CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761310Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

U.S. FOOD & DRUG ADMINISTRATION

*****Sponsor requested revised Meeting Minutes*****

IND 111915

MEETING MINUTES

ImmunoGen, Inc.
Attention: Jennifer Eaddy
830 Winter Street
Waltham, MA 02451

Dear Ms. Eaddy:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for mirvetuximab soravtansine (IMGN853).

We also refer to the teleconference between representatives of your firm and the FDA on January 20, 2022. The purpose of the teleconference was to discuss the overall data content and format for the planned mirvetuximab soravtansine BLA in support of the indication for the treatment of adult patients with folate receptor-alpha (FRα) positive platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens.

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 teleconference outcomes.

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

If you have any questions, contact Amy Tilley, Regulatory Project Manager at amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Amy Tilley
Regulatory Project Manager
Oncology 1 Group
Division of Regulatory Operations
for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation & Research

Gwynn Ison, MD
Acting Clinical Team Leader
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation & Research

Enclosure:

- Meeting Minutes
- Sponsor Slides

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	January 20, 2022 11:00 am – 12:00 pm EST
Meeting Location:	Teleconference
Application Number:	IND 111915
Product Name:	mirvetuximab soravtansine (IMGN853)
Indication:	Treatment of adult patients with folate receptor-alpha (FRα) positive platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens
Sponsor Name:	ImmunoGen, Inc.
Regulatory Pathway:	351(a) of the Public Health Service Act
Meeting Chair:	Gwynn Ison, MD, Acting Team Leader
Meeting Recorder:	Amy Tilley, Regulatory Project Manager

FDA ATTENDEES

Laleh Amiri Kordestani, MD, Director, DO1
Gwynn Ison, MD, Acting Clinical Team Leader, DO1
Christy Osgood, MD, Clinical Team Leader, DO1
Preeti Narayan, MD, Clinical Reviewer, DO1
Tara Berman, MD, Clinical Reviewer, DO1
Christina Brus, MD, Clinical Reviewer, DO1
Asma Dilawari, MD, Clinical Reviewer, DO1
Mirat Shah, MD, Clinical Reviewer, DO1
Hima Lingam, MD, Clinical Reviewer, DO1
Samina Jafri, PhD, Biologist, CDRH/OIR/DMGP/MPCB
Shyam Kalavar, MPH, CT, Scientific Reviewer, CDRH/OIR/DMGP/MPCB
Erik Bloomquist, PhD, Biostatistics Team Leader, OTS/OB/DBV
Xin Gao, PhD, Biostatistics Reviewer, OTS/OB/DBV
Salaheldin Hamed, PhD, Clinical Pharmacology Team Leader, OTS/OCP/DCPV
Guoxiang Shen, PhD, Clinical Pharmacology Reviewer, OTS/OCP/DCPV
Tiffany Ricks, PhD, Pharmacology Toxicology Supervisor, DHOT
Zhong Li, PhD, Senior Pharmaceutical Quality Reviewer, OPQ/OPMA/DBM/BMB1
Kristen Nickens, PhD, Product Quality Team Leader, OPQ/OBP/DBRRI

Eric Hales, PhD, Product Quality Reviewer, OMPT/CDER/OPQ/OBP/DBRRI
Amy Tilley, Regulatory Project Manager, ORO/DRO – Oncologic Diseases

SPONSOR ATTENDEES

Anna Berkenblit, MD, Senior Vice President, Chief Medical Officer
Mark Enyedy, President and CEO
Joe Wang, PhD, Executive Director, Biostatistics
Eric Westin, MD, Vice President, Clinical Development and Translational Sciences
Theresa Wingrove, PhD, Senior Vice President, Regulatory Affairs and Quality
(b) (4)

Jennifer Eaddy, Executive Director, Regulatory Affairs
(b) (4)

1.0 BACKGROUND

Mirvetuximab soravtansine (IMGN852, also known as MIRV) is an ADC (antibody drug conjugate) that binds to folate receptor 1 (FOLR1) or FRα, a glycophosphatidylinositol linked protein which shows limited normal tissue expression and high expression in several solid tumors, including serous epithelial ovarian cancer (EOC). MIRV consists of a humanized anti-FRα monoclonal antibody attached via linker to the cytotoxic maytansinoid, DM4. Maytansinoids are antimitotic agents that inhibit tubulin polymerization and microtubule assembly, resulting in cell cycle arrest and apoptosis. The Sponsor, Immunogen, has met with the FDA on multiple prior occasions to discuss the development of mirvetuximab soravtansine.

The objective of this Type B pre-BLA teleconference is to discuss the content and format of the planned submission of the BLA for mirvetuximab soravtansine. The proposed indication will be:

- Mirvetuximab soravtansine is an FRα-directed antibody-drug conjugate (ADC) indicated for the treatment of adult patients with folate receptor-alpha (FRα) positive platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer (PROC), who have received one to three prior systemic treatment regimens. Select patients for therapy based on an FDA-approved companion diagnostic.

The BLA submission is planned for March 2022. ImmunoGen seeks marketing approval for mirvetuximab soravtansine under the accelerated approval pathway.

The Sponsor plans that this initial BLA will be supported by one “pivotal” study (Study 0417, SORAYA) and 2 supporting studies including Study 0401 (FIH dose finding study)

and Study 0403 (FORWARD1 study, which failed to meet its primary endpoint and has been the topic of previous meetings). Study 0417 was discussed during a previous teleconference in 2019. The FDA advised that given the single arm study design, the primary endpoint should be ORR by blinded independent review committee (BICR), and that INV assessed ORR could be used as a sensitivity analysis. The FDA also advised that all responders should be followed for at least 6 months from the onset of response for duration of response (DOR).

Study 0417 (SORAYA)

Study 0417 (SORAYA) was a single arm study that has enrolled 106 patients with PROC in receipt of 1-3 prior lines of therapy, including bevacizumab, and whose tumors express FRα, as determined by the Ventana FOLR1 CDx Assay (FRα+ threshold ≥75% of cells staining positive), utilizing the PS2+ scoring method (referred to as FRα-high). Platinum resistant disease was defined as PD within 6 months from completion of minimum of 4 cycles of platinum-based therapy, including at least 1 line of therapy containing bevacizumab. In addition, to be eligible for this study, patients had to be "appropriate" for single agent chemotherapy as their next line of therapy, as determined by the Investigator.

Radiological assessments were performed at baseline and every 6 weeks during the first 36 weeks, then every 12 weeks until PD, death, start of new anticancer therapy, or withdrawal of consent. ORR was determined according to INV assessment according to RECIST 1.1. CT and/or MRI images were collected for determination of tumor response by BICR for a sensitivity analysis. Key secondary endpoints include duration of response (DOR) by INV and BICR, and safety.

Topline results for Study 0417:

One hundred six (n=106) patients were enrolled; 105 had measurable disease by INV and are included in the efficacy evaluable population. The platinum-free interval was 0-3 months for 37% and >3-6 months for 60%. Forty-eight percent (48%) of patients had 1-2 prior lines and 51% had 3 prior lines. All patients had received prior bevacizumab and 48% of patients received a prior PARP inhibitor. All patients had ECOG 0-1. The primary efficacy results of ORR by INV and BICR assessment are shown in Tables 7 and 8.

Table 7: Study 0417 Confirmed ORR by Investigator - Efficacy Evaluable Population

	All Patients (n=105)
Confirmed ORR, n (%)	34 (32.4)
95% CI	23.6, 42.2
Confirmed BOR, n (%)	
CR	5 (4.8)
PR	29 (27.6)
Stable Disease	48 (45.7)
Progressive Disease	20 (19.0)
Not Evaluable	3 (2.9)

Note: The denominator for the percentages is the number of patients in the INV Efficacy Evaluable population.
Note: Patients without at least one post-baseline RECIST assessment will be treated as not evaluable.
Source: Study 0417, Table 14.2.1.1.

Table 8: Study 0417 Confirmed ORR by BICR – Efficacy Evaluable Population

	All Patients (n=95)
Confirmed ORR, n (%)	30 (31.6)
95% CI	22.4, 41.9
Confirmed BOR, n (%)	
CR	5 (5.3)
PR	25 (26.3)
Stable Disease	53 (55.8)
Progressive Disease	8 (8.4)
Not Evaluable	4 (4.2)

Note: The denominator for the percentages is the number of patients in the BICR Efficacy Evaluable population.
Note: Patients without at least one post-baseline RECIST assessment will be treated as not evaluable.
Source: Study 0417, Table 14.2.1.2.

The duration of response by INV and BICR assessment are shown in Tables 9 and 10, respectively. It is notable that the median DOR by INV assessment is considerably shorter than the median DOR by BICR assessment, with half as many radiological PD events documented by INV as compared to BICR.

Table 9: Study 0417 Duration of Response using RECIST per Investigator – Efficacy Evaluable Population with Confirmed Complete or Partial Response

Measure	All Responders (N=34)
DOR Events, n (%)	
Radiological Progression	18 (53)
Death without Documented Progression	0 (0)
Censored, n (%)	
New Anti-Cancer Therapy Prior to Progression or Death	1 (3)
No Death or Progression	15 (44)
Progression or Death After Missing Two or More Consecutive Radiological Assessments	0 (0)
Kaplan-Meier Estimates for DOR, (Months)	
Median (95% CI)	5.9 (5.6, 7.7)
1st Quartile (95% CI)	4.2 (2.8, 5.7)
3rd Quartile (95% CI)	7.7 (6.9, NR)
Range	1.5+, 9.8
Kaplan-Meier Estimates for DOR Rate, (95% CI)	
At 3 months	0.84 (0.67, 0.93)
At 6 months	0.46 (0.25, 0.65)
At 9 months	0.23 (0.05, 0.47)

Note: Duration of response is defined as the time from the date of first response (complete or partial response) to the date of progressive disease or death from any cause, whichever occurs first.
NR=not reached; + = censored.
Source: Study 0417, Table 14.2.2.1.

Table 10: Study 0417 Duration of Response using RECIST per BICR – Efficacy Evaluable Population with Confirmed Complete or Partial Response

Measure	All Responders (N=30)
DOR, n (%)	
Radiological Progression	9 (30)
Death without Documented Progression	0 (0)
Censored, n (%)	
New Anti-Cancer Therapy Prior to Progression or Death	2 (7)
No Death or Progression	19 (63)
Progression or Death After Missing Two or More Consecutive Radiological Assessments	0 (0)

Table 10: Study 0417 Duration of Response using RECIST per BICR – Efficacy Evaluable Population with Confirmed Complete or Partial Response (Continued)

Measure	All Responders (N=30)
Kaplan-Meier Estimates for DOR, (Months)	
Median (95% CI)	11.7 (5.0, NR)
1st Quartile (95% CI)	5.0 (2.6, NR)
3rd Quartile (95% CI)	11.7 (NR, NR)
Range	1.4+, 11.7
Kaplan-Meier Estimates for DOR rate, (95% CI)	
At 3 months	0.85 (0.64, 0.94)
At 6 months	0.62 (0.37, 0.80)
At 9 months	0.62 (0.37, 0.80)

DOR = duration of response; CI = confidence internal; NR=not reached; + = censored.
Note: Duration of response is defined as the time from the date of first response (complete or partial response) to the date of progressive disease or death from any cause, whichever occurs first.
Source: Study 0417, Table 14.2.2.2.

Proposed confirmatory Study 0416

Study 0416 is a randomized (1:1) phase 3 study in patients with advanced PROC who have had 1-3 prior lines of therapy. Patients must have tumor expression of FR-α (high FRα expression as determined by PS2+ scoring method). The study is comparing MIRV with Investigator's choice of paclitaxel, PLD, or topotecan). The study is ongoing and will enroll a total of 430 patients. As of December 2021, 220 patients have been randomized and the Sponsor estimates the study will complete enrollment in mid-2022.

The design of Study 0416 was discussed with the FDA at a teleconference on September 30, 2019. The primary endpoint is PFS by INV assessment. The study has 90% power to detect a PFS HR of 0.7. An interim futility analysis for PFS will occur at 110 events and the Sponsor intends to stop if the HR for PFS is >1. The study also has 90% power to detect an OS HR of 0.6857. During the September 30, 2019, teleconference, although the FDA agreed that PFS could be by INV assessment, the FDA recommended that the Sponsor utilize co-primary endpoints of PFS and OS given the relatively short duration of survival in this treatment refractory setting. The FDA specifically advised that the targeted PFS improvement of 1.5 months may not be considered to be clinically meaningful or interpretable, since the imaging interval will be 1.5 months. The FDA also provided input on the need for prior bevacizumab in the enrolled population, and the Sponsor stated that "most patients" will have received prior bevacizumab. The FDA finally recommended that the SAP for study 0416 be submitted to the FDA for review prior to initiation of the study.

The FDA sent Preliminary Comments to ImmunoGen, Inc. on January 17, 2022.

2.0 DISCUSSION

Preamble:

We do not consider that the data from Study 0417 (SORAYA) will be acceptable to support a BLA submission for accelerated approval for mirvetuximab soravtansine, and we do not advise submitting your BLA based upon these data. Your assumption that the bar to which your product will be compared, an ORR of 13% from the AURELIA trial, is inaccurate. The FDA will consider the response rates for the individual chemotherapy agents from AURELIA for comparison, including an ORR of 30% (95% CI: 17, 44) for single agent paclitaxel and median DOR of 6.8 months. Given this, the proposed efficacy data for mirvetuximab soravtansine, including an INV-assessed ORR of 32% (95% CI: 23, 42) with median DOR 5.9 months, would not represent an improvement over the available therapies. In addition, you have not provided any information on BRCA or HRD status on all patients enrolled to Study 0417, although approximately half of patients enrolled have received prior PARP therapy. If patients with underlying BRCAm or HRD-positive tumors were enrolled and had not yet received a PARPi, approved PARPi's would also be considered available therapies to which the ORR for mirvetuximab soravtansine will be compared.

We also remind you of advice provided in September 2019 about the design of Study 0416, which you proposed to use as your confirmatory trial for regular approval. We reiterate that it is unlikely that the targeted 1.5 month improvement in PFS over control will be clinically meaningful considering notable toxicity, including a 30% G3 or higher TEAEs ("related") on Study 0417 and considerable ocular toxicity.

If you choose to submit this BLA, the application may need to be discussed at an Oncologic Drugs Advisory Committee.

Meeting Discussion: After review of additional information the Sponsor provided on the response rate of paclitaxel across other studies, specifically in FR alpha population, FDA agreed that single agent paclitaxel ORR from AURELIA trial is not an appropriate comparator for consideration for AA. As such, FDA agreed with the Sponsor's plan to submit their BLA for review. FDA noted that key review issues will include the toxicity profile of MIRV and the duration of response.

The Sponsor confirmed the FR alpha assay was locked down prior to conducting Study 0417. The Sponsor also confirmed that the PMA will be submitted to CDRH no later than 1 month after BLA submission.

During the BLA review, the FDA may request a blinded look at ORR and/or DOR from the ongoing phase 3 confirmatory trial 0416. The FDA recommended the Sponsor prepare for the possibility of such a request.

1. Does the FDA agree that ImmunoGen's overall BLA organization and content as described in the enclosed proposed Table of Contents (TOC) are appropriate and sufficient to support filing and review of the initial BLA for mirvetuximab soravtansine?

   FDA Response: See the Preamble. The proposed TOC appears sufficient to support submission of a BLA.

   Meeting Discussion: None.

2. Does the FDA agree that the proposed datasets (Attachment 3) to be provided as part of the initial BLA are adequate?

   FDA Response: See the Preamble. The proposed datasets in general appear acceptable for submission of a BLA. The key focus of the clinical review will be on Study 0417, and the proposed datasets for this study appear acceptable. Additional datasets or amendments to datasets may be requested and should be made available upon request during BLA review. Your proposal to include studies 0417, 0403, and 0401 in an integrated safety dataset seems acceptable.

   Meeting Discussion: None.

3. ImmunoGen would like to offer an Applicant Orientation Presentation meeting in support of the BLA. Does the FDA agree to an Applicant Orientation Presentation meeting after receipt of the mirvetuximab soravtansine BLA?

   FDA Response: See the Preamble. We generally advise on scheduling of an AOM upon receipt of a BLA.

   Meeting Discussion: None.

4. ImmunoGen will request Priority Review in the cover letter to the BLA application. Is it sufficient to include a brief position statement providing justification for eligibility for Priority Review in the cover letter of the BLA?

   FDA Response: See the Preamble. You may provide a justification for eligibility for Priority Review in the cover letter.

   Meeting Discussion: None.

5. Ventana Medical Systems, Inc. is developing an FRα companion diagnostic (CDx) to select patients appropriate for treatment with mirvetuximab soravtansine. With respect to the CDx, ImmunoGen plans to include a brief

summary on the history of the Ventana FOLR1 assay in Section 2.7.1 of the mirvetuximab soravtansine BLA. Does the FDA agree to this approach?

In addition, we seek guidance from the FDA on any other BLA content that will facilitate the concurrent review of the mirvetuximab soravtansine BLA and the Ventana FOLR1 Assay PMA.

FDA Response: See the Preamble. You should confirm that the investigational VENTANA FOLR1 assay (that includes the PS2+ scoring algorithm and cutoff) used for patient enrollment was locked down prior to its use in the 0417 trial.

Your proposal to include an overview of the history of the Ventana FOLR1 assay in the BLA is acceptable to aid reviewers.

We note that the PMA should be submitted at the same time to CDRH, but no later than 30 days after the BLA submission to CDER for a contemporaneous review and necessary action. The PMA should include all administrative elements of a PMA submission and all device-related information. This includes but is not limited to device description (including cutoffs and the scoring algorithm), software information, GMP/QSR information, analytical and clinical performance studies, bridging study data, all line data, as applicable, and any protocol deviations. You can refer to the following link for more information: https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-approval-pma.

Meeting Discussion: None.

6. Does the FDA agree to the proposed timing for submission of launch materials?

FDA Response: It is premature to comment on the timing of launch materials at this time.

Meeting Discussion: None.

7. ImmunoGen anticipates submitting the mirvetuximab soravtansine BLA in March 2022. The dates for the manufacture of the biologic components of the Antibody, Drug Substance, and Drug Product have been secured (see Table 6) to ensure that the manufacturing is ongoing at the time of the anticipated potential inspections. Is this schedule sufficient to facilitate pre-license inspection planning in support of the BLA?

FDA Response: See the Preamble. It is premature to comment on the timing of facility inspections, since we do not recommend that you submit your BLA at this time.

Meeting Discussion: None.

Following the teleconference, the Sponsor requested that the FDA provide feedback on the proposed manufacturing schedule of their CMOs below to ensure that manufacturing is ongoing at the time of the anticipated inspections.

Company Position and Supporting Information

Table 6: CMO Manufacturing Timeline

Material	Manufacturer/Location	Start of Manufacture Tentative Schedule
Antibody	(b) (4)	
Drug Substance		

Drug Product	(b) (4)

Post Meeting FDA Response: The proposed manufacturing schedule appears to be reasonable based on a submission date in March 2022.

As travel restrictions are eased or lifted, FDA will use a risk-based approach to prioritizing inspections. The prioritization strategy will consider the impact of product availability on public health; investigator safety; and travel restrictions still in place during the COVID-19 public health emergency. These considerations will be balanced with the goal to reduce any backlog of assigned inspections. Please refer to the "Resiliency Roadmap for FDA Inspectional Oversight", May 2021 (https://www.fda.gov/media/148197/download) for further information on FDA's prioritization plan for the inspectional oversight activities. At this time, we cannot predict when inspections of your manufacturing facilities may occur.

8. Does the FDA agree with ImmunoGen's proposed scope (content and data cutoff) for the 120-day safety update report; in the event of Priority Review, can the FDA confirm that the safety update would be required by day-90?

The proposal is to include updated safety info on Study 0417 covering the period from database lock of November 16, 2021 through the submission date of the BLA (projected for March 2022); 4 additional months of safety data will be included. This will be just for study 0417. The integrated safety analysis will not be updated. They propose including the following for Study 0417: extent of exposure, overview of TEAEs by SOC and PT, Ocular TEAEs and resolution, SAEs by SOC and PT, G3 or higher TEAEs, TEAs leading to discontinuation, delay, reduction, deaths. Narratives and CRFs will be provided for SAEs, deaths, discontinuations, G3 or higher pneumonitis, ocular, infusion related AEs.

FDA Response: See the Preamble. We agree with the proposed scope of safety data to be submitted for Study 0417. A 120-day safety update is required. You should submit CRFs for all patients enrolled on the study. Additional narratives above those described, may be requested during review.

Meeting Discussion: The FDA noted that the Sponsor's proposed submission of CRFs and narratives is acceptable. The Sponsor will provide additional CRFs and narratives upon request.

9. The estimated median DOR by investigator observed in Study 0417 at the time of the protocol-specified primary analysis is 5.9 months (95% CI: 5.6, 7.7). We would like to provide updated DOR data concurrent with the safety update report for labeling purposes. Can the FDA confirm that updated DOR data may be submitted concurrently with the safety update and that such an update would not extend the PDUFA action date?

FDA Response: We do typically request that an updated DOR (and corresponding dataset) be submitted at the time of safety update. However, see the Preamble.

Meeting Discussion: None.

Additional Comments:

1. **Submit in vitro ADME study reports in the application to support labeling.**

2. **To facilitate the FDA's review of the critical intermediate, drug substance, and drug product manufacturing process for mirvetuximab soravtansine, provide the information for all attributes, parameters, or controls proposed for routine commercial manufacturing as well as those evaluated during development and validation, in the tabular format provided below. Please provide a separate table for each unit operation. The tables should summarize information from Module 3 and may be submitted Module 3.2.R. Note, this Table does not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.**

Title: INSERT UNIT OPERATION

Process parameter / operating parameter /In-process control (IPC)/In-process tests (IPT)[1]	Proposed Range for Commercial Manufacturing[2]	Criticality classification[3]	Characterized Range from process development[2]	Manufacture range from historical experience (i.e., for pivotal clinical lots)	Manufacture range from process validation	Justification of the proposed commercial acceptable range[4] (or link to eCTD)	Comment[5]

[1]Terminology should be adapted to the one used by ImmunoGen, Inc.
[2]As applicable.
[3]For example, critical process parameter, non-critical process parameter, as described in Module 3.

[4]This could be a brief verbal description (e.g., "development range", "validation range", or "historical manufacturing experience", etc.) or links to the appropriate section of the eCTD.
[5]Optional.

Meeting Discussion: None.

3.0 OTHER IMPORTANT MEETING LANGUAGE

PREA REQUIREMENTS

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

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

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

pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

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

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

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

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

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

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[4] and Pregnancy and Lactation Labeling Final Rule[5] 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.
- The FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

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

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[6]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

NONPROPRIETARY NAME

On January 13, 2017, the FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the FDA

[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
[8] https://www.fda.gov/media/85061/download

intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

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

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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Sponsor slides

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/s/

AMY R TILLEY
02/08/2022 01:26:00 PM

GWYNN ISON
02/08/2022 02:07:47 PM

IND 111915

MEETING MINUTES

ImmunoGen, Inc.
Attention: Jennifer Eaddy
830 Winter Street
Waltham, MA 02451

Dear Ms. Eaddy:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for mirvetuximab soravtansine (IMGN853).

We also refer to the teleconference between representatives of your firm and the FDA on December 6, 2021. The purpose of the teleconference was to discuss the proposed [redacted] (b) (4)

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

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

If you have any questions, contact Amy Tilley, Regulatory Project Manager at amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Amy Tilley
Regulatory Project Manager
Oncology 1 Group
Division of Regulatory Operations
for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation & Research

Gwynn Ison, MD
Acting Clinical Team Leader
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation & Research

Enclosure:

- Meeting Minutes

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/s/

AMY R TILLEY
12/07/2021 04:47:32 PM

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12/07/2021 04:56:38 PM

IND 111915

MEETING MINUTES

ImmunoGen, Inc.
Attention: Jennifer Eaddy
Senior Director, Regulatory Affairs
830 Winter Street
Waltham, MA 02451

Dear Ms. Eaddy:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for mirvetuximab soravtansine (MIRV; IMGN853).

We also refer to the meeting between representatives of your firm and the FDA on September 30, 2019. The purpose of the meeting was to discuss the key elements of the design of the next Phase 3 study for MIRV, Study 0416, so that it may provide the definitive evidence needed to support approval. The secondary purpose of the meeting is to discuss the rationale for the proposed change in the FRα companion diagnostic scoring algorithm to be used in Study 0416.

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

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

If you have any questions, call Amy Tilley, Regulatory Project Manager at 301-796-3994.

Sincerely,

{See appended electronic signature page} *{See appended electronic signature page}*

Amy Tilley
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research

Sanjeeve Balasubramaniam, MD, MPH
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor Attachments

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2/Pre-Phase 3
Meeting Date and Time:	September 30, 2019 3:00 pm – 4:00 pm
Meeting Location:	WO22 Room 1309
Application Number:	IND 111915
Product Name:	mirvetuximab soravtansine (IMGN853).
Indication:	A monotherapy for the treatment of patients with FRα–positive platinum-resistant epithelial ovarian cancer, fallopian tube, or primary peritoneal cancers who have received no more than three prior systemic treatment regimens. Select patients for therapy based on an FDA-approved companion diagnostic test.
Sponsor:	ImmunoGen, Inc.
Meeting Chair:	Sanjeeve Balasubramaniam, MD, MPH Clinical Team Leader
Meeting Recorder:	Amy Tilley, Regulatory Project Manager

FDA ATTENDEES

Julia Beaver, MD, Director, DOP1
Sanjeeve Balasubramaniam, MD, MPH, Clinical Team Leader, DOP1
Laleh Amiri-Kordestani, MD, Supervisory Associate Direcotor, DOP1
Harpreet Singh, MD, Clinical Team Leader, DOP1
Tara Berman, MD, Clinical Reviewer, DOP1
Erik Bloomquist, PhD, Acting Biostatistics Team Leader, OTS/OB/DBV
Xin Gao, PhD, Biostatistics Reviewer, OTS/OB/DBV
Soma Ghosh, PhD, Chief, CDRH/OIR/DMGP/MPCB
Samina Jafri, PhD, Biologist, CDRH/OIR/DMGP/MPCB
Amy Tilley, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

Anna Berkenblit, MD, Senior Vice President, Clinical Development & Chief Medical Officer
Eric Westin, MD, Vice President, Clinical Development
Jiuzhou Wang, PhD, Senior Director, Biostatistics
Theresa Wingrove, PhD, Senior Vice President, Regulatory Affairs and Quality
Jennifer Eaddy, Senior Director, Regulatory Affairs

1.0 BACKGROUND

ImmunoGen requested a face-to-face Type B meeting with FDA to discuss key design elements of the next Phase 3 study for mirvetuximab soravtansine (MIRV), Study 0416, in order to gain approval of MIRV for the proposed indication. In addition, the sponsor would like to discuss the folate receptor alpha (FRα) companion diagnostic scoring method to be used in Study 0416. Finally, ImmunoGen would like to understand FDA's receptiveness to a potential accelerated approval pathway in advance of the completion of Study 0416, as the response rate of 44% in the Phase 1 Study 0401 was higher than expected for patients with medium and high FRα expression receiving MIRV compared to standard of care options in the patient population.

MIRV, also known as IMGN853, is a targeted antibody-drug conjugate (ADC) that binds FRα, a glycophosphatidylinositol-linked protein, which shows limited normal tissue expression and reportedly high expression in several solid tumors, most notably serous epithelial ovarian cancer (EOC). This ADC consists of a humanized anti- FRα monoclonal antibody attached via a cleavable disulfide-containing linker to the cytotoxic maytansinoid, DM4. Maytansinoids are antimitotic agents that inhibit tubulin polymerization and microtubule assembly, resulting in cell cycle arrest and apoptosis. The catabolites may also diffuse across the cell membrane and kill neighboring cells, enabling the conjugate to be active against tumors with heterogeneous expression of FRα.

MIRV is indicated for the treatment of patients with FRα-positive platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received no more than 3 prior systemic treatment regimens. Select patients for therapy will be chosen based on an FDA-approved companion diagnostic test.

MIRV is provided as a liquid formulation for IV administration. The dose is 6 mg/kg adjusted ideal body weight (AIBW) given once every 3 weeks until disease progression or unacceptable toxicity.

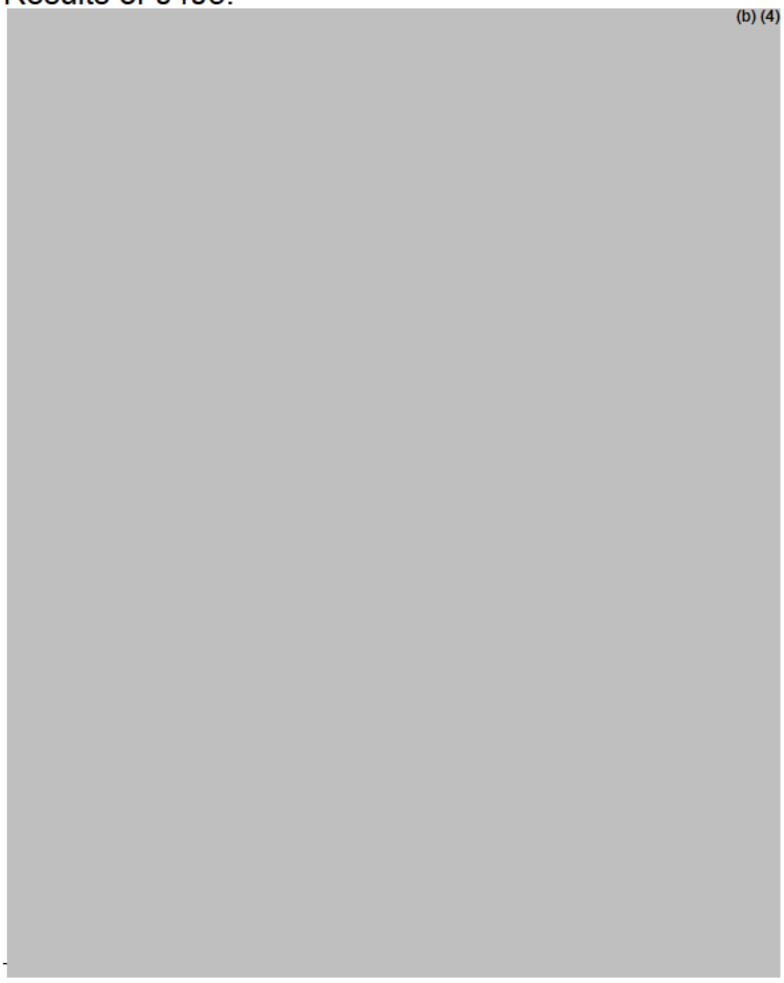
Clinical History:

- Study 0401 established the recommended Phase 2 dose and schedule of MIRV as a single-agent in patients with FRα-positive solid tumors who have relapsed or are refractory to standard therapies. Stage 1 was a dose escalation phase, examining 2 schedules: Schedule A (MIRV q3w) and Schedule B (MIRV on days 1, 8, and 15, every 28 days). Schedule A was selected for further development. Stage 2 included 3 EOC expansion cohorts and a single endometrial carcinoma cohort, each given MIRV at a dose of 6 mg/kg AIBW q3w. Two-hundred-six patients were enrolled (69 in dose escalation and 137 in dose expansion) in sites across the US and Canada, with the last patient visit occurring on March 19, 2018.

(b) (4)

- Study 0403 was a Phase 3, randomized study of MIRV versus investigator's choice single-agent chemotherapy intended to support initial registration. A total of 366 patients were randomized 2:1 to receive either MIRV or IC single-agent chemotherapy (paclitaxel [Pac], pegylated liposomal doxorubicin [PLD], or topotecan [Topo]). Eligibility criteria included patients with PROC who had received no more than 3 prior systemic treatment regimens. This study evaluated the efficacy and safety of IMGN853 in patients whose FRα status was determined using the 10X scoring method. This diagnostic study will re-evaluate slides previously stained with VENTANA FOLR1 (FOLR1-2.1) CDx Assay as part of ImmunoGen Study 0403 and Ventana Study D093147, to use the PS2+ method previously used in early development and in ImmunoGen's early phase clinical trials, Studies 0401 (b) (4) to determine FRα expression level by the PS2+ method at the at the 75% cutoff. This diagnostic study aims to evaluate the performance of VENTANA FOLR1 (FOLR1-2.1) CDx Assay as a companion diagnostic device for IMGN853, in the intended population of patients with revised cutoff of FRα expression ≥75%, determined using the PS2+ method.

Results of 0403:



Results of 0403 after post-hoc reevaluation of FRa score by PS2+ method:

Study 0416 Study Design

The study is designed to test the alternative hypothesis that survival function of PFS is different between MIRV and the investigator's choice (IC) chemotherapy arm (see "Comparator Arm" below).

Approximately 430 patients will be randomized 1:1 (approximately 215 patients in the MIRV and IC chemotherapy arms, respectively) over a period of approximately 18 months. The final analysis of PFS will be conducted when at least 330 events have occurred. The study will have 90% power to detect a PFS hazard ratio of 0.7. An interim futility only analysis for PFS will be conducted when at least 110 events have occurred. The study will stop if the observed hazard ratio for PFS at the futility only interim analysis is greater than 1. No alpha spending is needed for this futility analysis.

The final analysis of OS will be conducted when at least 300 events have occurred. There will be one interim analysis for OS at the time of final analysis of PFS, at which time approximately 200 (67%) deaths will have been observed. A Lan-DeMets alpha-spending function using an O'Brien-Fleming stopping boundary will be used to control overall type I error for OS at 2-sided alpha level of 0.05. The overall study will have 90% power to detect an OS hazard ratio of 0.6857.

Key Inclusion Criteria

- Platinum-resistant disease
- Progression on or after the most recent line of therapy, either radiographically or by Ca125
- Willing to provide archival tumor tissue block or slides or undergo procedure to obtain a new biopsy using a low risk, medically routine procedure for IHC confirmation of FRα positivity
- Tumor positivity for FRα expression as defined by the VENTANA-FOLR1 CDx Assay
- At least 1 lesion that meets the definition of measurable disease by RECIST v1.1 (radiologically measured by the investigator)
- At least 1 but no more than 3 prior systemic lines of anticancer therapy, for whom single agent chemotherapy is appropriate for the next line of treatment
    - Adjuvant ± Neoadjuvant will be considered as one line of therapy

- Maintenance therapy (e.g., bevacizumab, PARP inhibitors) will be considered as part of the preceding line (i.e., not counted independently)

- Therapy changed due to toxicity in the absence of progression will be considered as part of the same line (i.e., not counted independently)

- Hormonal therapy will be counted as a separate line of therapy unless it was given as maintenance

Key Exclusion Criteria

- Patients with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumors containing any of the above histologies, or low-grade or borderline ovarian tumors

- Patients with primary platinum-refractory disease, defined as those who did not respond to or who progressed within 3 months of front-line (first) exposure to platinum-containing chemotherapy

- Patients with prior wide-field radiotherapy affecting at least 20% of the bone marrow

- Patients with uncontrolled bleeding disorders

- Patients with >Grade 1 peripheral neuropathy

- Patients with active or chronic ocular disorders such as Sjogren's syndrome, Fuchs corneal dystrophy (requiring treatment), history of corneal transplantation, active herpetic keratitis, active ocular conditions requiring on-going treatment/monitoring such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, macular degeneration, presence of papilledema, and /or monocular vision

- Serious concurrent illness or clinically-relevant active infection, clinically-significant cardiac disease, history of cirrhotic liver disease (Child-Pugh Class B or C)

- History of hemorrhagic or ischemic stroke within six months prior to randomization

Comparator Arm

The investigator's choice chemotherapy arm consisting of paclitaxel, PLD, or topotecan was selected as the comparator arm, as these drugs are the most commonly used standard of care agents in the setting of PROC. Upwards of 67% of US patients with PROC are treated with single-agent chemotherapy (Ipsos Oncology Monitor 2019) such as Pac, PLD, or Topo. In the comparator arm of Study 0403, investigators chose PLD for 46% (54 out of 118 patients) of the patients enrolled, weekly Pac for 31% (37 out of 118 patients), and Topo for 23% (27 out of 118 patients).

FDA sent Preliminary Comments to ImmunoGen, Inc. on September 26, 2019.

2. DISCUSSION

Clinical Questions

1. Does FDA agree that PFS, as assessed by the investigator, may serve as the primary efficacy endpoint in the Phase 3 Study 0416 for patients with FRα-positive platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received at least one but no more than three prior systemic treatment regimens?

   FDA Response: Yes, PFS as assessed by the investigator may serve as the primary efficacy endpoint in the Phase 3 Study 0416. We recommend that you consider OS as a co-primary endpoint considering the results of your prior study and patient population. We note your targeted improvement in 1.5 months for PFS may not be clinically meaningful or interpretable with your 1.5-month imaging interval.

   Meeting Discussion: None.

2. Does FDA agree with BICR-assessed PFS as a sensitivity analysis in support of the primary endpoint?

   FDA Response: Yes.

   Meeting Discussion: None.

3. Does FDA agree that the key inclusion and exclusion criteria listed in Section 3.1.1.3 are appropriate for Study 0416?

   FDA Response: For inclusion criteria of patients with "*progression on or after the most recent line of therapy, either radiographically or by Ca125,"* only radiographic progression should be an eligibility criterion. Progression by Ca125 is not considered interpretable from a regulatory

standpoint. If you include patients who have not had prior bevacizumab, patients randomized to the control arm should receive bevacizumab plus single agent chemotherapy. If you choose to keep your current comparator choices without bevacizumab, at least half of the patients should have received prior bevacizumab in order to be relevant to the US population. The remaining key inclusion and exclusion criteria appear reasonable.

Meeting Discussion: The FDA recommended that if the sponsor chooses to include patients who have progressed by CA125 increase alone in the eligibility criteria, these patients should be eligible only if they meet GCIG criteria for CA125 progression. See Meeting Discussion for Question 4.

4. Does FDA agree with the choice of the comparator arm (Investigator's Choice (IC) chemotherapy) in Study 0416?

FDA Response: See response to Question 3.

Meeting Discussion: The FDA stated that the study population should be generalizable to the US population including exposure to prior bevacizumab. The sponsor's proposal to include patients for whom single agent therapy is appropriate is reasonable. Since the sponsor expects that a large fraction of the population will have had prior bevacizumab, the proposed comparator arm is appropriate.

Statistical Questions

5. Does FDA agree with the draft statistical analysis plan (SAP) for Study 0416?

FDA Response: The draft SAP appears acceptable. You should submit a finalized SAP and protocol to the agency prior to initiating the study. See also response to Question 1.

Meeting Discussion: None.

6. Specifically, does FDA agree with the proposed methods of analysis for the primary endpoint (INV-assessed PFS)?

FDA Response: Yes.

Meeting Discussion: None.

7. Specifically, does FDA agree with the proposed methods of analysis for the key secondary endpoints?

   FDA Response: See responses to Questions 9 and 10 for PRO endpoints.

   Meeting Discussion: None.

8. Does FDA agree with the methodology to establish overall type I error rate in the presence of an interim futility analysis?

   FDA Response: Yes, this appears acceptable.

   Meeting Discussion: None.

Patient Reported Outcomes Questions

9. Does FDA agree [redacted] (b) (4)

   FDA Response: There is insufficient information to fully interpret the data submitted on the proposed [redacted] (b) (4) due to the following reasons:

(b) (4)

See Additional Comments regarding what data to provide for the (b) (4) analyses.

(b) (4)

(b) (4)

Meeting Discussion: None.

10. Does FDA agree (b) (4)

FDA Response: We generally recommend (b) (4)

(b) (4)

Meeting Discussion: None.

CDRH Question

11. Does FDA concur that the use of the PS2+ scoring method for FRα expression represents an acceptable approach for patient selection in the proposed Study 0416?

FDA Response: Yes, provided the device is locked down prior to use for this trial.

Meeting Discussion: None.

Clinical Questions

12. With the new information described in this Briefing Document, might FDA reconsider its position on the use of single-arm data (with ORR as a surrogate endpoint), utilizing the PS2+ scoring method to select FRα-high expressing patients in support of accelerated approval?

    FDA Response: No. Post-hoc analyses of data from 0403 are not sufficient to support those results for accelerated approval using single-arm ORR data. Your diagnostic device should be analytically validated and locked down prior to analyzing any data from your trial(s).

    Meeting Discussion: The sponsor's proposal to conduct a new single-arm study in patients with PROC could support a regulatory action provided that the ORR and DOR surpass those of the best available therapy at the time of action. In such a study the patient population should have had treatment with prior bevacizumab or the results will be compared to ORR/DOR from bevacizumab plus chemotherapy. Inclusion of patients who are ineligible for bevacizumab should be a minority and criteria should be clearly prespecified and recorded by investigators. These criteria should be discussed with the agency prior to initiating the study. The confirmatory study should be fully accrued prior to any regulatory action.

    An alternative option could be to conduct the randomized trial with a coprimary endpoint of ORR. This would require necessary measures to maintain trial integrity. If the sponsor chooses this option, another meeting should be requested to discuss a more in-depth study design.

13. If FDA agrees that an accelerated approval may be an option, it is our intention to conduct a formal reread of Study 0403 tumor tissue slides based on the PS2+ scoring method. Would FDA comment on the acceptability of the diagnostic protocol synopsis described in Appendix 3 to support this potential path?

    FDA Response: See Response to Question 12.

    Meeting Discussion: None.

14. Does FDA agree that Study 0416, like the previous Phase 3 Study 0403, is a non-significant risk (NSR) study, and that an IDE is not required for the CDx used to select patients for the trial? If yes, may ImmunoGen submit an amendment to the IND that formally requests the NSR determination per FDA Guidance on the streamlined submission process for study risk determination for investigational diagnostics in oncology trials?

FDA Response: We have determined that the use of the investigational in vitro diagnostic (IVD) device (VENTANA FOLR1 (FOLR1-2.1) CDx Assay) in Study 0416 does not present a significant risk because it does not meet the definition of a significant risk (SR) device under § 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812). You should ensure that nonsignificant risk (NSR) procedures are used in obtaining any biopsies taken for testing with the investigational IVD.

An IDE application is not required to be submitted to or approved by us. However, use of the investigational IVD in your proposed clinical investigation being conducted in the United States is subject to the abbreviated requirements described in § 812.2(b) of the IDE regulation.

No additional formal submission for study risk determination (SR/NSR) is required.

Meeting Discussion: None.

Additional Comments:

Clinical Outcome Assessments

Comments regarding clinical trial design

(b) (4)

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Meeting Discussion: None.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

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

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric

labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

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

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

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

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

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

Formal Meetings Between the FDA and Sponsors or Applicants[3] to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[4]

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.[5]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[6] as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards.

Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[7] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

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[3] See the guidance for industry *"Formal Meetings Between the FDA and Sponsors or Applicants."*
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[5] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[6] https://www.fda.gov/media/88173/download
[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

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

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[8] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[9] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[10] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[11]

[8] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[9] https://www.fda.gov/media/88173/download
[10] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[11] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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[12] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[13]

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[14]

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

[12] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[13] https://www.fda.gov/media/109533/download
[14] https://www.fda.gov/media/85061/download

following information:

(1) Study phase

(2) Statement of whether the study is intended to support marketing and/or labeling changes

(3) Study objectives (e.g., dose finding)

(4) Population

(5) A brief description of the study design (e.g., placebo or active controlled)

(6) Specific concerns for which you anticipate the Division will have comments

(7) For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
- Other significant changes
- Proposed implementation date

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

UNITED STATES PATIENT POPULATION

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

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

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[15]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[16]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor attachments

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[15] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[16] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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

/s/

AMY R TILLEY
10/01/2019 03:41:01 PM

SANJEEVE BALASUBRAMANIAM
10/03/2019 07:41:09 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111915

MEETING MINUTES

ImmunoGen, Inc.
Attention: Theresa Wingrove, PhD
Vice President, Regulatory Affairs
830 Winter Street
Waltham, MA 02451

Dear Dr. Wingrove:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for mirvetuximab soravtansine (IMGN853).

We also refer to the meeting between representatives of your firm and the FDA on July 27, 2016. The purpose of the meeting was to reach agreement on the key elements of proposed Study 0403 that will be used to support the marketing application for IMGN853 in platinum resistant epithelial ovarian 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, contact Tracy Cutler, Regulatory Health Project Manager at (301) 796-9608 or Tracy.Cutler@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tracy L. Cutler, MPH, CCRP, CIP
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-Phase 3
Meeting Date and Time:	July 27, 2016; 1:00 pm – 2:00 pm
Meeting Location:	White Oak, Building 22, Room 1309
Application Number:	IND 111915
Product Name:	Mirvetuximab soravtansine (IMGN853)
Indication:	For use in patients with folate receptor alpha (FRα)-positive platinum-resistant epithelial ovarian cancer (EOC), primary peritoneal cancer or fallopian tube cancer who received at least one but no more than three prior systemic treatment regimens.
Sponsor/Applicant Name:	ImmunoGen, Inc.
Meeting Chair:	Laleh Amiri-Kordestani, MD
Meeting Recorder:	Tracy Cutler, MPH

FDA ATTENDEES

Geoffrey Kim, MD, Director, DOP1
Amna Ibrahim MD, Deputy Director, DOP1
Laleh Amiri-Kordestani, MD, Acting Clinical Team Leader, DOP1
Genevieve Schechter, MD, Clinical Reviewer, DOP1
Amanda Walker, MD, Clinical Reviewer, DOP1
Todd Palmby, PhD, Pharmacology/Toxicology Team Leader, DHOT
C.J. George Chang, DVM, MS, PhD, Pharmacology/Toxicology Reviewer, DHOT
Eric Hales, PhD, Product Quality Reviewer, OBP/DMA
Pengfei Song, PhD, Clinical Pharmacology Team Leader, DCPV
Jinzhong Liu, PhD, Clinical Pharmacology Reviewer, DCPV
Shenghui Tang, PhD, Biostatistics Team Leader, DBV
Laura Fernandes, PhD, Biostatistics Reviewer, DBV
Kristen Goldberg, Project Manager, OHOP
Tracy Cutler, MPH, Regulatory Health Project Manager, DOP1

SPONSOR ATTENDEES

Anna Berkenblit, MD, MMSc, Vice President, Chief Medical Officer
Ramola Bhandarkar, MS, Associate Director, Regulatory Affairs
Monette Cotreau, PhD, Executive Director, Clinical Pharmacology
Charles Morris, MB ChB MRCP (UK), Executive Vice President & Chief Development Officer

Rodrigo Ruiz-Soto, MD, Senior Medical Director
Joe Wang, PhD, Director, Biostatistics
Theresa Wingrove, PhD, Vice President, Regulatory Affairs

1.0 BACKGROUND

Mirvetuximab soravtansine (IMGN853) is an anti-folate receptor alpha (FRα) humanized monoclonal immunoglobulin G1 (IgG1) antibody that is conjugated to DM4 (a maytansinoid) by a hindered disulfide containing linker, sulfo-SPDB. The target, FRα, is a glycosylphosphatidylinositol-anchored cell surface protein encoded by the folate receptor 1 (FOLR1) gene. The following table summarized the ongoing clinical trials.

Table 2: Outline of All Trials with Mirvetuximab Soravtansine

Protocol No	Ph	Country CTA/IND Approvals	Study Title	Study Design	Study Population	No. of Patients as of 29APR16	FPFV	Study Status
0401	1	USA, Canada	FIH Study in Adults with Ovarian & other FRα+Solid Tumors	Open Label, Non-randomized	Adult Patients with R/R FRα+Solid Tumors	188	09 July 2012	Ongoing
(b) (4)								
0403 (Amend-ment 04 Approved in US, UK and Spain)	3	USA, UK, Spain	FORWARDI: Randomized, Open Label Phase 3 Study IMGN853 vs IC Agents (b) (4)	Open Label, Randomized Study IMGN853 vs the IC Agents (Pac, Topo, PLD)	Advanced EOC, Primary Peritoneal Cancer or Fallopian Tube Cancer.	Stage 1: 4 US patients, closed Stage 2 Amendment pending Stage 2: 0	03 Mar 2016	Ongoing

PLD: Pegylated Liposomal Doxorubicin
CTA: Clinical Trial Application NDA: New Drug Application R/R: Relapsed/Refractory
FPFV: First Patient First Visit

The first-in-human (FIH) study (Study 0401) results indicate mirvetuximab soravtansine is active in platinum-resistant ovarian cancer (OC) with a confirmed overall response rate (ORR) of 26% (1 CR and 11 PRs) for all patients (n=46) enrolled in the Ovarian Cancer Expansion cohort. For patients who had received 1-3 prior lines of therapy (regardless of FRα expression; n=23), the ORR was 39%; ORR was 44% (95% CI: 20%, 70%) in the subset of patients (n=16) with 1-3 prior therapies and medium/high FRα (≥50%) expression. The median PFS for the overall population was 4.8 months and 6.7 (95% CI: 3.9, 11) months in patients who had received 1- 3 prior therapies (Expansion Cohort 1).

As of January 31, 2016, 176 patients have been treated with IMGN853. At least one treatment-emergent adverse event (TEAE) was reported by 171 patients (97%). Treatment-emergent adverse events of Grade 1 or 2 were most common (100 patients, 57%), 58 patients (33%) reported Grade 3 TEAEs, eight patients (5%) reported Grade 4 and five patients (3%) experienced a Grade 5 TEAE.

The most common TEAEs, reported in ≥20% of patients included diarrhea (75 patients, 43%); nausea (68 patients, 39%); fatigue (65 patients, 37%); blurred vision (49 patients, 28%); headache (44 patients, 25%); vomiting (43 patients, 24%); neuropathy peripheral (42 patients, 24%); aspartate aminotransferase (AST) increased (40 patients, 23%); and abdominal pain (38 patients, 22%). Two adverse events of concern are interstitial pneumonitis and ocular toxicity. Almost 60% of patients on Study 0401 developed treatment-emergent eye disorders mild or moderate in severity. Most commonly reported eye disorder was blurred vision (46%) (Grade 1 -20%; Grade 2 - 24%). Other eye disorders included mild to moderate keratopathy (26%) and dry eye (15%). The occurrence of the TEAEs of diarrhea and eye disorders was more frequent in patients who had received more therapies prior to enrollment. The frequency of eye disorders has decreased after April 2015, compared to prior period probably due to the use of preservative-free lubricating eye drops, use of baby shampoo/soft cloth to clean eyes, warm compresses, use of UVA/UVB sunglasses, and avoidance of contact lenses. Currently the use of prophylactic corticosteroid eye drops is being explored in 40 patients (Cohort 5, Study 0401).

Two other clinical trials are being conducted. (b) (4)

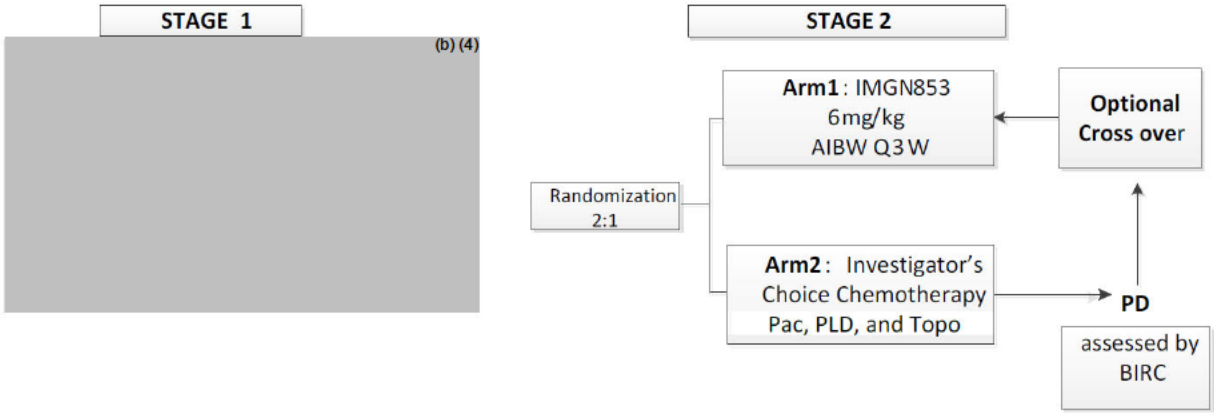
Study 0403 was originally designed with two stages. (b) (4)

However after discovering that the rate of ocular toxicity (blurred vision) was diminished to 35%, Stage I was abandoned. The Sponsor has revised the Study 403 protocol as a pivotal trial in which IGMN853 6 mg/kg AIBW q 3 weeks will be studied.

Revised Study 0403 is to be a 333 patient open label phase 3 pivotal trial in FRα positive platinum- resistant EOC patients with measurable disease who have received 1-3 prior lines of chemotherapy randomized 2:1 to IMGN853 6 mg/kg q 3 weeks or investigators choice (IC) of: 1) paclitaxel 80 mg/m^2 as an one hours IV infusion days 1, 8, 15 q 4 weeks, or 2) topotecan 4 mg/m^2 as a 30 minute infusion q 4 weeks or topotecan 1.25 mg/m^2 q 3 weeks as a 30 minute infusion; or, PLD 40 mg/m^2 as an IV infusion every four week. The co-primary endpoint is progression-free survival (PFS) confirmed by a blinded independent review committee (BIRC) in the ITT population and in the FRα high (≥75% of cells positive for FRα) population. Secondary endpoints include comparison of 1) the safety and tolerability of IMGN853 with that of selected standard of care chemotherapy, 2) the objective response rate (ORR), overall survival (OS), and duration of response (DOR) of patients randomized to IMGN853 or selected standard of care chemotherapy by BIRC assessments primarily and by investigator assessments secondarily, 3) progression free survival as assessed by the investigator, 4) evaluation of the pharmacokinetics (PK) of IMGN853, 5) assessment of the immunogenicity of IMGN853 (Anti-drug antibodies or ADA), and 6) assessment of the quality of life using the EORTC

QLQ/OV28 and EQ-5D-5L Questionnaire. Primary endpoints that will be evaluated include PFS in the ITT and in the FRα high group. Secondary endpoints include TEAES, and clinically significant ≥Grade 3 changes in laboratory tests, ORR using RECIST 1.1, GCIG CA-125 clinical response rate, time to event endpoints including PFS<DOR, and OS; immunogenicity using ADA, and QoL Multiple exploratory endpoints are also included. Tumor assessments, including radiological assessments by computerized tomography (CT) or magnetic resonance imaging (MRI) scans, will be performed at screening and subsequently every six weeks for the first 36 weeks then every twelve weeks until PD per RECIST 1.1, death or the initiation of subsequent anti-cancer therapy, whichever occurs first. All patients will be followed every three months (± 2 weeks) for survival until death, lost to follow-up or withdrawal of consent for survival. Crossover at time of BIRC confirmed progression will be allowed.

Study Schema:



Abbreviations: Pac: paclitaxel; PLD: pegylated liposomal doxorubicin; Topo: topotecan; BIRC: Blinded Independent Review Committee

With a median PFS for the IC arm estimated at 3.5 months, for the IMGN arm of 6.0 months, with exponential distribution, and a 2:1 ratio of FRα high to FRα, and a censoring rate of 20% a sample size of approximately 333 patients enrolled over 21 months is needed using a 2:1 randomization. Patients will be stratified by number of prior lines (1 or 2 vs. 3), FRα levels (≥75% tumor staining at ≥2+ intensity vs. ≥50% and <75% tumor staining at >2+ intensity) and IC chemotherapy (paclitaxel, PLD or topotecan). (b) (4)

Safety information would be available on ~ 360 patients treated with IMGN853 alone or in combination at time of the BLA submission.

The purpose of this meeting is to reach agreement on the key elements of the design of Study 0403 so that this clinical trial can provide definitive evidence of safety and efficacy to support

the regular approval of mirvetuximab soravtansine (IMGN853). Secondary purpose is to reach agreement on the nonclinical, clinical pharmacology, and CMC analytical comparability strategy.
FDA sent Preliminary Comments to ImmunoGen, Inc., on July 22, 2016.

2.0 DISCUSSION

2.1 Clinical

Question 1: Does the Agency agree that Progression Free Survival (PFS) may serve as the primary efficacy endpoint in support of the BLA in patients with folate receptor alpha (FRα)-positive platinum-resistant epithelial ovarian cancer (EOC), primary peritoneal cancer or fallopian tube cancer who received at least one but no more than three prior systemic treatment regimens?

FDA Response: Yes, use of PFS is acceptable in this platinum resistant population. Consideration of PFS as the primary endpoint for demonstration of efficacy for approval of drug products is based on the magnitude of the effect and the risk-benefit profile of the drug product. You should be aware that PFS is subject to ascertainment bias and the results of the analysis may be influenced by any imbalance in assessment dates, as tumor assessments will be performed every 6 weeks for both arms, or missing data between treatment arms. Also note that a statistically significant difference in PFS may not necessarily demonstrate a clinically meaningful difference.

Please adjust the type I error rate for multiple secondary endpoints (b) (4) **Secondary endpoints analyses are considered supportive only if the primary analysis is positive.** (b) (4) **We recommend OS as a key secondary endpoint.**

Sponsor Response: (b) (4)

(b) (4)

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(b) (4)

FDA Follow-Up Response: (b) (4)

Due to your proposal (b) (4) **DOP1 will need to provide written comments after consultation with the COA group and will also provide written advice** (b) (4)

Meeting Discussion: **No discussion took place during the meeting.**

Question 2: Does the Agency agree with the proposed analysis method of the primary endpoint, PFS, in all randomized patients (Intent-to-Treat, or ITT) and FRα high expression subgroup?

FDA Response: **Discuss your rationale for testing the hypothesis in the FRα high subgroup prior to testing in the ITT population which includes intermediate and high FRα expressing ovarian cancers, as the response rates are nearly identical in these populations. With your current design, the efficacy results may be driven by the FRα high subgroup resulting in a statistically significant improvement in the ITT population that is driven by this subgroup with minimal effect in the FRα intermediate subgroup. If this is the case, we anticipate that labeling would reflect this result.**

In addition, the stratified primary analyses should be based on the stratification factors used at randomization.

Sponsor Response: There is no plan to test the hypothesis in the FRα high subgroup prior to testing in the ITT population. The Hochberg procedure, rather than hierarchical testing procedure, will be used to control the overall Type I error (refer to Draft Statistical Analysis Plan page 17 Section VII.K Multiple Comparisons). While the ORRs are currently nearly identical in FRα high and intermediate subgroups, consistent with the drug's mechanism of action the drug's efficacy may be better in the FRα high subgroup with respect to response rate and/or PFS. The Sponsor acknowledges there may be potential labeling implications if the efficacy results are driven by the FRα high subgroup resulting in a statistically significant improvement in PFS in the ITT population with minimal effect in the FRα intermediate subgroup.

The stratified primary analyses will be based on the stratification factors used at randomization.

Meeting Discussion: **The Agency acknowledged the Sponsor's plan for controlling the Type I error and determined it to be acceptable.**

Question 3: Does the Agency agree with the methodology used in the simulation report to establish overall type I error rate in the presence of an interim futility analysis?

FDA Response: **Yes.**

Sponsor Response: **The Sponsor acknowledged the Agency's response.**

Meeting Discussion: **No discussion took place during the meeting.**

Question 4: Does the Agency agree with the crossover allowing patients in the comparator (Investigator's Choice of chemotherapy) arm the option to receive mirvetuximab soravtansine after BIRC confirmation of disease progression?

FDA Response: **Yes, crossover is acceptable for only those patients who have disease progression confirmed by the BIRC prior to crossover. Please ensure that you capture all subsequent therapies for all patients.**

Sponsor Response: Yes, the Sponsor acknowledged the Agency's response that crossover is acceptable for only those patients who have disease progression confirmed by the BIRC prior to crossover. The Sponsor will capture all subsequent therapies for all patients.

Meeting Discussion: **No discussion took place during the meeting.**

Question 5: Only patients whose tumor samples are FRα positive [≥50% tumor staining at ≥2+ intensity] by the Ventana Medical Systems Inc. (VMSI) FOLR1 2.1 CDx Immunohistochemistry Assay will be enrolled in Study 0403. Does the Agency agree with the Sponsor's choice to restrict study eligibility to those patients whose tumors are FRα positive by the Ventana assay?

FDA Response: Yes, it is acceptable to study platinum-resistant ovarian cancer patients with FRα expression ≥50%. Include a justification in the protocol for excluding patients with FRα negative or <50% staining.

Sponsor Response: A justification for excluding patients with FRα negative or <50% staining, consistent with the information presented in the briefing document, will be included in the protocol.

Meeting Discussion: **No discussion took place during the meeting.**

Question 6: Does the Agency agree with the choice of the comparator arm (Investigator's Choice Chemotherapy Arm) in Study 0403?

FDA Response: Yes.

Sponsor Response: The Sponsor acknowledged the Agency's response.

Meeting Discussion: **No discussion took place during the meeting.**

Question 7: Does the Agency agree that the key inclusion and exclusion criteria listed in Table 5 are appropriate for Study 0403?

FDA Response: Yes. Discuss whether patients will have to be refractory to bevacizumab or progressed on a bevacizumab combination for enrollment on this trial.

Sponsor Response: The Sponsor does not require patients to be enrolled in Study 0403 to be refractory or to have progressed on a bevacizumab combination. In the Study 0401 Cohort 1, approximately 60% (29/46) of patients received bevacizumab as part of a prior line of treatment. Response rates (ORR; 95% CI) were similar in patients who had been exposed to bevacizumab (21% (6/29); 8.0%, 39.7%) and those who have not (35.3% (6/17); 14.2%, 61.7%).

Meeting Discussion: **The Agency agreed with the Sponsor's proposal.**

Question 8: Does the Agency agree that the estimated patient experience is sufficient to adequately characterize the safety profile of mirvetuximab soravtansine to support a BLA for full approval in the proposed indication?

FDA Response: The adequacy of the safety database will be a review issue. In general, a database of >300 patients treated with the investigational product is usually adequate.

Sponsor Response: The Sponsor acknowledged the Agency's response.

Meeting Discussion: **No discussion took place during the meeting.**

2.2 Clinical Pharmacology (Written Response Requested)

Question 9: Does the Agency concur that a separate QT/QTc study is not required for mirvetuximab soravtansine program?

FDA Response: Possibly. Before we can decide whether a separate QT/QTc study is needed, please submit the data, analyses and the cardiac report of your Study 0401 for our review.

Sponsor Response: The Sponsor will submit these data analyses and cardiac report when available. The Sponsor requests clarification regarding the required elements of a cardiac safety report.

FDA Follow-Up Response: The table below lists the report elements. The table as well as the the items listed in the additional comments should be submitted together.

REPORT SECTION	IMPORTANT ELEMENTS
Synopsis	Concise summary of objectives, methods, key results and conclusions
Introduction	• Summary of clinical pharmacology of drug and preclinical/clinical cardiac safety • Description of therapeutic and high clinical exposure scenario
Objectives	Concise statement of cardiac study objectives
Data	• Description of clinical study design, doses and dose administration, subjects, timing PK/ECG measurements • If pooling studies, highlight any differences between studies in subject handling as well as ECG acquisition and measurements
Methods	• Method of QT correction for heart rate • Describe the data analysis plan (by-time analysis, categorical analysis, concentration-QTc analysis)
Results	• Summary of dataset, including subjects, observations, data transformations, missing data and outliers • Graphical exploratory analysis to evaluate model assumptions • Description of model and model development results

	• Description of final model results with GOF plots • Description of model predictions
Discussion	• Explain clinical relevance of results • Justification of the adequacy of the study (dose/exposure range, QTc correction, assay sensitivity …) • If drug prolongs QTc interval, describe patients at increased risk of QTc prolongation based on their intrinsic or extrinsic factors.
Conclusions	Discuss clinical relevance of findings in the context of ICH E14
Appendices	• Modeling analysis plan • Dataset specifications • Model scripts/codes Clinical Pharmacology Table

Please submit the QTc analysis report with the following items when they are ready for our further review:

a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
b. Electronic copy of the study report
c. Electronic or hard copy of the clinical protocol
d. Electronic or hard copy of the Investigator's Brochure
e. Annotated CRF
f. A data definition file which describes the contents of the electronic data sets
g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
j. Narrative summaries and case report forms for any
    i. Deaths
    ii. Serious adverse events
    iii. Episodes of ventricular tachycardia or fibrillation
    iv. Episodes of syncope
    v. Episodes of seizure
    vi. Adverse events resulting in the subject discontinuing from the study
k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com). If you use Holter recording and select 10-second segments to measure, submit either the entire Holter recording or at least the entire analysis windows.

l. A completed Highlights of Clinical Pharmacology Table

Advancing in this field – and possibly reducing the burden of conducting QT studies – depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at www.cardiac-safety.org/library.

If further clarification is needed, please officially send correspondence to the IND and/or contact the Regulatory Health Project Manager.

Question 10: Does the Agency concur that the completed and planned clinical pharmacology studies as outlined are adequate to support the proposed pivotal study and BLA submission?

FDA Response: Yes.

Sponsor Response: The Sponsor acknowledged the Agency's response.

2.3 Nonclinical Toxicology (Written Response Requested)

Question 11: The 3-month chronic toxicity study results are provided in the Briefing Package. Does the Agency agree that the 3-month toxicity study results are sufficient to support initiation of the phase 3 study (Study 0403) as well as the BLA?

FDA Response: Yes. The preliminary 3-month toxicity study data provided in your briefing package appear to be appropriate to support the initiation of your phase 3 clinical trial. A final determination on whether the safety of your drug product has been adequately assessed will be made after review of your BLA submission.

Sponsor Response: The Sponsor acknowledged the Agency's response.

Question 12: Does the Agency agree that additional toxicology studies of DM4 are not required for phase 3 and BLA?

FDA Response: Yes. The toxicology studies of DM4 described in your briefing package appear to be sufficient to support the initiation of your phase 3 clinical trial and BLA submission. A final determination on the adequacy of the data will be made after review of your BLA submission.

Sponsor Response: The Sponsor acknowledged the Agency's response.

Question 13: Based on our interpretation of the ICH S10 guidance, does FDA agree that a phototoxicity assessment of the conjugate mirvetuximab soravtansine is not required?

FDA Response: Yes.

Sponsor Response: The Sponsor acknowledged the Agency's response.

2.4 CMC (Written Response Requested)

Question 14: Study 0403 will [redacted] (b) (4) Does the Agency agree with the proposed test panels for the antibody intermediate, the conjugate drug substance and drug product for the assessment of analytical comparability?

FDA Response: The proposed test panels for the antibody intermediate, conjugated drug substance and drug product appear reasonable for the assessment of analytical comparability. However, your pre-meeting package indicates that the comparability assessments will be performed using plans that have not yet been finalized. The adequacy of the comparability assessments, including the comparability acceptance criteria and data, will be determined after review of the information submitted.

Regarding Table 14 (Manufacturing process changes [redacted] (b) (4)

Sponsor Response: The Sponsor acknowledged the Agency's response.

Question 15: ImmunoGen will submit the comparability data to the IND in early 2017 and at that time will request a Type B CMC meeting to review the comparability data, as well as the overall CMC commercialization strategy for mirvetuximab soravtansine. Assuming analytical comparability is demonstrated [redacted] (b) (4) does the Agency agree [redacted] (b) (4) without any additional study?

FDA Response: If analytical comparability is demonstrated, then it would be generally acceptable [redacted] (b) (4) **without the need for additional studies; however the need for any additional assessments will be determined at the time of review of the data submitted.**

We acknowledge your statements [redacted] (b) (4) **as appropriate.**

Be aware that, if [redacted] (b) (4) **not found to be comparable, it could jeopardize the interpretation of clinical data from Study 0403.**

We note your intent to initiate Study 0403 with clinical material manufactured [redacted] (b) (4)

(b) (4) **over the course of the study. Submit a plan for tracking the lot number and manufacturing process used for each patient administration.**

Provide a detailed description of the methodology and plans for validation of the assays that will be used for the detection of anti-drug antibodies (ADA). The qualification results should include data demonstrating that the assay is specific, sensitive and reproducible, and should include information on the sensitivity of the assay to product interference. The validated assay should be capable of sensitively detecting ADA responses in the presence of IMGN853 drug product levels that are expected to be present at the time of patient sampling. Information on the expected product levels that will be present in patient samples should be included to support use of the assay. An assay should also be developed that is able to delineate neutralizing ADA responses. Until an assay (s) has been developed and validated, patients samples should be banked under appropriate storage conditions.

Sponsor Response: The Sponsor acknowledged the Agency's response with regards to comparability. We will submit the plan for tracking drugs lots and the manufacturing process used for each patient administration.

In addition, the Sponsor acknowledged the Agency's recommendations on the ADA assay. Until a neutralizing ADA assay has been developed, the patient samples will be banked.

Additional Comments - Clinical

1. **Has the sample size been adjusted to allow for a 10-20% drop-out rate?**

   Sponsor Response: Yes.

   Meeting Discussion: **No discussion took place during the meeting.**

2. **Confirm that the Investigator choice of chemotherapy will be made prior to randomization and include information about the choice of chemotherapy to be made prior to randomization. If a patient declines the Investigator choice after randomization and prior to treatment how will this be handled?**

   Sponsor Response: The investigator will decide the choice of chemotherapy and discuss the same with the patient prior to randomization. The IRT/IVRS system from Y-PRIME includes a field for the IC agent chosen, which will be completed by the site before randomizing the patient.

   If a patient declines the investigator choice after randomization and prior to treatment, the patient will not be screened and randomized again, but will remain in the ITT population for efficacy analysis.

   Trends in the dropout rate after randomization and prior to treatment will be assessed as part of the monitoring plan and independent data monitoring committee (IDMC) review.

Meeting Discussion: **No discussion took place during the meeting.**

3. **The following concerns with regard to management of IMGN853 related toxicity were identified on review of the protocol:**

   a. **For IMGN853 Grade 2 or 3 thrombocytopenia, retreatment is allowed when platelet count is ≥80,000/µl. For the IC choices, platelet count must ≥100,000/µl for retreatment. Revise Table 2 to state the retreatment with IGMN853 is not allowed until the platelet count ≥100,000/µl (Grade 1).**

      Sponsor Response: Table 2 will be revised to state that retreatment with IMGN853 is not allowed until the platelet count is ≥100,000/µl (Grade 1).

      Meeting Discussion: **No discussion took place during the meeting.**

   b. **Provide evidence that retreatment of patients who have experienced Grade 3 pneumonitis secondary to IMGN853 that has resolved is safe or revise Table 6 to state that patients who develop Grade 3 pneumonitis must be removed from protocol.**

      Sponsor Response: There was one Grade 4 and no Grade 3 pneumonitis in Study 0401. The patient with Grade 4 pneumonitis was not retreated with IMGN853. Patients who develop Grade 3 pneumonitis will be permanently discontinued from Study 0403. Table 6 in the protocol will be revised.

      Meeting Discussion: **No discussion took place during the meeting.**

4. **In Section 5.6.1.6.1 of the protocol in the management of ocular toxicity the following is noted:**

   a. **The use of punctal plugs is recommended. However this information is not included in the meeting background package. How many patients have required punctal plugs? Have any complications such as infection been observed?**

      Sponsor Response: Two patients underwent punctal plugs placement among all those enrolled in the dose escalation and expansion cohorts of the phase 1 Study 0401 (n=184). There were no reported infections in either case. One punctal plug placement was complicated by Grade 1 excessive lacrimation that subsequently resolved without sequelae. There were no other reported complications.

      Meeting Discussion: **No discussion took place during the meeting.**

   b. **In Section 5.6.1.6.1 use of preservative-free lubrication (artificial tears) is not mentioned although its use is mentioned in the background information. Explain why punctal plugs would be used prior to lubrication.**

Sponsor Response: The use of lubricating artificial tears is required for all patients treated with IMGN853 in the FORWARD I trial and this requirement is highlighted in Section 5.9.1. For additional clarification, Section 5.6.1.6.1 has been modified to also include this requirement. For patients with persistent dry eyes despite the measures outlined in Section 5.6.1.6.1 (protective UVA/UVB sunglasses, use of soft soap, warm compresses at bedtime and the use of artificial tears), punctal plugs will be an optional intervention as an adjunct to - but not in place of - any of the above measures.

Section 5.9.2 will be modified to reflect the required use of prophylactic steroid eye drops in patients treated with IMGN853. A subset of patients treated in the phase 1 Study 0401 (cohort 5, steroid eye drops) has received prophylactic steroid eye drops as a required intervention (Prednisolone 1%). While data are available on only a small number of patients (n=18), preliminary analysis demonstrates a reduction of ocular adverse events in this subgroup, with 3/18 patients developing blurred vision (17%, 2/18 Grade 1 and 1/18 Grade 2). This rate compares favorably to the ocular AEs observed in Cohorts 1 and 3 (epithelial ovarian cancer patients who received lubricating eye drops) at 38% and 33% respectively.

Meeting Discussion: **No discussion took place during the meeting.**

c. Please plan to discuss Figure 7 and 8 found on pages 88 and 89 of the Briefing Book with respect to AUC and ocular toxicity.

Sponsor Response: The data provided on pages 88 and 89 of the Briefing Document will be discussed in the Investigator's Brochure (IB) and this change will be implemented at the next revision of the IB which will be no later than the annual update of the IB (March 31, 2017). In addition, a brief reference to these finding will be included in the protocol.

Meeting Discussion: **No discussion took place during the meeting.**

5. In Section 5.6.1.10, it states that IMGN853 will be discontinued for cardiac safety. Have any cases of cardiac toxicity related to IMGN853 been identified? If so please describe. If there is a specific potential risk of cardiac safety related to IMGN853 provide information about this risk.

Sponsor Response: Discontinuation for cardiac safety has been part of our standard protocol language. As of April 29, 2016, data cut off 7/184 (4%) patients have presented cardiac TEAEs deemed as possibly related. Hypertension was reported in four patients (Grade 2 in three patients and Grade 1 in one patient), Grade 1 tachycardia was reported in two patients and one patient reported Grade 1 prolonged QTc interval. The Sponsor does not believe there is a related cardiac safety risk.

Meeting Discussion: **No discussion took place during the meeting.**

6. **Discuss your reasons for using Protocol 0403 for the pivotal trial as this protocol had been amended five times. Prior to embarking on use of this protocol as pivotal, revise the protocol to include the amendments as appendices and exclude them from the body of the protocol. In addition please correct the discrepancies that were observed on review of the protocol.**

   Sponsor Response: Protocol 0403 was used because four patients had already been enrolled in Stage 1 and its revision is operationally more efficient than starting a separate pivotal protocol. As per FDA's recommendation, the Sponsor will reorganize the protocol and correct the discrepancies.

   Meeting Discussion: **No discussion took place during the meeting.**

7. **Have you considered** (b) (4) (b) (4)

   Sponsor Response: (b) (4)

   Meeting Discussion: **No discussion took place during the meeting.**

Additional Comments – Patient Reported Outcomes

Patient-Reported Outcome (PRO) and other clinical outcome assessment data will be carefully reviewed as part of the overall benefit-risk assessment of a regulatory submission and should be collected diligently with this in mind. While not regulatory requirements, the following comments are provided to maximize the quality and interpretability of PRO data.

Core Concepts: We recommend collecting and separately analyzing the following patient-reported core concepts:

- **Symptomatic adverse events;**
- **Physical function; and**
- **Disease-related symptoms (where appropriate).**

Additional PRO or functional measures that are important to patients could be considered based on the context of a given clinical trial, although parsimony is advised to minimize patient burden and improve the quality of data collected.

Instrument Selection: Support the PRO instrument(s) you intend to utilize by available data and/or published peer-reviewed literature guided by the principles laid out in the 2009 FDA Guidance for Industry entitled "Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" found at www.fda.gov/downloads/Drugs/Guidances/UCM19328.

In some cases, subscales or subsets of items from existing instruments may be utilized if

prospectively defined and psychometrically evaluated. Early consultation with FDA is strongly recommended regarding selection of appropriate measurement tool(s) for your particular clinical trial. Some suggestions for the measurement of the patient-reported core concepts are provided below:

- **Symptomatic adverse events (AEs): FDA considers the National Cancer Institute's PRO version of the common terminology criteria for adverse events (PRO-CTCAE) found at http://healthcaredelivery.cancer.gov/pro-ctcae/ to be a promising instrument. Provide a rationale for the selection of symptomatic adverse events that will be assessed.**

- **Physical function: We remain open to proposals for new and existing measures of physical function in cancer patients. One option that may be considered is use of the PROMIS® physical function item bank found at http://www.nihpromis.org/measures/measureshome.**

- **Disease-specific symptoms: Where appropriate and feasible, items of interest may include disease-specific symptoms that patients have reported as being important across advanced cancer settings, such as pain, anorexia, and fatigue, either individually, or within a composite "symptom score" with other important disease-specific symptoms (e.g., dyspnea and cough in lung cancer). Because measurement of time to symptom deterioration is challenging, consider enriching for symptomatic patients in the current trial or in a separate trial to measure symptom improvement.**

Trial Design Considerations:

- **Optimize the frequency and timing of assessments. Increased assessments early in therapy can maximize the amount of data available in both the investigational and control arms, particularly for patients who withdraw early.**

- **Prospectively put in place procedures for minimizing missing data, including obtaining PRO data from patients at time of early withdrawal, and include these procedures in the protocol. Reasons for missing PRO data at the overall score- and item-level should be documented and included in the analysis dataset.**

- **Where feasible, analyze measures of disease-related symptoms, symptomatic adverse events, and physical function as distinct concepts.**

- **Provide a pre-specified plan for the analysis of PRO data including the threshold for and interpretation of a meaningful change in score(s).**

- **Carefully record the use of concomitant medications that may affect the interpretation of the concept(s) being measured (e.g., use of concomitant pain medications when measuring pain).**

Labeling Considerations: Inclusion of PRO data in the product label will depend on the adequacy of submitted data, the strengths and limitations of the instrument within the given context of use, and the design and conduct of the trial.

- **If a claim of superiority in a particular PRO concept is sought, pre-specify the PRO hypothesis and test it within the statistical hierarchy of hypothesis testing in the clinical trial. Control the overall type I error rate for testing hypotheses based on primary and all secondary endpoints. Prospectively define the statistical analysis methods, especially procedures for handling missing values. Provide justification in advance for the endpoint definition, including what constitutes meaningful change, for FDA review and comment.**

- **PRO findings without a prospectively specified statistical analysis plan are considered descriptive. FDA will review these data as part of the totality of submitted information, and will evaluate and consider whether inclusion of descriptive PRO data in labeling is appropriate on a case-by-case basis, taking into consideration any factors that may affect the interpretability and reliability of the findings.**

Meeting Discussion: **No discussion took place during the meeting.**

Additional Comments - Clinical Pharmacology

1. **Please submit the following information and data to support the population pharmacokinetic analysis:**

   a. **SAS transport files (*.xpt) for all datasets used for model development and validation.**
   b. **A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**
   c. **Model codes or control streams and output listings for all major model building steps (e.g., base structural model, covariates models, final model, and validation model). Submit these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).**
   d. **A model development decision tree or table which gives an overview of modeling steps.**

   Submit the following for the population analysis reports:

   a. **The standard model diagnostic plots.**
   b. **Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.**
   c. **Model parameter names and units in tables. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1).**
   d. **A summary of the report describing the clinical application of modeling results.**

Reference ID: 5078954

2. **Please submit the following to support the exploratory exposure-response analyses for efficacy and safety:**

   a. **Analyses may include but not be limited to Kaplan-Meier analyses stratified by subgroups of drug exposure, univariate and multivariate logistic and/or Cox regression analyses, whichever are deemed appropriate to support dose selection or dose adjustment.**
   b. **Drug exposure to be used in the analyses may include but not be limited to trough concentration at steady-state, maximum concentration at steady-state, average concentration at steady-state or trough concentration after the first dose. A justification should be provided for the exposure metric that is used for the analysis.**
   c. **Response should at least include primary and key secondary endpoints for efficacy, overall safety events, and adverse events of interest.**

   Include the following in the exposure-response analysis reports:

   a. **A summary of baseline characteristics including but not limited to demographics, disease features and lab measurements, for all patients included in the analysis and subgroups based on drug exposures.**
   b. **Distribution of drug exposure(s) for the full population used in the analysis.**
   c. **A summary table of final model parameters with their corresponding units.**
   d. **Any plots deemed appropriate to support the clinical interpretation of modeling results.**
   e. **A summary describing the clinical application of modeling results.**

3. **Please refer the following popPK, ER relationship, and pharmacometric data and models submission guidelines for more information:**

   a. **http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf**
   b. **http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf**
   c. **http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm**

Meeting Discussion: **No discussion took place during the meeting.**

Reference ID: 5078954

3.0 OTHER IMPORTANT MEETING LANGUAGE

3.1 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.
Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

3.2 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 (cder-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.

3.3 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.

3.4 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.

3.5 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).

3.6 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

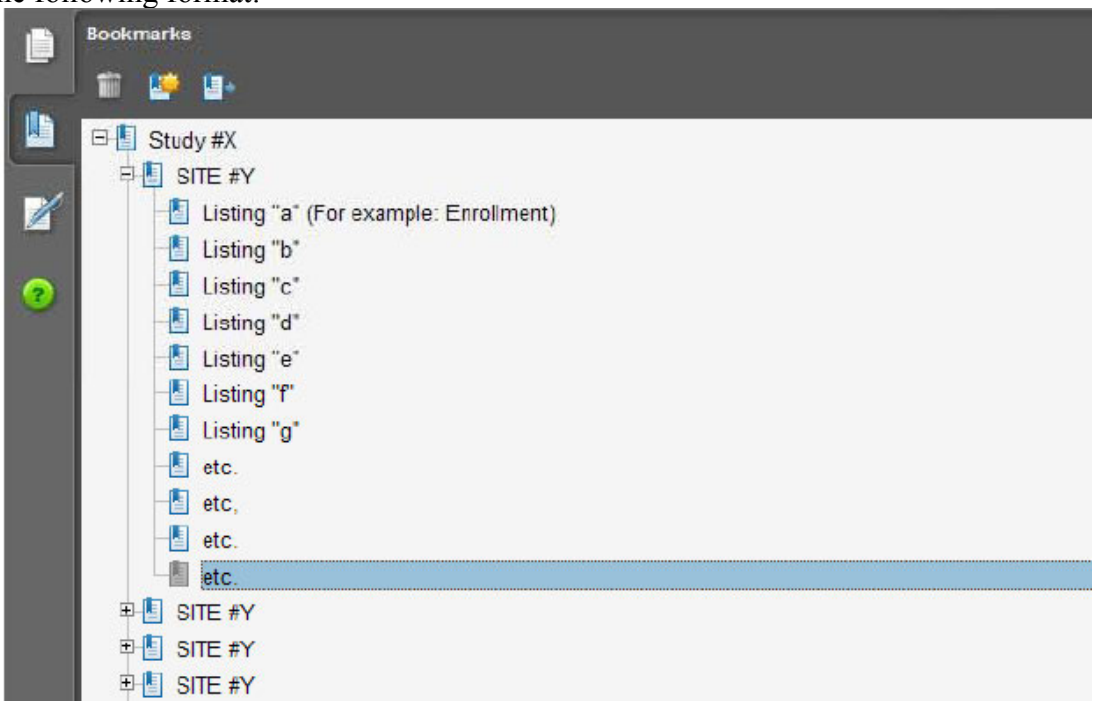
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, 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.

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

3.7 Patient-Focused Endpoints

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable

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

patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

3.8 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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues that required further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts used during the discussion at the meeting.

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

/s/

TRACY L CUTLER
08/09/2016

LALEH AMIRI KORDESTANI
08/09/2016