CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761289Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 125409

MEETING MINUTES

MedImmune, LLC (a wholly owned subsidiary of AstraZeneca)
Attention: Lynn Kerr
Director, US Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Kerr:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Imfinzi (durvalumab) and MEDI1123 (tremelimumab).

We also refer to the teleconference between representatives of your firm and the FDA on December 16, 2021. The purpose of the meeting was to discuss the safety and efficacy data from HIMALAYA and Study D4190C00022 (Study 22) for the treatment of patients with unresectable hepatocellular carcinoma.

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

If you have any questions, please call me at 240-402-6571 or email me at Christina.Leach@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Christina Leach, PharmD
Regulatory Health Project Manager
Division of Regulatory Operations-Oncologic Diseases for DO3
Office of Regulatory Operations
Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER)

[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.

Enclosure:

- Meeting Minutes

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

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: December 16, 2021, 1pm to 2pm, EST
Meeting Location: Zoom videoconference

Application Number: IND 125409

Product Name: Imfinzi (durvalumab) and MEDI1123 (tremelimumab)

Indication: Hepatocellular Carcinoma

Sponsor Name: MedImmune, LLC (a wholly owned subsidiary of AstraZeneca)
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Steven Lemery, MD, MHS; Director, Division of Oncology 3
Meeting Recorder: Christina Leach, PharmD; Regulatory Project Manager, DO3

FDA ATTENDEES

Steven Lemery, MD, MHS	Director, Division of Oncology 3 (DO3)
'Lola Fashoyin-Aje, MD. MPH	Deputy Director, DO3
Paul Kleutz, MD	Supervisory Associate Director, Office of Oncologic Diseases (OOD)
Jamie Brewer, MD	Clinical Team Lead, DO3
Sandra Casak, MD	Clinical Team Lead, DO3
Carmelo Blanquicett, MD, PhD	Clinical Reviewer, DO3
May Tun Saung, MD, PhD	Clinical Reviewer, DO3
Matthew Thompson, PhD, MPH	Supervisor, Division of Hematology, Oncology, Toxicology (DHOT)
Ram Sihag, PhD	Product Quality Team Lead
Xu (Michael) Di	Product Quality Reviewer
Candace Gomez-Broughton, Ph.D.	Microbiology Product Quality, Branch Chief
Madushini Dharmasena, Ph.D.	Microbiology Product Quality, Senior Pharmaceutical Quality Assessor

Jason Moore	Clinical Pharmacology Team Lead
Sriram Subramaniam	Clinical Pharmacology Reviewer
Joyce Cheng	Biostatistics Team Lead, Division of Biostatistics 5 (DBV)
Mengdie Yuan	Biostatistics Reviewer, DBV
Christina Leach, PharmD	Regulatory Project Manager, DO3
Amy Sessums, PharmD	Regulatory Project Manager, DO3

SPONSOR ATTENDEES

Name	**Title**
Karen McCullough, PhD	Vice President, Regulatory Affairs
Elinore Mercer, PhD	Executive Director, Regulatory Affairs
Ken Carlson, MSc	Director, Global Regulatory Lead, Regulatory Affairs
Lynn Kerr, BSc	Director, US Regulatory Lead, Regulatory Affairs
John Kurland, PhD	Global Product Leader
Osama Rahma, MD	Global Clinical Head
Alejandra Negro, PhD	Global Clinical Program Lead
Jason Clark, PhD	Executive Director, Statistics
Michelle Marcovitz, PhD	Statistical Science Associate Director
KyoungSoo Lim, MD	Associate Director, Clinical Pharmacology and Pharmacometrics
Denni Zborowski, MS	Statistical Programming Director
Carrie L. McCoy, MD	Principal Safety Physician

BACKGROUND

Regulatory

On October 20, 2021, MedImmune, LLC (a wholly owned subsidiary of AstraZeneca) (MedImmune), requested a Type B, Pre-BLA meeting with the FDA to discuss the acceptability of safety and efficacy data from HIMALAYA and Study D4190C00022 (Study 22) to support licensure of durvalumab (b) (4) in combination with tremelimumab for the treatment of patients with unresectable hepatocellular carcinoma. FDA granted the meeting on October 25, 2021.

Clinical Pharmacology
As part of the clinical pharmacology package for the proposed BLA submission, Medimmune proposes to submit:

- Updated population pharmacokinetic (PK) analyses using data from HIMALAYA and Study 22 for durvalumab (in addition to data from Study 002, Study 006, Study 010, DETERMINE, BASKET, POSEIDON) and tremelimumab (in addition to data from Study 1108, ATLANTIC, PACIFIC, CASPIAN, POSEIDON).

- Exposure-response analyses for efficacy (e.g., OS and PFS) and safety (e.g., Grade ≥3 treatment-related adverse of event (AE), AEs of special interest (AESI), AEs lead to discontinuation).

- An integrated summary of immunogenicity for tremelimumab in combination with durvalumab in the proposed patient population, summary of anti-drug antibodies (ADA) data against durvalumab and tremelimumab as well as comparison with historical durvalumab ADA, and evaluation of the potential impact of ADA on durvalumab or tremelimumab PK, safety, and efficacy.

The proposed clinical pharmacology package is in line with MedImmune's earlier overall clinical pharmacology plan that was agreed to by the Agency in the communication dated April 15, 2020.

Clinical
MedImmune has requested this Type B, Pre-sBLA meeting to discuss the acceptability of the efficacy and safety data from HIMALAYA and Study D4190C00022 (Study 22) to support MedImmune's proposed BLA (tremelimumab) and sBLA (durvalumab) submissions for the treatment of patients with unresectable hepatocellular carcinoma (HCC). The proposed dosing regimen is one dose of tremelimumab 300 mg in combination with durvalumab 1500 mg at Cycle 1, followed by durvalumab 1500 mg every 4 weeks as a single agent.

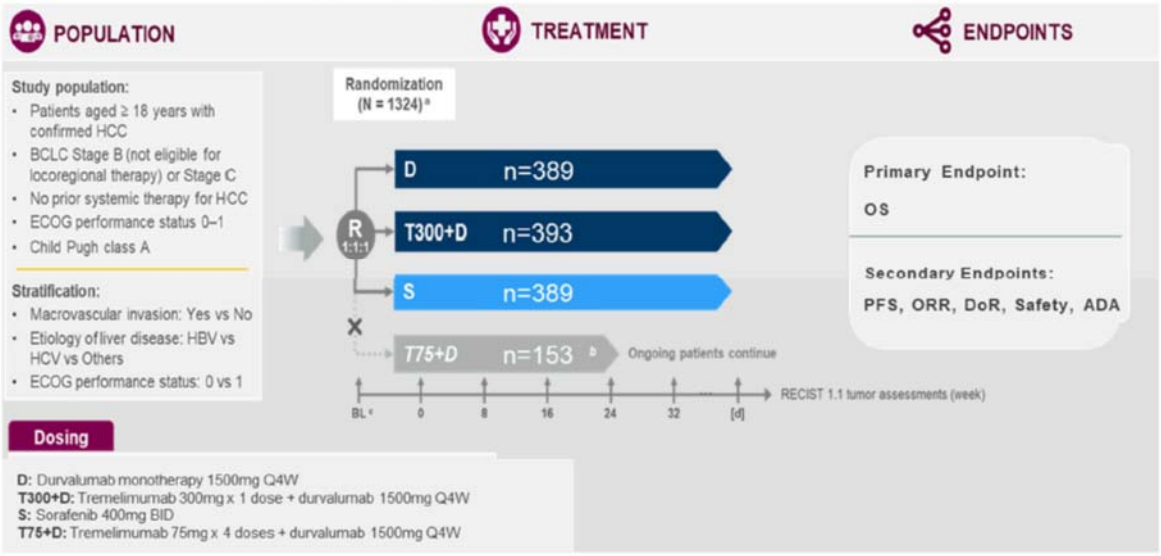
(b) (4)

HIMALAYA is a randomized, open-label, multi-center, global trial evaluating the efficacy and safety of durvalumab monotherapy and durvalumab plus tremelimumab combination versus sorafenib for the treatment of patients with unresectable HCC who are not eligible for locoregional therapy and have not received prior systemic therapy for HCC. The trial enrolled patients with Barcelona Clinic Liver Cancer (BCLC) stage B (not eligible for locoregional therapy) or stage C, Child-Pugh A classification liver disease, and no prior history of any systemic therapy for HCC. Patients were stratified by presence of microvascular invasion (yes vs no), etiology of liver disease (confirmed

Hepatitis B virus (HBV) versus confirmed HCV versus others), and performance status (ECOG 0 versus 1).

The primary endpoint was overall survival (OS) compared between the tremelimumab 300 mg × 1 dose plus durvalumab 1500 mg (T300+D) combination therapy arm versus the sorafenib 400 mg twice daily (S) arm. The key secondary endpoints were a non-inferiority evaluation of OS followed by superiority of the durvalumab 1500 mg (D) monotherapy versus S. The objective response rate (ORR), best overall response (BoR) and duration of response (DoR) according to RECIST 1.1 by blinded independent central review (BICR) were also secondary endpoints for the D versus S arms and T300+D versus S arms.

Figure 1 HIMALAYA: Study Design



Source: MedImmune meeting background package

Enrollment to the tremelimumab 75 mg x 4 doses and durvalumab 1500 mg treatment arm (T75+D) was closed based on an interim analysis conducted in Study 22 demonstrating a lack of added efficacy in the T75+D arm compared to the D arm. Patients in HIMALAYA already randomized and receiving treatment with T75+D could continue assigned study treatment, provided the Investigator and patient agreed it was in the best interest of the patient. Data for the T75+D arm will be provided in the Clinical Study Report for descriptive purposes only.

Patients in all treatment arms were to be treated until confirmed disease progression (Investigator assessment per RECIST 1.1), unacceptable toxicity, or another treatment discontinuation criterion was met. Treatment through progression was allowed at the Investigator's discretion for all arms if patients were considered to still be receiving benefit. Patients receiving the T300+D regimen could be rechallenged once with the

tremelimumab component of the combination at the Investigator's discretion based on specific criteria.

At the final data cut off (27 Aug 2021), a total of 555 events and 573 events had occurred across the T300+D and S arms, and across the D and S arms, respectively, leading to a maturity of 71% for the T300+D versus S comparison and 74% for the D versus S comparison. The top-line efficacy results for the primary analysis of OS for T300+D compared to S and secondary analyses comparing D to S for non-inferiority then superiority are summarized in Table 6 (taken from the meeting background package).

Table 6 **HIMALAYA Primary and Secondary Efficacy Evaluation – Overall Survival: OS12, OS18, OS24, and OS36; PFS; ORR; and DoR (FAS)**

	Number (%) of patients		
	D (N=389)	**T300+D (N=393)**	**S (N=389)**
Death, n (%)	280 (72.0)	262 (66.7)	293 (75.3)
HR [a]	0.86	0.78	NA
95% CI for HR [a]	0.73–1.02	0.66–0.92	NA
95.67% CI for HR [a,b]	0.73–1.03	NA	NA
2-sided p-value [b,c]	0.0674	0.0035	NA
Median OS (months) [95% CI] [d]	16.56 [14.06–19.12]	16.43 [14.16–19.58]	13.77 [12.25–16.13]

	Number (%) of patients		
	D (N=389)	**T300+D (N=393)**	**S (N=389)**
Total PFS events (%) a, d, e	345 (88.7)	335 (85.2)	327 (84.1)
	1.02 [0.88-1.19]	0.90 [0.77-1.05]	NA
	0.7736	0.1625	NA
Median PFS [95% CI] [d]	3.65 [3.19-3.75]	3.78 [3.68-5.32]	4.07 [3.75-5.49]
ORR (%) [95% CI]	17.0 [13.37-21.07]	20.1 [16.25-24.41]	5.1 [3.17-7.83]
Median DoR (months)	16.8	22.3	18.4

Source: MedImmune meeting background package

MedImmune reported that the observed adverse events in the T300+D arm and the D monotherapy arm were consistent with the known safety profiles of tremelimumab and

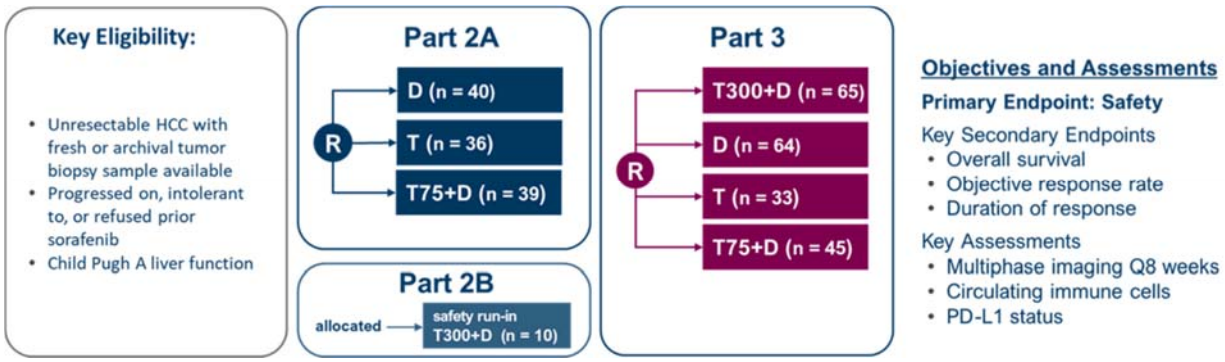
durvalumab, and consistent with the known safety profile of immune checkpoint inhibitor therapy.

Table 9 Adverse Events in Any Category in HIMALAYA (Safety Analysis Set)

	Number (%) of patients[a]		
Patients with:	**D (N = 388)**	**T300+D (N = 388)**	**S (N = 374)**
Any AE	345 (88.9)	378 (97.4)	357 (95.5)
Any AE of CTCAE Grade 3 or 4	144 (37.1)	196 (50.5)	196 (52.4)
Any AE with outcome of death	26 (6.7)	30 (7.7)	27 (7.2)
Any SAE (including events with outcome of death)	115 (29.6)	157 (40.5)	111 (29.7)
Any AE leading to discontinuation of study treatment	32 (8.2)	53 (13.7)	63 (16.8)
Any AE leading to dose delay [c]	95 (24.5)	134 (34.5)	178 (47.6)
Any infusion reaction AE [e]	11 (2.8)	20 (5.2)	2 (0.5)

Adapted from MedImmune meeting background package

Study 22 (D4190C00022)



Study 22 was a phase II, multicenter, open label, multi-part study evaluating the safety, tolerability, and activity of durvalumab monotherapy, tremelimumab monotherapy and durvalumab combined with tremelimumab or bevacizumab in patients with unresectable HCC, progressed or intolerant with sorafenib or another TKI. Data from this trial will be submitted to support the analysis of HIMALAYA.

At the final analysis, median OS was 17.05 months in both the T300+D and T arms compared with 12.91 months in the D arm and 11.30 months in the T75+D arm. The confirmed BICR-ORR according to RECIST 1.1 was 24.0% for patients in the T300+D arm (N=75) compared with 11.5%, 7.2%, and 9.5%, in the D (N=104), T (N=69), and T75+D arms (N=84), respectively.

FDA sent Preliminary Comments to MedImmune on December 14, 2021.

SPONSOR QUESTIONS AND FDA RESPONSES

Clinical

1. Does the Agency agree that the efficacy and safety data for tremelimumab in combination with durvalumab (T300+D) versus sorafenib (S) from the pivotal HIMALAYA study, with supportive data from Study 22, are sufficient to support a tremelimumab BLA and durvalumab sBLA for the proposed indication?

   FDA Response: Whether the data from HIMALAYA is sufficient to support a tremelimumab BLA and durvalumab sBLA for the proposed indication will be a review issue. A major review issue will be whether tremelimumab contributes to the treatment effect when added to durvalumab given the limited differences between the D + T and D arms in major efficacy endpoints observed in the HIMALAYA trial. FDA may consider whether to discuss the application at an Oncology Drug Advisory Committee meeting.

   MedImmune Response: The Sponsor would welcome further discussion on the Agency's perspective on contribution of tremelimumab to the combination. Please also see response to Question 2.

   Discussion during 12/16/21 Teleconference: Refer to discussion under question #2.

2. Does the Agency agree that the totality of the data demonstrate evidence of the contribution of tremelimumab and durvalumab to the T300+D regimen in the proposed patient population?

   FDA Response: Refer to FDA's response to question #1.

   MedImmune Response: The Sponsor looks forward to entering into a dialogue on this topic with the Agency.

   As described in the Briefing Document, the Sponsor's position is that HIMALAYA was a well-designed and executed study providing a robust result that illustrates the benefit of the contribution of tremelimumab in a population reflective of 1L uHCC patients. Consistency of the treatment effect of the addition of tremelimumab was observed in the primary endpoint and was supported by key secondary endpoints. Further, the effect of tremelimumab is consistent with biological rationale of CTLA-4 inhibition and was also demonstrated in Study 22, a key supportive study for this application.

Table 1 below [in response document which is attached] provides a summary of data across both studies that was summarized in the Briefing Document. The Sponsor is providing this again within this document to facilitate discussions with the Agency at the meeting.

Discussion during 12/16/21 Teleconference: FDA reiterated that the contribution of tremelimumab would be a review issue. FDA stated that MedImmune should address the lack of a (nominally) statistically significant effect on OS between tremelimumab plus durvalumab over durvalumab alone noting that the curves separate after approximately two years when fewer patients remained on study. Furthermore, FDA expressed concern that there was not an apparent difference in progression free survival between arms and the response rates were similar.

MedImmune stated that that they believe the data support approval in that the tremelimumab plus durvalumab arm was the arm that had a statistically significant effect versus the sorafenib arm and highlighted the estimated effect on OS at 36 months. MedImmune also believes that the results of Study 22 provides support for their position that tremelimumab contributes to the treatment effect in the combination arm.

Ultimately, FDA stated that this will be considered during the review of the applications and that AZ should address this issue in the applications and during the application orientation meeting if held.

3. Does the Agency agree (b) (4)

FDA Response: (b) (4)

MedImmune Response: The Sponsor acknowledges the Agency's feedback and looks forward to further discussion of this topic at the pre-BLA meeting. (b) (4)

(b) (4)

Discussion during 12/16/21 Teleconference: FDA acknowledged MedImmune's response. FDA also stated that MedImmune should address (in the applications) the constancy assumption with respect to post-progression therapy and address whether there could have been any other study design elements that could have biased the results towards a null effect between arms. MedImmune acknowledged.

Clinical Pharmacology

4. Does the Agency agree that the content of the proposed clinical pharmacology data package, including population pharmacokinetics (PopPK) and exposure response analyses, is acceptable to support the BLA review of tremelimumab in combination with durvalumab?

FDA Response: The proposed clinical pharmacology data package, including population PK, exposure-response analyses, and immunogenicity for durvalumab and tremelimumab, appears reasonable. The acceptability of the proposed data will be a review issue.

Prior to submission of the application, please also refer to the Clinical Pharmacology additional comments (regarding BLA submission plan and content) that were provided in the meeting minutes dated April 15, 2020.

MedImmune Response: The Sponsor confirms that the additional Clinical Pharmacology comments provided in the FDA meeting minutes from 15 April 2020 will be addressed within the dossier content. No further discussion of this topic at the 16 December 2021 meeting is requested.

Discussion during 12/16/21 Teleconference: None

CMC

5. Tremelimumab Drug Substance and Drug Product are manufactured by contract manufacturer (b) (4) and Drug Product is manufactured by contract manufacturer (b) (4) (b) (4) Planning discussions for manufacturing schedules with both contract manufacturers are ongoing for 2022. Would the Agency be willing to coordinate with the Sponsor on the specific timeframes and scope of the Pre-Approval Inspections of these facilities?

FDA Response: The need for facility inspections will be determined upon receipt of the sBLA. The Agency will work with MedImmune as much as possible for inspection planning. The most current manufacturing schedules should be provided to the Agency at the time of submission to facilitate the inspection planning process.

MedImmune Response: The Sponsor confirms that the manufacturing schedules for tremelimumab will be provided to the Agency at the time of the tremelimumab BLA submission. No further discussion of this topic at the 16 December 2021 meeting is requested.

Discussion during 12/16/21 Teleconference: None

Programming

6. Does the Agency agree that the proposed content/format of individual study datasets, pooled datasets, and the planned documentation to support the application reviews for tremelimumab in combination with durvalumab (b) (4) (b) (4) is acceptable?

FDA Response: Based on the information provided in the meeting briefing package, the proposal appears acceptable**;** however, FDA may request additional data analyses or summaries of data during review of the applications.

MedImmune Response: The Sponsor acknowledges this feedback. No further discussion of this topic at the 16 December 2021 meeting is requested.

Discussion during 12/16/21 Teleconference: None

Regulatory

7. Does the Agency agree with the Sponsor's proposal for an Application Orientation Meeting in support of the tremelimumab BLA review to occur shortly after the submission?

FDA Response: FDA agrees that an Application Orientation meeting may be warranted if such a meeting can be scheduled shortly after submission of the applications.

MedImmune Response: The Sponsor wishes to further discuss and clarify the Agency response provided. The Sponsor would like to clarify when the need for an Application Orientation Meeting would be determined and a decision communicated to the Sponsor. Additionally, the Sponsor would like to discuss whether a technical-walkthrough of the application would also be in scope.

Discussion during 12/16/21 Teleconference: FDA stated that an Application Orientation meeting could be helpful to the review teams, especially if the meeting occurs early during the review of the application. FDA recommended that MedImmune notify FDA regarding the timing of the Application submission to facilitate scheduling of the meeting. FDA stated that a technical walkthrough could be scheduled and either held or cancelled pending FDA's determination on whether the meeting would be helpful.

8. Does the Agency agree with the Sponsor's proposal to submit the durvalumab sBLA at the end of the validation period for the tremelimumab BLA to support the proposed T300+D indication? Does the FDA agree with the Sponsor's proposal

for inter-application hyperlinking between the tremelimumab BLA and durvalumab sBLA supporting the T300+D indication and cross-referencing between the sBLA for T300+D [redacted] (b) (4) applications?

FDA Response: FDA is unable to provide a response regarding the submission of the durvalumab sBLAs as it is unclear what is meant by the validation period. To facilitate efficient reviews, the PDUFA dates for each of the applications would optimally be aligned to occur on the same date. The proposal to use hyperlinking between the tremelimumab BLA and durvalumab sBLA is generally acceptable. The sBLA submission [redacted] (b) (4) should contain all necessary data and documents for review.

MedImmune Response: The Sponsor acknowledges the Agency's feedback, no further discussion of this topic at the 16 December 2021 meeting is requested.

Discussion during 12/16/21 Teleconference: None

9. Does the Agency agree with the Sponsor's plan to submit the Assessment Aid supporting the combination indication during the validation period of the tremelimumab BLA?

FDA Response: FDA agrees with the submission of Assessment Aid(s) to support the review of the proposed applications; however, the Assessment Aid(s) should be included in the original application submissions.

MedImmune Response: The Sponsor acknowledges the Agency's feedback, no further discussion of this topic at the 16 December 2021 meeting is requested.

Discussion during 12/16/21 Teleconference: None

10. Given the length of the extensive follow-up period for HIMALAYA and Study 22, does the Agency agree with the Sponsor's proposal to request a waiver for a 90- or 120-day safety update for the T300+D [redacted] (b) (4)

FDA Response: The proposal appears acceptable; however, if at any time MedImmune identifies any serious safety issue that should result in modifications to patient labeling, a safety update should be expeditiously submitted.

MedImmune Response: The Sponsor acknowledges the Agency's feedback, no further discussion of this topic at the 16 December 2021 meeting is requested.

Discussion during 12/16/21 Teleconference: None

11. Does the Agency agree that the magnitude of improvement of overall survival of T300+D versus sorafenib warrant Priority Review Designation given the current unmet medical need of patients with unresectable HCC?

FDA Response: No. A determination for Priority Review designation would not be made solely based on an improvement in effectiveness over sorafenib.

MedImmune Response: The Sponsor acknowledges the Agency's position, no further discussion of this topic at the 16 December 2021 meeting is requested.

Discussion during 12/16/21 Teleconference: None

FDA ADDITIONAL COMMENTS

12. At the time of the pre-BLA meeting, please provide the number of patients enrolled by country.

MedImmune Response: The Sponsor acknowledges this request and will provide the requested information within the HIMALAYA clinical study report.

Discussion during 12/16/21 Teleconference: FDA highlighted potential concerns with the enrollment of patients at clinical trial sites in countries where FDA cannot inspect (especially for reasons other than COVID). FDA recommended that MedImmune address this in the BLA and to the extent possible, ensure that sites can be inspected. MedImmune should also document that the care of patients in such countries was consistent with what would be expected to be applicable to patients in the US.

13. In the BLA submissions, specify how often patients receiving the T300+D regimen were rechallenged (i.e., with the tremelimumab component of the combination) and provide the criteria for each instance. Also clarify if any patient was rechallenged more than once. The submissions should also describe safety in patients who were rechallenged.

MedImmune Response: The Sponsor acknowledges this request and will provide the requested information within the HIMALAYA clinical study report. The Sponsor notes that, per protocol, patients were only allowed to be rechallenged one time with tremelimumab after disease progression. A total of 30 T300+D patients were rechallenged with a second dose of T300. Per the investigators assessment, patients were required to have radiologic progression in the absence of clinically significant symptoms of disease progression, and still able to derive clinical benefit from treatment in the opinion of the investigator. Patients experiencing symptomatic progression or clinically meaningful treatment toxicity were not eligible to rechallenge. The criteria for rechallenge is described in

section 7.2.1.3 of the protocol. Could the Agency please clarify if there are any additional and/or specific analyses that could address this Agency comment?

Discussion during 12/16/21 Teleconference: FDA requested that MedImmune provide the information regarding clinical effects (safety and efficacy) after rechallenge. Upon review of this data, additional analyses may be requested.

MedImmune stated that no new safety signals were identified and will provide the information in the applications.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. MedImmune confirmed that no late components will be submitted to either the original BLA for tremelimumab nor the supplemental BLA for durvalumab.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that at this time there is no need for a REMS.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

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

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain

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

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

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

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

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

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

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

PRESCRIBING INFORMATION

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

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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

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

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[6] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

[6] https://www.fda.gov/media/84223/download
[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[8] https://www.fda.gov/media/85061/download

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

- Assessment Aid[10]

NONPROPRIETARY NAME

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

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

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

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

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

at such time as FDA approves the BLA.

ATTACHMENTS AND HANDOUTS
MedImmune's responses to FDA Preliminary Comments

14 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

CHRISTINA L LEACH
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND125409

MEETING MINUTES

MedImmune, LLC (a wholly owned subsidiary of AstraZeneca)
Attention: Jamie Gillette, MS, RAC
Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

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

We also refer to the meeting between representatives of your firm and the FDA on April 28, 2017. The purpose of the meeting was to discuss and reach agreement on proposed study Protocol D419CC00002 (Study 002), to support the following proposed indications:

- (b) (4)
- durvalumab, in combination with tremelimumab, is indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC) (b) (4) (b) (4)
- tremelimumab, in combination with durvalumab, is indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC) (b) (4) (b) (4)

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

If you have any questions, call me at (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
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:	Type B
Meeting Category:	End-of-Phase 2
Meeting Date and Time:	April 28, 2017; 9:00 AM – 10:00 AM, EST
Meeting Location:	White Oak Building 22, Conference Room 1419
Application Number:	IND 125409
Product Names:	durvalumab tremelimumab
Indication:	(b) (4) [redacted]
Sponsor/Applicant Name:	MedImmune, LLC (a wholly owned subsidiary of AstraZeneca)
Meeting Chair:	Steven Lemery
Meeting Recorder:	Idara Udoh

FDA ATTENDEES
Center for Drug Evaluation and Research (CDER)
Division of Oncology Products 2, Office of New Drugs (OND)
Patricia Keegan, Director
Steven Lemery, Clinical Team Leader
Sandra Casak, Clinical Reviewer
Idara Udoh, Senior Regulatory Health Project Manager

OND Division of Hematology, Oncology, and Toxicology
Whitney Helms, Nonclinical Team Leader

Office of Clinical Pharmacology, Division of Clinical Pharmacology V
Hong Zhao, Clinical Pharmacology Team Leader

Office of Biostatistics, Division of Biometrics V (DBV)
Lisa Rodriguez, Biometrics Team Leader
Umaporn Siangphoe, Biometrics Reviewer

MEDIMMUNE ATTENDEES
Praveen Marapaka, Ph.D., Senior Director, Global Regulatory Affairs
Jamie Gillette, MSc., RAC, Director, Global Regulatory Affairs
Ken Carlsen, MSc., Director, Global Regulatory Affairs
Hesham Abdullah, M.D., Vice President, Oncology, Regulatory Affairs
Joan Buenconsejo, Ph.D., Director and Biometrics Team Leader
Shao-Chun Chang, M.D., Ph.D., Global Clinical Lead
Tony Ho, M.D., Global Medical Lead, Durvalumab Immuno-oncology
Robert Iannone, M.D., Head, Immuno-Oncology
Vijayvel Jayaprakash, MBBS, Ph.D., Medical Scientist, Immuno-Oncology
Lorin Roskos, Ph.D., Vice President, Clinical Pharmacology, Pharmacometrics and DMPK
Jill Walker, Ph.D., Executive Director, Diagnostics

MEETING PURPOSE

On March 1, 2017, MedImmune, LLC ("MedImmune") requested a Type B, End-of-Phase 2 (EOP2) meeting to discuss and reach agreement on proposed study, Protocol D419CC00002 (Study 002), to support the following proposed indications:

- (b) (4)
- durvalumab, in combination with tremelimumab, is indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC) (b) (4)
- tremelimumab, in combination with durvalumab, is indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC) (b) (4) (b) (4)

BACKGROUND

Chemistry, Manufacturing, and Controls (CMC)

Durvalumab is a human monoclonal immunoglobulin G1 kappa (IgG1κ) antibody specific for programmed death ligand 1 (PD-L1) and CD80. The protein has a molecular weight of approximately 149 kDa. The drug substance (DS) is produced in CHO cells. The clinical DS lots are manufactured at (b) (4) scales. The durvalumab drug product (DP) is supplied as a solution in 10 ml clear glass vials closed with an elastomeric stopper and a flip-off cap overseal and stored at 2°C to 8°C. Each vial contains 500mg of active pharmaceutical ingredient (API) at a final concentration of 50mg/ml. The DP is diluted with 0.9% saline or 5% dextrose and administered to patients by IV infusion.

Tremelimumab is a recombinant human monoclonal immunoglobulin G2 kappa (IgG2κ) antibody specific for the human cytotoxic T lymphocyte-associated antigen 4(CTLA-4). The protein has a theoretical molecular mass of 149,145 Da. The clinical DS lots are produced in

(b) (4) NS0 cells at (b) (4) scales. The tremelimumab DP is supplied as a solution in 20ml glass vials with a rubber stopper and aluminum seal and stored at 2°C to 8°C. Each vial contains (b) (4) mg of API at a concentration of 20mg/ml and the DP is administered to patients by IV infusion.

Nonclinical

The pharmacology/toxicology information needed to support a marketing application for durvalumab is currently being reviewed under Biologics Licensing Application (BLA) 761069. MedImmune states that completed studies supporting the clinical use of tremelimumab include Good Laboratory Practice (GLP)-compliant toxicology studies in monkeys of up to 6 months in duration, an embryofetal development study in monkeys, and pharmacology studies demonstrating its mechanism of action and activity.

Clinical

In the briefing package, MedImmune summarized the results from several studies in which patients with HCC received durvalumab as a single agent, tremelimumab as a single agent, or both products administered concurrently. Overall response rates (ORR) were 10.3% for durvalumab (4 responses out of 39 evaluable patients; 95% confidence interval (CI) 2.9%, 24.6%); 17.6% (3 responses out of 17 evaluable patients; 95% CI 6.2%, 41.0%) for tremelimumab 16 mg/kg every 90 days (Sangro et al. 2013); and 20% (8 responses out of 40 patients; 95% CI 6.2%, 41.0%) for durvalumab 20 mg/kg in combination with tremelimumab 1 mg/kg Q4W in the ongoing Study 022.

The proposed study (002) is a randomized, open-label, multi-national, parallel-group, active-controlled study which will enroll 1200 patients with unresectable Barcelona Clinic Liver Cancer (BCLC) Stage B and BCLC Stage C HCC, Child Pugh class A liver function, no prior systemic treatment, and ineligibility for locoregional treatment. Randomization will be stratified by macrovascular invasion (yes vs. no), etiology of liver disease (HBV vs. HCV vs. others), and ECOG performance status (0 vs. 1). Eligible patients will be randomly assigned in a 1:1:1:1 ratio to four treatment arms:

1. Durvalumab 1500 mg every four weeks
2. Durvalumab 1500 mg in combination with tremelimumab 75 mg every four weeks for 4 doses, followed by durvalumab as a single agent
3. Durvalumab 1500 mg in combination with a single dose of tremelimumab 300 mg followed by durvalumab as a single agent
4. Control arm: Sorafenib 400 mg twice daily.

The primary objective is the comparison of overall survival (OS) between durvalumab in combination with four doses of tremelimumab versus sorafenib. Assuming a median OS of 10 months in the sorafenib arm and a median OS of 14.3 months in the experimental arm (hazard ratio (HR) 0.70), a final analysis conducted in the intent-to-treat (ITT) population after 460 events (anticipated to occur approximately 39 months after enrollment of the first patient) will

have 96% power to demonstrate a statistically significant difference in OS at a 2-sided 4.45% significance level.

One interim analysis will be performed using a LanDeMets spending function to preserve a two-sided overall type I error of 0.05. If 74% of the target OS events (i.e., 339/460) occur at the time of the interim analysis, the 2-sided significance levels to be applied for the interim and final analyses would be 0.0183 and 0.0445, respectively. Enrollment will not be delayed by the interim analysis.

Key secondary objectives are the comparison of OS in the durvalumab plus a single dose of tremelimumab arm versus sorafenib and the comparison of OS in the durvalumab monotherapy arm versus sorafenib. To control the family-wise error rate (FWER) at 0.05 level, a multiple testing procedure with the following gatekeeping strategy will be used for the comparison of OS between each of the three new treatment regimens and sorafenib:

- Step 1: Test durvalumab plus tremelimumab for 4 doses arm versus sorafenib at the FWER of 0.05. If the result is significant, Step 2 proceeds.
- Step 2: Test durvalumab monotherapy arm and durvalumab plus a single tremelimumab dose arm at the FWER of 0.05 using Dunnett and Tamhane's step-up procedure (Dunnett and Tamhane, 1992). If the larger p-value is less than 0.05, both null hypotheses will be rejected.

Other secondary endpoints are time-to-progression (TTP), progression-free survival (PFS), ORR, disease control rate, duration of response (RECIST 1.1) of each arm versus sorafenib; same endpoints in a subset of patients with PD-L1 expression; assessment of quality of life using the QLQ-C30 and QLQ-HCC18 questionnaires; assessment of immunogenicity, pharmacokinetics (PK), and safety.

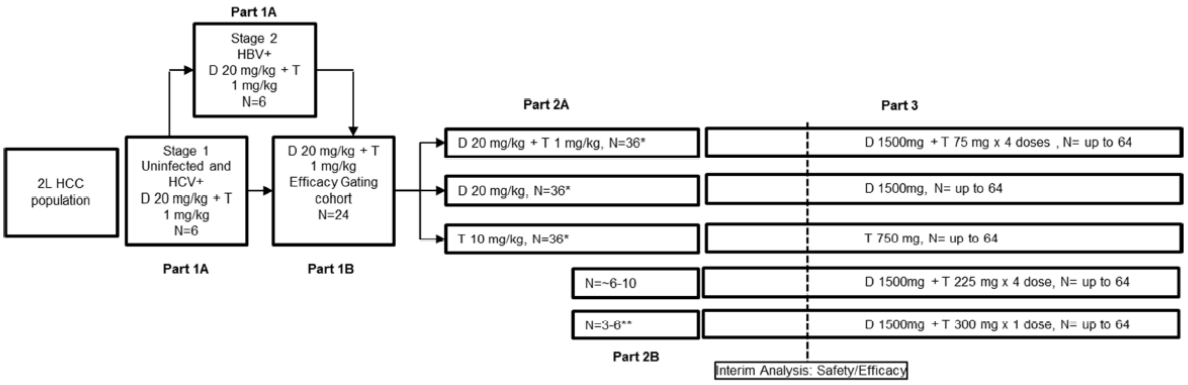
MedImmune stated sample sizes were determined for three key efficacy comparisons as follows:

- To compare Arm 1 versus 4, OS HR of 0.70 with a median OS of 14.3 and 10 months, and OS at 18 months of 42.3% and 28.7% in Arm 1 and 4, respectively. Assuming a median OS of 12 and 10 months in Arms 1 and 4, with a total of 460 events, a log-rank test with a two-sided significance level of 5% will provide 96% power to detect the HR=0.83.
- To compare Arm 2 versus 4, OS HR of 0.70 with a median OS of 14.3 and 10 months, and OS at 18 months of 42.3% and 28.7% in Arm 2 and 4, respectively. Assuming a median OS of 12 and 10 months in Arm 2 and 4, with a total of 460 events, a log-rank test with a two-sided significance level of 2.62% will provide 94% power to detect the HR=0.83.
- To compare Arm 3 versus 4, OS HR of 0.74 with a median OS of 13.6 and 10 months, and OS at 18 months of 40.5% and 28.7% in Arm 3 and 4, respectively. Assuming a median OS of 12 and 10 months in Arm 3 and 4, with a total of 460 events, a log-rank test with a two-sided significance level of 2.62% will provide 86% power to detect the HR=0.83.

Efficacy data will be analyzed using a log-rank test with stratification factors on the ITT population per the treatment arms assigned at randomization. The study is considered achieved if it demonstrates statistically different in OS in Arm 1 vs. 4.

The study will be conducted globally in North and South America, Europe, Oceania and Asia.

In addition to Study 002, MedImmune plans to submit data from the ongoing Study 022 as supportive information. MedImmune states that the study will be expanded to increase the number of patients and cohorts as follows:



Biomarker Development Strategy

Prior to completion of enrollment into Study 002, MedImmune plans to analyze PD-L1 expression on tumor cells and tumor infiltrating immune cells in patients enrolled in Study 022. In the event that an association between biomarker and increased activity is observed, MedImmune plans to validate the finding in Study 002. All patients screened for inclusion in Study 002 will be mandated to provide a formalin fixed paraffin-embedded tissue sample for testing; testing will be performed prior to database lock using a fully validated and locked assay developed under design control in a certified laboratory. All staff will be blinded to outcome data as testing will be performed prior to database lock and in a central laboratory independent of the clinical sites.

The statistical analysis plan (SAP) for the pivotal Study 002 will be updated to reflect the pre-specified analysis of the biomarker subgroup, prior to database lock.

DISCUSSION OF FDA RESPONSES TO SPONSOR QUESTIONS

MedImmune's position on Question #1-6 provided on pages 27-32 of briefing package.

1. **Does the Agency agree that the proposed Phase 3 study design is appropriate to support registration of durvalumab and durvalumab in combination with tremelimumab at the proposed dosing regimens?**

   FDA Response: In general, a randomized four-arm trial with OS as the endpoint is an appropriate design to obtain the data necessary to support labeling claims for durvalumab in

this indicated population. However, the trial should be revised to include a comparison between Arms 1 and 2 in order to provide evidence of the contribution of tremelimumab to durvalumab in Arm 2. MedImmune should revise the protocol to include a plan for an analysis comparing OS between Arm 2 and Arm 1 to support MedImmune's position that the combination regimen provides benefit over than observed with durvalumab administered as a single agent.

Additionally, provide data supporting the tolerability of the proposed dose of tremelimumab in Arm 3 or revise the protocol to include a 6-12 patient safety lead-in for this treatment arm prior to initiation of randomization.

MedImmune Response (provided via email 4/27/2017): The Sponsor acknowledges the Agency's comment. The comparison between the monotherapy durvalumab (Arm 1) and the combination arm (Arm 2) is one of the secondary objectives in the current protocol and will also be described in detail in the SAP. This approach, involving the evaluation of the totality of evidence in the context of benefit-risk based on a comparison between arms with respect to both efficacy and safety, is consistent with other ongoing sponsored Phase 3 studies and is aligned with prior FDA feedback (IND (b) (4)).

The Sponsor acknowledges the Agency's comment on the proposal regarding dose of durvalumab 1500 mg plus tremelimumab 300 mg.

As described in the briefing package, the same cumulative AUC tremelimumab exposure is expected with 300 mg single dose when compared with the standard dose of tremelimumab 75 mg Q4W for 4 doses; therefore, a similar safety profile is anticipated. Additionally, as part of the planned Phase 3 protocol, there is an established safety monitoring by the IDMC after 30 patients per arm. Finally, this durvalumab 1500 mg plus tremelimumab 300 mg dose regimen will be evaluated in the Phase 1/2 study 22 upon a planned amendment and is anticipated to enroll patients prior to the Phase3 study initiation. Available data from Study 22 will be provided to the FDA prior to initiation of randomization of the Phase 3 study.

Discussion During Meeting: MedImmune clarified that the protocol contains a proposal for comparison of Arms 1 and 2 as a secondary objective. The determination of the incremental benefit of the addition of tremelimumab to durvalumab during review of the efficacy supplement for durvalumab and BLA for tremelimumab will consider the totality of the efficacy results for all endpoints and the safety information across treatment arms. With regards to the proposed approach to justification of the doses in the combination therapy arm (Arm 3), the proposed approach described in MedImmune's April 27, 2017, response is acceptable. FDA advised that a modification of Study 002 to include a prospective plan for an adaptive modification to drop one of the combination arms (i.e., Arm 2 and/or 3) would be acceptable. MedImmune acknowledged the advice.

2. **Does the Agency agree that the patient population has been appropriately defined in this study** [redacted] (b) (4)

   FDA Response: Yes.

   MedImmune Response (provided via email 4/27/2017): The Sponsor acknowledges the Agency's response and has no further comment.

   Discussion During Meeting: No discussion occurred.

3. **Does the Agency agree that the proposed geographical recruitment and trial stratification criteria are appropriate and in turn, will support registration in this region?**

   FDA Response: Yes, FDA agrees that the proposed stratification factors are acceptable. However there is insufficient information regarding geographical recruitment to allow FDA to characterize the estimated proportion of patients to be enrolled in the US. Please refer to FDA's Response to question 7. In general, FDA will accept the results of foreign clinical studies if there is adequate justification for extrapolation of the treatment effects to the US population.

   MedImmune Response (provided via email 4/27/2017): The Sponsor acknowledges the Agency's response and has no further comment.

   Discussion During Meeting: No discussion occurred.

4. **Does the Agency agree that sorafenib is the most appropriate active comparator for this study?**

   FDA Response: FDA agrees that sorafenib is an acceptable active control for this study.

   MedImmune Response (provided via email 4/27/2017): The Sponsor acknowledges the Agency's response and has no further comment.

Discussion During Meeting: No discussion occurred.

5. **Does the Agency agree with the proposed endpoints and targeted magnitude of benefit?**

FDA Response: FDA agrees with OS as the preferred primary endpoint and that the targeted magnitude of effect is clinically meaningful. Although FDA does not object to the proposed secondary endpoints, please be aware that TTP, PFS-1, and disease control rate will not be included in labeling as these are not considered measures of clinical benefit. Therefore FDA strongly recommends that comparison of blinded independent review assessments of PFS and ORR be listed first in the hierarchical testing immediately following analyses of OS.

As an alternative to a blinded independent review of all patients, MedImmune may propose a pre-specified auditing procedure by a blinded independent review committee (BIRC) in the ITT population. Please see below additional FDA comments in regards to patient reported outcomes (PROs) if MedImmune proposes to include such data in labeling.

Please be advised that two Phase 3 studies are generally required for licensure. FDA may accept a single pivotal study to support licensure if results show a highly statistically significant effect on survival that is internally consistent across relevant subgroups. The results of the single pivotal trial should be sufficiently robust and so compelling that it would be unethical to repeat the study. Please also note that a single trial with a p-value close to 0.05 may not provide a sufficiently compelling and robust result. For further information please refer to the FDA document "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products" at http://www.fda.gov/cder/guidance/index.htm.

Furthermore, MedImmune should also evaluate PFS as assessed by a BIRC or an investigator assessment with pre-specified auditing procedure by BIRC in the ITT population other than time-to-first-progression.

MedImmune Response (provided via email 4/27/2017): The Sponsor acknowledges the Agency's response and agrees to prioritize PFS after OS in the multiplicity testing plan.

Discussion During Meeting: No discussion occurred.

6. **Does the Agency agree with the proposed statistical analysis approach to evaluate the efficacy endpoints, as well as the multiple testing procedure to control the overall Type 1 error rate?**

FDA Response: FDA does not disagree with the proposed methods. However, there is insufficient information for FDA to replicate and provide agreement with the proposed SAPs. MedImmune should determine the study sample size for OS based on assumptions of an exponential model, number of required events, an accrual period, a total follow-up, and a dropout rate. The sample size should also be described in the protocol and SAP in regards to important secondary objectives and control of type I error for the interim and final analyses.

Additionally, please detail the primary and secondary null hypotheses of the multiple testing gatekeeping procedure in the proposed protocol and SAP.

MedImmune Response (provided via email 4/27/2017): The Sponsor acknowledges the Agency's response. The assumptions used in the calculation of the sample size will be described in detail in the protocol and the SAP. The analyses to evaluate the primary and secondary objectives, as well as the multiplicity plan, will also be described in the protocol and the SAP.

Discussion During Meeting: No discussion occurred.

7. **Does the Agency agree that the proposed geographical recruitment and trial stratification criteria are appropriate and in turn, will support registration in this region?**

FDA Response: The selection of stratification criteria is MedImmune's choice. Insufficient information was provided to respond the question regarding geographical recruitment.

MedImmune Response (provided via email 4/27/2017): The Sponsor acknowledges the Agency's response and has no further comment.

Discussion During Meeting: No discussion occurred.

MedImmune's position on Question #7 provided on pages 33-34 of briefing package.

8. **Does the Agency agree** (b) (4)

FDA Response: No. Please see FDA's response to question 1 (b) (4)

MedImmune Response (provided via email 4/27/2017): The Sponsor acknowledges the Agency's response and has no further comment. Please also refer to the response to Question 1.

Discussion During Meeting: No discussion occurred.

MedImmune's position on Question #8 provided on page 34-35 of briefing package.

9. **AstraZeneca would like to discuss with the Agency the registrational utility of surrogate endpoints in this disease setting. Specifically, does the Agency agree that Time to Progression (TTP) (defined as time to progression or HCC-related death [i.e. non-HCC related deaths will be censored]), if included as another primary endpoint, with appropriate control of the overall type I error rate (for example the alpha could be split between overall survival and TTP), could form the basis of regulatory approval in advance of the overall survival result being available?**

   FDA Response: No. As discussed in FDA's "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" at https://www.fda.gov/downloads/drugsGuidanceComplianceRegulatoyInformation/Guidance/UCM071590.pdf), TTP is not considered an appropriate measure of activity due to inability to make a risk-benefit assessment as with PFS, and concerns regarding assessment and informative bias. However, FDA is amenable to evaluate the treatment effects based on ORR as assessed by a BIRC, provided that the magnitude and duration of response is clinically meaningful and likely to predict an effect on OS.

   If accelerated approval is requested based on demonstration of treatment effects on a tumor-based endpoint (i.e., PFS or ORR) in the ITT population, the endpoints should be assessed by a BIRC or a pre-specified auditing procedure by a BIRC. The auditing plan should include the percentage of patients, identification of imaging subsets, criteria in auditing all images, and comparison between locally-reviewing and auditing results. The proposed protocol and SAP should prospectively detail methods for assessing, measuring, and analyzing the endpoints, methods for censoring and handling incomplete and/or missing data as well as sensitivity analyses to evaluate the robustness of the results.

   MedImmune Response (provided via email 4/27/2017): The Sponsor acknowledges the Agency's willingness to consider an accelerated approval based on ORR and duration of response.

   The Sponsor proposes to conduct such an analysis after approximately 100 patients per arm with 24 weeks of follow up and not prior to last subject enrolled. No formal comparative efficacy analyses between the experimental arms and the control arm will be performed for the accelerated approval.

   Discussion During Meeting: The proposal to further revise the protocol to include a plan to conduct analyses of ORR as described in MedImmune's April 27, 2017 response in support of a possible request for accelerated approval is acceptable. MedImmune should request a meeting with FDA to discuss the results if they appear to meet the criteria for accelerated approval.

   FDA advised that the protocol include a description of the proposed analysis plan for ORR, and that a small alpha penalty be taken for this analysis. Formal statistical comparisons between arms may not be required; rather, FDA may rely on evaluation of the lower-bound

of the 95% CI around the experimental arms relative to the point estimate for the control and for durvalumab monotherapy, as well as relative to available therapy in external trials. In such an evaluation, FDA would consider DOR and the safety profile in considering whether the criteria for accelerated approval are met. At the time of the protocol submission, FDA may provide additional advice regarding the proposed analysis of ORR, including whether the CI should not be overlapping between arms.

MedImmune stated their plans for submitting a request for preliminary Breakthrough Therapy Designation advice. FDA stated that the request should be based on at least 20 patients with BIRC assessed, confirmed responses with follow-up for DOR for at least 6 months in all such patients. In addition, other supportive information such as investigator assessed responses in additional patients with shorter follow-up should be provided.

MedImmune's position on Question #9 provided on pages 35-36 of briefing package.

10. **Does the Agency agree with the AstraZeneca's proposed biomarker development strategy?**

    FDA Response: No. In order to seek claims based on a retrospective-prospective analysis, the assay used to identify sub-populations must be analytically validated. In addition, it would be premature to answer if the plan is adequate as no SAP has been provided.

    MedImmune Response (provided via email 4/27/2017): The Sponsor acknowledges the Agency's response. The Sponsor would ensure that prior to testing in Phase 3, the assay will be fully analytically validated and testing performed at a certified laboratory. In addition, the Phase 3 study SAP will be updated accordingly and shared with the Agency.

    Discussion During Meeting: MedImmune clarified that the validated assay may not be available for use at the time of initiation of the proposed study. FDA requested, and MedImmune agreed, to provide the plan for prospective/retrospective testing and analysis with the validated assay as a component of Study 002 protocol and SAP.

ADDITIONAL FDA COMMENTS

Clinical Pharmacology

11. Include in the proposed protocol a plan to perform exposure-response analyses of relationships between durvalumab and tremelimumab exposure and effectiveness, toxicity, and pharmacodynamic (PD) biomarkers.

    MedImmune Response (provided via email 4/27/2017): The Sponsor agrees to include the analyses and has no further comments.

Discussion During Meeting: No discussion occurred.

12. Include in the proposed protocol a plan to evaluate the effect of anti-drug antibodies on the PK, PD markers, efficacy, and safety of durvalumab and tremelimumab.

    MedImmune Response (provided via email 4/27/2017): The Sponsor agrees to include the analyses and has no further comments.

    Discussion During Meeting: No discussion occurred.

Clinical Outcome Assessments

13. 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-specifiy 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.

MedImmune Response (provided via email 4/27/2017): The Sponsor acknowledges the Agency's response and has no further comment.

Discussion During Meeting: No discussion occurred.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit Initial Pediatric Study Plans (iPSP) within 60 days **of this meeting**. Separate iPSPs should be provided for durvalumab and for tremelimumab. The iPSPs must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSPs should be submitted in PDF and Word format. Failure to include an Agreed iPSPs with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

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

specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a

clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

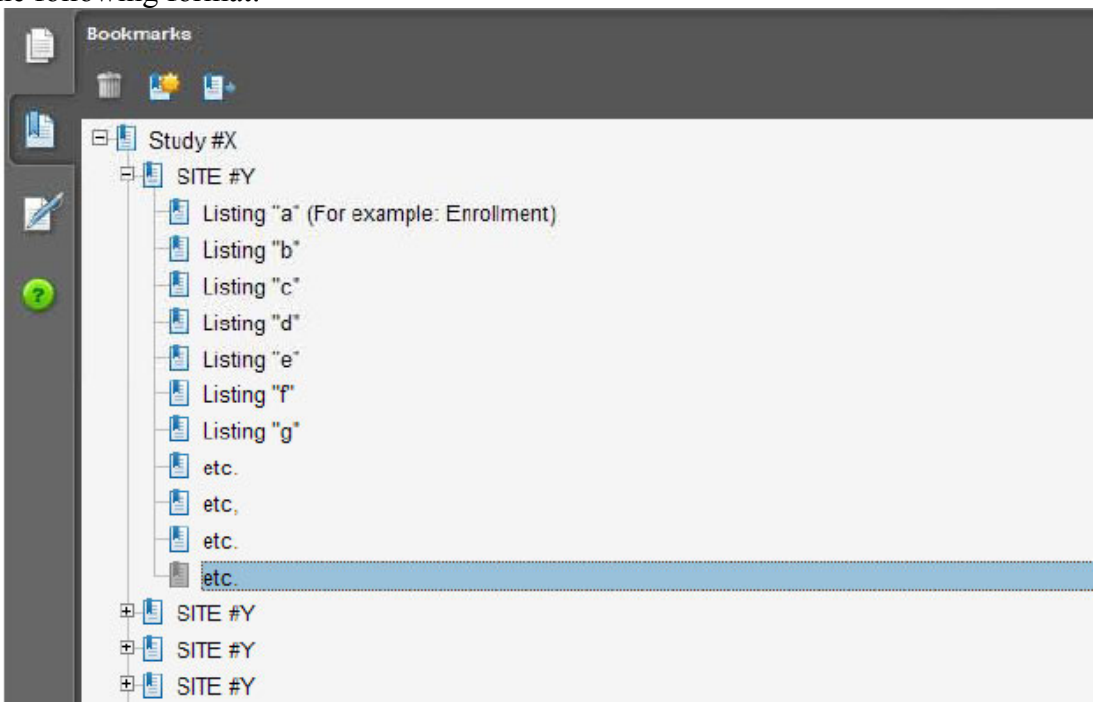
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)

f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

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



III. Request for Site Level Dataset:

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

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

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

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

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

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

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

References:

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

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

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

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.

ISSUES REQUIRING FURTHER DISCUSSION

No issues required further discussion.

ACTION ITEMS

No action items.

ATTACHMENTS AND HANDOUTS

No attachments and handouts.

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

/s/

IDARA UDOH
05/03/2017