Bioanalytical reports
 - Module 5: Study 202 Datasets/CRT package, TLF outputs
- Submission 3: **Planned Submission Date April 7, 2021**
 - Module 1:
 - Draft USPI (annotated except Clinical Module 2 and 5)
 - Request for Proprietary Name
 - Module 3:
 - Carton and container labeling (Draft) - Module 3 rolling portion of Module 1
 - Module 5: BIMO datasets
- Submission 4: **Planned Submission Date April 21, 2021**
 - Module 2: SCE with hyperlinks
 - Module 5: Full Study 202 CSR with appendices, CRF
- Submission 5: **Planned Submission Date May 21, 2021**
 - **Module 5:**
 - POP PK and ER modeling datasets and model files
 - POP PK and ER reports, TLFs
 - ISS Datasets and TLFs
- Submission 6: **Planned Submission Date June 28, 2021**
 - Module 1:
 - Annotated completed USPI
 - Assessment Aid
 - Module 2: Introduction, SCS, CO, SCP

Contents of the NDA

Proposed Integrated Safety Set (ISS)

Immunocore proposes to submit an ISS that consists of all patients who have received at least one dose of tebentafusp monotherapy regardless of dose, line of therapy, or cancer type. Based on the ISS statistical analysis plan (SAP) submitted to the IND, this includes approximately 508 patients.

Immunocore proposes to provide a post-submission safety and efficacy update covering the period from October 14, 2020, to approximately March 31, 2021, for IMCgp100-102 (safety) and IMCgp100-202 (safety and OS). This would be submitted by mid-May. Immunocore proposes to include listings and narratives of any newly observed SAEs or SAEs with an increase in severity not previously reported and for patients that discontinued treatment because of drug related SAEs. Immunocore plans to update the data on the primary endpoint for the ITT population, and also plans to update the labeling based on the new efficacy and safety data.

Nonclinical

Tebentafusp is a bispecific fusion protein consisting of a soluble T cell receptor (TCR) targeting antigen gp100 fused to an antibody single-chain variable fragment (scFv) targeting CD3. Gp100 is a membrane-associated glycoprotein expressed on normal melanocytes and tumors derived from melanocytes. Immunocore states that once the soluble TCR is engaged, the scFv effector can bind to CD3 on any T cell, redirecting the T cell to produce effector cytokines or kill the cell presenting the target peptide.

Clinical Pharmacology

Data to support the proposed dosing regimen of tebentafusp are derived from Studies IMCgp100-01, IMCgp100-102, and IMCgp100-202.

Clinical/Statistics

Uveal melanoma (UM) is a malignant neoplasm affecting vascular layers of the eye. It is genetically, biologically, and clinically distinct from cutaneous and other forms of melanoma. It primarily metastasizes to the liver. The prognosis for patients with metastatic uveal melanoma (mUM) is poor with overall survival (OS) < 6-12 months. There are no FDA approved therapies or standard of care.

IMCgp100-102 is an ongoing, open-label, single-arm, multi-center, dose finding with dose expansion study of IMCgp100 as a single agent in adult patients with metastatic uveal melanoma (mUM). The dose expansion portion of the trial comprised 2 cohorts. Cohort A enrolled patients with mUM in the second line setting with any prior liver-directed therapy. Cohort B enrolled patients with mUM in the second or third-line setting with up to one prior

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liver-directed therapy regimen. The primary endpoint of the dose expansion portion of the study was confirmed objective response rate (ORR) based on RECIST 1.1 as assessed by blinded independent central review (BICR). The study was closed to accrual February 2019.

The primary efficacy analysis was conducted on all patients enrolled in the dose expansion portion of the trial (N=127) with a minimum follow-up of 12 months (primary analysis data cut-off of March 20, 2020). The ORR based on BICR was 4.7% (6 PRs/127). DoR in the 6 patients who achieved PR was 8.7 months (95% CI: 5.6, 24.4).

The safety analysis was conducted on the full analysis set consisting of all patients who received tebentafusp in the dose escalation and expansion phases (N=146). The most common ($\geq 20\%$) TEAEs, any grade, were pyrexia (83%), pruritis (71%), nausea (70%), chills (67%), fatigue (65%), hypotension (46%), dry skin (44%), vomiting (43%), edema peripheral (40%), abdominal pain (38%), back pain (36%), headache (36%), rash maculo-papular (36%), rash (32%), periorbital edema (32%), arthralgia (29%), diarrhea (29%), hair color changes (29%), decreased appetite (27%), constipation (26%), cough (25%), erythema (22%), myalgia (21%), rash generalized (21%), abdominal pain upper (21%), dyspnea (21%), and skin hypopigmentation (21%).

The only \geq Grade 3 TEAE occurring in $\geq 10\%$ of patients was maculo-papular rash.

IMCgp100-202 is an ongoing, open-label, randomized, multi-center study of tebentafusp compared to investigator's choice (IC) therapy (dacarbazine, ipilimumab, or pembrolizumab) in HLA A*0201-positive patients \geq age 18 with previously untreated advanced uveal melanoma. Patients were randomly allocated in a 2:1 ratio with stratification based on LDH status to one of the following arms:

- Arm 1: Tebentafusp IV 20 mg C1D1, 30 mg C1D8, and then 68 mg weekly beginning C1D15.
- Arm 2: Investigator Choice (dacarbazine 1000 mg/m² IV Q21 days, ipilimumab 3 mg/kg IV Q21 days X 4 doses; pembrolizumab 2 mg/kg up to max 200 mg or 200 mg fixed dose IV Q21 days).

Patients are treated until radiographic progression (except for ipilimumab), unacceptable toxicity, investigator decision, or patient withdrawal of consent. Patients who received tebentafusp, pembrolizumab, or ipilimumab and experienced disease progression per RECIST 1.1 could continue treatment if they met the prespecified criteria. Crossover between treatment arms during the study was not permitted.

The primary endpoint was overall survival (OS). The primary endpoint was split into 2 primary objectives related to 1) OS in all patients randomized to tebentafusp versus all patient randomized to IC (intent-to-treat [ITT] 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 IC (Rash Analysis Set [RAS]). The amount of alpha allocated to the ITT analysis was 4.5% and the amount of alpha allocated to the rash analysis set was 0.5%,

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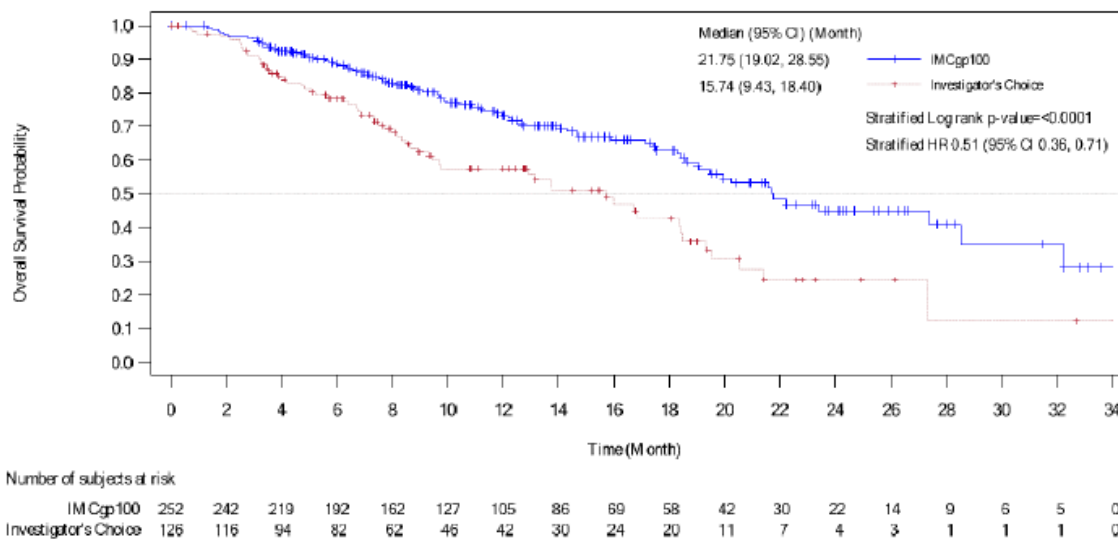
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controlling the overall experiment-wise error rate at 5%. The ITT OS analysis used a 2-sided log-rank test stratified by LDH status for generation of the p value. The HR was estimated using a Cox proportional hazards model stratified by LDH. Estimates of OS over time were provided by product-limit estimates presented by treatment arm. Median OS with a 95% CI was estimated by the method of Brookmeyer and Crowley. Secondary endpoints were progression-free survival (PFS), best overall response, and disease control rate (DCR).

As of the data cutoff date for the interim analysis (13 October 2020), 252 patients were randomized to receive tebentafusp and 126 patients randomized to IC. Based on a median follow-up of 13.3 months and 143 events (83 deaths [33%] in the tebentafusp arm and 60 deaths [48%] in the IC arm), the primary endpoint of OS favored tebentafusp with a hazard ratio (HR) of 0.51 (95% CI: 0.36, 0.71; $p < 0.0001$). The Kaplan-Meier estimates show that median OS was longer in the tebentafusp arm compared with the IC arm (21.7 vs. 15.7 months). The KM estimates of overall survival for the ITT set is shown below in the figure from the briefing package.

Figure 3: Kaplan-Meier Estimate of Overall Survival (ITT Set)



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

Based on median follow-up duration of 11.3 months, median PFS was 3.3 months (95% CI: 3, 5) and 2.9 months (95% CI: 2.9, 3.1) in the IC arm. ORR per investigator assessment was 8.3% (95% CI: 5.2, 12.5) for tebentafusp and 4.8% (95% CI: 1.8, 10.1) for IC.

DISCUSSION

CMC

1. The Sponsor proposes to submit up to 12 months of stability data on the registration batches in the initial Module 3 submission with additional stability data, up to 18 months, provided as an update during BLA review (without impacting BLA PDUFA action date). Does the FDA agree with the proposed plan for submission of stability data for the BLA?

FDA Response: The proposed plan to provide initial stability results for up to 12 months from commercial scale lots and submit additional stability data during the BLA review cycle is acceptable. Adequacy of the data to support product stability will be determined during the review of the BLA. FDA will consider the totality of stability evidence provided in the application to determine the expiration dates for the drug substance and drug product. Additional recommendations to leveraging stability data from clinical batches and process validation batches to determine shelf-life of the drug substance and drug product are provided to you in the written response from September 2020. For further information on this topic, consult ICH Q5C (Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products).

Discussion during the Meeting: Immunocore acknowledged FDA's comments. There was no discussion of this item during the meeting.

2. Based on the timing of the CMC Module 3 submission and planned commercial manufacturing for 2021, does the FDA envision performing specific pre-approval inspections (PAI), or will some inspections be performed in the post-marketing phase to occur at the time of manufacturing?

FDA Response: The need for facility inspections will be determined upon receipt of Module 3 of the BLA application. Detailed manufacturing process and facility information should be included in the submission. Clearly identify [REDACTED] ^{(b) (4)} for drug product manufacturing and [REDACTED] ^{(b) (4)} for drug substance manufacturing.

Discussion during the Meeting: Immunocore acknowledged FDA's comments. There was no discussion of this item during the meeting.

Clinical

3. Does the FDA agree with the proposed data cut-off dates for ISS in the BLA?

FDA Response: FDA agrees with the data cut-off dates proposed in the meeting package and the ISS SAP submitted to the IND. FDA has the additional comments:

- a. For studies 102 and 202, FDA agrees to the data cut-off dates but does not agree to the use of snapshot dates without further information or justification. For each study, include all safety data up to the cutoff date.
- b. FDA agrees to the use of a data cutoff /snapshot date of October 13, 2020 for Study 201.
- c. FDA agrees patients in Study 202 who received investigator's choice therapy are not necessary for analyses in the ISS.

Sponsor Response (received March 11, 2021): The sponsor acknowledges FDA agreement on proposed data cut off dates for the ISS and confirms that, for each study, all safety data up to the proposed cutoff date will be included. We would like to provide further clarification on data snapshot dates outlined in Table 1 below.

The sponsor first identifies a desired cutoff date which is intended to provide all data up to that date. The Sponsor then cleans the database up to the cutoff date. Once the data are sufficiently cleaned, a database snapshot (also referred to as an extract) is taken for analysis.

The proposed snapshot dates were therefore chosen to provide sufficient time after the cutoff dates and prior to the BLA submission for data purposes cleaning. The snapshot date is an internal metric for time to data cleaning.

Does this provide clarity to the FDA?

Table 1: Proposed study data cut off and data snapshot dates for the ISS

Parameter	Study				
	IMCgp100-01	IMCgp100-401	IMCgp100-201	IMCgp100-102	IMCgp100-202
ISS data cut off date ¹	11Aug17	14May19	13Oct20	20Mar20	13Oct20

Status	Final/Locked	Final/Locked	Follow-up ongoing	Primary Analysis Completed with above data cutoff date Follow-up ongoing	Interim Analysis for OS that passed pre-defined boundary completed based on this data cutoff date Follow-up ongoing
ISS snapshot (extract) date ²	N/A	N/A	21Jan21	15Jan21	22Jan21

¹Based on CSR data cut off dates (except for Study 201)

²Based on cleanest data extract for the BLA

Discussion during the Meeting: FDA stated that Immunocore's proposed approach is acceptable.

4. The Sponsor plans to submit a post-submission safety and efficacy update within the timeframe requested by the FDA. Does the Agency agree with the proposed content of the proposed post-submission safety and efficacy update? Does the FDA recommend a specific timeframe for the post submission safety and efficacy update submission that would enable efficient and timely review (data cut-off provided below may need to be updated based on FDA recommendation)?

FDA Response: FDA agrees with the proposed data cutoff and FDA will accept the update early if Immunocore chooses. FDA agrees with the inclusion of listings and narratives of any new SAEs, SAEs with an increase in severity, and SAEs that lead to treatment discontinuation. In addition, include listings and narratives for adverse events of special interest and severe or serious cardiac events (arrhythmias, syncope, and QTcF values > 500 msec). In the dataset submitted with the update, include a flag indicating new events.

FDA does not agree with the proposed submission of updated labeling. Updated labeling should only be submitted if the safety update changes the overall safety profile of tebentafusp in a meaningful way. In addition, FDA does not agree to updating the labeling based on the new efficacy data submitted with the post-submission safety update.

Sponsor Response (received March 11, 2021): The sponsor acknowledges and accepts FDA's recommendation. We followed this approach for the original narratives for Study IMCgp100-102 and Study IMCgp100-202.

With regards to the efficacy update, would the FDA be receptive to [REDACTED] (b) (4) [REDACTED] ?

Discussion during the Meeting: [REDACTED] (b) (4) [REDACTED]

[REDACTED] FDA stated that the Agency would consider the optimal approach for submission of the final protocol-specified OS analysis during the review of the BLA. FDA stated that it was acceptable to not submit the updated analysis at the time of the safety update because the data would not be expected to be fully cleaned at that time.

Regulatory

5. The Sponsor proposes following RTOR complete submission content plan for the planned BLA submission. Does the FDA agree with the proposed content and timing of each component of submission to be adequate and acceptable to support BLA review and approval?

FDA Response: In general, the proposed content and timing appears reasonable. However, Immunocore should submit datasets (ADSL.xpt, ADEX.xpt, ADAE.xpt, ADRS.xpt, ADPC.xpt and ADPP.xpt) from Study IMCgp100-01 to the BLA, as they will be required to evaluate the acceptability of the proposed dosing regimen e.g., for the assessment of dose-response relationships with tolerability and evaluation of PK including enabling the use of tebentafusp in patient sub-groups with organ impairment. Additional data sets may be requested if needed during the BLA review.

Sponsor Response (received March 11, 2021): The sponsor acknowledges FDA feedback on overall acceptability of the proposed RTOR submission plan and agrees to provide requested ADaM datasets for the Study IMCgp100-01 on April 7, 2021 (Table 2).

In addition, the sponsor would like to propose submission of only one annotated draft USPI for ease of review and to avoid tracking of multiple versions of the annotated draft USPI this would be submitted on June 28, 2021 (Table 2). Does the FDA agree?

Table 2 provides an updated RTOR submission plan is provided below for FDA agreement.

Table 2: Updated RTOR Submission Plan for tebentafusp BLA

Submission	Proposed Submission*	Planned FDA Submission Date
	Module 4 and Corresponding Module 2 documents Module 1 Administrative Information	Completed-Rolling submission 1 Submitted December 18, 2020
1	<p>Module 5: Study 01 Abbreviated CSR</p> <p>Study 102 CSR with Appendices, TLFs, Datasets/CRT package</p> <p>Module 2.4 Addendum: Repro/Embryo-fetal toxicity Integrated Summary</p> <p>Module 1: Debarment Certificate Financial Disclosure Forms Environmental Assessment Correspondence Regarding Meetings</p>	Complete Submitted February 26, 2021
2	<p>Module 1: USPI draft - Non-Annotated (minus Warnings and Precautions)</p> <p>Module 5: Study 202 Datasets/ CRT package Study 202 TLF outputs</p>	15 March 2021
	<p>Module 1: Portion of Module 1 (1.4.1 and 1.4.4)</p> <p>Module 3 and Module 2.3</p>	31 March 2021 (Part 2 of agreed Rolling Submission Plan)
3	Module 2:	7 April 2021

	<p>2.7.1 Summary of Bioanalytical reports w/references</p> <p>Module 5: BIMO datasets 5.3.1.4 Bioanalytical Reports (Part 1)</p> <p>Study IMCgp100-01 ADaM datasets</p> <p>Module 1 Request for Proprietary Name Draft Carton and Container Labeling Breakthrough Designation Application and Approval Letter</p>	
4	<p>Module 5: Full Study 202 CSR with appendices, case report forms, narratives 5.2 Tabular listings</p> <p>Module 2: 2.7.3 (SCE) with hyperlinks and references 2.7.6. Synopsis of Individual Studies</p>	21 April 2021
5	<p>Module 1: Draft USPI Non-Annotated (With Warnings and Precautions)</p> <p>Module 5: Pop PK and ER Modeling Datasets and model files Pop PK and ER Reports, TLFs ISS Datasets ISS TLFs 5.3.1.4 Bioanalytical reports (Part 2- 1 Report)</p>	21 May 2021
6	<p>Module 2: (with references) 2.2 Introduction 2.7.4 (SCS) 2.5 (CO) 2.7.2 (SCP)</p> <p>Module 1: Annotation completed draft USPI 1.9 Pediatric Administrative Information Assessment Aid</p>	28 June 2021

Text in green highlights updates from the previous RTOR submission plan version. Text in blue highlights updates based on FDA requests.

Discussion during the Meeting: FDA stated that the proposal appears acceptable.

FDA asked Immunocore if a manufacturing schedule would be provided in Module 3. Immunocore stated that they have provided approximate dates and they will provide specific dates when they become available. FDA recommended updating the manufacturing dates as soon as possible.

IC asked if they could submit certain clinical documents early if they are ready. FDA recommended that IC ask FDA first as unless received far in advance, it may be preferable to have all the documents in the same submission for ease of review.

FDA stated that having the Assessment Aid and BIMO data submitted early could be helpful during the review.

6. Does the FDA have any further recommendations for the timing of component submissions that should be considered to optimize FDA's review?

FDA Response: To facilitate FDA's review, the complete assessment aid (AA) should be submitted as soon as possible. The submitted AA should be free of promotional language. Because the review, and thus the associated AA, is a standalone document, it should not contain hyperlinks and references to other documents, other than to annotate a table or figure with its source. The AA is intended to provide the key background information for the disease, treatment landscape, protocol, and development, and to provide key results used in assessing risk:benefit in the intended use population. Results may be presented in the form of succinct summary paragraph(s) or tables. If tables are used, additional text that simply repeats findings in the tables is not necessary.

In addition, provide an updated RTOR submission plan as the February 26, 2021 submission did not include the USPI draft that was noted in the background.

Discussion during the Meeting: Immunocore acknowledged FDA comments. An updated RTOR submission plan is provided in Table 2 above. There was no discussion of this item during the meeting.

7. Does the FDA agree that the draft dossier table of contents includes all modules in support of a BLA submission and review?

FDA Response: The draft dossier table of contents appears acceptable. With the submission, in Section 1, include documents related to Breakthrough Therapy Designation.

Discussion during the Meeting: Immunocore acknowledged FDA's comments. There was no discussion of this item during the meeting.

8. Can the Sponsor initially submit responses via email, and then combine the formal responses to information requests (IRs) received during into a once weekly submission via electronic submission gateway?

FDA Response: FDA does not object to weekly, if needed, formal submissions via electronic gateway of previously emailed responses to information requests

as long as the responses are clearly identified and submitted to the appropriate module(s). Some formal submissions, for example, labeling may be requested more rapidly.

9. Can the sponsor submit a listing of each investigator site for Study 102 and 202 with accrual of patients at each site now to be utilized to sites for inspection?

FDA Response: FDA does not object to submission of investigator site and patient accrual at this time; however, all requested BIMO data should be submitted at the same time as selection of site inspection(s) takes into consideration more than patient accrual by site.

Sponsor Response (received March 11, 2021): The sponsor agrees to provide all requested BIMO data in Module 5 as noted in the updated RTOR submission plan. The BIMO data is planned to be submitted as part of the RTOR submission plan on 7 April 2021. See Table 2 above.

Discussion during the Meeting: There was no discussion of this item during the meeting.

10. Does the FDA have any recommendations on timing and frequency of annotated USPI submissions during the review?

FDA Response: The annotated USPI and Medication Guide should be submitted no later than the PDUFA clock triggering piece of the application.

Sponsor Response (received March 11, 2021): The Sponsor would like to propose submission of only one annotated draft USPI for ease of review and to avoid tracking of multiple versions of the annotated draft USPI this would be submitted on June 28, 2021 (See Table 2 above).

Discussion during the Meeting: There was no discussion of this item during the meeting.

11. Does the FDA agree that any HLA genotyping assay that is used in a clinical setting can be used for patient selection for tebentafusp treatment?

FDA Response: FDA does not agree that any HLA genotyping assay that is used in a clinical setting can be used for patient selection to receive tebentafusp treatment.

- a. Selecting patients with appropriate HLA allele(s) is considered essential for the safe and effective use of the corresponding therapeutic product tebentafusp. As FDA stated in previous communications (e.g., meetings on November 14, 2016), the use of HLA typing assays for selection of patients to receive treatment meets the definition of a companion diagnostic device

(CDx). Refer to the FDA guidance “In Vitro Companion Diagnostic Device - Guidance for Industry and Food and Drug Administration Staff” issued on August 6, 2014 for additional information.

At the time of the pre-BLA meeting, provide a plan as to how Immunocore will facilitate a CDx application for an HLA genotyping assay. Please note that FDA may require a De Novo submission or 510(k) submission, and not a PMA, for the new intended use as a companion diagnostic.

- b. FDA suggests that Immunocore partner with an HLA device manufacturer to conduct necessary studies and submit a premarket submission for the HLA typing assay intended for use as a CDx for patient selection. Immunocore may consider partnering with HLA device manufacturers who already have 510(k) clearance for other indications. For example, the SeCore assay is 510(k) cleared and has been used in Immunocore’s clinical study. Using this option, only limited studies would be necessary to obtain a companion claim.
- c. Assays used for patient selection should be adequately validated for the intended use. The studies needed to support a CDx claim may vary depending on what HLA assay(s) are used for the clinical trial and whether they are FDA-cleared.
 - i. For an FDA-cleared HLA device that was used in the clinical trials, please conduct an accuracy study that focuses on the specific HLA allele(s) needed for patient selection.
 - ii. For an HLA device that is not FDA cleared, studies typically required for a new HLA assay including but not be limited to the following: accuracy, limit of detection, interfering substances, repeatability and reproducibility, lot-to-lot, analytical specificity and cross-reactivity study, sample stability study, reagent stability study, carryover study, etc.
 - iii. If the HLA assay(s) submitted for FDA approval or clearance are different from the one used in the clinical trials, a bridging study should be conducted to demonstrate the analytical comparability of the assays and to establish clinical validity of the CDx device(s). For additional information on bridging studies, please see the following reference: *Journal of Biopharmaceutical Statistics*, 25:397-407, 2015.
- d. Immunocore may consider discussing the planned studies for the companion diagnostic device or submitting further questions to the FDA. For future discussions regarding the HLA devices, please follow the FDA Guidance: “Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program” published on May 7, 2019.

Sponsor Response (received March 11, 2021): The sponsor acknowledges that utilizing any assay would be too broad.

All tebentafusp trials used the 510K approved SeCore® HLA assay. This assay is currently utilized broadly for other life-threatening medical interventions, such as organ transplant, which are not included in the intended use of the 510K labeling. This assay's current intended use statement is broad in that it states the use is to identify HLA Class I and II antigens.

We acknowledge it is not time to discuss labeling, but as a means to anchor the above we note that the following is included in the proposed USPI:

- Section 1: ... treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma [see Dosage and Administration (2.1)].
- Section 2.1: Select patients for treatment of unresectable or metastatic uveal melanoma with BRAND based on a positive HLA-A*02:01 genotyping test [see Clinical Studies (14)].
- Section 14: Patients were required to be HLA-A*02:01 genotype positive identified by [REDACTED] (b) (4).

Therefore, the sponsor is of the opinion that this approach will meet the FDA request [REDACTED] (b) (4)

Does the FDA agree?

Discussion during the Meeting: FDA stated that use of the device is considered a companion diagnostic as the Device labeling is not cleared for selection of patients with tebentafusp.

Immunocore asked if a companion diagnostic application could be submitted as a Post-Marketing commitment. FDA stated that this approach can be considered as FDA acknowledged that IC has a plan in place to support labeling of a companion diagnostic.

FDA recommended a meeting with CBER with respect to the labeling for the CDx with representation from CDER. FDA requested that the plan to support the CDx and PMC should be included in the BLA submission.

FDA stated the review of the CDx application may be quick and recommended supporting the submission of the application as soon as possible.

12. Based on the safety and clinical experience with tebentafusp, the Sponsor is of the opinion that no REMs is required. Therefore, the Sponsor does not plan to submit a proposed REMS for tebentafusp with BLA. Does the Agency agree with this initial approach?

FDA Response: At this time, FDA agrees a REMS submission is not required to file the application. However, FDA will determine the need for a REMS during the review of the BLA

Discussion during the Meeting: Immunocore acknowledged FDA's comments. There was no discussion of this item during the meeting.

ADDITIONAL COMMENTS

13. Include with the financial information the financial disclosure data (clinical investigators, including sub-investigators, with disclosable financial interest and without disclosable financial interest) in an excel compatible format, e.g., .xls or .xpt.

Sponsor Response (received March 11, 2021): The sponsor agrees with FDA request and will submit financial disclosure information in the requested format.

Discussion during the Meeting: There was no discussion of this item during the meeting.

Clinical Pharmacology

14. In Immunocore's responses to the FDA preliminary comments ahead of the meeting scheduled on March 12, 2021, or within 30 days of receipt of these comments, provide the following information to support the proposed dosing regimen of tebentafusp:
- a. A tabular summary of the tebentafusp dosing regimens evaluated in Studies IMCgp100-01 and IMCgp100-102.
 - b. A detailed tabular summary of safety data from Studies IMCgp100-01 and IMCgp100-102, analyzed by dose cohort. This summary should include an overview of CRS events by grade (per ASTCT 2019 criteria) at each dose level.
 - c. A summary of the incidence of all Grade and Grade ≥ 2 CRS, Grade ≥ 3 rash, Grade ≥ 3 LFT increases, and treatment-emergent adverse events leading to dose modifications over time (by cycle), at the 20/30/68 mcg QW dosing regimen in Studies IMCgp100-102 and IMCgp100-202.
 - d. A tabular summary of efficacy data from Studies IMCgp100-01 and IMCgp100-102 by dosing cohort.

- e. Clarification regarding whether sparse PK samples have been collected in all patients in Study IMCgp100-202. Provide a tabular summary of studies that are included in the exposure-responses analyses for safety and efficacy, including information on studies from which dense and sparse PK sampling are available. Provide a summary of the current exposure-response analyses with safety and efficacy planned to support the proposed dosing regimen.
- f. A tabular summary of PRO endpoints collected in clinical studies including Study IMCgp100-102. This summary should include the PRO endpoints assessed and time points at which PRO data were collected relative to dosing and PK sampling. This information might enable assessment of the potential utility of exposure-response analyses with patient reported outcomes. Provide justification for the approach selected.

Sponsor Response (received March 11, 2021): We agree to provide tabular summary of safety data within 30 days for Study IMCgp100-102 at each dose level. This summary data will include an overview of CRS events by grade as adjudicated by the sponsor using the ASTCT 2019 criteria.

The sponsor will follow-up in the next 30 days to seek clarification on optimal way to present the tabular summary of safety events by cohorts on Study IMCgp100-01.

Accurate adjudication according to the ASTCT 2019 criteria is not possible for Study IMCgp100-01 due to the lack of available data in the study, which is now closed, relating to important parameters for grading such as oxygen use. However, the study data has already been adjudicated according to the Lee 2014 criteria and the Sponsor can provide the requested summaries based on this adjudication.

In addition, the sponsor agrees with FDA information requests listed below and will provide the requested information within 30 days of receipt of this feedback.

- a. A tabular summary of the tebentafusp dosing regimens evaluated in Studies IMCgp100-01 and IMCgp100-102.*
- c. A summary of the incidence of all Grade and Grade ≥ 2 CRS, Grade ≥ 3 rash, Grade ≥ 3 LFT increases, and treatment-emergent adverse events leading to dose modifications over time (by cycle), at the 20/30/68 mcg QW dosing regimen in Studies IMCgp100-102 and IMCgp100-202.*
- d. A tabular summary of efficacy data from Studies IMCgp100-01 and IMCgp100-102 by dosing cohort.*
- e. Clarification regarding whether sparse PK samples have been collected in all patients in Study IMCgp100-202. Provide a tabular summary of studies that are included in the exposure-responses analyses for safety and efficacy,*

including information on studies from which dense and sparse PK sampling are available. Provide a summary of the current exposure-response analyses with safety and efficacy planned to support the proposed dosing regimen.

A tabular summary of PRO endpoints collected in clinical studies including Study IMCgp100-102. This summary should include the PRO endpoints assessed and time points at which PRO data were collected relative to dosing and PK sampling. This information might enable assessment of the potential utility of exposure-response analyses with patient reported outcomes. Provide justification for the approach selected.

Discussion during the Meeting: FDA stated that the proposal is acceptable and acknowledged Immunocore's response.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- 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.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to [FDA.gov](https://www.fda.gov).²

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor’s initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD & C Act) for early evaluation in the pediatric

² <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF IPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.³

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length,

randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345,

Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h⁶ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁷. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested

⁶ <https://www.fda.gov/media/84223/download>

⁷ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁸

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ATTACHMENTS AND HANDOUTS

Response to FDA Preliminary Feedback received from Immunocore on March 11, 2021.

⁸ <https://www.fda.gov/media/85061/download>

RESPONSE TO FDA PRELIMINARY COMMENTS RECEIVED 9 MARCH 2021

QUESTION 1

The Sponsor proposes to submit up to 12 months of stability data on the registration batches in the initial Module 3 submission with additional stability data, up to 18 months, provided as an update during BLA review (without impacting BLA PDUFA action date). Does the FDA agree with the proposed plan for submission of stability data for the BLA?

FDA RESPONSE:

The proposed plan to provide initial stability results for up to 12 months from commercial scale lots and submit additional stability data during the BLA review cycle is acceptable. Adequacy of the data to support product stability will be determined during the review of the BLA. FDA will consider the totality of stability evidence provided in the application to determine the expiration dates for the drug substance and drug product. Additional recommendations to leveraging stability data from clinical batches and process validation batches to determine shelf-life of the drug substance and drug product are provided to you in the written response from September 2020. For further information on this topic, consult ICH Q5C (Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products).

SPONSOR RESPONSE:

The sponsor acknowledges FDA comments. No further discussion requested.

QUESTION 2

Based on the timing of the CMC Module 3 submission and planned commercial manufacturing for 2021, does the FDA envision performing specific pre-approval inspections (PAI), or will some inspections be performed in the post-marketing phase to occur at the time of manufacturing?

FDA RESPONSE:

The need for facility inspections will be determined upon receipt of Module 3 of the BLA application. Detailed manufacturing process and facility information should be included in the submission. Clearly identify (b) (4) for drug product manufacturing and (b) (4) for drug substance manufacturing.

SPONSOR RESPONSE:

The sponsor acknowledges FDA comments. No further discussion requested.

QUESTION 3

Does the FDA agree with the proposed data cut-off dates for ISS in the BLA?

FDA RESPONSE:

FDA agrees with the data cut-off dates proposed in the meeting package and the ISS SAP submitted to the IND. FDA has the additional comments:

- a. For studies 102 and 202, FDA agrees to the data cut-off dates but does not agree to the use of snapshot dates without further information or justification. For each study, include all safety data up to the cutoff date.
- b. FDA agrees to the use of a data cutoff/snapshot date of October 13, 2020 for Study 201.

FDA agrees patients in Study 202 who received investigator’s choice therapy are not necessary for analyses in the ISS.

SPONSOR RESPONSE:

The sponsor acknowledges FDA agreement on proposed data cut off dates for the ISS and confirms that, for each study, all safety data up to the proposed cutoff date will be included. We would like to provide further clarification on data snapshot dates outlined in Table 1 below.

The sponsor first identifies a desired cutoff date which is intended to provide all data up to that date. The Sponsor then cleans the database up to the cutoff date. Once the data are sufficiently cleaned, a database snapshot (also referred to as an extract) is taken for analysis.

The proposed snapshot dates were therefore chosen to provide sufficient time after the cutoff dates and prior to the BLA submission for data purposes cleaning. The snapshot date is an internal metric for time to data cleaning.

Does this provide clarity to the FDA?

Table 1: Proposed study data cut off and data snapshot dates for the ISS

Parameter	Study				
	IMCgp100-01	IMCgp100-401	IMCgp100-201	IMCgp100-102	IMCgp100-202
ISS data cut off date ¹	11Aug17	14May19	13Oct20	20Mar20	13Oct20
Status	Final/Locked	Final/Locked	Follow-up ongoing	Primary Analysis Completed with above data cutoff date Follow-up ongoing	Interim Analysis for OS that passed pre-defined boundary completed based on this data cutoff date Follow-up ongoing
ISS snapshot (extract) date ²	N/A	N/A	21Jan21	15Jan21	22Jan21

¹Based on CSR data cut off dates (except for Study 201)

²Based on cleanest data extract for the BLA

QUESTION 4

The Sponsor plans to submit a post-submission safety and efficacy update within the timeframe requested by the FDA. Does the Agency agree with the proposed content of the proposed post-submission safety and efficacy update? Does the FDA recommend a specific timeframe for the post submission safety and efficacy update submission that would enable efficient and timely review (data cut-off provided below may need to be updated based on FDA recommendation)?

FDA RESPONSE:

FDA agrees with the proposed data cut off and FDA will accept the update early if Immunocore chooses. FDA agrees with the inclusion of listings and narratives of any new SAEs, SAEs with an increase in severity, and SAEs that lead to treatment discontinuation. In addition, include listings and narratives for adverse events of special interest and severe or serious cardiac events (arrhythmias, syncope, and QTcF values > 500 msec). In the dataset submitted with the update, include a flag indicating new events.

FDA does not agree with the proposed submission of updated labeling. Updated labeling should only be submitted if the safety update changes the overall safety profile of tebentafusp in a meaningful way. In addition, FDA does not agree to updating the labeling based on the new efficacy data submitted with the post- submission safety update.

SPONSOR RESPONSE

The sponsor acknowledges and accepts FDA's recommendation. We followed this approach for the original narratives for Study IMCgp100-102 and Study IMCgp100-202.

With regards to the efficacy update, would the FDA be receptive to

(b) (4)

?

QUESTION 5

The Sponsor proposes following RTOR complete submission content plan for the planned BLA submission. Does the FDA agree with the proposed content and timing of each component of submission to be adequate and acceptable to support BLA review and approval?

FDA RESPONSE:

In general, the proposed content and timing appears reasonable. However, Immunocore should submit datasets (ADSL.xpt, ADEX.xpt, ADAE.xpt, ADRS.xpt, ADPC.xpt and ADPP.xpt) from Study IMCgp100-01 to the BLA, as they will be required to evaluate the acceptability of the proposed dosing regimen e.g. for the assessment of dose-response relationships with tolerability and evaluation of PK including enabling the use of tebentafusp in patient sub- groups with organ impairment. Additional data sets may be requested if needed during the BLA review.

SPONSOR RESPONSE:

The sponsor acknowledges FDA feedback on overall acceptability of the proposed RTOR submission plan and agrees to provide requested ADaM datasets for the Study IMCgp100-01 on April 7, 2021 (Table 2).

In addition, the sponsor would like to propose submission of only one annotated draft USPI for ease of review and to avoid tracking of multiple versions of the annotated draft USPI this would be submitted on June 28, 2021 (Table 2). Does the FDA agree?

Table 2 provides an updated RTOR submission plan is provided below for FDA agreement.

Table 2: Updated RTOR Submission Plan for tebentafusp BLA

Submission	Proposed Submission*	Planned FDA Submission Date
	Module 4 and Corresponding Module 2 documents Module 1 Administrative Information	Completed- Rolling submission 1 Submitted December 18, 2020
1	Module 5: Study 01 Abbreviated CSR Study 102 CSR with Appendices, TLFs, Datasets/CRT package Module 2.4 Addendum: Repro/Embryo-fetal toxicity Integrated Summary Module 1: Debarment Certificate Financial Disclosure Forms Environmental Assessment Correspondence Regarding Meetings	Complete Submitted February 26, 2021
2	Module 1: USPI draft - Non-Annotated (minus Warnings and Precautions) Module 5: Study 202 Datasets/ CRT package Study 202 TLF outputs	15 March 2021
	Module 1: Portion of Module 1 (1.4.1 and 1.4.4) Module 3 and Module 2.3	31 March 2021 (Part 2 of agreed Rolling Submission Plan)
3	Module 2:	7 April 2021

	<p>2.7.1 Summary of Bioanalytical reports w/references</p> <p>Module 5: BIMO datasets 5.3.1.4 Bioanalytical Reports (Part 1)</p> <p>Study IMCgp100-01 ADaM datasets</p> <p>Module 1 Request for Proprietary Name Draft Carton and Container Labeling Breakthrough Designation Application and Approval Letter</p>	
4	<p>Module 5: Full Study 202 CSR with appendices, case report forms, narratives 5.2 Tabular listings Module 2: 2.7.3 (SCE) with hyperlinks and references 2.7.6. Synopsis of Individual Studies</p>	21 April 2021
5	<p>Module 1: Draft USPI Non-Annotated (With Warnings and Precautions)</p> <p>Module 5: Pop PK and ER Modeling Datasets and model files Pop PK and ER Reports, TLFs ISS Datasets ISS TLFs</p> <p>5.3.1.4 Bioanalytical reports (Part 2- 1 Report)</p>	21 May 2021
6	<p>Module 2: (with references) 2.2 Introduction 2.7.4 (SCS) 2.5 (CO) 2.7.2 (SCP)</p> <p>Module 1: Annotation completed draft USPI 1.9 Pediatric Administrative Information Assessment Aid</p>	28 June 2021

Text in **green** highlights updates from the previous RTOR submission plan version.

Text in **blue** highlights updates based on FDA requests.

QUESTION 6

Does the FDA have any further recommendations for the timing of component submissions that should be considered to optimize FDA’s review?

FDA RESPONSE:

To facilitate FDA's review, the complete assessment aid (AA) should be submitted as soon as possible. The submitted AA should be free of promotional language. Because the review, and thus the associated AA, is a standalone document, it should not contain hyperlinks and references to other documents, other than to annotate a table or figure with its source. The AA is intended to provide the key background information for the disease, treatment landscape, protocol, and development, and to provide key results used in assessing risk: benefit in the intended use population. Results may be presented in the form of succinct summary paragraph(s) or tables. If tables are used, additional text that simply repeats findings in the tables is not necessary.

In addition, provide an updated RTOR submission plan as the February 26, 2021 submission did not include the USPI draft that was noted in the background.

SPONSOR RESPONSE:

The Sponsor acknowledges FDA comments. An updated RTOR submission plan is provided in Table 2 above.

QUESTION 7

Does the FDA agree that the draft dossier table of contents includes all modules in support of a BLA submission and review?

FDA RESPONSE:

The draft dossier table of contents appears acceptable. With the submission, in Section 1, include documents related to Breakthrough Therapy Designation.

SPONSOR RESPONSE:

No further discussion requested.

QUESTION 8

Can the Sponsor initially submit responses via email, and then combine the formal responses to information requests (IRs) received during into a once weekly submission via electronic submission gateway?

FDA RESPONSE:

FDA does not object to weekly, if needed, formal submissions via electronic gateway of previously emailed responses to information requests as long as the responses are clearly identified and submitted to the appropriate Module(s). Some formal submissions, for example, labeling may be requested more rapidly.

SPONSOR RESPONSE

No further discussion requested.

QUESTION 9

Can the sponsor submit a listing of each investigator site for Study 102 and 202 with accrual of patients at each site now to be utilized to sites for inspection?

FDA RESPONSE:

FDA does not object to submission of investigator site and patient accrual at this time; however, all requested BIMO data should be submitted at the same time as selection of site inspection(s) takes into consideration more than patient accrual by site.

SPONSOR RESPONSE:

The sponsor agrees to provide all requested BIMO data in Module 5 as noted in the updated RTOR submission plan. The BIMO data is planned to be submitted as part of the RTOR submission plan on 7 April 2021. See Table 2 above.

QUESTION 10

Does the FDA have any recommendations on timing and frequency of annotated USPI submissions during the review?

FDA RESPONSE:

The annotated USPI and Medication Guide should be submitted no later than the PDUFA clock triggering piece of the application.

SPONSOR RESPONSE:

The Sponsor would like to propose submission of only one annotated draft USPI for ease of review and to avoid tracking of multiple versions of the annotated draft USPI this would be submitted on June 28, 2021 (See Table 2 above).

QUESTION 11

Does the FDA agree that any HLA genotyping assay that is used in a clinical setting can be used for patient selection for tebentafusp treatment?

FDA RESPONSE:

FDA does not agree that any HLA genotyping assay that is used in a clinical setting can be used for patient selection to receive tebentafusp treatment.

- a. FDA suggests that Immunocore partner with an HLA device manufacturer to conduct necessary studies and submit a premarket submission for the HLA typing assay intended for use as a CDx for patient selection. Immunocore may consider partnering with HLA device*

manufacturers who already have 510(k) clearance for other indications. For example, the SeCore assay is 510(k) cleared and has been used in Immunocore's clinical study. Using this option, only limited studies would be necessary to obtain a companion claim.

- b. *Assays used for patient selection should be adequately validated for the intended use. The studies needed to support a CDx claim may vary depending on what HLA assay(s) are used for the clinical trial and whether they are FDA-cleared.*
- i. *For an FDA-cleared HLA device that was used in the clinical trials, please conduct an accuracy study that focuses on the specific HLA allele(s) needed for patient selection.*
 - ii. *For an HLA device that is not FDA cleared, studies typically required for a new HLA assay including but not be limited to the following: accuracy, limit of detection, interfering substances, repeatability and reproducibility, lot-to-lot, analytical specificity and cross-reactivity study, sample stability study, reagent stability study, carryover study, etc.*
 - iii. *If the HLA assay(s) submitted for FDA approval or clearance are different from the one used in the clinical trials, a bridging study should be conducted to demonstrate the analytical comparability of the assays and to establish clinical validity of the CDx device(s). For additional information on bridging studies, please see the following reference: Journal of Biopharmaceutical Statistics, 25:397-407, 2015.*
- c. *Immunocore may consider discussing the planned studies for the companion diagnostic device or submitting further questions to the FDA. For future discussions regarding the HLA devices, please follow the FDA Guidance: "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program" published on May 7, 2019.*

SPONSOR RESPONSE:

The sponsor acknowledges that utilizing any assay would be too broad.

All tebentafusp trials used the 510K approved SeCore[®] HLA assay. This assay is currently utilized broadly for other life-threatening medical interventions, such as organ transplant, which are not included in the intended use of the 510K labeling. This assay's current intended use statement is broad in that it states the use is to identify HLA Class I and II antigens.

We acknowledge it is not time to discuss labeling, but as a means to anchor the above we note that the following is included in the proposed USPI:

- **Section 1:** ... treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma [see Dosage and Administration (2.1)].
- **Section 2.1:** Select patients for treatment of unresectable or metastatic uveal melanoma with BRAND based on a positive HLA-A*02:01 genotyping test [see Clinical Studies (14)].
- **Section 14:** Patients were required to be HLA-A*02:01 genotype positive identified by (b) (4)

Therefore, the sponsor is of the opinion that this approach will meet the FDA request (b) (4)

Does the FDA agree?

QUESTION 12

Based on the safety and clinical experience with tebentafusp, the Sponsor is of the opinion that no REMs is required. Therefore, the Sponsor does not plan to submit a proposed REMS for tebentafusp with BLA. Does the Agency agree with this initial approach?

FDA RESPONSE:

At this time, FDA agrees a REMS submission is not required to file the application. However, FDA will determine the need for a REMS during the review of the BLA

SPONSOR RESPONSE

The Sponsor acknowledges FDA's acceptability of initial REMS proposal. No further discussion is requested during the meeting.

Additional Comments

13. *Include with the financial information the financial disclosure data (clinical investigators, including sub-investigators, with disclosable financial interest and without disclosable financial interest) in an excel compatible format, e.g., .xls or .xpt.*

SPONSOR RESPONSE:

The sponsor agrees with FDA request and will submit financial disclosure information in the requested format.

Clinical Pharmacology

14. *In Immunocore's responses to the FDA preliminary comments ahead of the meeting scheduled on March 12, 2021, or within 30 days of receipt of these comments, provide the following information to support the proposed dosing regimen of tebentafusp:*

- b. A detailed tabular summary of safety data from Studies IMCgp100-01 and IMCgp100-102, analyzed by dose cohort. This summary should include an overview of CRS events by grade (per ASTCT 2019 criteria) at each dose level.*

SPONSOR RESPONSE

We agree to provide tabular summary of safety data within 30 days for Study IMCgp100-102 at each dose level. This summary data will include an overview of CRS events by grade as adjudicated by the sponsor using the ASTCT 2019 criteria.

The sponsor will follow-up in the next 30 days to seek clarification on optimal way to present the tabular summary of safety events by cohorts on Study IMCgp100-01.

Accurate adjudication according to the ASTCT 2019 criteria is not possible for Study IMCgp100-01 due to the lack of available data in the study, which is now closed, relating to important parameters for grading such as oxygen use. However, the study data has already been adjudicated according to the Lee 2014 criteria and the Sponsor can provide the requested summaries based on this adjudication.

In addition, the sponsor agrees with FDA information requests listed below and will provide the requested information within 30 days of receipt of this feedback.

- a. *A tabular summary of the tebentafusp dosing regimens evaluated in Studies IMCgp100-01 and IMCgp100-102.*
- c. *A summary of the incidence of all Grade and Grade ≥ 2 CRS, Grade ≥ 3 rash, Grade ≥ 3 LFT increases, and treatment-emergent adverse events leading to dose modifications over time (by cycle), at the 20/30/68 mcg QW dosing regimen in Studies IMCgp100-102 and IMCgp100-202.*
- d. *A tabular summary of efficacy data from Studies IMCgp100-01 and IMCgp100-102 by dosing cohort.*
- e. *Clarification regarding whether sparse PK samples have been collected in all patients in Study IMCgp100-202. Provide a tabular summary of studies that are included in the exposure-responses analyses for safety and efficacy, including information on studies from which dense and sparse PK sampling are available. Provide a summary of the current exposure-response analyses with safety and efficacy planned to support the proposed dosing regimen.*

A tabular summary of PRO endpoints collected in clinical studies including Study IMCgp100-102. This summary should include the PRO endpoints assessed and time points at which PRO data were collected relative to dosing and PK sampling. This information might enable assessment of the potential utility of exposure-response analyses with patient reported outcomes. Provide justification for the approach selected.

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

/s/

NATALIYA N FESENKO
03/17/2021 10:36:28 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 114314
Request Receipt Date	12/22/2020
Product	Tebentafusp (IMCgp100)
Indication	Metastatic uveal melanoma (MUM)
Drug Class/Mechanism of Action	Bifunctional biologic fusing gp100 affinity enhanced T-cell receptor (targeting domain) with CD3 (effector domain)
Sponsor	Immunocore
ODE/Division	OOD/DO3
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	2/18/2021

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

- Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

Immunocore requests Breakthrough Therapy Designation for tebentafusp (IMCgp100) for the treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma (mUM).

- Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?**

YES NO

- Was the BTDR submitted to a PIND?**

YES NO

If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

- Consideration of Breakthrough Therapy Criteria:**

- Is the condition serious/life-threatening¹?

YES NO

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

- Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- YES, the BTDR is adequate and sufficiently complete to permit a substantive review
 Undetermined
 NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

- i. Only animal/nonclinical data submitted as evidence
- ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTDR Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation

Reviewer Signature: { See appended electronic signature page }
 Team Leader Signature: { See appended electronic signature page }
 Division Director Signature: { See appended electronic signature page }

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Disease Background

Uveal melanoma (UM) is a form of melanoma affecting the iris, ciliary body, or choroid (collectively referred to as the uvea). It has a distinct pathophysiology as well as clinical and molecular characteristics compared to other types of melanoma. There are no drugs specifically approved for metastatic UM (mUM). UM responds poorly to cytotoxic chemotherapy and radiotherapy. UM is not generally sensitive to checkpoint inhibitors. The prognosis for patients with

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

mUM is poor with a median survival of < 12 months. The 1-year OS rate for UM in recent meta-analyses is approximately 40%.

Tebentafusp

Tebentafusp is a bispecific protein therapeutic comprising a soluble, affinity-enhanced T cell receptor (TCR; targeting domain) fused to an antibody single-chain variable fragment targeting CD3 (scFv; effector domain). The TCR recognizes a peptide derived from gp100, a melanocyte lineage antigen expressed exclusively in normal melanocytes (e.g. skin and hair follicle) and tumors derived from melanocytes (i.e. melanoma), that is presented on the cell surface by human leukocyte antigen – A*02:01 (HLA-A0201).

Submission for BTDR

The following submission was evaluated as part of the BTDR review: Breakthrough Therapy Designation Request submitted to IND 114314 on December 22, 2020 (SDN 296).

\\CDSESUB1\evsprod\ind114314\0292\m1\us\17-fast-trac\break-therpy-des-req.pdf

8. Information related to endpoints used in the available clinical data:

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

Immunocore requested BTDR based upon overall survival (OS) results in a randomized controlled trial.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

OS has been used as the primary endpoint to support traditional approval for the treatment of patients with melanoma. OS is a clinical endpoint that directly measures the clinical benefit of a drug and would support traditional approval.

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
 - *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
 - *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*
- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval. **Not applicable.**

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

There are no available FDA-approved therapies for patients with metastatic uveal melanoma.

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*

- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

A review of CDERS electronic document archival system (DARRTS) and list of CDER approvals available on www.fda.gov did not identify any breakthrough therapy requests for mUM.

11. Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

In support of the BTDR, Immunocore presented efficacy and safety data from the first prespecified interim analysis of Study IMCgp100-202.

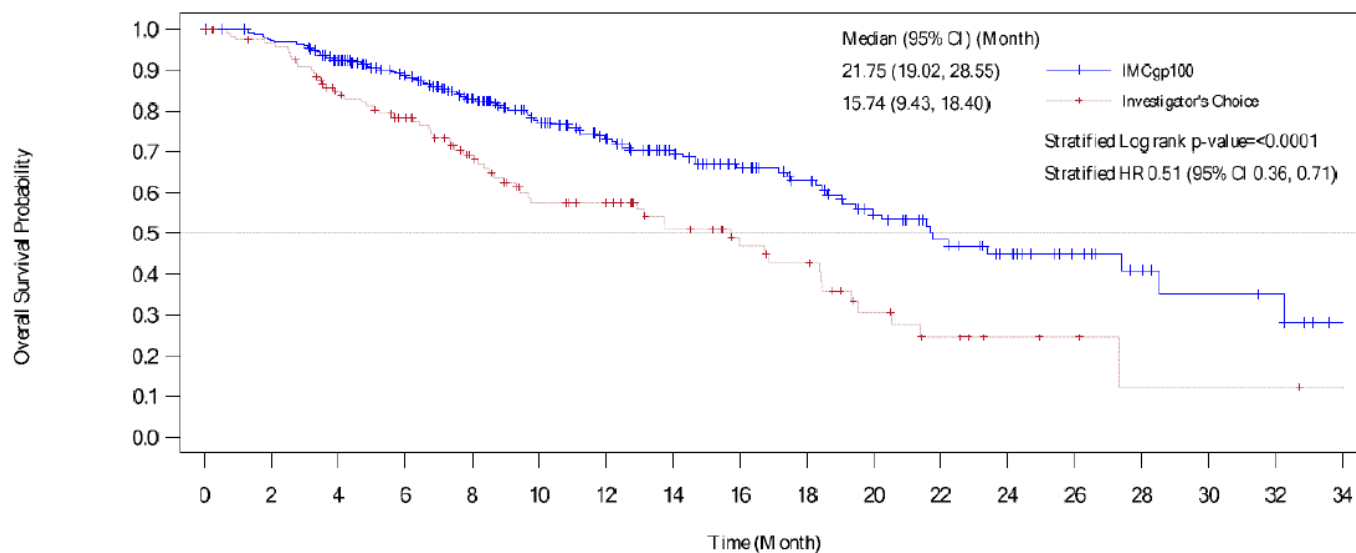
IMCgp100-202 is an open-label, randomized, multi-center study to evaluate the efficacy and safety of tebentafusp in adult HLA-A*02:01-positive patient with previously untreated mUM. Patients were randomized (2:1) to received tebentafusp or Investigator's choice (dacarbazine, ipilimumab, or pembrolizumab). Randomization was stratified by lactate dehydrogenase (LDH) status. Treatment continued until radiographic progression (except for ipilimumab), unacceptable toxicity, investigator decision, or patient withdrawal. Crossover between was not permitted. The primary endpoint was OS. Key secondary endpoints were progression-free survival (PFS), best overall response, and disease control rate.

The first interim analysis was to be performed after approximately 60% of the events (150 deaths of 250 planned). From 12 October 2017 to 13 October 2020, 378 patients were randomly assigned to receive either tebentafusp (n=252) or investigator's choice (n=126). Based on a median follow-up duration of 13.3 months and 143 events (~60% of total events), the primary end point of OS favored tebentafusp with a hazard ratio (HR) of 0.51 (95% CI:0.36, 0.71; p< 0.0001). The Kaplan-Meier (KM) estimates (not yet mature) suggest a median OS of 28.6 months for tebentafusp compared with 15.7 months for investigator's choice. The KM curves for the OS are shown in the figure below, copied from the BTDR submitted by the Sponsor.

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Figure 1 Kaplan-Meier Estimate of Overall Survival (ITT Set)



Number of subjects at risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
IM Cgp100	252	242	219	192	162	127	105	86	69	58	42	30	22	14	9	6	5	0
Investigator's Choice	126	116	94	82	62	46	42	30	24	20	11	7	4	3	1	1	1	0

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

b. Include any additional relevant information. Consider the following in your response:

- Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.
- Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.
- Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.

Immunocore included limited safety data for Study IMCgp100-202. A total of 245 patient (97%) in the tebentafusp arm and 111 (82%) in the Investigator's choice arm received at least one dose of study drug and comprise the safety analysis set. The frequency of Grade 3 or higher events was 55% in the tebentafusp arm and 37% in the investigator choice arm. The incidence of serious treatment-emergent adverse events was 29% in the tebentafusp arm and 23% in the investigator's choice arm. The rates of TEAEs resulting in death were similar between the two arms. None of the deaths in either arm were considered treatment-related.

Adverse events are associated with the mechanism of action and include skin events and systemic symptoms associated with cytokine release such as hypotension, pyrexia, and fatigue. The Sponsor reports that most cytokine release syndrome (CSR) events observed across the development program were mild to moderate in severity. To date there have been no fatal episodes of CRS.

12. Division's recommendation and rationale (pre-MPC review):

GRANT:

Provide brief summary of rationale for granting:

Based on the data submitted by Immunocore, DO3 recommends granting the proposed request for breakthrough therapy designation for Tebentafusp (IMCgp100) for the treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

Unresectable and metastatic UM is a serious disease with unmet need. Based on a planned interim analysis of the randomized study IMCgp100-202, the primary endpoint of OS, which favored the tebentafusp arm with a hazard ratio (HR) of 0.51 (95% CI:0.36, 0.71; p< 0.0001), provided evidence of clinical benefit for tebentafusp in this population.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

A pre-BLA meeting has been granted and is scheduled for March 2021.

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES NO

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation
Deny Breakthrough Therapy Designation

Reviewer Signature: { See appended electronic signature page }
Team Leader Signature: { See appended electronic signature page }
Division Director Signature: { See appended electronic signature page }

Revised 3/18/19/M. Raggio

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

/s/

MARGARET C THOMPSON
03/04/2021 06:43:36 PM

STEVEN J LEMERY
03/05/2021 08:22:55 AM



IND 114314

MEETING MINUTES

Immunocore LLC
Attention: Mark Moyer, M.S.
Senior Vice President, Head of Regulatory Affairs
Six Tower Bridge, 181 Washington Street, Suite 540
Conshohocken, PA 19428

Dear Mr. Moyer:¹

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tebentafusp (IMCgp100).

We also refer to the teleconference between representatives of your firm and the FDA on March 3, 2020. The purpose of the meeting was to discuss the clinical development plan for tebentafusp (IMCgp100).

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

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

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

IND 114314
Page 2

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C

Meeting Category: Guidance

Meeting Date and Time: Tuesday, March 3, 2020, 1:00 PM – 2:00 PM EST

Meeting Location: Teleconference

Application Number: IND 114314

Product Name: Tebentafusp (IMCgp100)

Proposed Indication: Treatment of HLA A*0201 positive patients with metastatic uveal melanoma

Sponsor Name: Immunocore LLC

FDA ATTENDEES

Steven Lemery, M.D., Director (acting), OOD/DO3
Margaret Thompson, M.D., Clinical Reviewer OOD/DO3
Sirisha Mushti, Ph.D., Statistical Reviewer OB/DBV
Lisa Rodriguez, Ph.D., Statistical Reviewer OB/DBV
Matt Thompson, Ph.D., Nonclinical Reviewer, CDER/DHOT
Jens Fricke, Ph.D., Product Quality Team Leader, OPQ/OBP
Willie Wilson, Ph.D., Product Quality Team Leader, OPQ/OBP
Nataliya Fesenko, Pharm.D., Regulatory Project Manager, ORO-OD

SPONSOR ATTENDEES

Shaad Abdullah, M.D., FACP, Clinical Program Lead
David Berman, M.D., Ph.D., Head of Research and Development
Mohammed Dar, M.D., Chief Medical Officer & Head of Clinical Development
Chris Holland, M.S., Head of Biometrics
Mark Moyer, M.S., Head of Regulatory Affairs, Pharmacovigilance and Project Management, Project Leader for tebentafusp
Koustubh Ranade, Ph.D., Head of Translational Medicine

BACKGROUND

Regulatory

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

Clinical

Tebentafusp (IMCgp100) is a bispecific protein comprising a soluble, affinity-enhanced T cell receptor (TCR) fused to an antibody single-chain variable fragment targeting CD2. The TCR recognizes a peptide derived for gp100, a melanocyte lineage antigen expressed exclusively in normal melanocytes and tumors derived from melanocytes, i.e., melanoma, that is presented on the cell surface by human leukocyte antigen A*02:01.

IMCgp100 is under evaluation in two ongoing clinical trials of adult patients with uveal melanoma sponsored by Immunocore: Study IMCgp100-102 and Study IMCgp100-202.

Study IMCgp100-102 is an open-label, single-arm, multi-center, dose finding with dose expansion study of IMCgp100 as a single agent in adult patients with metastatic uveal melanoma (mUM). The dose expansion portion of the trial comprises two cohorts. Cohort A enrolls patients with mUM in the second-line setting after disease progression following systemic treatment with a checkpoint inhibitor with any prior liver-directed therapy. Cohort B enrolls patients with mUM in the second or third-line setting with up to one prior liver-directed therapy regimen.

The primary endpoint of the dose expansion portion of the study is confirmed objective response rate (ORR) based on RECIST v.1.1 as assessed by blinded independent central review (BICR). The main secondary efficacy endpoints are duration of response (DOR), progression free survival (PFS), and overall survival (OS). The study was closed to accrual February 2019 with 127 patients entered. The primary analysis for the study will include all 127 patients with a minimum of 53 weeks follow-up.

The meeting package included preliminary results based on a planned interim analysis of the first 75 patients enrolled in the cohort expansion portion of the trial with a minimum follow-up of 43 weeks. Overall response evaluated by IRC was 4% (3 PRs,

95% CI: 0.8%, 11.2%). The waterfall plot for these patients is copied from the meeting package below.

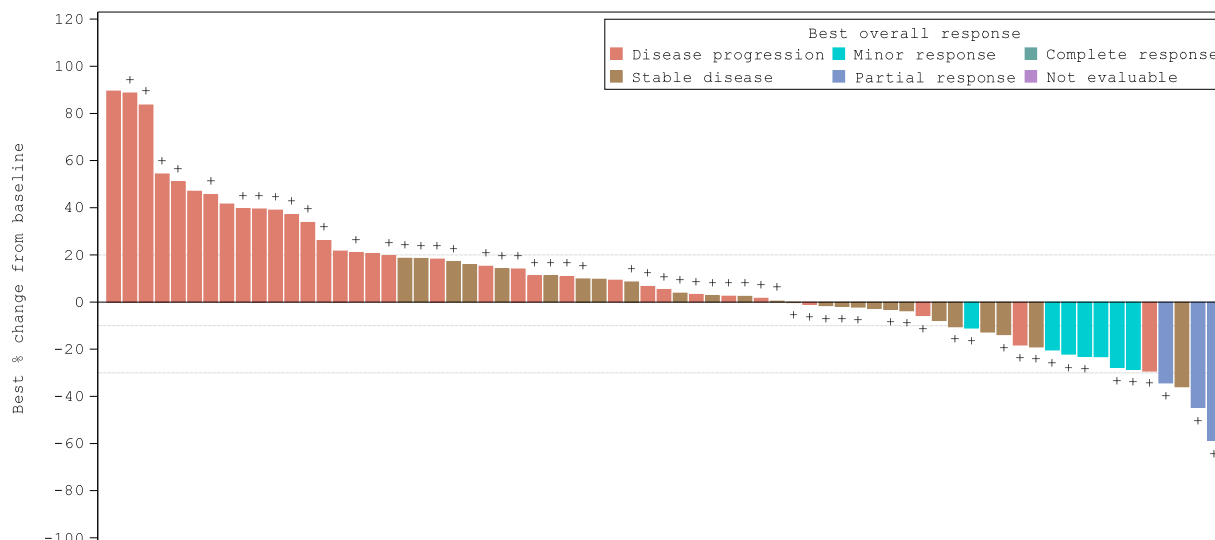


Figure: Waterfall plot for interim analysis population in IMCgp100-102 (+ indicates prior Immune Checkpoint Inhibitor)

Study IMCgp100-202 is a randomized, open-label, multi-center study of IMCgp100 compared to investigator's choice therapy (dacarbazine, ipilimumab, or pembrolizumab) in HLA A*0201-positive patients with previously untreated advanced uveal melanoma. Patients will be randomly allocated in 2:1 ratio to IMCgp100 vs. investigator's choice therapy with stratification based on LDH status.

The primary endpoint is overall survival (OS). The primary analysis of OS in all randomized patients will be conducted using a 2-sided log-rank test stratified by LDH status for generation of the p-value. The hazard ratio (HR) will be estimated using a stratified Cox-proportional hazards model using the Efron approach for handling ties, together with the associated profile likelihood 95% confidence intervals (CIs) for the HR. Assuming a 2:1 randomization ratio, 219 events (deaths) are needed to provide 80% power to detect a 0.67 HR for OS with a 2-sided significance level of 0.05 (1-sided 0.025). The sample size of the trial was originally planned at 327 patients.

These analyses will be performed using a 3-stage adaptive group sequential design:

- The first analysis will re-assess sample-size using conditional power.
- The interim analysis will include an assessment of all relevant clinical outcomes to include OS, PFS, and ORR.
- The final analysis.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

Secondary efficacy objectives are ORR, PFS, DOR, time to response, and disease control rate (DCR) using RECIST v1.1.

The study is ongoing with 275 patients randomized as of December 31, 2019. Immunocore is proposing the following amendments: elimination of the resizing analysis, extending accrual to 369 patients, addition of a second interim analysis, and refinement in timing of the original interim analysis.

Proposed Approval Pathway

Immunocore proposes submitting a BLA for tebentafusp for potential accelerated approval, based on final analysis of Study IMCgp100-102, or regular approval, based on final analysis of Study IMCgp100-102 and Study IMCgp100-202, with a proposed indication for the treatment of HLA A*0201-positive patients with mUM. Immunocore anticipates the following key timeline events:

- IMCgp100-102: primary topline results May 2020 (Clinical Study Report planned for August 2020).
- IMCgp100-202: first interim analysis topline results August 2020, second interim analysis topline December 2021, primary analysis topline 2024.

FDA sent Preliminary Comments to Immunocore on February 21, 2020.

DISCUSSION

Clinical/Statistical

1. Immunocore is proposing two changes to the randomized Study IMCgp100-202 including a) removing the protocol specified unblinded sample size re-estimation and b) adding a second interim analysis. A blinded sample size re-estimation was performed indicating an increase from 327 to 369 patients and the number of target events from 219 to 250. In addition, the timing of the currently planned interim analysis will be updated. These changes are primarily being made to increase the probability of a successful trial and to have the opportunity to stop the trial early in case of outstanding efficacy. Does FDA agree with the proposed amendments (details can be found in Section 15.5.11 Proposed Protocol Amendments)?

FDA Response: Insufficient information was provided for FDA to answer this question. Please provide further details regarding the “blinded sample size re-estimation” for FDA’s clarification. Clarify if Immunocore’s blinded analysis was based on the data accrued to-date from Study IMCgp100-202 or was the study

design re-visited after the obtaining the interim topline results for Study IMCgp100-102.

Specify clearly which aspect has led to an increase in the number of events from 219 to 250; Provide a reference for the sample size re-estimation method and specify if the type-I error is controlled at 5% with such an increase in the number of events. Furthermore, the meeting background document did not provide details regarding the stopping rules (and alpha spending) for the proposed interim analyses.

Immunocore Response (received February 26, 2020): To clarify, the sample size was re-estimated without consideration of any data accrued in Study IMCgp100-202. Rather, the study design was re-visited based on interim OS from Study IMCgp100-102 in addition to OS data from a recently published meta-analysis (Rantala et. al, 2019). The availability of these data has rendered the per-protocol, un-blinded sample size re-estimation not necessary. The increase in the sample size from 327 to 369 and the number of events from 219 to 250 was based on these updated assumptions and also the desire to increase the power of the study from 80% to 90%.

Regarding the interim analyses, the alpha-spending procedure (Lan-DeMets) and boundary type (O'Brien-Fleming), which are well-established for their ability to control the overall Type I error rate at desired levels, are unchanged from the original protocol and statistical analysis plan. However, the number of interim analyses and timing of the analyses are different. The original protocol called for one analysis at 70% of the events while the proposed amendment calls for analyses at 50% and 80% of the required events. The extra interim analysis was added to provide an opportunity to stop the trial early in case of outstanding efficacy. All interim analyses will be conducted only after patient recruitment is complete. Further details will be provided in the amended protocol and statistical analysis plan.

Discussion during the meeting: FDA stated that the response appears to address FDA's concern.

2. Rash is an expected and on-target AE (due to gp100+ melanocytes in the skin). In study IMCgp100-01, and subsequently observed in study IMCgp100-102, patients who developed a rash shortly (e.g. same day or within first few days) after the first dose of tebentafusp had superior OS compared to those who did not have a rash.

Given the strong biological rationale, the observation of this association in two studies, the onset of rash so close to randomization (thus limiting immortal time bias) and the importance of providing this information to HCPs, Immunocore proposes to add a dual primary objective to Study IMCgp100-202 to formally test

this hypothesis for overall survival by assigning some alpha to the comparison of tebentafusp patients who experience rash within the first week versus all other patients (i.e., tebentafusp patients without a rash + control arm patients; described in Section 15.5.12 Proposal for Analysis of Rash Association with OS for IA of Study 202). The majority of the alpha to be spent will remain with the original primary objective based on the ITT comparison of tebentafusp versus the control arm by randomized assignment. Immunocore realizes that this is a novel approach but is of the opinion that it is in the best interest for patients that this be formally tested in the ongoing IMCgp100-202 since a new study in such a rare patient population will take a very long time. Does the FDA have any comments that should be considered?

FDA Response: FDA would not agree that an analysis comparing the survival of patients who experience rash within the first week of receipt of tebentafusp versus all other patients could support approval. The analysis, as noted in the meeting package, is not based on a randomized population and any analysis performed on patients without rash will be considered by FDA to be exploratory (alpha cannot be interpreted in this setting).

Notwithstanding FDA's primary concern, it is also not clear why a comparison between patients who do not have a rash includes both patients who receive tebentafusp as well as those who do not. Also, rash is non-specific and likely involves skin cells beyond melanocytes.

Finally, if tebentafusp is determined to be effective, the proposed analysis would result in many patients who did not have rash discontinuing the drug after one week. Although this may be of value if there is a certain relationship between rash and efficacy, if the relationship is not causal, then patients could be harmed by stopping early.

Immunocore Response (received February 26, 2020): We acknowledge the feedback from FDA and would like to take the opportunity during the meeting to discuss this topic in more detail.

Immunocore is of the opinion that the rash observed with tebentafusp is gp100-specific, associated with a unique clinical presentation (e.g. phenotypically characteristic, rapid and predictable onset), related to the tebentafusp mechanism of action, and based on carefully defined criteria for a composite term for rash.

Immunocore understands that an analysis based on early onset rash is unique and not standard and would not be acceptable as a co-primary objective by the FDA. (b) (4)

Immunocore would like to

focus the discussion on whether such an analysis can be performed as a co-primary objective while still maintaining the integrity of the ITT analysis.

Immunocore originally intended to include all patients randomized in the rash-OS analysis and thus proposed to pool the non-rash, tebentafusp patients with the control arm. If there is remaining time and based on FDA's comment, Immunocore would appreciate any further feedback on optimal ways to conduct a rash analysis regardless of whether such an analysis is exploratory or co-primary. For example, would comparing tebentafusp rash patients to all control arm patients be more informative?

Discussion during the meeting: Immunocore proposes to include a minor alpha spend for the rash hypothesis (b) (4)

Immunocore acknowledged the concern regarding the pooling of patients in both the experimental and control arms and would propose an analysis of patients with rash with all patients in the control arm. FDA stated that the Agency would still consider this analysis as exploratory. Immunocore acknowledged.

Immunocore stated that enrollment is expected to be completely enrolled at the time of the proposed analysis in patients with or without rash. Immunocore expects that the vast majority of patients will also have discontinued study treatment and therefore would not expect the analysis to affect which treatment a patient would receive post progression.

FDA stated that ultimately, this would be Immunocore's risk regarding splitting alpha; however, it would not appear to affect the integrity of the trial related to the analysis of OS in the ITT population. FDA stated, however, that this could impact the power to assess for a treatment effect in the ITT population (increasing the risk for a negative trial) and suggested that if Immunocore was going to do such an analysis, that Immunocore consider a smaller alpha spend. Irrespective, FDA would consider the analysis based on rash as exploratory. Immunocore acknowledged.

3. The topline results for IMCgp100-102 will be shared with the FDA to discuss potential for BLA for accelerated approval based on this study alone. Immunocore plans to discuss with FDA once available.

If the FDA is of the opinion that the primary results (provided around May 2020) from IMCgp100-102 cannot support a BLA alone, and given the promising OS observed to date (supported by association with rash and durable responses), would the FDA consider a Real-Time Oncology Review (RTOR) pilot program (Immunocore understands that formal request needs to be made once topline is available) to initiate BLA review based on the IMCgp100-102 CSR, and have the first interim analysis for Study IMCgp100-202 trigger the PDUFA start date

(expected about 3 months after topline from IMCgp100-102)? If yes, Immunocore would like to know the logistics of applying for this pilot program and how the submissions are made to enable such?

FDA Response: No. FDA cannot agree with a request for RTOR without an understanding of the data that would be submitted in a BLA. Given the reported response rate of 4% in Study IMCgp100-102, FDA believes that data from the randomized study will be necessary to support approval. Therefore, a request for RTOR should not be initiated until after Immunocore has conducted an analysis demonstrating substantial evidence of effectiveness (e.g., if a pre-specified boundary is crossed for the primary endpoint at one of the interim or final analyses of efficacy of Study IMCgp100-202).

FDA reminds Immunocore that the RTOR program does not guarantee approval nor does it guarantee a decision will be made prior to the PDUFA date.

Immunocore Response (received February 26, 2020): Immunocore notes in FDA's response to Question 3 that RTOR needs to be requested based on the data to support potential review/approval. We will consider formally applying for this based on availability of such data. We will share the primary analysis results from Study IMCgp100-102 when available, and if promising we will request a discussion to see if there is a path forward.

Discussion during the meeting: There was no further discussion of this item during the meeting.

4. Since IMCgp100 may confer most benefit to UM patients in OS rather than formal RECIST response, would a propensity score analysis comparing OS from Study IMCgp100-102 to real world patient-level data from the recent Khoja et. al. meta-analysis in metastatic uveal melanoma (Section 15.6 Use of Real-World Data) be helpful to the FDA to fully review the final Study IMCgp100-102 results for potential accelerated approval? If so, prior to conducting any endpoint analyses, Immunocore would like to collaborate with FDA by submitting the SAP and propensity score modeling results for review.

FDA Response: No. Patients enrolled in Immunocore's trial is expected to be fundamentally different than those enrolled in a published meta-analysis of patients enrolled up to 20 years ago. A propensity score analysis cannot control for unknown confounding prognostic factors.

Immunocore Response (received February 26, 2020): FDA's initial response is clear and Immunocore has no further questions or need for clarification.

Discussion during the meeting: There was no further discussion of this item during the meeting.

5. Based on fast track designation granted on April 1, 2019, does FDA agree to grant a rolling BLA submission for this BLA (Section 11.3 Timelines for Study Analyses and Potential Submissions)?

FDA Response: Products receiving fast track designation for a specific indication are eligible for a rolling submission for that indication (if FDA agrees to file the application). A request for rolling review will generally be considered at the time of the pre-BLA meeting.

Immunocore Response (received February 26, 2020): FDA's initial response is clear and Immunocore has no further questions or need for clarification.

Discussion during the meeting: There was no further discussion of this item during the meeting.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to [FDA.gov](https://www.fda.gov).²

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants³ to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric

² <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

³ See the guidance for industry "*Formal Meetings Between the FDA and Sponsors or Applicants.*"

U.S. Food and Drug Administration

Silver Spring, MD 20993

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product development, please refer to FDA.gov.⁴

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁵ and Pregnancy and Lactation Labeling Final Rule⁶ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively

⁴ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁵ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁶ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.⁷

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,⁸ as well as email access to the eData Team (cdere-data@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁹ that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

⁷ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

⁸ <https://www.fda.gov/media/88173/download>

⁹ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.¹⁰ For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide¹¹ (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.¹² When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.¹³

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the

¹⁰ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

¹¹ <https://www.fda.gov/media/88173/download>

¹² <https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

¹³ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in

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the development process. For more information, please see the FDA website entitled *Study Data Standards Resources*¹⁴ and the CDER/CBER Position on Use of SI Units for Lab Tests website.¹⁵

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.¹⁶

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product

¹⁴ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

¹⁵ <https://www.fda.gov/media/109533/download>

¹⁶ <https://www.fda.gov/media/85061/download>

development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

- (1) Study phase
- (2) Statement of whether the study is intended to support marketing and/or labeling changes
- (3) Study objectives (e.g., dose finding)
- (4) Population
- (5) A brief description of the study design (e.g., placebo or active controlled)
- (6) Specific concerns for which you anticipate the Division will have comments
- (7) For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ATTACHMENTS AND HANDOUTS

Immunocore response received on February 26, 2020

SPONSOR QUESTIONS AND FDA RESPONSES

1. Immunocore is proposing two changes to the randomized Study IMCgp100-202 including a) removing the protocol specified unblinded sample size re-estimation and b) adding a second interim analysis. A blinded sample size re-estimation was performed indicating an increase from 327 to 369 patients and the number of target events from 219 to 250. In addition, the timing of the currently planned interim analysis will be updated. These changes are primarily being made to increase the probability of a successful trial and to have the opportunity to stop the trial early in case of outstanding efficacy. Does FDA agree with the proposed amendments (details can be found in Section 15.5.11 Proposed Protocol Amendments)?

FDA Response: Insufficient information was provided for FDA to answer this question. Please provide further details regarding the “blinded sample size re-estimation” for FDA’s clarification. Clarify if Immunocore’s blinded analysis was based on the data accrued to-date from Study IMCgp100-202 or was the study design re-visited after the obtaining the interim topline results for Study IMCgp100-102.

Specify clearly which aspect has led to an increase in the number of events from 219 to 250; Provide a reference for the sample size re-estimation method and specify if the type-I error is controlled at 5% with such an increase in the number of events. Furthermore, the meeting background document did not provide details regarding the stopping rules (and alpha spending) for the proposed interim analyses.

Immunocore Response to Question #1

Thank you for the response.

To clarify, the sample size was re-estimated without consideration of any data accrued in Study IMCgp100-202. Rather, the study design was re-visited based on interim OS from Study IMCgp100-102 in addition to OS data from a recently published meta-analysis (Rantala et. al, 2019). The availability of these data has rendered the per-protocol, unblinded sample size re-estimation not necessary. The increase in the sample size from 327 to 369 and the number of events from 219 to 250 was based on these updated assumptions and also the desire to increase the power of the study from 80% to 90%.

Regarding the interim analyses, the alpha-spending procedure (Lan-DeMets) and boundary type (O’Brien-Fleming), which are well-established for their ability to control the overall Type I error rate at desired levels, are unchanged from the original protocol and statistical analysis plan. However, the number of interim analyses and timing of the analyses are different. The original protocol called for one analysis at 70% of the events while the proposed amendment calls for analyses at 50% and 80% of the required events. The extra interim analysis was added to provide an opportunity to stop the trial early in case of outstanding efficacy. All interim analyses will be conducted only after patient recruitment is complete. Further details will be provided in the amended protocol and statistical analysis plan.

2. **Rash is an expected and on-target AE (due to gp100+ melanocytes in the skin). In study IMCgp100-01, and subsequently observed in study IMCgp100-102, patients who developed a rash shortly (e.g. same day or within first few days) after the first dose of tebentafusp had superior OS compared to those who did not have a rash.**

Given the strong biological rationale, the observation of this association in two studies, the onset of rash so close to randomization (thus limiting immortal time bias) and the importance of providing this information to HCPs, Immunocore proposes to add a dual primary objective to Study IMCgp100-202 to formally test this hypothesis for overall survival by assigning some alpha to the comparison of tebentafusp patients who experience rash within the first week versus all other patients (i.e., tebentafusp patients without a rash + control arm patients; described in Section 15.5.12 Proposal for Analysis of Rash Association with OS for IA of Study 202). The majority of the alpha to be spent will remain with the original primary objective based on the ITT comparison of tebentafusp versus the control arm by randomized assignment. Immunocore realizes that this is a novel approach but is of the opinion that it is in the best interest for patients that this be formally tested in the ongoing IMCgp100-202 since a new study in such a rare patient population will take a very long time. Does the FDA have any comments that should be considered?

FDA Response: FDA would not agree that an analysis comparing the survival of patients who experience rash within the first week of receipt of tebentafusp versus all other patients could support approval. The analysis, as noted in the meeting package, is not based on a randomized population and any analysis performed on patients without rash will be considered by FDA to be exploratory (alpha cannot be interpreted in this setting).

Notwithstanding FDA's primary concern, it is also not clear why a comparison between patients who do not have a rash includes both patients who receive tebentafusp as well as those who do not. Also, rash is non-specific and likely involves skin cells beyond melanocytes.

Finally, if tebentafusp is determined to be effective, the proposed analysis would result in many patients who did not have rash discontinuing the drug after one week. Although this may be of value if there is a certain relationship between rash and efficacy, if the relationship is not causal, then patients could be harmed by stopping early.

Immunocore Response to Question #2

We acknowledge the feedback from FDA and would like to take the opportunity during the meeting to discuss this topic in more detail.

Immunocore is of the opinion that the rash observed with tebentafusp is gp100-specific, associated with a unique clinical presentation (e.g. phenotypically characteristic, rapid

and predictable onset), related to the tebentafusp mechanism of action, and based on carefully defined criteria for a composite term for rash.

Immunocore understands that an analysis based on early onset rash is unique and not standard and would not be acceptable as a co-primary objective by the FDA. (b) (4)

Immunocore would like to focus the discussion on whether such an analysis can be performed as a co-primary objective while still maintaining the integrity of the ITT analysis.

Immunocore originally intended to include all patients randomized in the rash-OS analysis and thus proposed to pool the non-rash, tebentafusp patients with the control arm. If there is remaining time and based on FDA's comment, Immunocore would appreciate any further feedback on optimal ways to conduct a rash analysis regardless of whether such an analysis is exploratory or co-primary. For example, would comparing tebentafusp rash patients to all control arm patients be more informative?

3. **The topline results for IMCgp100-102 will be shared with the FDA to discuss potential for BLA for accelerated approval based on this study alone. Immunocore plans to discuss with FDA once available.**

If the FDA is of the opinion that the primary results (provided around May 2020) from IMCgp100-102 cannot support a BLA alone, and given the promising OS observed to date (supported by association with rash and durable responses), would the FDA consider a Real-Time Oncology Review (RTOR) pilot program (Immunocore understands that formal request needs to be made once topline is available) to initiate BLA review based on the IMCgp100-102 CSR, and have the first interim analysis for Study IMCgp100-202 trigger the PDUFA start date (expected about 3 months after topline from IMCgp100-102)? If yes, Immunocore would like to know the logistics of applying for this pilot program and how the submissions are made to enable such?

FDA Response: No. FDA cannot agree with a request for RTOR without an understanding of the data that would be submitted in a BLA. Given the reported response rate of 4% in Study IMCgp100-102, FDA believes that data from the randomized study will be necessary to support approval. Therefore, a request for RTOR should not be initiated until after Immunocore has conducted an analysis demonstrating substantial evidence of effectiveness (e.g., if a pre-specified boundary is crossed for the primary endpoint at one of the interim or final analyses of efficacy of Study IMCgp100-202).

FDA reminds Immunocore that the RTOR program does not guarantee approval nor does it guarantee a decision will be made prior to the PDUFA date.

Immunocore Response to Question #3

Immunocore notes in FDA's response to Question 3 that RTOR needs to be requested based on the data to support potential review/approval. We will consider formally applying for this based on availability of such data. We will share the primary analysis results from Study IMCgp100-102 when available, and if promising we will request a discussion to see if there is a path forward.

4. **Since IMCgp100 may confer most benefit to UM patients in OS rather than formal RECIST response, would a propensity score analysis comparing OS from Study IMCgp100-102 to real world patient-level data from the recent Khoja et. al. meta-analysis in metastatic uveal melanoma (Section 15.6 Use of Real-World Data) be helpful to the FDA to fully review the final Study IMCgp100-102 results for potential accelerated approval? If so, prior to conducting any endpoint analyses, Immunocore would like to collaborate with FDA by submitting the SAP and propensity score modeling results for review.**

FDA Response: No. Patients enrolled in Immunocore's trial are expected to be fundamentally different than those enrolled in a published meta-analysis of patients enrolled up to 20 years ago. A propensity score analysis cannot control for unknown confounding prognostic factors.

Immunocore Response to Question #4

FDA's initial response is clear and Immunocore has no further questions or need for clarification.

5. **Based on fast track designation granted on April 1, 2019, does FDA agree to grant a rolling BLA submission for this BLA (Section 11.3 Timelines for Study Analyses and Potential Submissions)?**

FDA Response: Products receiving fast track designation for a specific indication are eligible for a rolling submission for that indication (if FDA agrees to file the application). A request for rolling review will generally be considered at the time of the pre-BLA meeting.

Immunocore Response to Question #5

FDA's initial response is clear and Immunocore has no further questions or need for clarification.

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

/s/

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