

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761115Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 122694

MEETING MINUTES

Immunomedics, Inc.
Attention: Diane Whiteley
Senior Director
300 The American Road
Morris Plains, NJ 07950

Dear Ms. Whiteley:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sacituzumab govitecan (IMMU-132, hRS7-SN38).

We also refer to the meeting between representatives of your firm and the FDA on October 12, 2017. The purpose of the meeting was to obtain FDA guidance on clinical, clinical pharmacology, and regulatory questions in preparation of the planned BLA filing.

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 Rajesh Venugopal, Senior Regulatory Project Manager at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Rajesh Venugopal, MPH, MBA
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

Laleh Amiri-Kordestani, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA
Meeting Date and Time: Thursday, October 12, 2017/11:00 AM – 12:00 PM
Meeting Location: 10903 New Hampshire Avenue White Oak Building 22
Conference Room: 1313, Silver Spring, MD 20903

Application Number: IND 122694
Product Name: sacituzumab govitecan (IMMU-132, hRS7-SN38)
Indication: Relapsed/refractory, metastatic, triple-negative breast cancer (mTNBC) after at least two prior therapies for metastatic disease
Sponsor/Applicant Name: Immunomedics, Inc.

Meeting Chair: Rajesh Venugopal, MPH, MBA
Meeting Recorder: Laleh Amiri-Kordestani, MD

FDA ATTENDEES

Julia Beaver, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Laleh Amiri-Kordestani, MD, Medical Team Leader, DOP1
Lynn Howie, MD, Medical Reviewer, DOP1
Tatiana Prowell, MD, Medical Reviewer, DOP1
Hui Zhang, PhD, Biostatistics Reviewer, OB/DBV
Shenghui Tang, PhD, Biostatistics Team Leader, OB/DBV
Salaheldin Hamed, PhD, Clinical Pharmacology Reviewer, DCP V
Pengfei Song, PhD, Clinical Pharmacology Team Leader, DCP V
Todd Palmby, PhD, Pharm/Tox Supervisor, DHOT
Joshua Bungler, PhD, CMC Reviewer, Division of Biotechnology Review and Research I, OBP
Qing (Joanna) Zhou, PhD, CMC Team Leader, Division of Biotechnology Review and Research I, OBP
Rajesh Venugopal, MPH, MBA, Senior Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

Diane Whiteley, Senior Director, Regulatory Affairs, Immunomedics, Inc.
William A. Wegener, MD, PhD, Chief Medical Officer, Immunomedics, Inc.
(b) (4) Regulatory Consultant, (b) (4)
(b) (4) Consultant, Senior Medical Writer, (b) (4)
(b) (4) Consultant, (b) (4)
Usama Malik, Chief Business Officer, Immunomedics, Inc.
Behzad Aghazadeh, Chairman of the Board, Immunomedics, Inc.

BACKGROUND

Immunomedics is requesting a pre-BLA meeting to discuss content and data for the planned submission of the initial BLA for sacituzumab govitecan (IMMU-132) for the indication of relapsed/refractory, metastatic triple-negative breast cancer in patients who have received at least two prior therapies for metastatic disease. The Sponsor is seeking Accelerated Approval for this BLA under 21 CFR Part 314, Subpart E.

IMMU-132 is an antibody-drug conjugate (ADC) where SN-38, the active metabolite of irinotecan, is conjugated to hRS7, a humanized monoclonal antibody which targets Trop-2, human trophoblast cell-surface antigen. The primary mechanism of action of IMMU-132 is by delivery of SN-38 to tumor cells. After binding to Trop-2, the ADC is internalized and antibody bound SN-38 is released into the tumor cell.

The regulatory history for IMMU-132 is as follows:

- December 22, 2014: IMMU-132 received Fast Track Designation for the “treatment of patients with triple-negative breast cancer (TNBC) who have failed no more than two prior therapies for metastatic disease.”
- February 25, 2015: EOP2 meeting where the Sponsor sought Agency advice for acceptable trial design for a registration trial of IMMU-132 in the treatment of patients with relapsed/refractory mTNBC. At that time the Sponsor committed to conducting a randomized Phase 3 trial and to seek a Special Protocol Assessment (SPA) and submit a Statistical Analysis Plan for review. The Agency confirmed that progression-free survival (PFS) would be an acceptable primary endpoint for the planned Phase 3 Study.
- June 25, 2015: WRO guidance provided regarding the Sponsor’s approach to the evaluation of quality of life, and based on a revised estimate of PFS to discuss the proposed registration strategy for IMMU-132 in patients with relapsed/refractory mTNBC including the possibility of accelerated approval.
- November 24, 2015: SPA was provided for the proposed Phase 3 study IMMU-132-05, “An international, multicenter, open-label, randomized Phase 3 trial of sacituzumab govitecan (IMMU-132) compared to treatment of physician’s choice in patients with relapsed/refractory metastatic (stage IV) triple negative breast cancer who received at least 2 prior treatments.”
- February 4, 2016: Breakthrough Therapy Designation was granted for IMMU-132 for the treatment of patients with relapsed/refractory metastatic TNBC who have received at least two prior therapies for metastatic disease based on data from the TNBC cohort of the ongoing Phase 1/2 study in epithelial malignancies.
- May 9, 2016: Type B Multidisciplinary Breakthrough Therapy meeting was held to discuss the updated safety and efficacy data from the ongoing Phase 1/2 study IMMU-132-01 focusing on the metastatic TNBC patients treated to date. There was

discussion of a regulatory strategy to possibly include the accelerated approval of IMMU-132 on the basis of IMMU-132-01. It was determined that there were not adequate data for a biological licensing application (BLA) at that time, but the Agency agreed that a single-arm trial demonstrating a confirmed objective response rate determined by blinded central review that is better than available therapy with a supportive mature duration of response could support accelerated approval for the treatment of patients with relapsed/refractory mTNBC after at least two prior therapies for metastatic disease. For accelerated approval, it would be important for the confirmatory trial to be underway if not fully accrued.

- November 14, 2016: Type B EOP2 meeting was held to discuss nonclinical/clinical pharmacology development strategies for IMMU-132. It was confirmed that genotoxicity studies would be required for BLA submission and product labeling. Based on genotoxicity studies, it was confirmed that embryo-fetal development studies did not appear to be warranted for the proposed indication.
- March 17, 2017: A Type C Written Response Meeting indicated that the Agency concurred that the Phase 3 materials manufactured with a new clone (b) (4) were analytically comparable to the Phase 2 materials manufactured using the (b) (4) (b) (4) clone (b) (4). It was also agreed that additional nonclinical safety studies beyond the ongoing 3-month repeat-dose monkey toxicology study (pending review of the study report) are not required for filing. The Agency indicated the requirements for stability data (6 months' stability data for both drug substance (DS) and drug product (DP)).
- April 24, 2017: The Agency provided feedback regarding the proposed Phase 3 study design and advised consideration of modifications and standardization of the Treatment of Physician's Choice Arm. The Agency agreed that the proposed study could support a regulatory submission.
- June 29, 2017: The Agency provided written responses which agreed that the package of at least 100 patients with metastatic TNBC who received 10 mg/kg of IMMU-132 after having received at least two prior therapies, with a minimum follow up of 4 months, appeared to be acceptable to support submitting a BLA. Additionally, it was agreed that the proposal to submit complete efficacy and safety data for the target population of mTNBC patients and safety data for the safety population of patients regardless of tumor type and IMMU-132 was acceptable but also required the inclusion of ECG and laboratory data. The Agency agreed with the proposed approach to collect and submit tumor scans for ICR in patient with CR, PR or with at least 20% of reduction of their lesions based on local radiographic assessment as adequate for filing. The anticipated safety database of approximately 300 patients exposed to study drug over all tumor types was agreed to be sufficient for filing.

The Sponsor seeks to obtain FDA guidance regarding their proposed submission of data and analyses from IMMU-132-01 in this pre-Biological Licensing Application meeting. This study is a Phase 1/2, open-label, basket design in adult patients with epithelial cancers including

ovarian, endometrial, cervical, breast (TNBC and non-TNBC), prostate, lung, and others. Eligible patients must have stage IV disease at the time of study entry. The primary objective is to evaluate the safety and tolerability of IMMU-132 as a single agent administered on days 1 and 8 of a 21 day cycle in patients with advanced epithelial cancers. The secondary objective is to evaluate the PK, immunogenicity, and efficacy of IMMU-132. The primary endpoint is objective response rate (ORR) with independent central review (ICR) of those tumor scans assessed to have a response.

The Sponsor identified a subpopulation of 110 mTNBC patients in the IMMU-132-01 study that had received at least 2 lines of prior therapy for metastatic disease and consistent with the target population of the BLA. These patients are included regardless of dose of IMMU-132 received. After chart review, 98 of these patients were found to have been treated with at least two previous chemotherapies (excluding hormonal and targeted agents) which was considered to be consistent with the inclusion criteria for the proposed Phase 3 study.

Analysis of the ORR in the total population of 110 patients was assessed as 37/110 (33.6%) and 32/98 (32.6%) when the 12 patients who had not received two lines of cytotoxic chemotherapy were excluded. Based on ICR, the ORR were assessed as 35/110 (31.8%) and 30/98 (30.6%) respectively.

The most common adverse events regardless of causality occurring in $\geq 25\%$ of patients include nausea, neutropenia, diarrhea, anemia, vomiting, fatigue, alopecia, constipation, rash, abdominal pain, and leukopenia. Grade 3 or greater events occurred in 41% of patients with most of these events being neutropenia, leukopenia, diarrhea, and anemia. Three patients discontinued due to adverse events including due to infusion reaction, rash/mucositis, and fatigue. There were not treatment associated deaths reported.

The Sponsor indicates that the multicenter, open-label, randomized Phase 3 study, IMMU-132-05, in patients with mTNBC refractory or relapsing after at least two prior chemotherapies for their advanced disease is currently prepared for initiation in Q3 2017.

The Sponsor proposes to submit a claim of efficacy based on the 110 mTNBC patients who had received at least one dose of IMMU-132 at 10 mg/kg. The primary endpoint is ORR as assessed by the investigator with those assessed as having a response to undergo ICR. They propose that the safety analyses will be conducted using the 110 patients who were treated with IMMU-132 with mTNBC who had received two prior therapies. The proposed safety evaluation will include all 110 patients treated in the mTNBC target population (n=110) and will be assessed in terms of AEs, laboratories, vital signs, AEs \geq grade 3, drug related AEs, AEs leading to treatment discontinuation, SAEs, AEs leading to death, with narratives provided for all SAEs, deaths on study, and AEs leading to treatment discontinuation.

The Sponsor intends to identify patients with mild renal and hepatic impairment based on laboratory parameters of ALT, AST and bilirubin and serum creatinine to summarize the safety of IMMU-132 for patients with mild renal and hepatic impairment in the Integrated Summary of Safety. The Sponsor proposes pharmacokinetic evaluation with exposure-toxicity and

exposure-response assessments using a model based approach. Immunogenicity will be assessed based on the occurrence of human anti-human antibodies (HAHA) against IMMU-132. Cardiac safety data will be submitted as well.

DISCUSSION

1. *The overall number of patients with metastatic triple-negative breast cancer in pivotal study IMMU-132-01 is 148, comprising patients irrespective of the line of treatment and the IMMU-132 dose received. Among these patients, the Applicant identified 110 patients who had received at least 2 lines of prior therapy for metastatic disease as the intended target population for a BLA application under accelerated approval, in line with the agreements with FDA during a face-to-face meeting held on 9 May 2016. The Applicant plans to perform comprehensive analyses of efficacy and safety based on the population of 110 patients to support the claim of efficacy and to characterize the safety of IMMU-132 in the intended target population for this BLA.*

Furthermore, the Applicant has identified through medical review of oncological history data a cohort of 98 patients that form a subgroup within the larger group of 110 patients (see Section 6.3). These 98 patients have received at least 2 lines of prior standard chemotherapy for metastatic disease (i.e. excluding hormonal or other non-chemotherapy treatment), thereby corresponding to the eligibility criteria for Phase 3 study IMMU-132-05 that is currently under preparation. While the Applicant does not consider this cohort as the target population for the BLA, it is planned to provide selected analyses of efficacy endpoints as sensitivity analyses to demonstrate the robustness of the treatment effect of IMMU-132. Does the FDA agree with this approach?

FDA Response: Yes.

Meeting Discussion: No discussion took place.

2. *Patients in trial IMMU-132-01 were required to have adequate renal and hepatic function in order to participate in the trial, i.e. to have creatinine ≤ 2 x ULN, bilirubin ≤ 1.5 ULN, and AST and ALT ≤ 3 x ULN (or 5 x ULN in case of known liver metastases). Furthermore, patients with Gilbert's disease were excluded from trial participation. Therefore, the Applicant expects that there will not be any patient data available to characterize the safety of IMMU-132 in patients with moderate or severe renal or hepatic impairment.*

a) The Applicant intends to identify patients with mild renal and hepatic impairment based on laboratory parameters of ALT, AST, and bilirubin (hepatic impairment) and of serum creatinine and proteinuria (renal impairment) and to summarize the safety of IMMU-132 for patients with mild renal and hepatic impairment in the Integrated Summary of Safety (see Section 6.4.3). Does the FDA agree with this approach?

FDA Response: Yes.

Meeting Discussion: No discussion took place.

b) To fulfil the requirement of section 505(i) of the Federal Food, Drug, and Cosmetic Act to periodically update the pending NDA/BLA with new safety information, the Applicant intends to file 4 months after the initial BLA submission a safety update report in the same format as the integrated safety summary of the BLA. Hence, the Applicant will provide an updated Module 2.7.4 in conjunction with an Appendix of tables, listings, and figures pertaining to safety, as well as narratives for patients who experienced drug-related SAEs (including related fatal AEs) or discontinued treatment because of drug-related AEs since the data cut-off date for the original BLA. This 4-month safety update report will include updated safety information for the mTNBC target population and for the safety population (i.e. all patients treated with IMMU-12 regardless of cancer type and IMMU-132 dose). Does the Agency concur with the proposed strategy towards the 4-month safety update report?

FDA Response: Both the initial safety submission as well as the safety update should include information regarding AEs, including SAEs, SAE narratives and death narratives regardless of attribution to the study drug.

Depending on your data cut-off date, an earlier safety update may be more appropriate.

Meeting Discussion: The Sponsor indicated that they will submit the BLA in March 2018 with a proposed data cut-off of December 1, 2017 for the 90 day safety update which would allow the planned submission of the safety update of June 2018. The Agency stated that this would be acceptable.

c) Statistical analyses will be performed as outlined in Section 6.4, with comprehensive efficacy analyses and a comprehensive analysis of safety for the mTNBC target population and with separate safety analyses for the entire safety population i.e. all patients regardless of cancer type, line of treatment, and IMMU-132 dose. Does the Agency agree that the planned statistical analyses as described in Section 6.4 are adequate and sufficient to support BLA filing?

FDA Response: Yes, the efficacy analyses appear acceptable. Please note that the duration of response would be an important supportive result. For the safety analyses, we recommend inclusion of all AEs and SAEs regardless of attribution.

Meeting Discussion: No discussion took place.

- 3. A population pharmacokinetic analysis will be conducted using nonlinear mixed effects modeling of sparse data collected from patients of the mTNBC target population of study IMMU-132-01.*

Does the Agency agree that the planned population PK analysis as described in Section 6.4.4 is adequate to evaluate the population PK, exposure-response, and important covariates impacting the PK of IMMU-132 in the mTNBC target population?

FDA Response: Yes.

Meeting Discussion: No discussion took place.

- 4. The administration of IMMU-132 will be in a clinical setting by healthcare providers. Prior to the administration, healthcare providers will ensure that the patient has a full understanding of the risks pertaining to IMMU-132 as well as the clinical benefit. These discussions will be in lieu of providing the full prescribing information to the patients. For this reason, Immunomedics is proposing to not conduct a label comprehension study, as the healthcare providers will be on hand during administration of the product. Does the Agency agree that this proposal is acceptable and that based on the clinical setting of administration, no label comprehension studies are necessary?*

FDA Response: The prescribing information is written for healthcare providers rather than patients. Based on the limited information provided in this meeting package, labeling comprehension studies of the prescribing information are not necessary.

The PATIENT COUNSELING INFORMATION section (section 17) of the prescribing information contains a summary of the most important information for healthcare providers to convey to patients for the safe and effective use of the product.

Patient comprehension studies should be considered if you are developing patient labeling (e.g., labeling that is directed towards the patient, such as Medication Guides, Patient Information, and Instructions for Use).

Meeting Discussion: No discussion took place.

- 5. It is the position of Immunomedics that since IMMU-132 has been shown to be safe and well tolerated, data for IMMU-132 substantiate a positive benefit/risk profile, and the indication for which approval is being sought is well understood, an Oncologic Drugs Advisory Committee meeting would not be necessary. Does the Agency agree?*

FDA Response: At this time there is no ODAC meeting being considered. However, this will be a review issue.

Meeting Discussion: No discussion took place.

- 6. The proposed eCTD content plan for Modules 1, 2, 4, and 5 is provided in the Appendix to this Briefing Document (Section 11.1). The Sponsor welcomes any comments that the Agency might have at this time regarding the proposed content and structure of these modules.*

FDA Response: We have no additional comments.

Meeting Discussion: No discussion took place.

7. *Immunomedics is in the process of identifying potential proprietary name candidates for IMMU-132. The Sponsor is evaluating candidates which they believe will adhere to the most recent guidance provided by FDA. Immunomedics is planning to submit a name request during the IND phase. Due to the fast-track designation of IMMU-132, Immunomedics intends to request a 90-day review period for the proprietary name.*

Given the orphan, Breakthrough Therapy and Fast Track designations of IMMU-132, Immunomedics will look to submit two potential proprietary names and ask that they be reviewed simultaneously by FDA. Is this approach acceptable for the Agency?

FDA Response: You may submit two proposed proprietary names in a submission and specify the primary choice. However, the Agency only reviews one proposed proprietary name at a time. The alternate name will not be evaluated unless the primary name is found to be unacceptable. If the primary name is found unacceptable, you will need to submit a new request for proprietary name review. Under PDUFA IV, FDA committed to 90 day review of proposed proprietary names for BLA products and 180 day review of proposed proprietary names for IND products. However, for products designated as breakthrough therapy drugs, we target a 90 day review, when feasible, and we will work closely with you with the goal of having an acceptable proprietary name for your product prior to your BLA action date. We refer you to our **Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Name** available at <https://www.fda.gov/downloads/Drugs/Guidances/ucm075068.pdf>.

Meeting Discussion: No discussion took place.

8. *Immunomedics is not planning on including previously submitted or previously-issued paper-based documents (such as FDA meeting minutes; or documents related to submissions for Fast Track Designation, Breakthrough Therapy Designation, and SPA) as these are currently on file at FDA. Does FDA agree with this approach?*

FDA Response: Provision of previously submitted paper based documents will facilitate the Agency's review. You should submit scanned copies of previous documents electronically with the BLA submission. These submissions should be hyperlinked.

Meeting Discussion: No discussion took place.

9. *IND 122694 cross-references IND 155621 for CMC information regarding IMMU-132. Both IND 122694 and IND 115621 are sponsored by Immunomedics. IND 115621 has now been identified by Immunomedics to be the repository for CMC information to be cross referenced. On 30 March 2017, the Sponsor submitted an amendment stating its intent to maintain all CMC information under IND 115621, and included a Letter of Authorization for IND 122694 to cross reference IND 115621 for all CMC information. Immunomedics plans to submit the CMC pre-BLA Meeting Request to IND 122694. Does FDA agree?*

FDA Response: Yes.

Meeting Discussion: No discussion took place.

ADDITIONAL DISCUSSION

- **The Agency would like the Sponsor to provide the imaging charter for BCIR within the BLA.**
- **The Agency notified the Sponsor that they have concerns about the methodology using a single blinded reviewer without adjudication for the BICR and may request additional information within the review period.**

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our July 31, 2017, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on PDUFA V and the Program is available at

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (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, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies 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* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

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 Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) 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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. As of **May 5, 2017**, the following submission types: **NDA**, **ANDA**, and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

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 following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

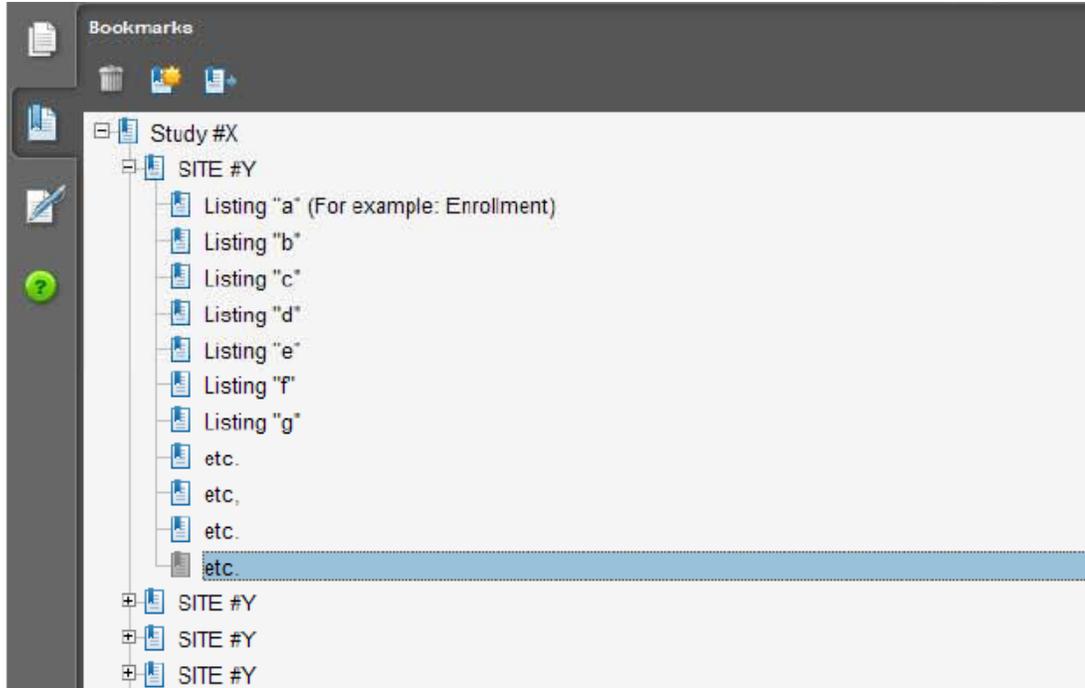
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which Sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other Sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAJESH VENUGOPAL
10/17/2017

LALEH AMIRI KORDESTANI
10/18/2017



IND 122694

MEETING MINUTES

Immunomedics, Inc.
Attention: Diane Whiteley
Senior Director
300 The American Road
Morris Plains, NJ 07950

Dear Ms. Whiteley:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sacituzumab govitecan (IMMU-132, hRS7-SN38).

We also refer to the meeting that was to occur between representatives of your firm and the FDA on June 29, 2017. On June 28, 2017, you requested to have the face to face meeting cancelled and have the two questions (Question #6 and #15) be further discussed with clarification via email rather than meet face to face.

The purpose of the meeting was to discuss and seek follow-up FDA guidance on sacituzumab govitecan's clinical and nonclinical development strategy to support licensure as additional data have been obtained since the previous Type B meetings held with the Agency in these disciplines.

A copy of the official minutes of the email clarification to Question #6 and #15 is enclosed for your information along with the our preliminary responses to the rest of the questions. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Rajesh Venugopal, Senior Regulatory Project Manager at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Rajesh Venugopal, MPH, MBA
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

Laleh Amiri-Kordestani, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

Enclosure: Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2

Meeting Date and Time: June 29, 2017/9:00 AM – 10:00 AM
Meeting Location: [Insert meeting location]

Application Number: IND 122694
Product Name: sacituzumab govitecan (IMMU-132, hRS7-SN38)
Indication: Treatment of patients with relapsed/refractory, metastatic, triple-negative breast cancer who have received at least two prior therapies for metastatic disease

Sponsor/Applicant Name: Immunomedics, Inc.

Meeting Chair: Laleh Amiri Kordestani, MD
Meeting Recorder: Rajesh Venugopal, MPH, MBA

FDA ATTENDEES

Julia Beaver, MD, Acting Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Laleh Amiri Kordestani, MD, Medical Team Leader, DOP1
Lynn Howie, MD, Medical Reviewer, DOP1
Hui Zhang, PhD, Biostatistics Reviewer, OB/DBV
Shenghui Tang, PhD, Biostatistics Team Leader, OB/DBV
Todd Palmby, PhD, Pharm/Tox Supervisor, DHOT
Tiffany Ricks, PhD, Pharm/Tox Reviewer, DHOT

SPONSOR ATTENDEES

Diane Whiteley, Senior Director, Regulatory Affairs, Immunomedics, Inc.
William A. Wegener, MD, PhD, Chief Medical Officer, Immunomedics, Inc.
Heather Horne, Senior Director, Clinical Research & Data Management, Immunomedics, Inc.

(b) (4) Regulatory Consultant, (b) (4)
(b) (4) CMC Consultant, (b) (4)
(b) (4) Consultant to Immunomedics, Inc. (b) (4)

BACKGROUND

The sponsor has requested a Type B End-of-Phase 2 (EOP2) meeting to seek guidance from the Agency regarding the clinical and non-clinical development strategy for IMMU-132 as they seek licensure for this agent for patients with triple negative breast cancer (TNBC) who have had progressive disease despite at least two previous therapies for metastatic disease. The goal of this meeting is to update the clinical and non-clinical plan for an initial BLA for consideration of accelerated approval, to obtain feedback on the CMC validation strategy, and to discuss the data needed to support a BLA filing in December 2017 as well as define review timelines and any additional information needed for the filing process or as a commitment or condition of possible approval of IMMU-132.

IMMU-132 is an antibody-drug conjugate (ADC) consisting of SN-38, an active metabolite of irinotecan, with a CL2A linker to hRS7, a humanized monoclonal antibody that targets Trop-2, human trophoblast cell-surface antigen. Trop-2 is a glycoprotein antigen expressed in many epithelial cancers. The primary mechanism of action of IMMU-132 is through delivery of SN-38 to tumor cells after the antibody binds to Trop-2, is internalized in the tumor cell and SN-38 is released into the tumor.

Per Sponsor, in pre-clinical models, IMMU-132 demonstrated improved and selective antitumor effects when compared to irinotecan. In cynomolgus monkeys, IMMU-132 was well-tolerated with decreased blood counts being the primary adverse effects.

There is currently an ongoing Phase 1/2 study of IMMU-132 as a basket trial in patients with relapsed/refractory metastatic epithelial cancers including TNBC, ovarian, hormone refractory prostate cancer, lung cancer (both small cell and non-small cell), squamous cell carcinoma of the head and neck, esophageal, gastric, colorectal, pancreatic, hepatocellular, renal (clear cell) and urinary bladder cancers. The Phase 1 portion of the study is completed and the MTD and a maximum acceptable dose were established. The ongoing Phase 2 portion of the study is evaluating the safety and activity of IMMU-132 in the previously listed malignancies. Based on encouraging results in the metastatic TNBC cohort, this group has been expanded. A safety and efficacy cohort of 100 patients with relapsed/refractory mTNBC who have received at least two prior therapies for metastatic disease will be used to support the efficacy claim of IMMU-132 and to provide a primary safety database for the planned BLA.

Based on data in the meeting package from the data cutoff point of August 2016, 32 patients met the requirement for Independent Central Review.

Objective Response Rate	21/69 (30%)
Complete Response	2/69 (3%)
Partial Response	19/69 (28%)
Median time to response	1.9 months (1.3 to 13.4 months)
Clinical Benefit Rate	46%
Median duration of response	8.9 months

In mid-February 2017, enrollment of the TNBC cohort was completed. Of the 148 patients with TNBC enrolled, 17 patients had received a dose level of IMMU-132 at a different dose level than that selected for development and 21 others had not received at least two prior therapies in the metastatic setting. This left a total of 110 patients in the TNBC cohort who met the criteria for efficacy evaluation of having had at least two prior regimens in the metastatic setting prior to study entry and having been treated with IMMU-132 at the 10 mg/kg dose level. Response rates are captured in the table below. To confirm local assessment of response, the scans of patients with local response or tumor shrinkage of at least 20% underwent independent central review. Fifty-six/110 patients qualified for independent review and the best overall response of 6 additional patients is pending (4 patients with partial response awaiting confirmatory scans and 2 patients with scan discs pending receipt for ICR). The following table is updated based on an Information Request response on June 19, 2017.

Data available as of 6/19/2017	Investigator Assessed Response	Independent Central Review*
Overall Response Rate	32.7% (36/110)	28.1% (31/110)
Complete Response	1.8% (2/110)	3.6% (4/110)
Partial Response	30.9% (34/110)	24.5% (27/110)
Median time to objective response	2.0 mos (1.5-13.4 mos)	
Clinical benefit rate (CR + PR + SD \geq 6 months)	43.6% (48/110)	
Median duration of response	8.4 mos (4.8, 11.6 95% CI)	
*Sponsor note: Incomplete data limits comparison with local results. Best overall response of 6 additional patients remains to be determined and is not included. Data are pre-database lock and considered preliminary.		

The most common adverse events (AEs) occurring in \geq 25% of patients included neutropenia, diarrhea, anemia, vomiting, fatigue, alopecia, constipation, rash, abdominal pain, and leukopenia. Grade \geq 3 AEs were reported in 41% of the patients. Thirty-nine percent of these events were neutropenia. The incidence of febrile neutropenia was 7%. Other grade 3-4 events occurring in $>$ 10% of patients included leukopenia (16%), anemia (14%) and diarrhea (13%). Three patients discontinued due to AEs: grade 3 rash/mucositis, grade 3 infusion reaction, and grade 2 fatigue. There were no treatment related deaths reported.

The target population for submission of the BLA is patients with relapsed/refractory metastatic TNBC who have received at least 2 prior therapies for metastatic disease. Data submitted will include all TNBC patients enrolled with relapsed/refractory metastatic disease and at least one prior treatment, however analyses will be conducted only in the target population of those who have received at least 2 prior therapies for metastatic disease and who were treated with IMMU-132 at 10 mg/kg in order to support the proposed indication statement.

Assessment of tumor response will be based on local review using RECIST 1.1. The primary endpoint is objective response rate (PR + CR) with responders requiring a confirmatory response assessment no sooner than 4 weeks later. Response rates will be given for the efficacy and the per-protocol population. Independent Central Review (ICR) will be conducted for tumor scans

from patients who were determined to have an objective response by local radiologists or at least 20% reduction of their locally determined target lesions. Local vs. ICR assessments of response will be tabulated for comparison and concordance of local vs. ICR results will be determined.

For the planned BLA, the claim of efficacy for IMMU-132 will be derived from study IMMU-132-01 with the target population of patients with relapsed/refractory mTNBC who have received at least 2 prior therapies for metastatic disease. The safety analysis for the target population as well as the use of IMMU-132 in all patients regardless of cancer type, line of treatment, and IMMU-132 dose will be based on study IMMU-132-01 and the results will be documented in the clinical study report (CSR) for study IMMU-132-01. The Sponsor proposes that Module 2.7.3 along with the tables, listings, and figures in the CSR for IMMU-132-01 will fulfill the requirements of an Integrated Summary of Efficacy. It is proposed that Module 2.7.4 along with the tables, listings, and figures of the CSR will fulfill the requirements of an Integrated Summary of Safety.

Regulatory History to Date:

- December 22, 2014: IMMU-132 received Fast Track Designation for the “treatment of patients with triple-negative breast cancer (TNBC) who have failed no more than two prior therapies for metastatic disease.”
- February 25, 2015: An EOP2 Meeting was held to discuss trial designs that would be acceptable for IMMU-132 in the treatment of patients with relapsed/refractory mTNBC. The Sponsor committed to conducting a randomized Phase 3 trial to seek an SPA for this trial and to submit a Statistical Analysis Plan (SAP) along with its SPA. At that time the Agency confirmed that progression-free survival (PFS) would be an acceptable primary endpoint for the planned Phase 3 trial.
- November 24, 2015: Special Protocol Assessment (SPA) was provided for the Sponsor’s proposed Phase 3 study IMMU-132-05, “An international, multicenter, open-label, randomized Phase 3 trial of sacituzumab govitecan (IMMU-132) compared to treatment of physician’s choice in patients with relapsed/refractory metastatic (stage IV) triple negative breast cancer who received at least two prior treatments.
- February 4, 2016: Breakthrough Therapy Designation granted for IMMU-132 in the treatment of patients with relapsed/refractory metastatic TNBC who have received at least 2 prior therapies for metastatic disease based on data from the TNBC cohort of the Sponsor’s ongoing Phase 1/2 study in epithelial malignancies.
- May 9, 2016: A Type B multidisciplinary Breakthrough Therapy meeting was held to discuss updated safety and efficacy data from the ongoing Phase 1/2 study IMMU-132-01 with emphasis on the results in TNBC patients treated to date. There was discussion of a regulatory strategy to possibly include accelerated approval for IMMU-132 on the basis of the results of IMMU-132-01. It was determined that there was not adequate data for a biological licensing application (BLA) at that time but stated that a single-arm trial demonstrating a confirmed objective response rate (ORR) by central blinded review that demonstrates that IMMU-132-01 is better than available therapy with supporting mature duration of response, in an adequate number of patients, could support accelerated approval for the treatment of patients with relapsed/refractory mTNBC after at least 2 prior therapies for metastatic disease. For accelerated approval, it would be important for the confirmatory trial to be underway if not fully accrued.

- November 14, 2016: A Type B EOP2 meeting was held to discuss nonclinical/clinical pharmacology development strategies for IMMU-132. FDA confirmed that genotoxicity studies would be required for a BLA submission and labeling of IMMU-132.
- March 17, 2017: A Type C Written Response Meeting indicated that the Agency concurred that the Phase 3 materials manufactured with a new clone (b) (4) were analytically comparable to the Phase 2 materials manufactured using the (b) (4) (b) (4) clone (b) (4). It was also agreed that additional nonclinical safety studies beyond the ongoing 3-month repeat-dose monkey toxicology study (pending review of study report) are not required for filing. The Agency indicated the requirements for stability data (6 months' stability data for both drug substance (DS) and drug product (DP)). The Agency requested further clarification of the validation strategy and the Sponsor requests further agency feedback regarding this at the upcoming meeting.
- April 24, 2017 The Agency provided feedback regarding the proposed Phase 3 study design and advised consideration of modifications and standardization to the Treatment of Physician's Choice Arm. The Agency agreed that the proposed study could support a regulatory submission.

The Sponsor seeks to update the Agency regarding the proposed plan of development for this agent which has been given Breakthrough Therapy designation for the treatment of patients with metastatic TNBC who have progressed after 2 lines of chemotherapy. The Sponsor proposes to submit data for the clinical package from all patients with TNBC enrolled in this study, however analyses will be conducted only in the target population of patients with at least 2 prior therapies for metastatic disease and treated with IMMU-132 at a dose of 10 mg/kg in support of the indication statement. The Sponsor proposes to submit for the following for the safety analysis:

- All patients treated in the target population will be included
- Treatment exposure to IMMU-132 will be defined as the number of treatment cycles, dose delays, dose reductions, and treatment discontinuations
- Safety will be assessed in terms of AEs, laboratory studies, vital signs, performance status, and ECG changes
- Analyses will include frequency tables for all AEs, AEs grade ≥ 3 , drug related AEs, AEs leading to treatment discontinuation, SAEs and AEs leading to death
- Narratives will be provided for all SAEs, deaths on study, and AEs leading to treatment discontinuation
- Severity of AEs and laboratory parameters will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0 toxicity grades

For the safety population that includes all patients regardless of cancer type, line of treatment, and IMMU-132 dose, selected safety information will be presented:

- Demographics and baseline characteristics
- Treatment exposure including dose delays, reductions, and discontinuations
- AEs including SAEs and fatal events
- ECG and laboratory data from this population are not planned to be included in the initial BLA

DISCUSSION

1. *Does the Agency agree that the proposed clinical package, consisting of at least 100 patients with metastatic TNBC who received 10 mg/kg of IMMU-132 after having at least 2 prior therapies, with a minimum follow-up duration of 4 months, will be sufficient to support the proof of efficacy for a submission of a BLA for accelerated approval of IMMU-132 in the following indication:*

“Sacituzumab govitecan is indicated for the treatment of patients with relapsed/refractory, metastatic, triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease”?

FDA Comment: Your clinical package, consisting of at least 100 patients with metastatic TNBC who received 10 mg/kg of IMMU-132 after having at least 2 prior therapies, with a minimum follow-up duration of 4 months appears to be acceptable.

Meeting Discussion:

No meeting discussion took place.

2. *With the unmet medical need identified in these patients, and the Breakthrough Therapy Designation granted on 04 Feb 2016, does the Agency agree with the Sponsor’s plan to submit a BLA, where at the time of submission, the Phase 3 study will have been enrolling patients for at least 3 months, and with a post-marketing commitment to complete the Phase 3 confirmatory study?*

FDA Comment: At the previous meeting on May 9, 2016, it was agreed that your Phase 3 study should have been enrolling patients for at least 3 months at the time of BLA submission. In the event of an accelerated approval, the confirmatory trial completion and submission of data will be a post-marketing requirement per accelerated approval regulations.

Meeting Discussion:

No meeting discussion took place.

3. *All patients in this basket trial were required to be refractory to or to have relapsed after at least one prior standard therapeutic regimen as assessed by investigator. Compliance with this criterion was documented via a CRF tick box. Confirmation of eligibility based on TNBC histology was to be documented on the CRF as part of the eligibility checklist and captured via CRF tick box.*

Additionally, it is confirmed by medical review that the patients have received at least 2 prior therapies for metastatic disease, with chemotherapy, biological or targeted agents included as qualifying prior therapies, but not hormonal or HER2 agents (either given prior to

achieving triple negative status or for any other reason). Does the Agency agree that these methods are adequate to ensure the accuracy of the data collected?

FDA Comment: In the written responses from the Agency on April 25, 2017, the Agency agreed that two prior standard therapeutic regimens must be standard of care chemotherapy regimens (not endocrine or non-chemotherapy based regimens). Please clarify what biological or targeted agents are considered to be acceptable as prior therapies. In addition, when you present your BLA for accelerated approval, you will need to justify why the IMMU-132 ORR is better than available therapy as this differs based on line of therapy (e.g., second line metastatic or third line metastatic).

Meeting Discussion:

No meeting discussion took place.

4. *Does the Agency agree with the Sponsor's proposal to submit complete efficacy and safety data for the target population, and to submit selected safety parameters for the safety population, as outlined in Sections 6.3.1 and 6.3.2?*

FDA Comment: Yes. In addition, you should submit ECG and laboratory data from this population in the initial BLA.

Meeting Discussion:

No meeting discussion took place.

5. *Does the Agency agree that the proposed analytical methods and statistical analyses to be used in study IMMU-132-01 (Section 6.3) will be sufficient to support a submission of a BLA for accelerated approval of IMMU-132?*

FDA Comment: Yes.

Meeting Discussion:

No meeting discussion took place.

6. *The primary endpoint will be the objective response rate i.e. patients with confirmed PR or CR based on local assessment. ICR will be conducted for tumor scans from patients who achieved an objective response by local radiologists or at least 20% reduction of their locally determined target lesions, as described in Section 6.3.1 and based on the discussions in the multidisciplinary breakthrough therapy meeting held with FDA on 9 May 2016. Does the Agency concur with this approach?*

FDA Comment: Yes, however during the review we may request additional IRC reads.

Sponsor's Discussion Point and Question Submitted June 28, 2017:

We would like clarification of your comment that you may request additional ICR reads.

As agreed with FDA to confirm local responses, from the target group of 110 patients to be submitted for consideration of accelerated approval, we have collected and submitted scans for independent reads for all 56 of those patients who had an objective response or at least 20% reduction of their lesions based on local radiology assessment?

Does FDA agree our approach to collection and independent review of specified scans is acceptable and adequate for filing?

FDA Response to Sponsor's Discussion Point and Question: Yes we agree with the proposed collection and review of scans, and that this plan is adequate for filing.

7. *The Sponsor is using paper based case report forms to collect the data from the sites and enter them into the ClinPlus electronic database system. The Clinical database was recently migrated from an ACCESS front end/SQL backend legacy system to the 21 CFR part 11-compliant based ClinPlus system. The Sponsor performed 100% source data verification and 100% data review. Furthermore, native logical checks to the ClinPlus database were run and external, independent data management experts were engaged to audit the Sponsor's data environment, processes, and database to ensure GCP compliance. The SAP and CSR for BLA filing will be based on this audited data environment. The Sponsor is not planning to submit individual paper CRFs. To facilitate FDA review, the Sponsor will provide an annotated CRF as well as narratives of all SAEs, deaths on treatment, and all AEs leading to discontinuation of treatment for the complete safety population. The clinical data or SAS data sets will be provided in CDISC Study Data Tabulation Model (SDTM) and analysis of clinical data will be in CDISC Analysis Data Model (AdAM). Does the Agency concur that this will be sufficient for BLA filing?*

FDA Comment: Yes.

Meeting Discussion:

No meeting discussion took place.

8. *PK/ADA sample analysis from patient serum samples is performed as described in Section 6.3.3. Samples are tested at Immunomedics under GLP with methods validated in accordance with the FDA Guidance for Industry: Bioanalytical Method Validation (2001). It is planned to use Excel to calculate simple statistics (mean values, standard deviations, etc.) and MedCalc or Prism GraphPad for most other statistical calculations. In addition, we plan to calculate PK parameters in house by using the program PK Solutions (Eugene OR; <http://www.pksolutions.com/index.htm>). A report describing the methods and calculations in detail will be provided to the Agency. Moreover, we ask to defer preparation of a PopPK analysis for initial BLA. Human PK/ADA data will be provided in the required SDTM/ADaM data formats. Does the Agency agree with this approach?*

FDA Comment: Yes. Your proposed submission plan appears reasonable. However, we strongly encourage you to submit the population PK report and exposure-response analyses at the time of initial BLA submission.

Meeting Discussion:

No meeting discussion took place.

9. *The Sponsor has conducted two genotoxicity studies to date. The first was GLP study #CTP1595_r1b entitled “Assessment of Genotoxicity of SN-38 Using the In Vitro Mammalian Cell Micronucleus Test (OECD 487)” and the second was GLP study #CYP1595_R1a entitled “Assessment of Genotoxicity of SN-38 Using Bacterial Reverse Mutation Test (OECD 471).” Does the Agency agree that these tests are sufficient and that no further genotoxicity study needs to be performed on the SN-38 prior the initial BLA submission for accelerated approval?*

FDA Comment: The genotoxicity studies described in your meeting briefing package appear sufficient to support a BLA submission in patients with advanced cancer. The final decision on the adequacy of the resulting data will be determined following review of your BLA submission.

Meeting Discussion:

No meeting discussion took place.

10. *Based on the two previously discussed genotoxicity studies, does the Agency agree that no embryo-fetal toxicity study needs to be performed prior the initial BLA submission for accelerated approval?*

FDA Comment: The genotoxicity and repeat-dose toxicology data described in your meeting briefing package appear sufficient to provide information on which to base labeling recommendations for use in pregnancy as described in ICH S9. Embryo-fetal development studies do not appear to be warranted to support a BLA submission for the proposed indication. The final decision on the adequacy of the genotoxicity data will be determined following review of your BLA submission.

Meeting Discussion:

No meeting discussion took place.

11. *Does the Agency agree that no additional nonclinical studies, beyond those described in the Briefing Document, will be needed prior to a BLA submission for accelerated approval, and that the current nonclinical package is sufficient to support a submission of a BLA for accelerated approval of IMMU-132?*

FDA Comment: We have not identified any additional nonclinical studies that will be needed prior to a BLA submission at this time. We will agree to what nonclinical studies constitute a complete package to support a BLA submission in a future pre-BLA meeting.

Meeting Discussion:

No meeting discussion took place.

12. *Does the Agency agree that the planned IMMU-132 safety database, comprising approximately 300 patients exposed to study drug across all tumor types, will be sufficient to support accelerated approval of the BLA?*

FDA Comment: Yes, this will be adequate for review in support of the BLA.

Meeting Discussion:

No meeting discussion took place.

In their Written Responses letter dated 17 March 2017, the FDA requested clarification with regard to the Sponsor's CMC validation strategy for IMMU-132. On May 3, 2017, the Sponsor submitted a response to this request to IND 115621 (Serial Number 0085; to which IND 122694 is crossreferenced), clarifying key points of the validation strategy. Also, the Sponsor included 2 additional questions in their response document to obtain FDA concurrence on the proposed validation strategy. Since the Sponsor has not yet received a response, it is respectfully requested that this issue be addressed during the EOP2 meeting.

13. *Does FDA agree Immunomedics' proposed validation strategy for the payload described above is acceptable to support an initial BLA for accelerated approval for IMMU-132 in the proposed indication?*

FDA Comment: Please refer to the June 15, 2017, correspondence issued under IND 115621 as the repository for general CMC information regarding IMMU-132-01. As directed in the correspondence, please provide written responses to FDA's comments within 30 days of the correspondence and any subsequent requests for CMC-only meeting requests, to IND 115621. We recommend that you also submit an associated letter of cross-reference to IND 122694.

Meeting Discussion:

No meeting discussion took place.

14. *Does FDA agree Immunomedics' proposed validation strategy for the antibody intermediate described above is acceptable to support an initial BLA for accelerated approval for IMMU-132 in the proposed indication?*

FDA Comment: Please refer to the June 15, 2017, correspondence issued under IND 115621 as the repository for general CMC information regarding IMMU-132-01. As directed in the correspondence, please provide written responses to FDA's comments within 30 days of the correspondence and any subsequent requests for CMC-only meeting requests, to IND 115621. We recommend that you also submit an associated letter of cross-reference to IND 122694.

Meeting Discussion:

No meeting discussion took place.

15. *For this single-study submission, the applicant proposes that Module 2.7.3 in conjunction with the tables, listings, and figures in the CSR for study IMMU-132-01 will fulfill the requirements of an Integrated Summary of Efficacy. Accordingly, it is proposed that Module 2.7.4, in conjunction with the tables, listings, and figures of the CSR, will fulfill the requirements of an Integrated Summary of Safety. Does the Agency agree with this proposal?*

FDA Comment: No. The Agency considers the ISE and ISS to be critical components of the clinical efficacy and safety portions of a marketing or licensing application. Module 5, specifically section 5.3.5.3, Reports of Analyses of Data from More than One Study, is the appropriate location for the ISE and ISS. Refer to the Guidance for Industry titled "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document", which can be found at <https://www.fda.gov/downloads/drugs/guidances/ucm136174.pdf>.

Sponsor's Discussion Point and Question Submitted June 28, 2017:

We believe that all information as foreseen in the integrated summaries on efficacy and safety will be presented in the dossier in a format congruent with what is being requested in the guidance, you referred us to.

The above mentioned guidance for industry titled "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document" will be taken into consideration fully.

In line with this guidance, we will provide detailed summaries of efficacy and safety in Module 2, Sections 2.7.3, Summary of Clinical Efficacy, and 2.7.4, Summary of Clinical Safety. These summary documents will consist mostly of text, with tables and figures incorporated as needed. The Sections 2.7.3 and 2.7.4 will provide data summaries, not a complete exposition.

The FDA Guidance, Section C, allows for special cases, such as NDAs/BLAs based on single studies, to split the ISE and ISS across Module 2 and Module 5, with the narrative portion located in Section 2.7.3 or 2.7.4 and the appendices of tables, figures, and datasets located in Section 5.3.5.3.

The applicant therefore suggests that Sections 2.7.3 and 2.7.4 will be sufficiently detailed to serve as the narrative portion of the ISE and ISS, while they will still be concise enough to meet the suggested size limitations for Module 2.

Furthermore, we intend to provide all tables, listings and figures presenting efficacy and safety data for the target population as well as the safety population for this BLA in CSR IMMU-132-01 (Module 5.3.5.2).

Therefore, we think that providing these tables, listings and figures again in the ISE and ISS in Module 5.3.5.3 will be redundant to the presentations in the CSR.

We therefore suggest that the narrative portions of ISE/ISS in Modules 2.7.3 and 2.7.4 together with the complete set of tables, listings and figures in the CSR fulfil the requirements for an ISE and ISS.

In line with the FDA Guidance, we will provide clear explanations in Modules 2 and 5 of where the different components of the ISE and ISS are located. Furthermore, hyperlinks will be set to allow the FDA reviewers full electronic navigation.

Would the Agency agree with this way forward, which factually provides all information as in the integrated summaries of efficacy and safety but reduces redundancies in the overall BLA?

FDA Response to Sponsor's Discussion Point and Question: Yes, we agree with this proposed plan for submission.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (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, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies 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* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

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 (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page 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.

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 start 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

Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages Sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to Sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>.

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 the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

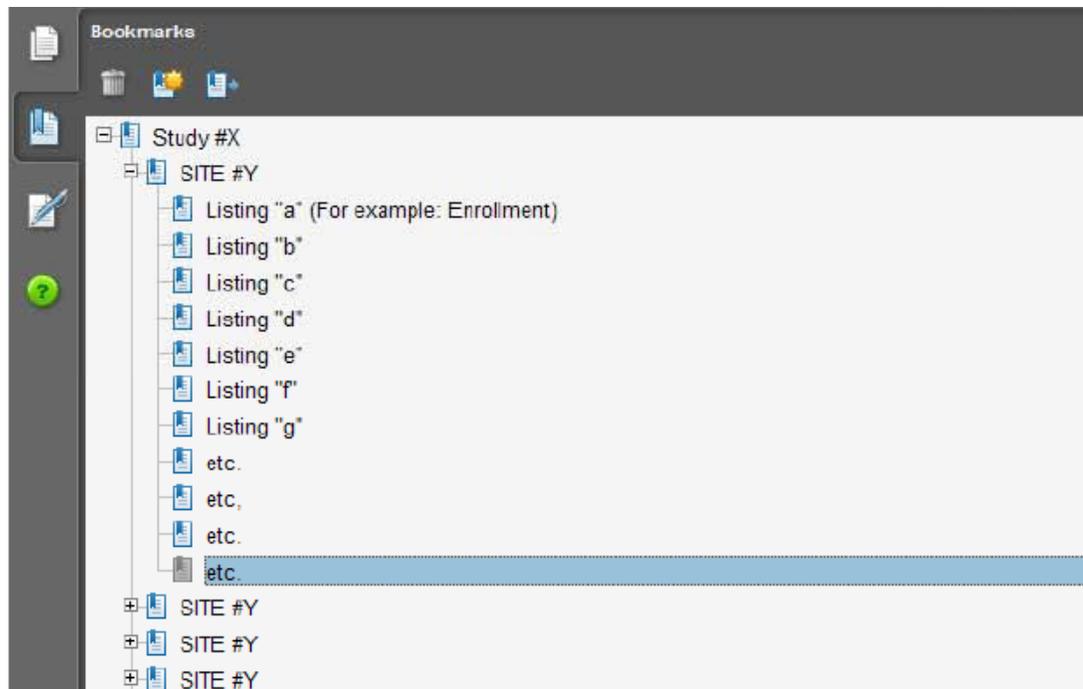
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which Sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other Sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAJESH VENUGOPAL
06/29/2017

LALEH AMIRI KORDESTANI
06/29/2017



IND 122694

MEETING MINUTES

Immunomedics, Inc.
Attention: Diane Whiteley
Senior Director
300 The American Road
Morris Plains, NJ 07950

Dear Ms. Whiteley:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for hRS7-SN38 (IMMU-132, sacituzumab govitecan).

We also refer to the teleconference between representatives of your firm and the FDA on November 14, 2016. The purpose of the meeting was to discuss nonclinical/clinical pharmacology development strategies for the drug development of sacituzumab govitecan.

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

If you have any questions, call Rajesh Venugopal, Senior Regulatory Project Manager at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Rajesh Venugopal, MPH, MBA
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

Julia Beaver, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: November 14, 2016/9:00 AM – 10:00 AM
Meeting Location: Teleconference

Application Number: IND 122694
Product Name: Sacituzumab govitecan
Indication: Treatment of patients with relapsed/refractory, metastatic, triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease

Sponsor/Applicant Name: Immunomedics, Inc.

Meeting Chair: Julia Beaver, MD
Meeting Recorder: Rajesh Venugopal, MPH, MBA

FDA ATTENDEES

Amna Ibrahim, MD, Deputy Director, DOP1
Julia Beaver, MD, Medical Team Leader, DOP1
Gwynn Ison, MD, Medical Officer, DOP1
Salaheldin Hamed, PhD, Clinical Pharmacology Reviewer, DCP V
Pengfei Song, PhD, Clinical Pharmacology Team Leader, DCP V
John K. Leighton, PhD, Director, DHOT
Todd Palmby, PhD, Pharm/Tox Supervisor, DHOT
Tiffany Ricks, PhD, Pharm/Tox Reviewer, DHOT
Wen Jin Wu, PhD, Chemistry Reviewer, OBP
Wendy Weinberg, PhD, Chemistry, Team Lead, OBP
Rajesh Venugopal, MPH, MBA, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

David Goldenberg, ScD, MD, Chairman & Chief Scientific Officer
Cynthia L. Sullivan, MS, MBA, President & CEO
William Wegener, MD, PhD, Chief Medical Officer
Thomas Cardillo, PhD, Executive Director, Preclinical Research
Edmund Rossi, PhD, Associate Vice President, Process Development & Manufacturing
Robert M. Sharkey, PhD, Senior Director, Scientific and Regulatory Affairs
Diane Whiteley, Senior Director, Regulatory Affairs

BACKGROUND

IMMU-132 is an antibody-drug conjugate, consisting of an antibody targeting human Trop2 (hRS7), a CL2A linker, and a topoisomerase-1 inhibitor, SN-38 (active metabolite of irinotecan). The purpose of the current meeting is to discuss the nonclinical and clinical pharmacology data needed to support an initial BLA submission for potential approval under an accelerated approval pathway. In the meeting briefing package, the Sponsor described an ongoing, 3-month repeat-dose toxicity study in Cynomolgus monkeys and the study design for a PK study in rabbits to compare hRS7 IgG used in the manufacture of Phase 1/2 and Phase 3 IMMU-132. The Sponsor has not conducted genotoxicity studies or an assessment of embryo-fetal developmental toxicity. The Sponsor is requesting guidance on the nonclinical and clinical pharmacology regulatory strategy.

The Agency sent Preliminary Comments to Immunomedics, Inc. on November 7, 2016.

DISCUSSION

- 1. Reference is made to the email from FDA, dated August 15, 2016, which Nonclinical reviewers confirmed that the proposed study design for the 3-month repeat-dose toxicity study appears reasonable. For confirmation, does FDA agree with the study design of the 3-month repeat dose toxicity study that will be conducted during the confirmatory Phase 3 clinical study?*

FDA Response:

The proposed study design for the 3-month repeat-dose toxicity study in Cynomolgus monkeys appears reasonable. The ICH S9 Guidance for Industry: Nonclinical Evaluation of Anticancer Pharmaceuticals available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM085389.pdf>, recommends that the results of 13-week GLP-compliant toxicology studies are expected prior to initiation of Phase 3 clinical trials, as noted in the meeting minutes from the End of Phase 2 meeting on February 25, 2015. You may complete the 3-month toxicology study concurrently with the Phase 3 clinical trial; however, you should submit, at minimum, an audited draft report including a signed histopathology report before enrollment of more than 50 patients on the arm of the proposed Phase 3 clinical trial that will include administration of IMMU-132.

In addition, the final report for this study should be provided in your original BLA submission regardless of whether you are seeking accelerated or regular approval.

Meeting Discussion:

The Sponsor requested to submit audited draft reports for the 3 month study in the initial BLA submission and submit the final reports for this study within 2 months of the initial BLA submission. The Agency clarified that final study reports are expected to support the

pivotal registration trial and marketing application. The Agency will follow-up with a post meeting written comment with a final determination.

- 2. Does FDA agree that the rabbit study supports comparability of hRS7 IgG sourced from the current clone material compared with the new clone material?*

FDA Response:

As stated in meeting minutes from the Type B meeting held on May 9, 2016, the need for an additional nonclinical study(ies) will depend on the outcome of the analytical CMC assessment. If nonclinical studies are needed, a rabbit PK study may provide supportive data, but would be insufficient as a standalone study to support comparability of hRS7 sourced from current and new clone material. In addition, your meeting briefing package did not provide information on the pharmacological relevance or target binding in rabbits. At this time, it is unclear if the proposed rabbit study would provide useful information in addition to the analytical CMC assessment and the 3-month repeat-dose study in monkeys comparing IMMU-132 sourced from Phase 1/2 and Phase 3 material.

Meeting Discussion:

No meeting discussion took place.

- 3. FDA stated in its Minutes dated February 27, 2015, that genotoxicity studies should be conducted to support anticancer pharmaceuticals. No genotoxicity studies have been performed with IMMU-132 to date. Does FDA agree that no genotoxicity study needs to be performed prior to the initial BLA filing for Accelerated Approval?*

FDA Response:

No. IMMU-132 will be regulated under a Biological License Application (BLA). There is no regulatory BLA pathway equivalent to a 505(b)(2) NDA, which allows reliance on the Agency's previous findings of safety and efficacy as reflected in approved labeling. Therefore, you may not rely on the package insert of irinotecan to provide the genotoxicity data on the payload of IMMU-132 (i.e., SN-38 or govitecan) needed to support submission of your BLA. You may not rely on published literature reporting the results of studies conducted with specific irinotecan products approved or under development for which you do not have a written right of reference. Conduct genotoxicity studies according to recommendations in ICH S2 that are compliant with GLP regulations (21 CFR part 58) to support an initial BLA submission and product labeling of IMMU-132. These studies may be conducted with the payload small molecule component of IMMU-132 (i.e., SN-38). As stated in ICH S9, if in vitro assays are positive, an in vivo assay may not be needed.

Meeting Discussion:

The Sponsor stated that they would conduct a GLP compliant Ames test using SN-038 Phase 3 material and asked whether this would be sufficient. The Agency stated that an

assay for chromosomal damage would also be needed and concurred with the Sponsor that this could be an in vitro micronucleus test that would also need to be GLP compliant.

4. *FDA stated in its Minutes dated February 27, 2015, that an assessment of embryo-fetal toxicity should be conducted to support a marketing application for anticancer pharmaceuticals. Does FDA agree that no embryo-fetal toxicity study needs to be performed prior to the initial BLA filing for Accelerated Approval?*

FDA Response:

Your justification for not conducting an embryo-fetal toxicity assessment provided in your meeting briefing package is inadequate and not acceptable. You need to provide adequate information on which to base labeling recommendations for use in pregnancy. As stated in ICH S9, if an adequate battery of GLP-compliant genotoxicity studies demonstrate that the small molecule portion of IMMU-132 is genotoxic and if IMMU-132 or the small molecule targets rapidly dividing cells in general toxicity studies, embryo-fetal developmental toxicity studies may not be needed to support a BLA submission for the proposed indication. See our response to Question 3.

Meeting Discussion:

The Sponsor will address the need for an embryo-fetal toxicity study when the results for genotoxicity studies are available.

5. *Does FDA agree that no additional nonclinical studies need to be performed prior to an initial BLA filing for Accelerated Approval? If not, does FDA agree that any additional required nonclinical studies can be conducted during the Phase 3 confirmatory study, and included in a Supplemental BLA submission?*

FDA Response:

We have not identified any additional nonclinical studies, beyond those described in the above responses that will be needed prior to a BLA submission at this time; however, it is premature to make a final determination about what nonclinical studies are needed to support a BLA submission given the nonclinical and clinical data currently available. The need for additional nonclinical studies will be addressed at your pre-BLA meeting.

Meeting Discussion:

No meeting discussion took place.

6. *Does FDA agree that the Company's response to the Agency's clinical pharmacology comments, conveyed to Immunomedics by email on July 21, 2014, have been adequately addressed in order to proceed with the initiation of the Phase 3 Confirmatory study as well as the initial BLA for Accelerated Approval?*

FDA Response:

Your clinical pharmacology components appear adequate. We remind you that you should determine appropriate doses of IMMU-132 in patients with renal and/or hepatic impairment. See also responses to Questions 7 and 8.

Meeting Discussion:

FDA stated that organ impairment studies are not required at the time of accelerated approval or the Phase 3 study however, this information may be required in the post-marketing setting. The Sponsor stated that a discussion regarding these studies will be initiated at a later time.

7. *In our initial BLA submission for Accelerated Approval, we propose that the results of Chemistry, Manufacturing and Controls (CMC) comparability and nonclinical studies (i.e., 3-month repeat dose monkey toxicology study, and PK study in rabbits) be sufficient to bridge our to-be-marketed drug product with the drug product used in the Phase 2 clinical trial. Does FDA agree?*

FDA Response:

No. You should provide clinical PK data to adequately bridge your to-be-marketed product (new clone) with the product used in the Phase 2 study (old clone). The clinical PK bridging data are not required for Phase 3 trial initiation if the comparability and nonclinical data are acceptable. See response to Question 2.

Meeting Discussion:

The Sponsor stated that an initial subset of 10 patients in the Phase 2 trial will be administered drug product manufactured with a new clone to support a PK bridge to the drug product manufactured with the old clone. The Agency stated that this is acceptable pending review of the analytical comparability and PK data. The Agency stated it is the Sponsor's choice to collect the PK samples in patients with different tumor types to support the PK bridge.

8. *Reference is made to the FDA Special Protocol – Agreement Letter dated November 24, 2015. As stated in the FDA Special Protocol – Agreement Letter, the Agency agrees that the design and planned analysis of Study IMMU-132-05 adequately addresses the objectives necessary to support regulatory submission. It does not require serum collection in all patients over multiple cycles for use in examining dose-response relationship. However, we*

expect that the continued collection of data from patients enrolled in the Phase 1/2 will provide sufficient information to address this PK issue. Does FDA agree that this will be sufficient for the initial BLA for Accelerated Approval?

FDA Response:

Yes, this proposal is acceptable for the initial accelerated approval BLA. However, you should collect sparse PK samples from all patients in addition to the proposed rich sampling in a subset of 20 patients in your proposed Trial IMMU-132-05 to enable population PK analyses, exposure-safety, and exposure-efficacy analyses.

Meeting Discussion:

The Sponsor clarified that sparse PK samples will be collected from all patients treated with the drug on Trial IMMU-132-05. The Agency stated that this is acceptable.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (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, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies 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 PSP 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 PSP, including a PSP 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* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

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 (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page 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.

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 start 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 Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide

feedback to Sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

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 the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to Sponsors 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), Sponsors 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 following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

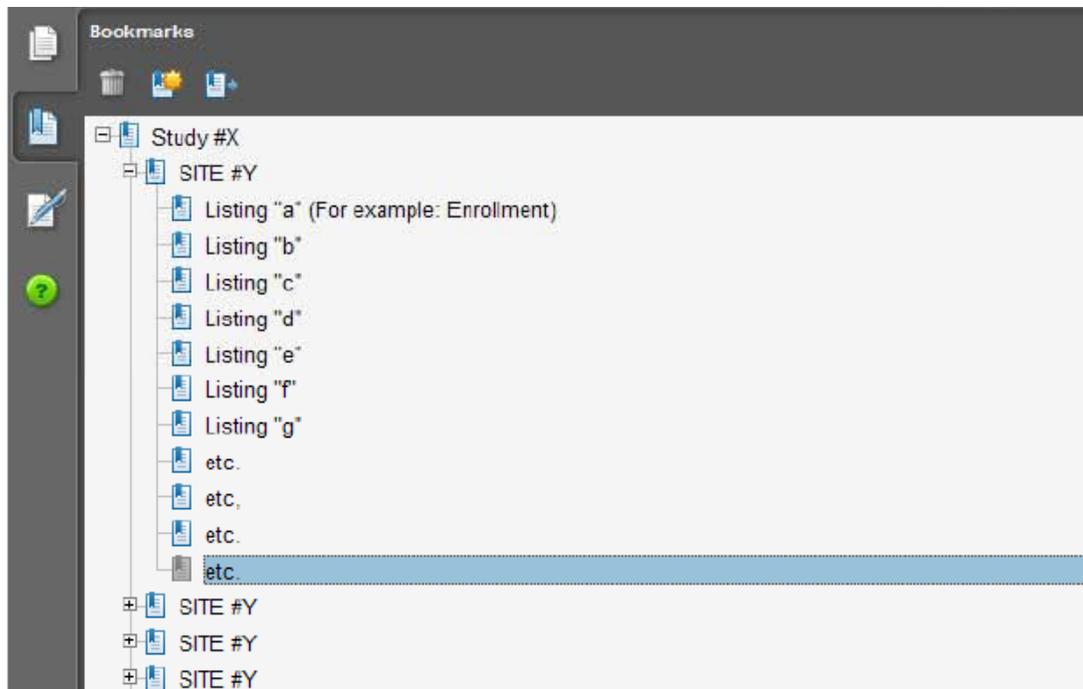
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which Sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other Sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is

maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAJESH VENUGOPAL
11/21/2016

JULIA A BEAVER
11/21/2016

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	122694
Request Receipt Date	12/8/15
Product	Sazituzumab govitecan (IMMU-132)
Indication	Sacituzumab govitecan is indicated for the treatment of patients with relapsed/refractory, metastatic, triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease.
Drug Class/Mechanism of Action	Antibody-drug conjugate containing humanized anti-Trop-2 antibody (hRS7) linked to SN38
Sponsor	Immunomedics
ODE/Division	OHOP/ DOP1
Breakthrough Therapy Request Goal Date (within <u>60</u> days of receipt)	2/7/16

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. 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):

Sacituzumab govitecan is indicated for the treatment of patients with relapsed/refractory, metastatic, triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease.

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold? YES NO

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:

3. Consideration of Breakthrough Therapy Criteria:

a. Is the condition serious/life-threatening? YES NO

If 3a 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:

b. 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?

- 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 therapy/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 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 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

5. 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.

6. 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.

Breast cancer is the most commonly diagnosed malignancy in women, and the second leading cause of cancer deaths in women in the US, with 231,840 new cases of breast cancer and 40,000 deaths estimated in 2015. Triple-negative breast cancer, TNBC, is an aggressive subtype of breast cancer that comprises approximately 10-20% of all breast cancer diagnoses, and is characterized by an absence of tumor expression of estrogen receptor (ER), progesterone receptor (PR), or HER2/neu¹. Therefore, patients with metastatic TNBC are typically not amenable to treatment with hormonal or HER2-directed therapies, and instead can only receive cytotoxic chemotherapies. There is no single standard chemotherapy for the treatment of mTNBC, and the median survival for patients newly diagnosed with metastatic breast cancer is approximately 10-13 months^{2,3}.

FDA-approved cytotoxic chemotherapies for metastatic breast cancer regardless of subtype include gemcitabine, docetaxel, paclitaxel, nab-paclitaxel, capecitabine, ixabepilone, and eribulin.

IMMU-132 is an antibody-directed chemotherapy that targets Trop-2, which is expressed on tumor cells, and preferentially delivers SN-38 intracellularly to the Trop-2 expressing cancer cells. According to the Sponsor, non-clinical studies support the hypothesis that IMMU-132 is taken up into tumor cells by binding to Trop-2. Thereafter, SN-38 is released into the tumor cells, with minimal (<2%) release into circulation^{4,5}. SN-38 is the active metabolite of irinotecan, and it acts to cause DNA strand breaks.

Regulatory history:

- *IMMU-132 received fast-track designation for the “treatment of patients with triple-negative breast cancer (TNBC) who have failed no more than two prior therapies for metastatic disease” on 12/22/14.*
- *Special Protocol Assessment (SPA) Agreement was given to the Sponsor’s proposed Phase 3 study IMMU-132-05, “An International, Multicenter, Open-Label, Randomized Phase III Trial of Sacituzumab govitecan (IMMU-132) compared to Treatment of Physician’s Choice in Patients with Relapsed/Refractory Metastatic (IV) Triple Negative Breast Cancer Who Received at Least 2 Prior Treatments” on November 24, 2015.*

7. 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.

*The sponsor is using results from the Phase I/II study IMMU-132-01 to support the BTDR. Efficacy is a secondary endpoint in study IMMU-132-01 and includes assessment of **objective response rate (ORR)** and **duration of response (DOR)**.*

The Phase 3 trial (which was granted a SPA agreement) has progression-free survival (PFS) as the primary endpoint and overall survival (OS) and ORR as key secondary endpoints.

- b. The Division of Oncology Products 1 has accepted the following clinical trials endpoints in metastatic TNBC. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease.

Clinical trial endpoints that have been used to support approval of drugs used in metastatic breast cancer include: overall response rate (ORR), time to progression (TTP), progression-free survival (PFS), and overall survival (OS).

The endpoint of ORR (CR+ PR) has been used by the FDA previously to give both regular and accelerated approvals for drugs used in the treatment of metastatic breast cancer. Regular approvals based upon response rate have been granted for two agents, including ixabepilone (single arm trial, third line setting) and abraxane (505b2 pathway; non-inferiority trial, second line setting). Accelerated approvals have been granted for two agents in the second line metastatic breast cancer setting, capecitabine and docetaxel. Both of these approvals were based upon response rate.

- 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.

There are no biomarkers in this population (triple negative breast cancer) that would be considered likely to predict clinical benefit, as hormone receptor status and HER2 status do not apply and the current drug being submitted for breakthrough therapy is not a targeted therapy.

8. 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.

The table below depicts the available therapies for patients with metastatic triple negative breast cancer who have received at least 2 prior lines of therapy in the metastatic setting. Eribulin was approved in the third line metastatic setting based on a randomized control trial of 762 patients who had received at least two prior lines of therapy compared to physician's choice chemotherapy. Eribulin was approved based on an improvement in overall survival. In addition, the results in the patients with metastatic TNBC who have been treated with IMMU-132 in the ongoing IMMU-132-01 study are depicted at the bottom of the table, for reference.

Chemotherapies in \geq Third Line Metastatic Breast Cancer

Chemotherapy	Setting	ORR	DOR	OS
Eribulin ^a	\geq Third line	11%	4.2 months	13.1 months vs. 10.6 months (physician's choice chemotherapy) HR 0.81 (95%CI: 0.66-0.99)
Ixabepilone ^a	\geq Third line	12.4% (95% CI 6.9%-19.9%)	6 months	
IMMU-132	Breakthrough requested for \geq Third Line (Median Fourth Line Studied in the trial)	34% (26% confirmed)	11.5 months	

^aApproved for Metastatic Breast Cancer Drugs@FDA, study results did included all subgroups (including TNBC)

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

There have been no agents in TNBC that have received breakthrough therapy designation. Three agents were granted breakthrough therapy designation in hormone receptor (HR) positive metastatic breast cancer, one based on ORR. As HR positive breast cancer is distinct from TNBC with respect to natural history and approved agents BTDRs between the two subgroups should not be compared.

10. 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 design, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Study ID	Phase	Design	Endpoints	Treatment group	Number subjects enrolled	Results
IMMU-132-01	I/II	Open-label, multicenter, single arm, multi-dose	ORR DOR	Metastatic TNBC	60	ORR 34% (Confirmed ORR 26%) DOR 11.5 months

The study supporting the BTDR is an ongoing Phase I/II trial (Study IMMU-132-01). This is a multi-center, open-label study of IMMU-132 in patients with previously treated, advanced/ metastatic epithelial tumors. The tumors eligible for enrollment include breast (triple-negative,) ovarian, prostate (hormone refractory), lung, head and neck (squamous), esophageal, colorectal, pancreatic, gastric, renal cell, urothelial, endometrial, and hepatocellular cancers. Patients must have received and relapsed after at least one standard chemotherapy regimen for their metastatic disease, and had to have measurable disease with no single lesion measuring ≥ 7 cm in diameter.

The primary study objective is to assess the safety and tolerability of IMMU-132 given every 3 weeks in these patients. Secondary objectives are to obtain data on pharmacokinetics, immunogenicity, and efficacy of IMMU-132.

The interim efficacy results reported by the Sponsor have been limited to include the 60 patients with relapsed/refractory metastatic TNBC who have received at least 1 taxane and who have received at least at least 2 prior therapies, including adjuvant therapy. Patients received 10 mg/kg IV of IMMU-132 on days 1 and 8 of a 21 day cycle.

Preliminary clinical results: The 60 patients with metastatic TNBC had a median of 3 prior chemotherapies in the metastatic setting, and a median of 5 prior chemotherapies including adjuvant therapy, and were thus heavily pretreated. Most patients (70%) had an ECOG performance status of 1. Fifty-eight patients were assessable for response. Twenty patients achieved an objective response, including CR or PR by RECIST 1.1, giving an objective response rate of 34%. This ORR includes two patients with CR and 18 patients with PR. Confirmatory CT scan was obtained 4-6 weeks after initial scans showing a confirmed response (PR or CR) in 15 of the 20 patients (26% confirmed response rate with two CRs and 13 PRs). An additional 23 patients achieved stable disease (SD).

Duration of response (DOR) for the 20 patients with RECIST response was calculated using the Kaplan-Meier method (censoring for ongoing patients). The median duration of response was 11.5 months (95% CI 7.6- 11.5 mos for 30% maturity rate). Of the 15 patients with confirmed responses, 8 had durations of response greater than 6 months, 3 had durations of response greater than 9 months, and 11 are still responding.

b. Include any additional relevant information.

- ***Safety data:*** *The Sponsor has reported that IMMU-132 has a manageable toxicity profile, with the primary dose-limiting toxicity being neutropenia. In 119 patients with cancer who have received the proposed Phase 3 dose of 10 mg/kg every 3 weeks, the main grade 1-4 adverse events include diarrhea (37%), nausea (35%), neutropenia (26%), fatigue (25%), and vomiting (25%). Severe adverse events (G3-4) have occurred less frequently, with the most common being neutropenia (15%), diarrhea (6%), anemia (6%) febrile neutropenia (4%). This safety profile is acceptable for the population being studied and in fact is improved over conventional chemotherapies used for metastatic TNBC.*
- *In summary, our assessment of the data submitted on the 60 patients with TNBC from Study IMMU-132-01 is supportive of breakthrough therapy. Patients with mTNBC have incurable disease with a life expectancy of approximately 12 months and therefore represents a life-threatening medical condition. The 60 patients enrolled in study IMMU-132-01 and treated with IMMU-132 had received a median of 3 lines of prior therapy (with some patients having received up to 8 prior lines of therapy) in the metastatic setting and thus represent patients treated in the fourth line metastatic TNBC. Although many chemotherapies are approved for metastatic breast cancer, there are only 2 therapies specifically approved as a later line of therapy, including eribulin and ixabepilone. Based upon the data from the studies supporting these two approvals, an expected response rate to available single agent chemotherapies in this later setting would be approximately 10-15%, compared with the 26% confirmed response rate of IMMU-132. In addition, 8 patients who have responded to IMMU-132 have durable (≥ 6 months) with 11 having ongoing responses, as noted with the current median duration of response of 11.5 months. Although this duration is not mature it suggests preliminary clinical evidence of substantial improvement over available therapies. Finally, the data submitted indicates that IMMU-132 is well-*

tolerated with a toxicity profile that is considerable improved over the majority of the available chemotherapeutic options in this refractory setting.

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

GRANT :

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:

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

- a. *The Division has recently granted a Special Protocol Assessment Agreement to the Sponsor's proposed Phase 3 trial, IMMU-132-05. The trial will be an international, multicenter, open-label, randomized trial of IMMU-132 compared to physician's choice of chemotherapy in patients with relapsed/refractory triple negative breast cancer who have received at least 2 prior treatments. This trial will randomize 328 patients 1:1 to either IMMU-132 or the choice of Eribulin, Capecitabine, Gemcitabine, or Vinorelbine. Stratification factors include number of prior therapies (2-3 vs. ≥ 4) and region (North America vs. Europe). The primary trial endpoint is progression free survival, with overall survival as the key secondary endpoint. The statistical plan is designed so that a 67% improvement in PFS in this population would be considered to be meaningful. The PFS estimate in this population varies from 1.7-4.2 mos (3 months average), therefore to achieve a 67% improvement in median PFS from 3 to 5 months (HR 0.6), a sample size of 328 patients (305 events) would achieve 99% power with a two-sided type 1 error rate of 5%, based on an accrual rate of 18.2 patients per month and minimum follow-up of 9 months. For the secondary endpoint of overall survival, with enrollment of 328 patients (204 events) a two-sided 5% type 1 error rate, the study will have 82.5% power to detect a 5 month improvement in OS from 10 months on the control arm to 15 months on the IMMU-132 arm. Other secondary endpoints in this trial will include overall response rate, duration of response, time to onset of response, quality of life, and safety endpoints.*

13. List references, if any:

1. **American Cancer Society Statistics 2015:**
<http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2015/>
2. **Mancini MA, et al. Standard of care and promising new agents for triple negative metastatic breast cancer. Cancers 6: 2187-2223, 2014.**
3. **Andre F, et al. Optimal strategies for the treatment of metastatic triple-negative breast cancer with currently approved agents. Annals of Oncology 23 (6): vi46-vi51, 2012.**
4. **Goldenberg DM, et al. Trop-2 is a novel target for solid cancer therapy with sacituzumab govitecan (IMMU-132, and antibody drug conjugate ADC). Oncotarget 6 (26): 22496, 2015.**

5. Sharkey RM, et al. Enhanced delivery of SN-38 to human tumor xenografts with an anti-Trop-2-SN-38 antibody conjugate (Sacituzumab govitecan). Clin Cancer Res. Published OnlineFirst June 23, 2015; doi:10.1158/1078-0432.CCR-15-0670.

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

15. 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}

5-7-15/M. Raggio

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GWYNN ISON
02/01/2016

JULIA A BEAVER
02/01/2016



IND 122694

MEETING MINUTES

Immunomedics, Inc.
Attention: Diane Whiteley
Senior Director
300 The American Road
Morris Plains, NJ 07950

Dear Ms. Whiteley:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for hRS7-SN38 (IMMU-132).

We also refer to the meeting between representatives of your firm and the Agency on February 25, 2015. The purpose of the meeting was to discuss your proposed registration strategy for IMMU-132 in patients with relapsed/refractory metastatic triple-negative breast cancer.

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 Rajesh Venugopal, Regulatory Project Manager at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Rajesh Venugopal, MPH, MBA
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

Patricia Cortazar, MD
Clinical Team Leader
Scientific Liaison Breast Oncology Group
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: February 25, 2015/3:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: IND 122694
Product Name: hRS7-SN38 (IMMU-132)
Indication: For treatment of patients with breast/ [REDACTED] (b) (4)
cancers

Sponsor/Applicant Name: Immunomedics, Inc.

Meeting Chair: Patricia Cortazar, MD
Meeting Recorder: Rajesh Venugopal

FDA ATTENDEES

Geoffrey Kim, MD, Acting Deputy Director, DOP1
Patricia Cortazar, MD, Medical Team Leader, DOP1
Gwynn Ison, MD, Medical Officer, DOP1
Todd Palmby, PhD, Supervisor, Pharmacology/Toxicology, DOP1
Tiffany Ricks, PhD, Pharmacology/Toxicology Reviewer, DOP1
Hui Zhang, PhD, Biostatistics Reviewer, OB/DBV
Shenghui Tang, PhD, Biostatistics Team Leader, OB/DBV
Sarah Dorff, PhD, Pharmacogenomics Reviewer, OCP
Qi Liu, PhD, Clinical Pharmacology Team Leader, OCP/DCP V
Pengfei Song, PhD, Clinical Pharmacology Reviewer, OCP/DCP V
Brian Booth, PhD, Clinical Pharmacology Deputy Director, OCP/DCP V
Amy McKee, MD, Medical Team Leader, DOP1
Rosane Charlab-Orbach, PhD, Pharmacogenomics Team Leader, OCP
Christy Cottrell, Chief, Project Management Staff, DOP1
Rajesh Venugopal, MPH, MBA, Senior Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

David M. Goldenberg, ScD, MD, Chairman & Chief Scientific Officer, Immunomedics, Inc.
Francois Wilhelm, MD, PhD, Chief Medical Officer, Immunomedics, Inc.
Robert M. Sharkey, PhD, Senior Director, Scientific Affairs, Immunomedics, Inc.
Diane Whiteley, Senior Director, Regulatory Affairs, Immunomedics, Inc.

External Consultant

(b) (4)

BACKGROUND

IMMU-132 is an antibody-directed chemotherapy, which delivers the topoisomerase-1 inhibitor, SN-38 (an active metabolite of irinotecan), into epithelial cancers. Specifically, it is a humanized RS7 IgG (hRS7) linked to SN-38, and the antibody binds to Trop-2 (aka epithelial glycoprotein-1 and trophoblastic cell-surface antigen), which is expressed on epithelial cancers (more so than on normal cells), including breast cancer.

In January 2015, IMMU-132 was granted fast-track designation for the treatment of patients with triple negative breast cancer (TNBC) who have failed no more than 2 prior therapies for metastatic disease. This was based upon data from a phase 1/2 study, IMMU-132-01, in patients with various epithelial cancers, including TNBC. In that study, 34 patients with metastatic TNBC receiving a median of 4 prior therapies were treated and 17 had assessable disease. In this population, there were 5 patients with a PR (29%) and 8 patients with SD (47%). They reported a clinical benefit rate for at least 6 months of 46%.

Study (IMMU-132-01) is ongoing, and is enrolling patients with all epithelial tumors, including patients with triple-negative breast cancer. In the current meeting package, an update was provided to report that 170 patients have received IMMU-132 at starting doses of 8 mg/kg (n=82), 10 mg/kg (n=76), 12 mg/kg (n=9), and 18 mg/kg (n=3) on days 1 and 8 q 21 days.

Efficacy and safety data on 34 patients with TNBC are presented in the meeting package. These results include an objective response rate (CR+PR) in 31 evaluable patients with TNBC of 23%, which included 1 CR. The Sponsor reported a clinical benefit rate ≥ 4 months of 54% and a clinical benefit rate ≥ 6 months of 39% in this patient population. These responses included patients with PR and SD.

The key adverse event with IMMU-132 is neutropenia. In patients treated at the 10 mg/kg dose, the incidence of G3 neutropenia was 16%, the incidence of G4 neutropenia was 4%, and the incidence of febrile neutropenia was 8%. These figures were similar with the 8 mg/kg dose, with G3 neutropenia in 21%, G4 neutropenia in 6% and febrile neutropenia in 3%. The incidence of other adverse events was comparable at 8 mg/kg and 10 mg/kg. Information on other adverse events in the TNBC population is shown in the Sponsor's Table 3.

Table 3. TNBC: Adverse event profile in patients with TNBC (N = 34 Patients).
Criteria: Grade 1-4 Adverse Events for overall incidence \geq 10% or any Grade 3 or 4 severity.

Adverse Events	All Grades	Grade 3	Grade 4
Diarrhea	11 (32%)	1 (3%)	0
Nausea	12 (35%)	0	0
Vomiting	6 (18%)	0	0
Neutropenia	12 (35%)	8 (24%)	2 (6%)
Febrile Neutropenia	1 (3%)	0	1 (3%)
Anemia	6 (18%)	1 (3%)	0
Leucopenia	3 (9%)	1 (3%)	0
Lymphopenia	2 (6%)	1 (3%)	0
Fatigue	9 (26%)	0	0
Alopecia	7 (21%)	0	0
Pruritus	4 (12%)	0	0
Caecitis	1 (3%)	1 (3%)	0

The current proposal is for an international, multi-center, open-label, randomized phase 3 trial of sacituzumab govitecan compared to treatment of physician's choice, in patients with relapsed/refractory metastatic (Stage IV) triple negative breast cancer. Randomization will be 1:1, and the plan will be to enroll 300 patients with TNBC who have received between 2-5 prior chemotherapy regimens.

Treatment will consist of either sacituzumab govitecan given 10 mg/kg IV on days 1 and 8 every 21 days or physicians choice of: eribulin 1.4 mg/m² IV on days 1 and 8 every 21 days, capecitabine 1250 mg/m² orally twice per day BID for 2 weeks on and 1 week off, or gemcitabine 1250 mg/m² IV on days 1 and 8 every 21 days.

Randomization will be stratified by location (North America vs. Europe), hormone status of the primary breast tumor (HR+ vs. HR-), number of prior therapies (2-3 vs. 4-5), and whether the disease is relapsed or refractory (refractory is defined as disease progression within less than one year of adjuvant therapy).

The Sponsor will request archived slides for documentation of tumor Trop-2 expression, but this will not be required for study eligibility. A whole blood sample will also be collected prior to receiving IMMU-132, in order to determine UGT1A1 genotype, although these results will only potentially be used for retrospective assessment of toxicity.

The primary study endpoint will be PFS, measured by blinded, independent central review. Secondary endpoints will include OS, independently-determined overall response rate (ORR), duration of response (DOR), time to onset of response according to RECIST 1.1., safety, quality of life (QOL), incidence of dose delays and dose reductions, and percentage of patients who discontinued therapy due to adverse event. In addition, the Sponsor will conduct an exploratory exposure-response analysis for PFS, OS and safety in relation to UGT1A1 status.

The statistical analysis specifies a plan to detect a 50% improvement in the primary endpoint of PFS compared with the control arm. For example, literature estimates of PFS in metastatic TNBC vary from 1.7- 3.0 months. Therefore, the following examples are provided, depending upon the duration of PFS detected in the control arm:

- For an estimate of median PFS of 1.7 months in the control monotherapy arm, a 50% improvement in PFS would consist of a median PFS of 2.55 months on the IMMU-132 arm, with HR 0.67. Sample size would be 300 patients (1:1 randomization), and would achieve 94% power for a bilateral type 1 error of 5%. Accrual rate 18 months, follow-up of 9 months.
- For an alternative estimate of median PFS of 3 months in the control arm, 50% improvement in PFS would consist of median PFS of 4.5 months on the IMMU-132 arm, with HR 0.67. Sample size of 300 patients would achieve 92.5% power for a bilateral type 1 error of 5%. Same accrual rate and follow-up.

The Sponsor also provided literature examples of OS in patients with TNBC receiving capecitabine or other physician's choice, and report median of OS duration around 8.2 months. Another example from patients with TNBC randomized to eribulin had median OS 12.9 months. As a result, with the proposed sample size of 300 patients, the study would have 80% power to detect a 50% improvement in OS in the IMMU-132 arm to approximately 15 months.

DISCUSSION

Regulatory/Clinical

1. *Based upon the unmet medical need for new treatments for patients with relapsed/refractory metastatic triple-negative breast cancer, would an original BLA based upon the current data, as well as an expanded enrollment of the ongoing phase 1/2 study, be acceptable for conditional approval? In addition, we will initiate a randomized, controlled, confirmatory phase 3 study in the target population (as described in Section 10.4.1 and in the attached protocol synopsis for Study IMMU-132-05).*

FDA Response:

No, we do not agree. An unconfirmed ORR of 23% in 31 patients from a single-arm study of IMMU-132-01 would not be sufficient on its own to support a BLA approval. The data on efficacy and safety from study IMMU-132-01 is limited and could only be supportive for subsequent study.

Meeting Discussion:

The Agency reiterated the issues with the Sponsor's proposal to submit the results of a single arm study to support accelerated approval. Since IMMU-132-01 is still ongoing, the Agency is willing to review updated efficacy and safety data on additional patients. The Sponsor is committed to conducting a randomized trial and may seek a Special Protocol Assessment (SPA) in the future. The Sponsor agrees to submit a Statistical Analysis Plan (SAP) along with their SPA.

The Sponsor is also planning to assess potential enrichment strategies. The Agency recommends assessing available instruments to evaluate patient reported outcome measures. The Agency recommended a separate meeting to discuss patient reported outcome measures.

2. *Key safety and efficacy data are presented in Section 10. Does FDA agree that the Sponsor has generated sufficient clinical safety and efficacy data to proceed to conduct the proposed phase 3 study IMMU-132-05 in patients with relapsed/refractory metastatic triple-negative breast cancer?*

FDA Response:

See response to Question # 1.

It is unclear whether your proposed dosing regimen (10 mg/kg on Days 1 and 8 of a 21-day cycle) is optimal, as you pool clinical efficacy and safety data from multiple dose levels. You should conduct integrated dose-response and exposure response analyses to justify the proposed 10 mg/kg dosing regimen before commencing the phase 3 trial.

Meeting Discussion:

The Sponsor agreed to provide exposure response and dose response analyses to justify the proposed dosing regimen.

3. *The key design elements of IMMU-132-05 are provided in Section 10.4.1 and in the attached draft phase 3 protocol synopsis. Does FDA agree with the proposed design of this confirmatory registration study with particular focus on:*
- a. *Inclusion/exclusion criteria*
 - b. *Primary endpoint*
 - c. *Key secondary endpoints*
 - d. *Stratification*
 - e. *Sample size*
 - f. *Statistical analysis?*

FDA Response:

- a. **Your proposed inclusion/exclusion criteria seem reasonable.**
- b. **Your proposal to use PFS by blinded independent review is acceptable** (b) (4)

- c. **Clarify how Quality of Life will be assessed, including whether you plan to use a validated tool to assess this.**

- d. We assume [REDACTED] (b) (4) [REDACTED] considering that you plan to target patients with triple negative breast cancer.
- e. **Sample size**
- For the time-to-event endpoint PFS, the sample size calculation should be driven by number of PFS events. Please modify your sample size determination.
 - You have proposed potential sample size re-estimation at the time of the interim analysis. You should pre-specify details on sample size re-estimation before the interim analysis is conducted.
- f. **SAP- See also response to 3b.**
- Your have proposed an interim efficacy analysis for PFS. Please note that an interim efficacy PFS analysis may not provide an accurate or reproducible estimate of the treatment effect size due to inadequate follow-up, missing assessments, disagreements between radiological reviewers and/or disagreements between investigator and independent assessments. Therefore, we recommend removing the interim efficacy PFS analysis. In addition, we recommend an interim analysis for futility based on number of PFS events, instead of number of patients.
 - If you plan to claim any efficacy based on secondary endpoints, you should make adjustment for multiplicity in testing secondary endpoints in order to maintain the overall type I error rate at two-sided 0.05 level.
 - For your proposed stratified log-rank test and Cox proportional hazards regression model for PFS and OS, we recommend that you reduce the number of stratification factors, as we are concerned with potential sparse data in some of the strata. In addition, to estimate the hazard ratio and 95% confidence interval of PFS and OS, please use stratified Cox proportional hazards regression model with treatment arm as the only covariate.

Meeting Discussion:

The Agency reiterated that PFS is a reasonable endpoint, provided that the results are statistically significant and clinically meaningful, and that treatment with IMMU-132 has a favorable benefit risk profile.

Additional Comments:

1. See “Guidance for Industry: S9 Nonclinical Evaluation for Anticancer Pharmaceuticals” for a list of nonclinical studies that should be conducted during development of pharmaceuticals intended to treat patients with advanced cancer.

- **To support continued development of IMMU-132 for patients with late stage or advanced cancer, results from 3-month repeat-dose toxicology studies following the intended clinical schedule of administration should be provided prior to initiating phase 3 clinical trials and to support submission of a marketing application. We also refer you to nonclinical comments sent to you following review of your original IND 115621 regarding the design of a repeat-dose toxicology study in Cynomolgus monkeys (Study No. (b) (4) 160.03). Future repeat-dose toxicology studies should include an adequate number of animals and at least three dose levels of the test article and a concurrent control. In general, non-rodent studies should consist of at least 3 animals/sex/group with an additional 2 animals/sex/group for recovery, if appropriate. For recommendations on design of toxicity studies, see the “Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients,” or CFSAN Redbook [<http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/ingredientsadditivesgraspackaging/ucm2006826.htm>].**
 - **An assessment of embryo-fetal toxicity should be conducted to support a marketing application for anticancer pharmaceuticals (See ICH S9). We recommend that you submit a future meeting request for our feedback on the appropriateness of your proposed plan to assess embryo-fetal toxicity with IMMU-132. This request should include your proposed assessment and adequate justifications supporting your proposal.**
 - **Genotoxicity studies should be conducted to support a marketing application for anticancer pharmaceuticals (See ICH S9).**
2. **We remind you of the clinical pharmacology comments conveyed to you by email on July 21, 2014.**
 3. **You should also develop an assay for the neutralizing anti-drug antibodies.**
 4. **Regarding your plan to explore the relationship between IMMU-132 safety and UGT1A1 genotype, consider evaluating other UGT1A1 reduced function alleles in addition to UGT1A1*28.**
 5. **We recommend that you request an end-of-phase 2 CMC meeting to discuss your product to be used in your pivotal clinical trial and an overview of your CMC plans for licensure.**

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies 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 PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP 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 at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND Sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a web page 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. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

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 the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests \(http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm\)](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator

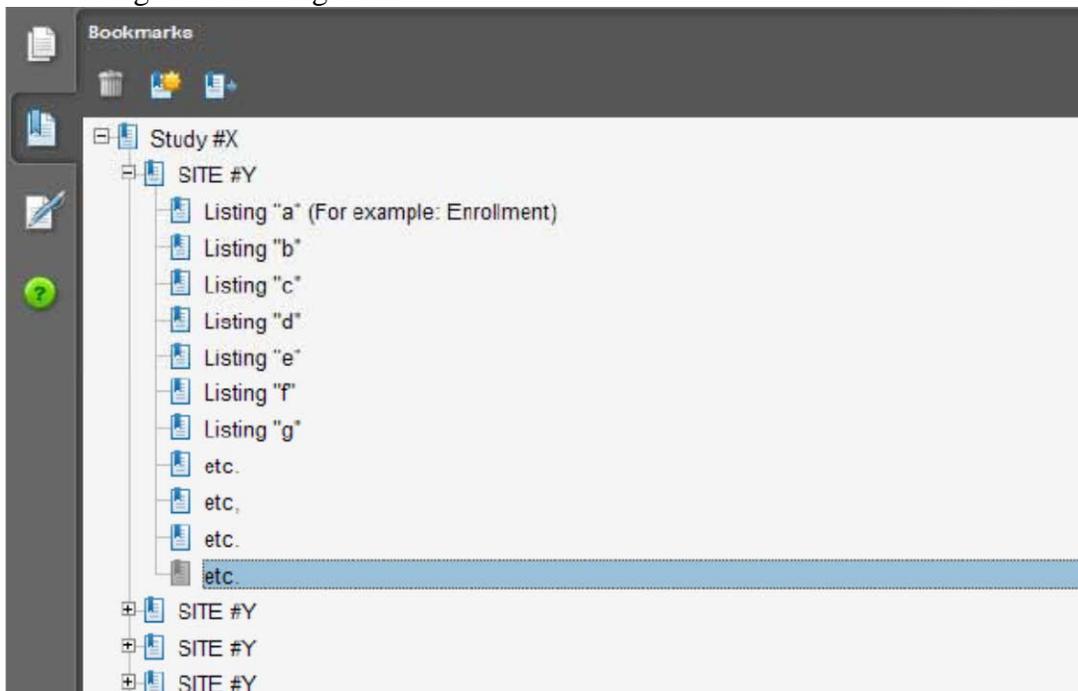
- c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, by site, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which Sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other Sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:

- a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
- b. Subject listing for treatment assignment (randomization)
- c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
- d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
- e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
- f. By subject listing, of AEs, SAEs, deaths and dates
- g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
- h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
- i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
- j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal phase 2 and phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item 1	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>).

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>).

For general help with eCTD submissions: ESUB@fda.hhs.gov.

ATTACHMENTS AND HANDOUTS

A copy of the slide presentation during the meeting is attached.

9 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAJESH VENUGOPAL
02/27/2015

PATRICIA CORTAZAR
02/27/2015