CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761270Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 124702

MEETING MINUTES

AstraZeneca Pharmaceuticals, L.P.
Attention: Martin Mao, M.S., R.A.C.
Regulatory Affairs Director, Oncology
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. Mao:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for durvalumab (MEDI4736) and tremelimumab (MEDI1123).

We also refer to the teleconference between representatives of your firm and the FDA on July 30, 2021. The purpose of the meeting was to discuss the acceptability of the available data from the prespecified progression-free survival (PFS) and overall survival (OS) analyses and the safety/tolerability data from Study D419MC00004, entitled "A Phase III, Randomized, Multi-Center, Open-Label, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination with Platinum-Based Chemotherapy for First-Line Treatment in Patients with Metastatic Non-Small-Cell Lung Cancer (NSCLC) (POSEIDON)," to support a proposed Biologics License Application (BLA) for tremelimumab in combination with durvalumab and platinum-based chemotherapy for the proposed indication, first-line treatment of adult patients with metastatic NSCLC, with no sensitizing epidermal growth factor receptor (*EGFR*) mutation or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations.
A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

If you have any questions, contact me at 301-348-1823, or at Jana.Highsmith@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jana Highsmith
Regulatory Health Project Manager
Division of Oncology 2
Division of Regulatory Operations for
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	Friday, July 30, 2021, 9:00-10:00 a.m., EDT
Meeting Location:	Teleconference
Application Number:	IND 124702
Product Name:	tremelimumab (MEDI1123) and durvalumab (MEDI4736)
Proposed Indication:	Tremelimumab in combination with durvalumab and platinum-based chemotherapy is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC), with no sensitizing epidermal growth factor receptor (*EGFR*) mutations or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations.
Sponsor Name:	AstraZeneca Pharmaceuticals, L.P.
Regulatory Pathway:	351(a) of the Public Health Service Act
Meeting Chair:	Nicole Drezner, M.D.
Meeting Recorder:	Jana Highsmith

FDA ATTENDEES

Harpreet Singh, M.D.	Director, DO2
Nicole Drezner, M.D.	Clinical Team Lead, DO2
Oladimeji Akinboro, M.D.	Clinical Reviewer, DO2
Emily Wearne, Ph.D.	Pharmacology/Toxicology Team Lead (Acting), DHOT
Melissa Pegues, Ph.D.	Pharmacology/Toxicology Reviewer, DHOT
Pallavi Mishra-Kalyani, Ph.D.	Biometrics Team Lead, DBV
Xiaoxue Li, Ph.D.	Biometrics Reviewer, DBV
Hong Zhao, Ph.D.	Clinical Pharmacology Team Lead, DCPII
Emasenyie Isikwei, M.D.	Clinical Pharmacology Reviewer, DCPII
Ram Sihag, Ph.D.	Product Quality Team Lead, DBRRIII
Xu “Michael” Di	Product Quality Reviewer, DBRRIII
Candace Gomez-Broughton, Ph.D.	OPMA Team Lead, DBM
Jana Highsmith	Regulatory Health Project Manager, DORO/OOD-DO2

SPONSOR ATTENDEES

Cristian Massacesi, M.D.	Senior Vice President, Head of Late Development
Gregory Rossi, Ph.D.	Vice President, Global Franchise Head
Jacques Mascaro, Ph.D., MBA	Senior Vice President, Regulatory Affairs

Karen McCullough, Ph.D.	Executive Director, Regulatory Affairs
Caleb Briggs, Pharm.D., RAC	Senior Director, Regulatory Affairs
Martin Mao, M.S., RAC	Director, Regulatory Affairs
Phil Jewsbury, Ph.D.	Global Product Leader
Lee Krug, M.D.	Global Clinical Head
Xiaojin Shi, M.D. M.Sc.	Global Clinical Program Lead
Helen Mann, M.Sc.	Director, Biometrics Team Leader
Lynne Poole, M.Sc.	Statistical Science Director
Jimmy He, Ph.D.	Clinical Pharmacologist
Katrina Baggett	Statistical Programming Director
John McKnight, D.Phil., MBA	Director, Regulatory CMC
Joanne Shipman, M.S.	Associate Director, Regulatory CMC
William Wang, Ph.D.	V.P. of Purification Process and Analytical Sciences
Miriam Marotti, M.D.	Principal Safety Physician
Maryam Rafie-Kolpin, Ph.D., DABT	Project Toxicology Lead

BACKGROUND

Regulatory

On June 7, 2021, AstraZeneca Pharmaceuticals , L.P., (AstraZeneca) submitted a Type B, pre-Biologics License Application (BLA) meeting request to discuss the acceptability of the available data from the prespecified progression-free survival (PFS) and overall survival (OS) analyses and the safety/tolerability data from Study D419MC00004, entitled “A Phase III, Randomized, Multi-Center, Open-Label, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination with Platinum-Based Chemotherapy for First-Line Treatment in Patients with Metastatic Non-Small-Cell Lung Cancer (NSCLC) (POSEIDON),” to support a proposed Biologics License Application (BLA) for tremelimumab in combination with durvalumab and platinum-based chemotherapy for the proposed indication, first-line treatment of adult patients with metastatic NSCLC, with no sensitizing epidermal growth factor receptor (*EGFR*) mutation or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations.

Clinical

AstraZeneca Pharmaceuticals L.P., referred to as ‘the Applicant’ hereafter, proposes to submit a BLA for tremelimumab in combination with durvalumab and platinum-based chemotherapy and a supplemental BLA (sBLA) for durvalumab in combination with tremelimumab and platinum-based chemotherapy, for the first-line treatment of patients with metastatic NSCLC with no sensitizing *EGFR* or *ALK* genomic tumor aberrations.

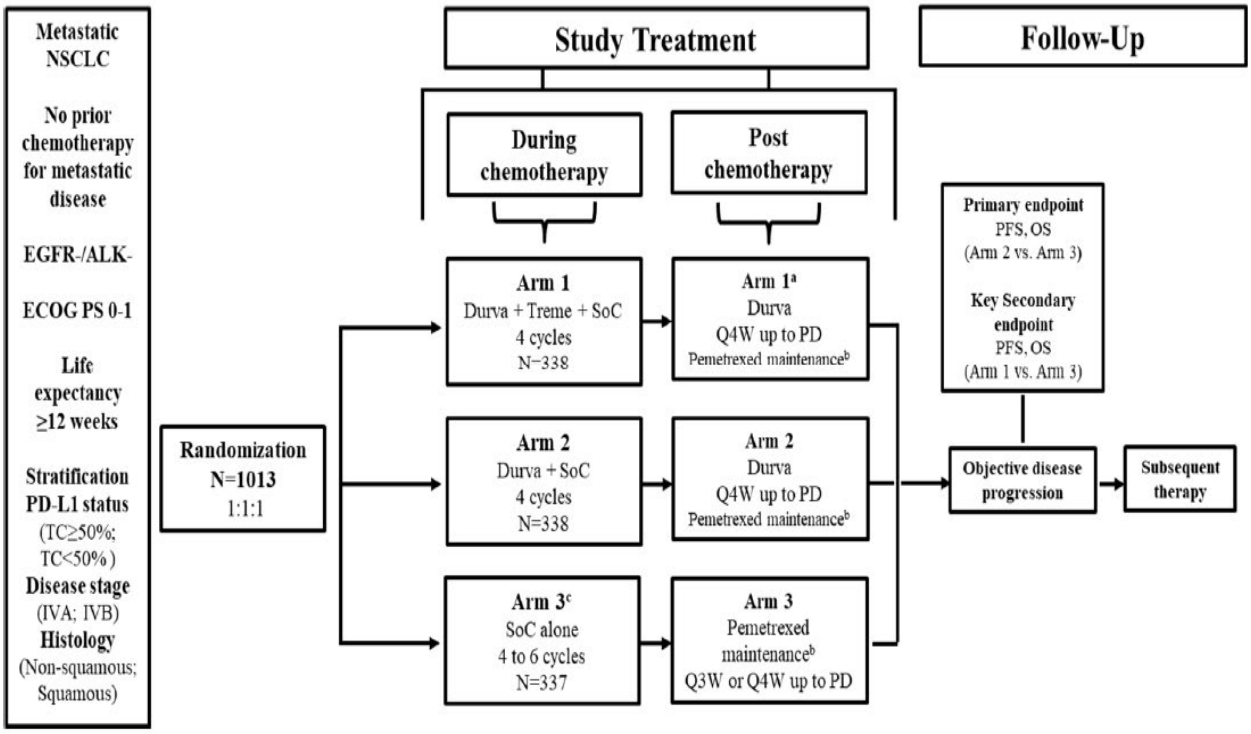
The Applicant proposes that the results of the POSEIDON trial comprise the primary efficacy and safety data in support of the BLA/sBLA.
POSEIDON is an international, multicenter, randomized, open-label trial that enrolled 1,013 patients with previously untreated metastatic NSCLC without sensitizing *EGFR* or *ALK* genomic tumor aberrations. Patients were randomized 1:1:1 to the treatment arms described below with randomization stratified by histology (non-squamous vs. squamous), disease stage (IVA vs IVB), and tumor PD-L1 status (tumor cells [TC] ≥50% vs TC <50%); tumor PD-L1 status was determined with the VENTANA SP263 IHC assay.

Treatment arms were:

- Arm 1: durvalumab 1500mg intravenously (IV) plus tremelimumab 75mg IV plus histology-based platinum-based chemotherapy every 3 weeks (Q3W) for up to 4 cycles followed by durvalumab 1500mg IV every 4 weeks (Q4W), with or without pemetrexed depending on the platinum-doublet received, until objective disease progression or unacceptable toxicity or withdrawal of consent.
  A single additional dose of tremelimumab 75mg IV was administered at week 16.
- Arm 2: durvalumab 1500mg IV plus histology-based platinum-based chemotherapy Q3W for up to 4 cycles followed by durvalumab 1500mg IV Q4W, with or without pemetrexed depending on the platinum-doublet received until objective disease progression or unacceptable toxicity or withdrawal of consent.
- Arm 3: histology-based platinum-based chemotherapy for up to 6 cycles with or without pemetrexed maintenance depending on the platinum-doublet received.

Details of the study design are summarized in the figure below.

Figure 1 Study design – POSEIDON



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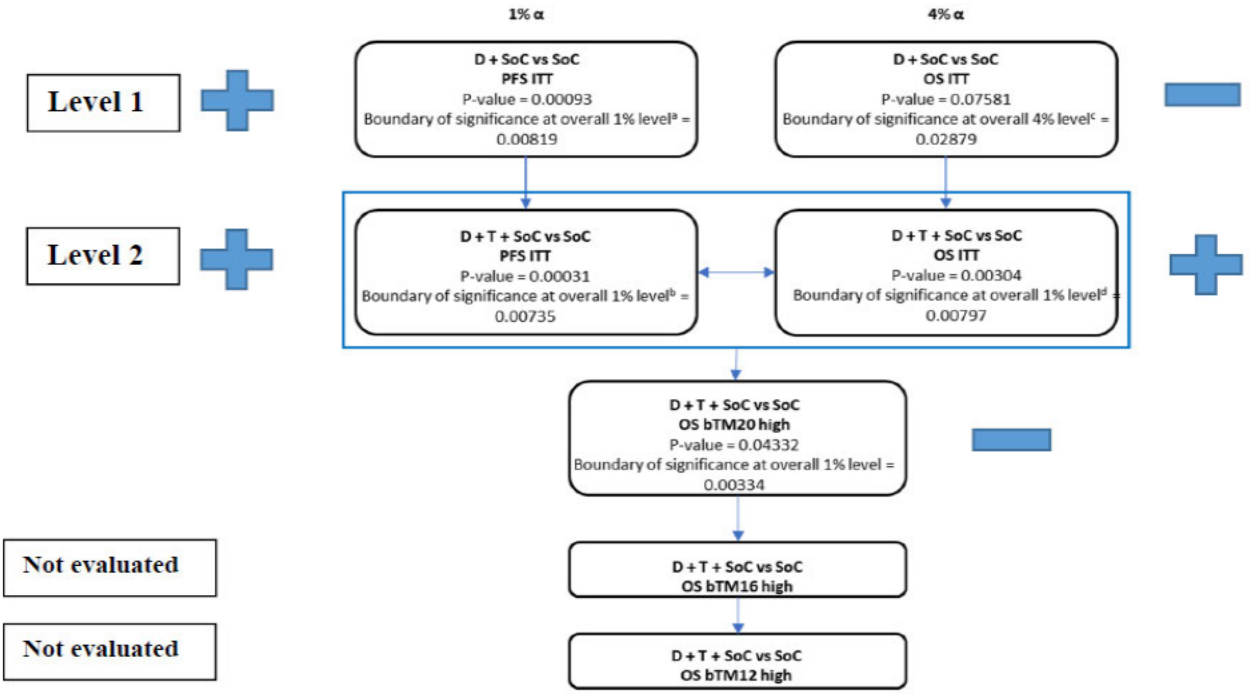
The co-primary endpoints were overall survival (OS) and progression-free survival (PFS) as assessed by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) in the durvalumab plus chemotherapy arm compared with the chemotherapy-only arm in the overall intent-to-treat (ITT) population. Key secondary endpoints included:

> i) OS and PFS as assessed by BICR per RECIST 1.1 in the durvalumab plus tremelimumab plus chemotherapy arm compared with the chemotherapy-only arm in the overall ITT population; and
> ii) OS in the durvalumab plus tremelimumab plus chemotherapy arm compared with the chemotherapy-only arm in the sub-population of patients with blood tumor mutational burden ≥20.

The alpha re-cycling strategy employed for a two-sided overall type 1 error control of 0.05 and overall outcomes based on this strategy are illustrated below:

Figure 2 Outcomes of the Multiple testing procedure (MTP)



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The key efficacy and safety outcome measures across the arms of the POSEIDON trial are summarized in tables 1 and 2, respectively, below:

Table 1: Summary of efficacy outcome measures from the POSEIDON trial

	D + T + Chemo (*N*=338)	D + Chemo (*N*=338)	Chemo (*N*=337)
OS [a]			
Number of events (%)	251 (74)	264 (78)	285 (85)
Median, months (95% CI)	14.0 (11.7, 16.1)	13.3 (11.4, 14.7)	11.7 (10.5, 13.1)
HR [b] (95% CI)	0.77 (0.65, 0.92)	0.86 (0.72, 1.02)	-
p-value	0.003	0.08	-
Alpha (pre-specified)	0.008	0.029	-
PFS per BICR[c]			
Number of events (%)	238 (70)	253 (75)	258 (77)
Median, months (95% CI)	6.2 (5.0, 6.5)	5.5 (4.7, 6.5)	4.8 (4.6, 5.8)
HR [b] (95% CI)	0.72 (0.60, 0.86)	0.74 (0.62, 0.89)	-
p-value	0.0003	0.0009	-
Alpha (pre-specified)	0.0074	0.0082	-
ORR per BICR [d]			
%	39	42	24
Odds ratio [b] (95% CI)	2.00 (1.43, 2.81)	2.26 (1.61, 3.19)	-
Nominal *p*-value	<0.001	<0.001	-
DoR [d]: Median, months (IQR)	9.5 (5.0 – NR)	7.0 (3.9 – NR)	5.1 (3.7 – 7.5)

D=Durvalumab; Chemo=chemotherapy; CI=confidence interval; DoR=duration of response; HR=hazard ratio; IQR=interquartile range; *N*=number; NR=-not reached; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; T=tremelimumab.
[a] Final OS analysis: data cut-off =March 12, 2021; median follow-up=34.9 months.
[b] HR comparing trial arm to chemotherapy alone.
[c] Final PFS analysis: data cut-off=July 24, 2019; median follow-up=10.3 months.
[d] Based on ad-hoc analysis conducted to determine the confirmed objective response.

A descriptive comparison of OS for the D + T + Chemo arm vs the D + Chemo arm was performed: HR=0.92 (95% CI: 0.78, 1.10).

Table 2: Key safety outcome measures from the POSEIDON Trial

	D + T + Chemo (*N*=330) %	**D + Chemo (*N*=334) %**	**Chemo (*N*=333) %**
Any grade AE	97	96	96
Grade 3-4 AE	53	55	52
Death resulting from AE	12	10	9
SAE	44	40	35
Treatment discontinuation from AE	22	20	15
Dose-delay/interruption from AE	57	56	43
Chemotherapy dose-reduction from AE	12	10	16
Infusion reactions	4.2	3.0	2.1
Any grade imAE	34	19	-
Grade 3-4 imAE	10	7	-
Serious imAE	10	6	-
imAE leading to death	0.6	0.3	-

AE=adverse event; D=Durvalumab; Chemo=chemotherapy; imAE=immune-mediated adverse event; *N*=number; SAE=serious adverse event; T=tremelimumab.

The Applicant proposes to demonstrate the contribution of tremelimumab to the treatment effect of the combination regimen of durvalumab plus tremelimumab plus chemotherapy by comparing the efficacy outcomes of Arms 1 and 2.

In addition to the efficacy and safety data from the POSEIDON trial, the Applicant proposes to submit supportive efficacy data for the combination of durvalumab plus tremelimumab from two randomized first-line treatment trials in advanced/metastatic NSCLC (MYSTIC and NEPTUNE) as well as efficacy data from a randomized trial in extensive stage small cell lung cancer (ES-SCLC) (CASPIAN). The efficacy results from these trials will not be pooled but will be summarized separately for each of the trials in Module 2.7.3 Summary of Clinical Efficacy. The clinical study reports for each of these trials, containing their statistical program outputs and datasets, will be provided separately in Module 5. Key details of the design of the three trials are summarized in table 3 below.

The Applicant also proposes to submit supportive data from trials that have evaluated the safety and/or efficacy of durvalumab plus tremelimumab with or without chemotherapy. The supportive safety data will be submitted in two pools:

- Durvalumab plus Tremelimumab plus Chemotherapy Pool: This pool will contain 596 patients from the POSEIDON and CASPIAN trials (see table 3 below).
- Durvalumab plus Tremelimumab only Pool: This pool will contain 2,280 patients from across 9 clinical trials and several solid tumor types in the clinical development program for durvalumab plus tremelimumab. The key details of these trials are summarized in table 3 below.

The proposed Summary of Clinical Safety will contain the primary safety data from the POSEIDON trial. The safety data from the two safety pools will be summarized alongside that from the POSEIDON trial.

Table 3: Proposed supportive trials for efficacy and or safety

Trial Name (Number)	Tumor type(s)	Trial Design	Relevant arm(s)
Efficacy and Safety Data			
MYSTIC (D419AC00001)	1L locally-advanced or metastatic NSCLC	Phase III, open-label, multi-center RCT	D+T (*n*=372) [a] Chemo (*n*=373)
NEPTUNE (D419AC00003)	1L locally-advanced or metastatic NSCLC	Phase III, open-label, multi-center RCT	D+T (*n*=410) Chemo (*n*=413)
CASPIAN (D419QC0001)	1L Extensive stage SCLC	Phase III, open-label, multi-center RCT	D+T+EP (*n*=268) [b] EP (*n*=269)
Safety Data alone			
Study 010 (D4190C00010)	Advanced solid tumors	Phase I, dose-escalation and dose-expansion	D+T (*n*=341)
Study 006 (D4190C00000)	Advanced NSCLC	Phase Ib, dose-escalation and dose-expansion	D+T (*n*=355)
Japan 002 (D4190C00002)	Advanced solid tumors (Japanese pts)	Phase I, dose-escalation and dose-expansion	D+T (*n*=124)
Study 22 (D4190C0002)	Advanced HCC	Phase I/II, open-label, multi-center RCT	D+T (*n*=127)
CONDOR (D4193C00003)	Recurrent or metastatic HNSCC	Phase II, open-label, multi-center RCT	D+T (*n*=133)
EAGLE (D4193C00002)	Recurrent or metastatic HNSCC	Phase III, open-label, multi-center RCT	D+T (*n*=246)
ARCTIC (D4191C00004)	2L+ locally-advanced or metastatic NSCLC	Phase III, open-label, multi-center RCT	D+T (*n*=173)

1L=first-line; 2L=second-line; Chemo=chemotherapy; D=durvalumab; EP=etoposide plus platinum; HCC=hepatocellular carcinoma; HNSCC=head and neck squamous cell carcinoma; *n*=number; NSCLC=non-small cell lung cancer; pts=patients; RCT=randomized controlled trial; SCLC=small cell lung cancer; T=tremelimumab.

[a] MYSTIC's safety database contains 371 patients exposed to durvalumab plus tremelimumab

[b] CASPIAN's safety database contains 266 patients exposed to durvalumab plus tremelimumab plus chemotherapy

Regarding the data submission, the Applicant proposes a structure/content BD in pages 260 – 280 of the meeting package. The Applicant will provide datasets for each of the trials specified above per the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) version 1.3 and as analysis datasets per the CDISC Analysis Data Model (ADaM) version 2.1. However, the datasets for the safety pools described above will be provided as analysis datasets only. Given that the data cut-off timepoints for the final PFS analysis (July 24, 2019) and OS analysis (March 12, 2021) were different in the pivotal POSEIDON trial, the Applicant proposes to submit two Case Report Tabulation (CRT) packages corresponding to all the data that supported analyses at each of these data cut-off timepoints. However, there will be only one Clinical Study Report (CSR) summarizing the PFS and OS outcomes in the pivotal study.

The Applicant proposes to submit an sBLA for durvalumab approximately two months after submitting the BLA for tremelimumab to facilitate updating the durvalumab USPI. A hyper-linking strategy for both applications is illustrated in figure 7 (page 44) of the meeting package.

FDA sent Preliminary Comments to AstraZeneca on July 26, 2021.

SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

1. Does the Agency agree that the assessment of the overall benefits and risks of tremelimumab+ durvalumab + SoC chemotherapy (“T + D + SoC”), based on the final PFS and OS analysis and safety/tolerability data from the POSEIDON study are sufficient to support a tremelimumab BLA and durvalumab sBLA in the proposed patient population?

   FDA Response: No. The POSEIDON study results do not demonstrate a meaningful difference between Study Arms A and B and therefore do not adequately justify the addition of tremelimumab to the combination. Despite the statistical significance of the analysis of OS for the comparison of T+D+SOC vs. SOC, a clinically insignificant difference of 0.7 months in median OS was observed in the T+D+SOC arm compared to the D+SOC arm. Furthermore, no evidence of benefit of the T+D+SOC arm over the D+SOC arm was observed in the descriptive analysis of OS for the comparison of D+SOC vs. T+D+SOC (HR 0.92 [95% CI 0.78, 1.10]).

   AstraZeneca’s 07/29/2021 Email Response: POSEIDON is a robust, randomized, well controlled study investigating durvalumab (D) + SoC vs SoC and tremelimumab (T) +D+SoC vs SoC, which demonstrated positive, alpha-controlled results in analyses of PFS (T+D+SoC and D+SoC) and OS (T+D+SoC) across primary and key secondary analyses. The Applicant acknowledges the Agency’s position regarding the additive clinical benefit of

tremelimumab as measured by median OS and OS hazard ratio. AstraZeneca agrees that evaluation of medians and hazard ratios are informative measures in characterizing the clinical effect of a treatment, however, in a study such as POSEIDON where non-proportional hazards (NPH) are evident, these metrics alone may be insufficient to fully assess the benefit of T+D+SoC and may underestimate the clinical benefit offered by the regimen. The Applicant proposes that the totality of the POSEIDON clinical evidence should be considered in evaluating COC as well as benefit overall. In addition to considering OS HR and medians, (2) landmark OS and long-term survival benefits in general, (3) durable responses, and (4) the overall safety and tolerability profile should be considered.

Mechanism of action and non-proportional hazards
The Kaplan-Meier (KM) curves observed in the POSEIDON study are consistent with the mechanistic understanding of the role of CTLA-4 inhibition when added to a chemotherapy + PD-L1 regimen. Both CTLA-4 and PD-L1 function to promote effective anti-tumor T-cell responses. These responses once triggered, can persist, even in the absence of continued therapy, complementing the short term tumour growth control delivered through chemotherapy-mediated tumor cell killing and leading to prolonged survival benefit. PD-L1 blockade primarily acts to strengthen pre-existing anti-tumor T-cell responses, which in a sub-set of patients lead to prolonged survival benefit observed as a tail in the survival curve. CTLA-4 blockade primarily acts to promote new anti-tumor T-cell responses, which can then be further strengthened by PD-L1 blockade. Addition of CTLA-4 to PD-L1 blockade therefore increases the proportion of patients in whom an active anti-tumor T-cell response is achieved, increasing the proportion of patients who achieve long term benefit, and further lifting the tail of the survival curve.

Clinically, this results in delayed separation of the curves and non-proportional hazards observed in the complementary log-log plots. Owing to this delayed separation, the real and clinically-meaningful benefit of adding CTLA-4 to the regimen may be understated by measures traditionally referenced in oncology, such as magnitude of the median OS and the OS HR. In such a situation, the OS HR may be rightly interpreted as an average estimate of the observed benefit and should be evaluated carefully alongside the totality of the curve.

Contribution of Tremelimumab
To inform the contribution of each agent to the regimen, AstraZeneca has also compared the two treatment arms using descriptive statistics. As noted above, the OS curves between T+D+SoC and D+SoC separated after approximately 10 months, consistent with the mechanistic understanding of this therapeutic regimen. A consistently higher OS rate of T+D+SoC compared to both D+SoC and SoC is noted throughout the whole KM curves, including the initial limited separation. This consistent and sustained effect provides reassurance that the

overall treatment effect is robust and unlikely to represent a chance finding. The Applicant acknowledges that the magnitude of survival benefit assessed in terms of OS HR demonstrates an incremental improvement (HR: 0.92; 95% CI: 0.776, 1.100), however the clinical benefit of this regimen is most clearly observed in the long term, becoming apparent in the evaluation of OS over time. Numerically higher OS rates at landmarks show this effect in quantifiable terms: 24 months (32.9% vs. 29.6% on T+D+SoC and D+SoC, respectively) and 36 months (25.3% vs. 20.3%, respectively). This improvement in percentage of patients surviving at each measured timepoint represents a meaningful benefit to those patients.
This sustained effect is also evident in the evaluation of duration of response (DoR) within POSEIDON. In the patients with a confirmed ORR (BICR, RECIST 1.1), patients treated with T+D+SoC achieved median DoR of 9.5 months compared with 7.0 months for patients treated with D+SoC. At 12 months, 49.7% of patients on T+D+SoC had remained in response compared with 38.9% of patients on D+SoC, and at 18 months, 40.7% of patients on T+D+SoC had remained in response compared with 29.6% of patients on D+SoC.
The challenge of metrics traditionally used in oncology to fully describe the benefit of such a regimen with non-proportional hazards is observed in other studies of IO combinations utilizing CTLA-4 inhibition in 1L mNSCLC, including CheckMate-227. This study demonstrated a similar delay in separation of the curves associated with the mechanistic action of the regimen. The size of clinical benefit seen for the addition of CTLA-4 in POSEIDON (HR 0.92 [95% CI 0.776, 1.100]) is consistent with the effect observed in CheckMate-227 for the addition of ipilimumab to nivolumab in the approved indication of PDL1$\geq$1% 1L mNSCLC (HR=0.90 [95% CI, 0.77 – 1.07]). (Hellmann et al).

Safety of the regimen and value to patients
In addition to the clinical benefit described above, the safety profile observed in the POSEIDON study was consistent with the well characterized safety profiles of the tremelimumab plus durvalumab combination, durvalumab monotherapy, and SoC chemotherapies. The most commonly reported AEs were hematologic and gastrointestinal events and in line with the concomitant use of chemotherapies. The majority of AEs were CTC grade 1 or 2. As expected, imAEs were numerically higher in the T+D+SoC arm than the D+SoC arm, mainly driven by low-grade diarrhea/colitis, dermatitis/rash, and endocrinopathies. These events were generally manageable with standard treatment guidelines. There was no increased toxicity that impacted the ability of patients to receive the combination of T+D+SoC compared with D+SoC.
The T+D+SoC regimen in POSEIDON included a short-course regimen of 5 doses of tremelimumab, intended to balance the immune activating effects of CTLA-4 against potential of toxicity from prolonged exposure. This dosing allows for a full course of SoC chemotherapy, and contrasts with the existing approved nivolumab and ipilimumab regimen which utilizes a short course of 2 cycles of chemotherapy together with nivolumab and ipilimumab treatment until

progression. While difficult to compare toxicity across trials, this safety profile of POSEIDON offers the potential for an IO+IO regimen which is distinct and valuable to patients.

Conclusion
The POSEIDON study demonstrates that the T+D+SoC regimen, when compared to SoC chemotherapy, leads to a statistically significant and clinically meaningful improvement in OS as well as a manageable toxicity profile. It is the position of the Applicant that these data constitute substantial evidence that the regimen is safe and effective. AstraZeneca acknowledges the Agency's position regarding the additive clinical benefit of tremelimumab as measured by median OS and OS hazard ratio. However, assessment of differences between treatment arms is subject to interpretation, and given the mechanism of CTLA-4 action, OS medians and hazard ratios are likely to understate the true, long-term clinical benefit offered by the addition of tremelimumab to the regimen. The Applicant maintains that an assessment of the totality of the evidence is crucial to fully describe its value.

Discussion During the 07/30/2021 Meeting: FDA acknowledged AZ's position regarding the difficulty in relying on median survival times or hazard ratios when non-proportional hazards (NPH) are present. FDA agreed that the issue of NPH is a concern in many immunotherapy studies, and there is a challenge in appropriately characterizing treatment benefit when NPH is observed. However, it is difficult to determine whether the difference in estimated survival rates between the two experimental arms of 1.6% at 12 months, 3.3% at 24 months, or 5% at 36 months represents a clinically meaningful incremental benefit to patients. In particular, the confidence intervals of these rates are likely to be overlapping and the 36 month timepoint is subject to censoring in both arms , both of which further detracts from determining the potential clinical benefit of adding tremelimumab to the combination therapy. Given the remaining uncertainty in the additional clinical benefit of adding tremelimumab to the combination therapy, FDA reiterates its position that the contribution of components is not established for the T+D+SOC arm, rendering the efficacy results of this arm difficult to interpret with regards to the overall benefit risk assessment of the combination.

AZ asked for clarification of whether the determination of contribution of components for POSEIDON would be a review issue for the BLAs. FDA discouraged AZ from filing applications for the proposed indications given the issues described; however, FDA stated that if applications are filed, whether the contribution of components has been demonstrated will be considered by the agency during review.

2. Does the Agency agree that the proposed strategy to demonstrate the contributions of durvalumab and tremelimumab to the treatment regimen of tremelimumab plus durvalumab in combination with SoC chemotherapy is acceptable for a BLA review?

FDA Response: No. See FDA Response to Question 1.

Discussion During the 07/30/2021 Meeting: See FDA discussion under Question 1.

3. Does the Agency agree that the Applicant's proposed content and presentation of efficacy and safety data are acceptable to support the BLA review?

FDA Response: See FDA Response to Question 1.

Discussion During the 07/30/2021 Meeting: FDA agrees that the proposed content and presentation of efficacy and safety data are acceptable to support BLA review.

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 and chemotherapy?

FDA Response: See FDA Response to Question 1.

Discussion During the 07/30/2021 Meeting: FDA agrees with the content of the proposed clinical pharmacology data package.

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

FDA Response: See FDA Response to Question 1.

Discussion During the 07/30/2021 Meeting: FDA stated that AZ will be required to submit the manufacturing schedule for all facilities at the time of BLA submission.

6. Does the Agency agree that the proposed content/format of individual study datasets, pooled datasets, and the planned documentation to support the tremelimumab BLA review is acceptable?

   FDA Response: See FDA Response to Question 1.

   Discussion During the 07/30/2021 Meeting: FDA has no objections to the content and format proposed for the BLA.

7. Does the Agency agree with the Applicant's proposal to request a waiver for the 90 or 120-Day Safety Update for the BLA?

   FDA Response: See FDA Response to Question 1.

   Discussion During the 07/30/2021 Meeting: FDA stated that a 90-day or 120-day safety update will be required.

8. Does the Agency agree with the Applicant's proposal for an Application Orientation Meeting in support of the tremelimumab BLA review for tremelimumab + durvalumab + SoC chemotherapy to occur shortly after the submission?

   FDA Response: See FDA Response to Question 1.

   Discussion During the 07/30/2021 Meeting: FDA stated it would be acceptable to hold an Application Orientation Meeting and datasets walkthrough meeting.

9. Does the Agency agree with the Applicant's approach and timing for submitting a corresponding durvalumab sBLA to BLA 761069 after the tremelimumab BLA submission?

   FDA Response: See FDA Response to Question 1.

   Discussion During the 07/30/2021 Meeting: FDA had no objections to the proposal.

ADDITIONAL COMMENTS

Chemistry, Manufacturing, and Controls (CMC)

10. To facilitate the Agency's review of drug substance (DS) and drug product (DP) manufacturing processes for tremelimumab, provide the information for process parameters and in-process control, as applicable, in the following tabular format. Please provide a separate table for each unit operation. The tables should

summarize information from module 3 and may be submitted either to module 1 or module 3R.

Process Parameter /Operating Parameter / In-Process Control	Proven Acceptable Range/ Control Limits/Targets[1] for Commercial Manufacturing Process	Criticality Classification[2]	Characterized Range/ Control Limits/Targets[1] tested in Process Development Studies	Manufactured Range/ Control Limits/Targets[1] used for Pivotal Study Lots	Manufactured Range/ Control Limits/Targets[1] used in Process Validation	Justification of the Proposed Commercial Acceptable Range[3]	Comment[4]

[1]As applicable
[2]For example, critical process parameter, key process parameter, non-critical process parameter, as described in module 3.
[3]This could be a brief verbal description or links to the appropriate section of the eCTD.
[4]Optional.

11. To facilitate the Agency's review of the control strategy for tremelimumab, provide information for quality attributes and process and product related impurities for DS and DP in the following tabular format. The tables should summarize information from module 3 and may be submitted either to module 1 or module 3R.

Quality Attributes and Process and Product Related Impurities for DS and DP	Criticality Classification[1]	Impact[2]	Source[3]	Analytical Method [4]	Proposed Control Strategy[6]	Justification of the Proposed Control Strategy[6]	Comment[7]

[1]For example, critical quality attribute or non-critical quality attribute.
[2]What is the impact of the attribute, e.g. contributes to potency, immunogenicity, safety, efficacy.
[3]What is the source of the attribute or impurity, e.g. intrinsic to the molecule, fermentation.
[4]List all the methods used to test an attribute in-process, at release, and on stability. For example, if two methods are used to test identity then list both methods for that attribute.
[5]List all the ways the attribute is controlled, for example, in-process testing, validated removal, release testing, stability testing.
[6]This could be a brief verbal description or links to the appropriate section of the eCTD.
[7]Optional.

The FDA is providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(a) BLA submission.

12. All facilities should be registered with the FDA at the time of the 351(a) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

13. The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to the following:

    a. Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
    b. Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).
    c. Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
    d. Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).
    e. Information and summary results from the shipping validation studies (3.2.S.2.5).
    f. Drug substance bioburden and endotoxin release specifications (3.2.S.4).
    g. Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the

methods should be provided in addition to the compendial reference numbers (3.2.S.4).

14. The CMC Drug Product section of the 351(a) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry *"Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products"* at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf

15. The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate:

    a. Identification of the manufacturing areas and type of fill line (e.g. open, RABS, isolator), including area classifications.
    b. Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.
    c. Parameters for filling and plunger placement for the pre-filled syringes (if applicable).
    d. Parameters for filling and capping for the vials (if applicable.
    e. A list of all equipment and components that contact the sterile drug product (i.e. the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.
    f. Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.
    g. Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.

16. The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

    a. Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.

b. Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.
c. In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
d. Isolator decontamination summary data and information, if applicable.
e. Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.
f. Information and summary results from shipping validation studies. For prefilled syringes, the effects of varying air pressure on pre-filled syringe plunger movement and potential breaches to the integrity of the sterile boundary during shipment should be addressed. Include data demonstrating that the pre-filled syringe plunger movement during air transportation does not impact product sterility.
g. Validation of capping parameters, using a container closure integrity test (if applicable).
h. Lyophilizer sterilization validation summary data and information (if applicable).

17. The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

a. Container closure integrity testing. System integrity should be demonstrated initially and during stability. Data demonstrating the maintenance of container closure integrity after the assembly of the pre-filled syringe and autoinjector should be included. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.
b. Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the

compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.

c. Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).

d. Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time.

e. Microbiological studies in support of the post-reconstitution and/or post-dilution storage conditions (if applicable). Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, bracket the drug product concentrations that would be administered to patients, and use the label-recommended reconstitution solutions and diluents. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> *Antimicrobial Effectiveness Testing*, plus typical skin flora or species associated with hospital-borne infections. *In lieu* of this data, the product labeling should recommend that the post-reconstitution and/or post-dilution storage period is not more than 4 hours.

Clinical Pharmacology

FDA has the following recommendations regarding the clinical pharmacology sections of the BLA submission:

Apply the following advice in preparing the clinical pharmacology sections of the BLA submission:

18. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

19. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.

20. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.

    a. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
    b. Identify individual subjects with dose modifications; the time to the first dose reduction, interruption, or discontinuation; the reasons for dose modifications in the datasets.

21. Submit the following for the population pharmacokinetic analysis reports:

    a. Standard model diagnostic plots
    b. Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line, and the population prediction line
    c. Model parameter names and units in tables.
    d. Summary of the report describing the clinical application of modeling results.
    e. Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

22. Submit the following information and data to support the population pharmacokinetic analysis:

    a. SAS transport files (*.xpt) for all datasets used for model development and validation.
    b. A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
    c. Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
    d. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers, and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships, and

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for pharmacometric data and models submission guidelines.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- FDA will make a final determination regarding the need for REMS during the review of the BLA.
- 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 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 to be submitted at

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

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.
- 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

[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

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.

SUBMISSION FORMAT REQUIREMENTS

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

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

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.

[6] http://www.fda.gov/ectd

[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[8] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[9]. 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

[8] https://www.fda.gov/media/84223/download

[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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*.[10]

ADVANCING ONCOLOGY DECENTRALIZED TRIALS

FDA Oncology requests that applicants submitting data to support NDA/BLA applications to voluntarily add flags to datasets in order to discriminate between REMOTE assessments and TRIAL SITE assessments. The intent is to allow FDA to learn from trials conducted in the COVID-19 pandemic that permitted some aspects of trial conduct to be performed remote from trial sites to reduce potential COVID exposure. The FDA hopes to learn more about the opportunities and challenges of these REMOTE modifications in order to foster use of "decentralize" aspects of clinical trials prospectively in the post-COVID era.

For details please refer to: https://www.fda.gov/about-fda/oncology-center-excellence/advancing-oncology-decentralized-trials.

For the purposes of this document, **"REMOTE"** is considered obtaining the assessment at a location outside of the standard clinical trial site assessment location noted in the initial protocol. **"TRIAL SITE"** is considered the location of clinics, laboratory, and imaging facilities local to the investigator site

ONCOLOGY PILOT PROJECTS

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

[10] https://www.fda.gov/media/85061/download

including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[11]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[12]

NONPROPRIETARY NAME

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

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

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

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

ATTACHMENTS AND HANDOUTS

13 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

[11] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program

[12] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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

/s/

JANA L HIGHSMITH
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