CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215310Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 126721

MEETING MINUTES

Millennium Pharmaceuticals, Inc.
Attention: Guilin Huang, MBA, RAC
Senior Director, Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Mr./Ms. Huang:[1]

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

We also refer to the teleconference between representatives of your firm and the FDA on November 10, 2020. The purpose of the meeting was to discuss whether your Study 101 is adequate to support a planned New Drug Application for mobocertinib under the accelerated approval regulations (21 CFR 314, Subpart H).

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

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

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

- Meeting Minutes

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

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	November 10, 2020; 2:00 PM – 3:00 PM, EST
Meeting Location:	N/A; Teleconference
Application Number:	IND 126721
Product Name:	mobocertinib
Indication:	Treatment of adult patients with epidermal growth factor receptor (*EGFR*) exon 20 insertion mutation–positive metastatic non–small cell lung cancer (NSCLC), as detected by a United States (US) Food and Drug Administration (FDA)-approved test, who have received prior platinum-based chemotherapy.
Sponsor Name:	Millenium Pharmaceuticals, Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetics Act
Meeting Chair:	Erin Larkins
Meeting Recorder:	Idara Udoh

FDA ATTENDEES

Harpreet Singh, Director, Division of Oncology 2 (DO2)
Erin Larkins, Clinical Team Lead, DO2
Nicole Drezner, Clinical Team Lead, DO2
Luckson Mathieu, Clinical Reviewer, DO2
Erica Nakajima, Clinical Reviewer, DO2
Oladimeji Akinboro, Clinical Reviewer, DO2
Katie Chon, Clinical Reviewer, DO2
Liza Stapleford, Clinical Reviewer, DO2
Satinder Choudhary, Clinical Reviewer, DO2
Whitney Helms, Nonclinical Team Lead, Division of Hematology, Oncology, and Toxicology (DHOT)
Amy Skinner, Nonclinical Reviewer, DHOT
Xing Wang, Product Quality Team Lead, Office of New Drug Products (ONDP)
Pallavi Mishra-Kalyani, Statistics Team Lead, Division of Biometrics (DB)
Somak Chatterjee, Statistics Reviewer, DB
Idara Udoh, Senior Regulatory Health Project Manager, Division of Regulatory Operations (DORO)
Jacqueline Glen, Regulatory Health Project Manager, DORO
Emily Pak, Regulatory Health Project Manager, DORO
Rama Kamesh Bikkavilli, Reviewer, Center for Devices and Radiological Health

Cristina Attinello, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Janine Stewart, Safety Evaluator, OSE

SPONSOR ATTENDEES
Krisztina Nemenyi, Vice President, Global Program Lead
Tatiana Ishida, Vice President, Global Regulatory Affairs
Guilin Huang, Senior Director, Global Regulatory Affairs
Sebastian Bilitza, PharmD Fellow, Global Regulatory Affairs
Lisa Dupont, Director, Regulatory CMC
Minal Mehta, Senior Medical Director, Clinical Science
Debbie Berg, Senior Scientific Director, Clinical Science
Shu Jin, Associate Scientific Director, Clinical Science
Michael Hanley, Scientific Director, Clinical Pharmacology
Celina Griffin, Associate Director, Pharmacovigilance
Jianchang Lin, Director, Statistics
Veronica Bunn, Senior Statistician, Statistics
Mark Lin, Director, Global Outcomes Research
Sylvie Vincent, Scientific Director, Translational Medicine
Francis Wolenski, Senior Toxicologist, Drug Safety Research & Evaluation
(b) (4)
Sarah Piloto, Regulatory Affairs, Thermo Fisher Scientific

BACKGROUND

Meeting Purpose
Millenium submitted a meeting request on September 17, 2020, to discuss whether Study 101 is adequate to support a planned New Drug Application for mobocertinib under the accelerated approval regulations (21 CFR 314, Subpart H).

Regulatory
On April 23, 2020, mobocertinib (TAK-788) was granted Breakthrough Therapy Designation for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutation whose disease has progressed on or after platinum-based chemotherapy based on a reported confirmed overall response rate (ORR) of 43% (95% CI 25, 63) in 28 patients. Among the 12 responders, 58% had a duration of response (DOR) ≥6 months and 50% had (DOR) ≥12 months.

On June 3, 2020, Fast Track designation was granted for the development of mobocertinib for the treatment of metastatic NSCLC harboring EGFR exon 20 insertion mutation.

Nonclinical

Mobocertinib is an irreversible inhibitor of the EGFR family of proteins, including EGFR with exon 20 activating insertions and the common activating mutations (exon 19 deletions and L858R) with or without the T790M resistance mutation. Millenium has completed in vitro studies pharmacology and hERG assays assessing the activity of mobocertinib and its two major metabolites; in vivo activity studies; safety pharmacology studies; ADME, phototoxicity, and genotoxicity studies, toxicology studies of up to 13 weeks duration in two animal species, and a pilot embryo-fetal development study in rats demonstrating increased embryofetal lethality at maternal exposures equivalent to human exposures at the recommended phase 2 dose (RP2D). Millenium plans to submit all nonclinical data to the NDA in a December 2020 submission.

Clinical Pharmacology

The pharmacokinetics (PK) of mobocertinib and its active metabolites (AP32960 and AP32914) were evaluated in the ongoing clinical trial, Study AP32788-15-101, in patients with NSCLC with EGFR exon 20 insertion mutations. A median T_{max} of 4 hours was observed following oral administration of mobocertinib. The single-dose C_{max} and $AUC_{0\text{-}24h}$ increased in a dose proportional manner in the dose range of 5 to 180 mg. However, steady state C_{max} and $AUC_{0\text{-}24h}$ following multiple doses increased in a less than dose proportional manner across the dose range of 5 to 180 mg. The terminal elimination half-life ($t_{1/2}$) of TAK-788 could not be characterized due to the daily dose regimen and the short washout period. A mean effective $t_{1/2}$ of approximately 15 (range=6-27) hours was estimated based on accumulation across the once daily doses of 20 to 160 mg. Accumulation ratios of 1.23 to 1.52 were observed in the dose range of 20 to 120 mg QD. At 160 mg QD, the geometric mean accumulation ratio following repeated doses was 1.06, suggesting autoinduction of mobocertinib apparent clearance is likely probably *via* CYP3A4 induction. The emerging finding of autoinduction by mobocertinib at the 160 mg QD dose is consistent with the results of *in vitro* induction studies that have shown concentration-dependent CYP3A4 induction by mobocertinib and its active metabolites (AP32960 and AP32914), suggesting a possible risk for drug-drug interactions (DDIs) due to induction of CYP3A4 and other co-regulated enzymes/ transporters by mobocertinib as a potential perpetrator. The relative systemic exposures of the active metabolites (AP32960 and AP32914) in the terms of combined molar $AUC_{0\text{-}24h}$ were approximately 62% (%CV: 25%) and 8% (%CV: 13%) to the parent drug respectively. The elimination half-life of AP32960 and AP32914 was similar to that of the parent drug, indicating formation rate-limited metabolite kinetics.

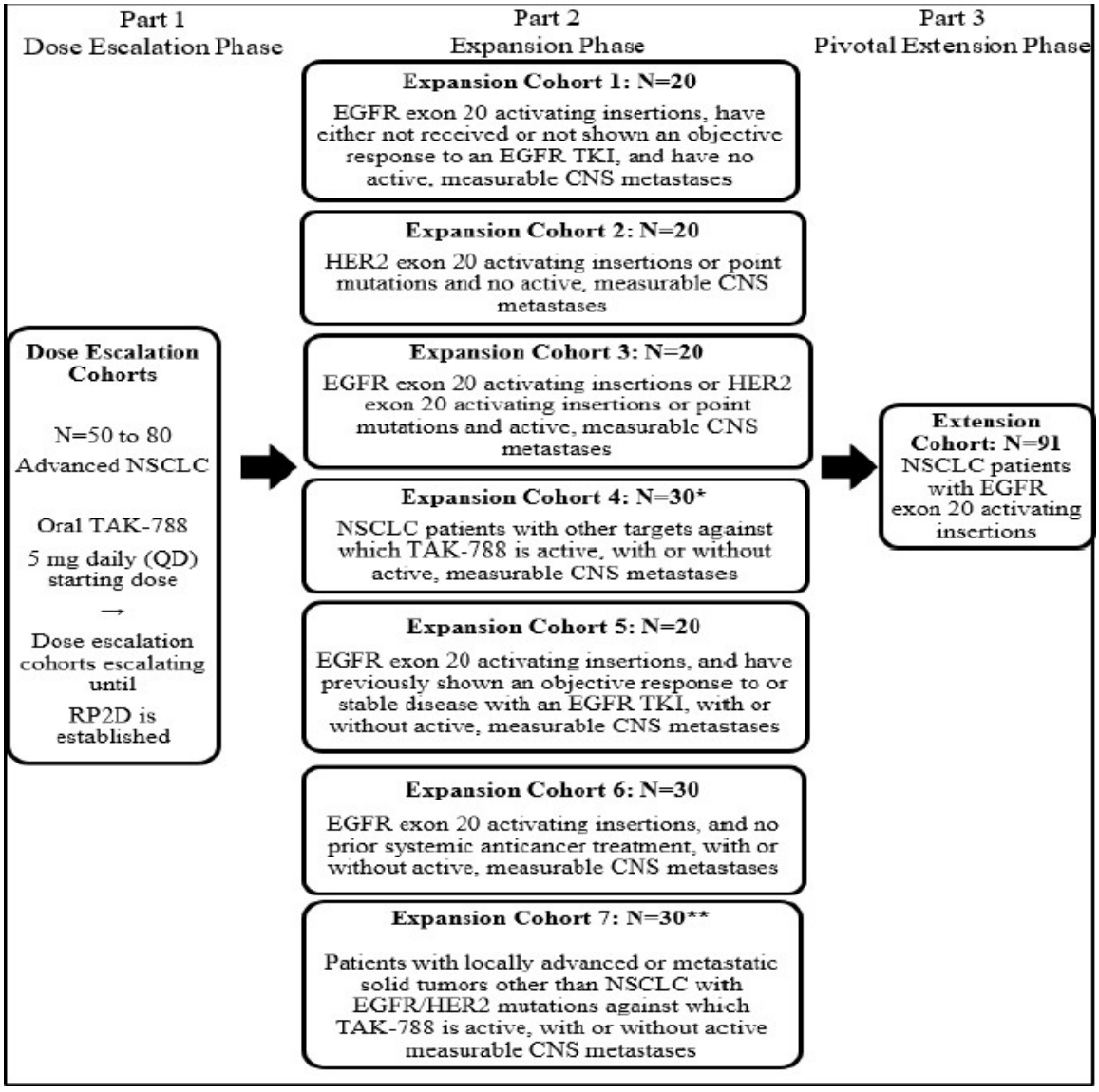
The clinical pharmacology development plan was reviewed and found to be generally acceptable (Final written response issued Aug 10, 2020).

Clinical

Study AP32788-15-101
Study AP32788-15-101 is an open-label, multi-center, three-part, dose escalation (3+3 design), dose expansion, and dose extension study of mobocertinib as a single agent in patients with metastatic NSCLC and other solid tumors. The study design is presented

in Figure 1 below (abstracted from the meeting briefing package). Cohorts 1 to 6 are limited to patients with NSCLC. The recommended phase 2 dose (RP2D) determined in Part 1 and used in Parts 2 and 3 is 160 mg once daily.

Figure1: Study AP32788-15-101 Study Design



Millennium provides efficacy results as of a data cut-off date of May 29, 2020, for the pooled prior platinum analysis set which consists of 114 patients with metastatic NSCLC with EGFR exon 20 insertion mutations previously treated with platinum-based chemotherapy who received mobocertinib at the 160 mg daily in Part 1 (n = 6), Expansion Cohort 1 of Part 2 (n = 28), and Part 3 (n =86). The confirmed ORR

assessed by independent review committee (IRC) in the pooled prior platinum analysis set is 26% (95% CI: 19, 35) with median DOR of 17.5 months. At the time of data cut-off, 63% of patients had follow-up of ≥6 months since onset of response.

In the Part 3 full analysis set, consisting of 96 patients who received at least one dose of mobocertinib, including 10 patients who had not previously received platinum-based chemotherapy, the ORR is 23% (95% CI: 15, 32).

The most common treatment emergent adverse events (TEAE) for the pooled prior platinum set were diarrhea (92%), rash (45%), vomiting (40%), decreased appetite (39%), nausea (37%), paronychia (35%), dry skin (32%), pruritus (24%), back pain (21%), cough (21%), and decreased weight (21%). Grade ≥3 TEAEs occurred in 66% of patients, with diarrhea the most common Grade ≥3 TEAE (22%). Serious adverse events occurring in ≥5% of patients were diarrhea (8%) and dyspnea (7%).

Real World Data (RWD) Proposal (Study TAK-788-5002)
Millennium plans to collect and conduct an analysis of RWD for a "historical benchmark cohort" of patients with NSCLC and EGFR exon 20 insertion mutations in order to provide an understanding of the natural history, treatment patterns and treatment outcomes with available therapies. Millennium preliminarily reports an ORR of 11.5% to 16.4% from the Flatiron HER database for previously treated patients with NSCLC harboring EGFR exon 20 insertion mutations receiving "physician-directed therapy" in Study TAK-788-5002.

Proposal for Rolling Submission
Millenium proposes a rolling submission for the NDA.

- Part 1: Submit by end of December 2020, to include nonclinical sections, and certain Module 1 documents.
- Part 2: Submit by end of February 2021, to include CMC, clinical sections, and labeling, as well as remaining Module 1 documents.

Study intended to verify clinical benefit - Study TAK-788-3001
Study TAK-788-3001 is an ongoing, open-label, multicenter, randomized study of mobocertinib in approximately 318 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations who have not previously received systemic treatment. Millennium reports that 37 patients have been enrolled into the study as of September 4, 2020.

Randomization is stratified by the presence of central nervous system (CNS) metastases at baseline (yes vs. no) and race (Asian vs. non-Asian). Patients will be randomized 1:1 to receive mobocertinib as a single agent (Arm A) or platinum-based chemotherapy (Arm B).

The primary efficacy endpoint for this study is progression-free survival (PFS) assessed by blinded independent review committee (BIRC) according to RECIST version 1.1. The primary analysis of PFS will be a stratified log rank test. Key secondary endpoints are confirmed ORR as assessed by IRC per RECIST v1.1 and overall survival (OS).

Study TAK-788-3001 will use an adaptive event-size reassessment approach for the primary endpoint and a sequential testing procedure for type I error control. One interim analysis is planned for futility, sample-size re-estimation, or efficacy after approximately 70% of the minimum total expected PFS events (159 of 227 events) have been observed. Assuming the median PFS for platinum-doublet chemotherapy is 6.5 months and the median PFS for mobocertinib is 10 months, a minimum total of 227 events will provide approximately 90% power to detect hazard ratio (HR) = 0.65 and will have a minimal detectable HR of 0.77 (approximately 2-month improvement in median PFS). An O'Brien-Fleming Lan-DeMets alpha spending function will be used to control the overall two-sided alpha level at 0.05. If the interim analysis is statistically significant per the pre-specified alpha boundary, the study will be stopped for efficacy and key secondary endpoints will be tested sequentially at the two-sided 0.05 level. If the interim analysis is not statistically significant per the pre-specified alpha boundary, the study will either be stopped for futility (if the futility criteria are met) or the total event size for the final analysis will be re-estimated using a conditional power approach, with an event cap of 270, if the results of the interim analysis fall in a "promising zone". The Cui-Hung-Wang (CHW) testing procedure will be applied at the final analysis to control type I error for event size re-estimation. The adaptation rule will be prepared by an independent design statistician who is not directly involved in the study conduct and will adopt an asymmetric step function for event size increase.

DISCUSSION

PREAMBLE

FDA has concerns regarding the ongoing, randomized trial, Study TAK-788-3001. While we acknowledge it is limited, the available data for response rate with mobocertinib in treatment-naïve patients with NSCLC harboring EGFR exon 20 insertion mutations (ORR 20%) suggests that single agent therapy with mobocertinib may not be appropriate in this patient population. FDA recommends Millenium consider investigating mobocertinib in combination with standard of care first-line therapy rather than continuing the study as currently designed. If Millenium elects to continue the study as designed, the protocol should be modified to incorporate an earlier analysis for futility.

In addition, given that anti-PD-(L)1 antibody, either alone or in combination with platinum-based chemotherapy, is the current standard of care in the U.S. for the first-line treatment of metastatic NSCLC, the use of a control arm of platinum-based chemotherapy is problematic, as patients will be foregoing therapy shown to improve OS outcomes and use of this control arm may limit the applicability of the results to the

US patient population. Given that a significant percentage (43%) of patients in the pooled prior platinum analysis set in Study AP32788-15-101 received prior treatment with immunotherapy, it appears this is an accepted treatment for patients with NSCLC harboring EGFR exon 20 insertion mutations, in which case a more appropriate control for Study TAK-788-3001 would be platinum-based chemotherapy plus an anti-PD(L)1 antibody.

Millenium's Response (received via email on November 9, 2020): The Sponsor acknowledges the Agency's advice, and would like to gain further understanding on the Agency's recommendation.

Discussion During Meeting: FDA reiterated the concerns expressed in the Preamble. Millenium indicated that they would take these comments under advisement and stated that they are already in the process of planning for a randomized trial assessing mobocertinib in combination with platinum-based chemotherapy. FDA urged Millennium to submit a meeting request to discuss the proposed study once they have clarified the design.

1) Does the Agency agree that the clinical results from Study 101 are adequate to support the submission of an NDA under the accelerated approval regulations (21 CFR 314 Subpart H) for mobocertinib as a treatment for adult patients with *EGFR* exon 20 insertion mutation-positive metastatic NSCLC who have received prior platinum-based chemotherapy?

FDA Response: Based on the data provided in the meeting background package, it is unclear whether the results are adequate to support the filing of an NDA. Please provide ORR and DOR results for the following subgroups of patients among the 114 patients in the pooled prior platinum analysis set: (a) patients who received prior treatment with platinum-based chemotherapy but no prior treatment with an anti-PD-(L)1 antibody and (b) patients who received both prior platinum-based chemotherapy and an anti-PD-(L)1 antibody (either concurrently or sequentially). In addition, provide information on the actual proportion of responders (not Kaplan-Meier estimates) with DOR ≥6 months and DOR ≥12 months for the pooled prior platinum analysis set and the two specified subgroups.

Furthermore, in order to allow adequate evaluation of the DOR, the majority, if not all, responders should have at least 6 months of follow-up past onset of response, as previously communicated during the August 10, 2020 meeting between FDA and Millenium. Given your stated plan to perform an updated analysis of ORR and DOR based on a November 2020 cut-off date, at which time all responders will have a follow-up of 6 months past onset of response, FDA recommends that data from this November 2020 analysis be used in the initial NDA submission rather than the currently available data based on a cut-off date of May 29, 2020. Given the observed response rate, FDA will not be able to

evaluate the ability of the results to support approval without this updated DOR data.

Millenium's Response (received via email on November 9, 2020): The Sponsor acknowledges the FDA's comments and is hereby providing ORR and DOR results as assessed by investigator and independent review committee (IRC) for the following two subgroups.

a) patients who received prior treatment with platinum-based chemotherapy but no prior treatment with an anti-PD-(L)1 antibody.

b) patients who received both prior platinum-based chemotherapy and an anti-PD-(L)1 antibody (either concurrently or sequentially).

In addition, the actual proportion of responders with DOR ≥6 months and DOR ≥12 months as assessed by investigator and IRC for the pooled prior platinum analysis set and the two specified subgroups (a and b) are also provided below. The ORR and median DOR are similar for the pooled prior platinum analysis set and the two specified subgroups.

Table 1 Investigator Assessed ORR and DOR for Pooled Prior Platinum Analysis Set and Subgroups with or without Prior anti-PD-(L)1 Antibody

	Mobocertinib 160 mg Patients without Prior Anti-PD-(L)1 Antibody N=66	Mobocertinib 160 mg Patients with Prior Anti-PD-(L)1 Antibody N=48	Mobocertinib 160 mg Overall N=114
Confirmed Objective Response n (%)	**22 (33.3)**	**18 (37.5)**	**40 (35.1)**
(95% CI)	(22.20, 46.01)	(23.95, 52.65)	(26.38, 44.59)
Confirmed Disease Control n (%)	**52 (78.8)**	**37 (77.1)**	**89 (78.1)**
(95% CI)	(66.98, 87.89)	(62.69, 87.97)	(69.35, 85.28)
Descriptive Duration of Confirmed Response (months)			
Median (95% CI)	**5.55 (3.75, 6.01)**	**5.44 (3.84, 13.90)**	**5.52 (4.96, 5.59)**
Min, Max	3.2, 19.3	3.7, 22.1	3.2, 22.1
>= 3 months n (%)	22 (100.0)	18 (100.0)	40 (100.0)
>= 4 months n (%)	15 (68.2)	12 (66.7)	27 (67.5)
>= 5 months n (%)	15 (68.2)	11 (61.1)	26 (65.0)
>= 6 months n (%)	**6 (27.3)**	**7 (38.9)**	**13 (32.5)**
>= 12 months n (%)	**1 (4.5)**	**5 (27.8)**	**6 (15.0)**

	Mobocertinib 160 mg Patients without Prior Anti-PD-(L)1 Antibody N=66	Mobocertinib 160 mg Patients with Prior Anti-PD-(L)1 Antibody N=48	Mobocertinib 160 mg Overall N=114

Note: Prior treatment with Anti-PD-(L)1 antibody can be either concurrent or sequential with prior treatment of platinum-based chemotherapy

Table 2 IRC Assessed ORR and DOR for Pooled Prior Platinum Analysis Set and Subgroups with or without Prior anti-PD-(L)1 Antibody

	Mobocertinib 160 mg Patients without Prior Anti-PD-(L)1 Antibody N=66	Mobocertinib 160 mg Patients with Prior Anti-PD-(L)1 Antibody N=48	Mobocertinib 160 mg Overall N=114
Confirmed Objective Response n (%)	**18 (27.3)**	**12 (25.0)**	**30 (26.3)**
(95% CI)	(17.03, 39.64)	(13.64, 39.60)	(18.51, 35.39)
Confirmed Disease Control n (%)	**52 (78.8)**	**37 (77.1)**	**89 (78.1)**
(95% CI)	(66.98, 87.89)	(62.69, 87.97)	(69.35, 85.28)
Descriptive Duration of Confirmed Response (months)			
Median (95% CI)	**4.65 (3.71, 6.01)**	**5.57 (3.71, 17.51)**	**5.55 (3.71, 6.01)**
Min, Max	1.8, 17.5	3.6, 20.3	1.8, 20.3
>= 3 months n (%)	17 (94.4)	12 (100.0)	29 (96.7)
>= 4 months n (%)	9 (50.0)	8 (66.7)	17 (56.7)
>= 5 months n (%)	9 (50.0)	8 (66.7)	17 (56.7)
>= 6 months n (%)	**5 (27.8)**	**5 (41.7)**	**10 (33.3)**
>= 12 months n (%)	**1 (5.6)**	**3 (25.0)**	**4 (13.3)**

Note: Prior treatment with Anti-PD-(L)1 antibody can be either concurrent or sequential with prior treatment of platinum-based chemotherapy

Mobocertinib provides a potentially valuable option for patients suffering with EGFR exon 20 insertion mutation–positive NSCLC previously treated with platinum-based chemotherapy.

The Sponsor agrees with the Agency to include data from the November 2020 data cut-off in the initial NDA submission. At the data cut-off of May 2020, more than 80% of responders as assessed by investigator and IRC have at least 5

months of follow-up post onset of response (63% have 6 months or more and 20% have 5-<6 months). It is anticipated that all responders will have had the opportunity to have at least 6 months of follow up, at the planned November 2020 data cut-off. It is anticipated that topline data from the November 2020 data cutoff will be available as early as January 2021. Our proposed plan is to share the topline data from the November 2020 data cut with the Agency around mid-January via e-mail correspondence. We hope the Agency will be able to provide feedback regarding whether the results could support approval, while we continue to prepare the initial NDA submission currently planned for February 2021.

In order to enable the initial NDA submission by February 2021:

- We propose the STDM and ADaM datasets from the November 2020 data cut-off will be included in Module 5 of the initial NDA submission.
- The updated ORR and DOR from the November 2020 data cut-off will be provided in the initial NDA submission within Module 2.5 and Module 2.7.3, along with the topline data (tables, listings and figures) to be provided in Module 5. The CSR and clinical Module 2 documents will contain the full results from the May 2020 data cut-off.
- The efficacy section in the proposed USPI will be based on the November 2020 data cut-off.

Would this approach be acceptable for the Agency?

Discussion During Meeting: FDA acknowledged Millenium's response and agreed the proposed approach is acceptable. FDA indicated that the Assessment Aid should include efficacy data based on the November 2020 data cut-off date rather than the May 2020 cut-off date. It would be acceptable for the Assessment Aid to include safety data based on the May 2020 cut-off date with updated safety information to be provided in the 120-day safety update.

FDA does not object to Millenium contacting them via email with topline results from the November 2020 data cut-off. Whether the results will support a specific indication will largely depend upon the duration of response (DOR) data. In the NDA submission, Millenium will need to present an argument to demonstrate that mobocertinib represents an improvement over available therapy.

2) Does the Agency agree with the sponsor's proposal for submission of updated DOR data based on a November 2020 data cutoff?

FDA Response: Please refer to FDA Response to Question 1.

Millenium's Response (received via email on November 9, 2020): The Sponsor acknowledges the Agency's feedback to Question 1 and would like to discuss further within the context of Question 1.

Discussion During Meeting: Refer to Discussion During Meeting for Question 1.

3) Does the Agency agree with the sponsor's approach to provide a contemporaneous context for the RWD from Study TAK-788-5002?

FDA Response: FDA agrees to Millenium's approach to provide contemporaneous natural history information with RWD from Study TAK-788-5002. However, the results of Study TAK-788-5002 will be considered exploratory, and no formal comparisons between the real-world cohort of this study and Study AP32788-15-101 will be considered.

Millenium's Response (received via email on November 9, 2020): The Sponsor acknowledges the Agency's comments, and no further discussion on Question 3 is required at the November 10, 2020 meeting.

Discussion During Meeting: No discussion occurred.

4) Can the Agency please comment on the proposed rolling review NDA submission plan and Real Time Oncology Review (RTOR)?

FDA Response: In general, the proposal is acceptable. FDA acknowledges the proposed companion diagnostic (CDx) submission timeline and further comments about CDx review timelines can be provided once the PMA supplement is submitted and being reviewed.

Millenium's Response (received via email on November 9, 2020): The Sponsor acknowledges the Agency's comments, and no further discussion on Question 4 is required at the November 10, 2020 meeting.

Discussion During Meeting: No discussion occurred.

ADDITIONAL FDA COMMENTS

Nonclinical

5) It is unclear from the meeting package whether Millenium plans to include any assessment of the genotoxicity of the major active human metabolites of mobocertinib in the planned NDA submission. Please include any available in vitro or in silico data regarding the genotoxicity of these two metabolites.

Millenium's Response (received via email on November 9, 2020): The Sponsor acknowledges the Agency's comments. We are providing the following

response to address the Agency's comment and no further discussion on this topic is required at the November 10, 2020 meeting.

The genotoxic potential of mobocertinib was assessed following the recommendations of ICH S9 and S2(R1), and included both in vitro and in vivo assessments. An assessment of the genotoxicity of the major active metabolites of mobocertinib (AP32960 and AP32914) is not planned in the NDA submission.

Mobocertinib was not mutagenic in a GLP-compliant bacterial reverse mutation assay, nor was it clastogenic in a GLP-compliant in vitro mammalian chromosome aberration assay using human peripheral blood lymphocytes. Mobocertinib did not induce chromosome damage in immature erythrocytes in a GLP-compliant micronucleus test in Sprague-Dawley rats administered mobocertinib.

A formal in silico assessment of the mutagenic potential of the 2 major active mobocertinib metabolites, AP32960 and AP32914, was not conducted and is not planned for the NDA submission. However, a preliminary in silico analysis (*see Appendix 1*) using both rules based and statistically based software is provided to address the Agency's comments about these 2 metabolites.

In conclusion, there is no evidence that AP32960 and AP32914 possess genotoxic potential. An assessment of the genotoxicity of the major active metabolites of mobocertinib (AP32960 and AP32914) is not planned in the NDA submission. The alerting structures of the metabolites identified by in silico analysis were identical to those found in mobocertinib, which was negative for mutagenicity (with and without S9 fraction) in a bacterial reverse mutation assay. In a mammalian chromosomal aberration assay using HBPLs, mobocertinib was not clastogenic, and while there was a statistically significant increase in aberrant metaphases after incubation with the S9 fraction, the increase was not dose dependent and was not considered indicative of genotoxic potential. Lastly, in an in vivo rat study there was no mobocertinib-related increase in the proportion of micronucleated immature erythrocytes, which indicates that mobocertinib did not induce chromosome damage. Plasma levels of the metabolites were at least 2-fold greater in the rat micronucleus study than in patients at the recommended 160 mg dose.

Discussion During Meeting: No discussion occurred.

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 stated that an inclusion of a REMS is not required for filing of the planned NDA. FDA will make a final determination regarding whether a REMS will be required during the NDA review.

- 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.

In addition, we note that a CMC-only pre-submission meeting was held on July 21, 2020. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

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.

FDA acknowledges receipt of your Agreed Initial Pediatric Study Plan (iPSP) submitted on May 7, 2020, and also refers to our May 29, 2020, letter confirming our agreement with this iPSP. Because your planned marketing application was not submitted prior to August 18, 2020 and consistent with the advice in our May 29, 2020 letter indicating agreement with your iPSP, you will need to amend the iPSP to address the new PREA requirements, as amended by FDARA section 504 to section 505B of the FD&C Act regarding molecularly targeted oncology drugs. This amended iPSP should addresses the target of this product and its potential relevance to one or more pediatric cancers and describe the 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) and/or any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation and justification for this approach.

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 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.

Meeting 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

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

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 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

[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

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.

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.[6]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[7] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

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[6] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

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

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

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

Additional information can be found at FDA.gov.[8]

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

[8] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

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

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

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

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

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[9] and the CDER/CBER Position on Use of SI Units for

[9] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

Lab Tests website.[10]

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.[11]

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.[12]

SECURE EMAIL COMMUNICATIONS

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

MANUFACTURING FACILITIES

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

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

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[10] https://www.fda.gov/media/109533/download
[11] http://www.fda.gov/ectd
[12] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[13] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[14]. 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,

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

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

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*.[15]

ONCOLOGY PILOT PROJECTS

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

- RTOR[16]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

Assessment Aid[17]

ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

ACTION ITEMS

No action items.

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[15] https://www.fda.gov/media/85061/download
[16] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[17] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

ATTACHMENTS AND HANDOUTS
No attachment and handouts.

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

/s/

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CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 126721
Request Receipt Date	February 25, 2020
Product	TAK-788
Indication	For the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy
Drug Class/Mechanism of Action	Tyrosine kinase inhibitor (TKI)
Sponsor	Millenium Pharmaceuticals, Inc.
ODE/Division	Office of Oncologic Diseases/Division of Oncology 2
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	April 24, 2020 (Technical 60 day date: April 25, 2020)

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

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

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

   TAK-788 is indicated for the treatment of patients with metastatic NSCLC with EGFR exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy.

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

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

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

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

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

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

Reference ID: 4591835

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

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

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

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

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

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

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

Deny Breakthrough Therapy Designation ☐

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

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

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

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

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

Drug description

According to the sponsor, TAK-788 (formerly AP32788) is an irreversible tyrosine kinase inhibitor (TKI) targeting targeting epidermal growth factor receptor (EGFR) with exon 20 insertions. TAK-788 forms a covalent bond with cysteine 797 in EGFR, which results in sustained inhibition of EGFR signaling.

Information regarding the disease and intended population for the proposed indication

Lung cancer is the leading cause of cancer and cancer-related mortality worldwide[1] and the leading cause of cancer-related deaths in the US[2].

EGFR exon 20 mutations occur in approximately 1.7%[3] – 4 % [4] of all EGFR mutations in NSCLC and consist of in-frame insertions in exon 20, leading to activation of the downstream AKT and MEK pathways. These mutations induce a pattern of in vitro and in vivo resistance to EGFR-TKIs and are reported to increase the affinity of EGFR for adenosine triphosphate (ATP), thus decreasing the efficacy of TKI inhibition (Yasuda et al, Lancet Oncol 2012). EGFR exon 20 insertion mutations occur in the same group of patients and tumors with classic EGFR mutations (i.e., women, non-smokers, adenocarcinoma histology) are resistant to clinically achievable doses of EGFR inhibitors approved to date, including gefinitib, erlotinib, neratinib, afatinib, and dacomitinib.

The drug's relation to existing therapy(ies)

Currently there is no FDA-approved targeted therapy for patients with EGFR exon 20 insertion mutation-positive tumors.

Refer to Section 9 below for a summary of conventional systemic therapies that are currently available for EGFR wild-type tumors.

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

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

Objective response rate (ORR) per RECIST v.1.1 and duration of response in a multi-cohort study were submitted by the Sponsor to support this breakthrough therapy designation request.

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

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

Both overall survival and progression-free survival have been used to support approvals in NSCLC. Additionally, objective response rate (ORR) with duration of response has been considered clinically meaningful and supportive of accelerated approvals.. In cases of tumors with low incidence, including NSCLC harboring less common genomic tumor aberrations, ORR of large magnitude associated with durable responses has been accepted to support regular approval.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

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

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Currently there is no FDA-approved target therapy for patients with EGFR exon 20 insertion mutation-positive tumors.

Patients with advanced NSCLC and tumors harbouring EGFR exon 20 insertion mutations are treated with conventional systemic therapies that are available for EGFR wild-type tumors, including first-line platinum-containing chemotherapy and/or an anti-PD(L)1 antibody. Upon progression, subsequent available therapies include: single agent anti-PD(L)1 antibody (nivolumab, pembrolizumab or atezolizumab) and single agent chemotherapy (docetaxel, pemetrexed) or docetaxel in combination with ramucirumab. A summary of the trial and approval endpoints are shown in the following table.

Of note, docetaxel with ramucirumab is used infrequently in favor of single agent immunotherapy or chemotherapy. This is due to the additive toxicity of the combination regimen and largely due to the rapid uptake of immunotherapy in clinical practice post 2015. In addition, many ongoing trials utilize single agent docetaxel as a control arm in the second line metastatic NSCLC setting. DO2 considers this acceptable given the additive toxicity and marginal OS benefit of docetaxel plus ramucirumab.

Table 1: Biologic/Drug Approved for 2nd-line metastatic NSCLC

	Clinical Trial	Approval Endpoint
Single Agent checkpoint inhibitor		
Nivolumab	RCT* of nivolumab vs. docetaxel for nonsquamous NSCLC (Checkmate-057)	median OS 12.2 vs. 9.4 mo [HR 0.72 (0.60, 0.89)] mPFS 2.3 vs. 4.2 mo [HR 0.92 (0.77, 1.11)] **ORR 19% (95% CI 15, 24) vs. 12% (95% CI 9, 17)**
Pembrolizumab	RCT of pembrolizumab vs. docetaxel for PD-L1 positive metastatic NSCLC (KEYNOTE-010)	Pembrolizumab 10 mg/kg vs. docetaxel mOS 12.7 vs. 8.5mo [HR 0.61 (95% CI 0.49, 0.75)] mPFS 4.0 vs. 4.0 mo [HR 0.79 (0.66, 0.94)] **ORR 19% (95% CI 15, 23) vs. 9% (95% CI 7, 13)**
Atezolizumab	RCT of atezolimab vs. docetaxel for metastatic NSCLC (OAK)	mOS 13.8 vs. 9.6 mo [HR 0.74 (95% CI 0.63, 0.87)] mPFS 2.8 vs. 4.0 mo (HR 0.95 (0.82, 1.10) **ORR 14% (95% CI 11, 17) vs. 13% (95% CI 10, 17)**
Single Agent Chemotherapy		
Docetaxel	RCT docetaxel vs. vinorelbine/Ifosfamide (TAX320 trial)	mOS 5.7 vs. 5.6 mo (Risk Ratio, Mortality 0.82 (95% CI 0.63, 1.06) mTTP 8.3 vs. 7.6 weeks **ORR 5.7% (95% CI 2.3, 11.3) vs. 0.8% vs. (95% CI 0.0, 4.5)**
Pemetrexed	RCT pemetrexed vs. docetaxel (study JMEI)	Exploratory OS analysis by histology (non-squamous) mOS 9.3 vs. 8.0 [HR 0.89 (95% CI 0.71-1.13)]
Combination Therapy		
Docetaxel plus ramucirumab	RCT ramucirumab/docetaxel vs. placebo/docetaxel (REVEL study)	N=1253 mOS 10.5 vs. 9.1 m (HR 0.86 (95% CI 0.75, 0.98) PFS 4.5 v.s 3.0 months [HR 0.76 (0.68, 0.86) **ORR 23% (95% CI 20, 26) vs. 14% (95% CI 11, 17)**

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

On March 9, 2020, Janssen Research and Development received breakthrough designation for JNJ-61186372. The indication is in patients with metastatic NSCLC with EGFR exon 20 insertion mutations who have been previously treated with platinum-based chemotherapy. Data to support the breakthrough designation was derived from Cohort D of EDI1001 study, an ongoing, dose-finding, multi-cohort study to evaluate the safety, tolerability and preliminary activity of JNJ-61186372 in patients with EGFR or MET mutations. Objective response rate was observed in 12 of 29 patients (ORR 41%, 95% CI 23.5, 61). The median duration follow-up time was 9.4 months, the median duration of response was 6.8 months (95% CI: 3.19, 16.1), and the median duration of treatment was 9.2 months.

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Table 2: Clinical Trial Supporting the BTDR

Study ID	Trial Design	No. of Patients	Treatment Group	Results to support BTD
AP32788-15-101	Single arm, dose- finding, activity estimating	Total enrolled: 136 RP2D in 2nd-line: (n=28)	Dose escalation: (n=6) Cohort expansion: (n=22)	EGFR exon 20 insertion, 2nd-line population (n=28) ORR 43% (95% CI 25, 63) DoR 10.2 months (range 5, 14)

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

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

Efficacy data to support the BTDR is derived from study AP32788-15-101, an ongoing, dose-finding, multi-cohort study to evaluate the safety, tolerability and preliminary activity of TAK-788 in patients with EGFR exon 20 mutations. TAK-788 is administered 160mg once daily until disease progression, unacceptable toxicity or withdrawal of consent.

From the study, 28 patients received at least one line of systemic platinum-based chemotherapy in the metastatic setting. Objective response rate was observed in 12 of 28 patients (ORR 43 %, 95% CI 25, 63). The median duration of response is 10.2 (range: 5, 14) months with 58% of patients responding for > 6 months and 50% of patients responding for > 12 months. The sponsor reports that 11/12 confirmed responders were followed up for at least 6 months.

Safety data were provided for 136 patients enrolled in study AP32788-15-101 with a data cutoff of January 27, 2020. The most common adverse events ($\geq$ 20%) were diarrhea, nausea, decreased appetite, vomiting, rash, fatigue, dry skin, anemia, and stomatitis. The most common grade $\geq$ 3 adverse events were diarrhea, hypertension, increased lipase, anemia, stomatitis, dyspnea, hypoxia, nausea, and vomiting. The safety profile of TAK-788 is, in general, consistent with the drugs of anti-EGFR class.

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

☒ GRANT:

Provide brief summary of rationale for granting:

The division considers the ORR (43%, 95% CI 25, 63) with median duration of response 10.2 months (95% CI: 5, 14) observed with TAK-788 as preliminary clinical evidence of a substantial improvement over the currently available therapies.

Reference ID: 4591835

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

☐DENY:

Provide brief summary of rationale for denial:

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

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

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

The division supports the ongoing efforts of the sponsor to complete the analysis of 91 additional patients onto the "EXCLAIM" extension cohort (Part 3) of the study. All patients in the extension phase have an EGFR exon 20 insertion mutation documented by a local test before enrollment, with retrospective confirmation of this mutation by an analytically validated central test. Enrollment in Part 3 of the study began in February 2019, and enrollment completed in December 2019. The study is conducted in the US, Europe, and Asia.

ThermoFisher Scientific is in communication with CDRH regarding the Oncomine Diagnostic Target test to be approved as the companion Dx test for TAK 788.

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

14. List references, if any:

1. WHO, GLOBOCAN 2018: Estimated Cancer, Incidence, Mortality and Prevalence Worldwide in 2018. http://gco.iarc.fr/today/home

2. NCI, Surveillance, Epidemiology, and End Results Program: Cancer Stat Facts, 2019 https://seer.cancer.gov/statfacts/html/lungb.html

3. Zhang Yue-Lun, Yuan J-Q at al. The Prevalence of EGFR Mutation in Patients with Non-Small Cell Lung Cancer: a Systematic Review and Meta-Analysis. Oncotarget, Vol.7, No. 48, October 12, 2016

4. Yasuda H, Kobayashi Sand Costa DB: EGFR exon 20 insertion mutations in non-small-cell lung cancer: Preclinical data and clinical implications. Lancet Oncol 13: e23-e31, 2012.

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

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

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}

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

Revised 3/18/19/M. Raggio

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

/s/

LUCKSON N MATHIEU
04/14/2020 11:59:35 AM

ERIN A LARKINS
04/14/2020 12:27:18 PM

B HARPREET SINGH
04/14/2020 08:54:26 PM

IND 126721

MEETING MINUTES

Millennium Pharmaceuticals, Inc.
Attention: Sharon Cang, MS, RAC
Associate Director, Global Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Cang:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AP32788.

We also refer to your February 19, 2019, correspondence, requesting a meeting to discuss the proposed randomized trial, Protocol TAK-788-3001, intended to support the proposed indication for AP32788 for the first-line treatment- of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations and the acceptability of the proposed overall registration strategy for TAK-788 for this proposed indication. Our preliminary responses to your meeting questions are enclosed. You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301)796-0704.

Sincerely,

See appended electronic signature page}

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	May 29, 2019
Meeting Location:	CDER WO 22 – Room 1311
Application Number:	IND 126721
Product Name:	TAK-788
Indication:	First-line treatment of patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) with epidermal growth factor (EGFR) exon 20 insertion mutations.
Sponsor/Applicant Name:	Millennium Pharmaceuticals, Inc., A wholly owned subsidiary of Takeda Pharmaceutical Company

FDA ATTENDEES

Center for Drug Evaluation Research

Office of Hematology and Oncology Products

Patricia Keegan, M.D.,	Division Director, DOP2
Erin Larkins, M.D.,	Medical Team Leader, DOP2
Luckson Mathieu, M.D.,	Clinical reviewer, DOP2
Gina Davis, M.T.,	Senior Regulatory Health Project Manager, DOP 2
Whitney Helms, Ph.D.,	Supervisor, DHOT
Dubravka Kufrin, Ph.D.,	Toxicology Reviewer, DHOT

Office of Clinical Pharmacology

Jeanne Fourie-Zirkelbach, Ph.D.,	Team Lead, Clinical Pharmacology
Krithika Arun Shetty, Ph.D.,	Clinical Pharmacology Reviewer

Center for Devices and Radiologic Health

Office of InVitro Radiology

Karen Bijwaard, M.S.,	Reviewer, Office of InVitro Radiology
Soma Ghosh, Ph.D.,	Acting Branch Chief, Office of InVitro Radiology

SPONSOR ATTENDEES

Sharon (Shengqun) Cang	Associate Director, Global Regulatory Affairs
Guilin Huang	Director, Global Regulatory Affairs
Jesus Gomez-Navarro	Vice President, Clinical Science
Shuanglian Li	Medical Director, Clinical Science
Andy Chi	Senior Director, Biostatistics
Jian Zhu	Senior Statistician, Biostatistics
Mark Lin	Director, Global Outcomes Research

Sylvie Vincent	Scientific Director, Translational Medicine
Steven Zhang	Associate Scientific Director, Clinical Pharmacology
Celina Griffin	Associate Director, PV Sciences
Rachael Brake	Senior Director, Global Program Lead

BACKGROUND

On August 22, 2015, Ariad Pharmaceuticals (now Millennium Pharmaceuticals, Inc., a subsidiary of Takeda LLC) submitted a meeting request, written responses only, to discuss the nonclinical program regarding the investigational product AP32788 as well as plans for the first-in-human study. The final meeting minutes issued on October 15, 2015.

The original IND was submitted on December 29, 2015, for Protocol AP32788-15-101, entitled, "A Phase 1/2 Study of the Safety, Pharmacokinetics, and Anti-Tumor Activity of the Oral EGFR/HER2 Inhibitor AP32788 in Non-Small Cell Lung Cancer." The study may proceed letter issued on January 28, 2016.

On March 9, 2018, Ariad submitted a new protocol, Protocol TAK-788-1001, entitled, "Phase 1, Randomized, Double-blind, Placebo-Controlled, Single Rising Dose Study to Evaluate Pharmacokinetics, Safety, and Tolerability of TAK-788 Followed by Crossover Evaluation of the Effects of a Low-Fat Meal on TAK-788 Pharmacokinetics in Healthy Subjects".

Nonclinical
TAK-788 is an irreversible inhibitor of the EGFR family of proteins, including EGFR with exon 20 activating insertions and the common activating mutations (exon 19 deletions and L858R) with or without the T790M resistance mutation. ARIAD has completed safety pharmacology studies, ADME and genotoxicity studies, and toxicology studies of up to 4 weeks duration in two animal species. FDA previously discussed the expectations for embryo-fetal development (EFD) studies and metabolite coverage to support an NDA and for 13-week toxicology studies in two species prior to initiation of a clinical trial intended to support registration.

Clinical Pharmacology
Millennium provided available PK, safety and efficacy data from the ongoing phase 1/2 study, Study AP32788-15-101, and from the low fat food effect study TAK-788-1001 to justify the proposed TAK-788 dosage of 160mg QD PO with or without a low fat meal for Study TAK-788-3001. Based on data from the escalation stage of Study AP32788-15-101, the 160 mg QD dosage was identified as the MTD and the RP2D and evaluated further in the expansion and extension cohorts. Based on currently available PK data, steady state systemic exposures do not meaningfully increase at doses greater than 120 mg QD, potentially due to auto-induction of CYP3A-mediated metabolism. Based on efficacy data available as of 14th September 2018, Millennium reports an unconfirmed ORR of 53.8% (CI: 33.4-73.4) at the160 mg QD PO dosage in NSCLC

patients with EGFR exon 20 insertion mutations who have been previously treated with at least 1 prior line of systemic anticancer therapy (n=28). Millennium indicates the higher incidence of GI AEs observed at the 160 mg QD dosage compared to lower dosages will be clinically managed using therapeutic interventions and dose reductions as appropriate.

Based on the results of the low-fat food effect study TAK-788-1001, a low fat meal does not appear to have a clinically meaningful impact on TAK-788 systemic exposure. Millennium hypothesizes that co-administration with food might mitigate GI AEs.

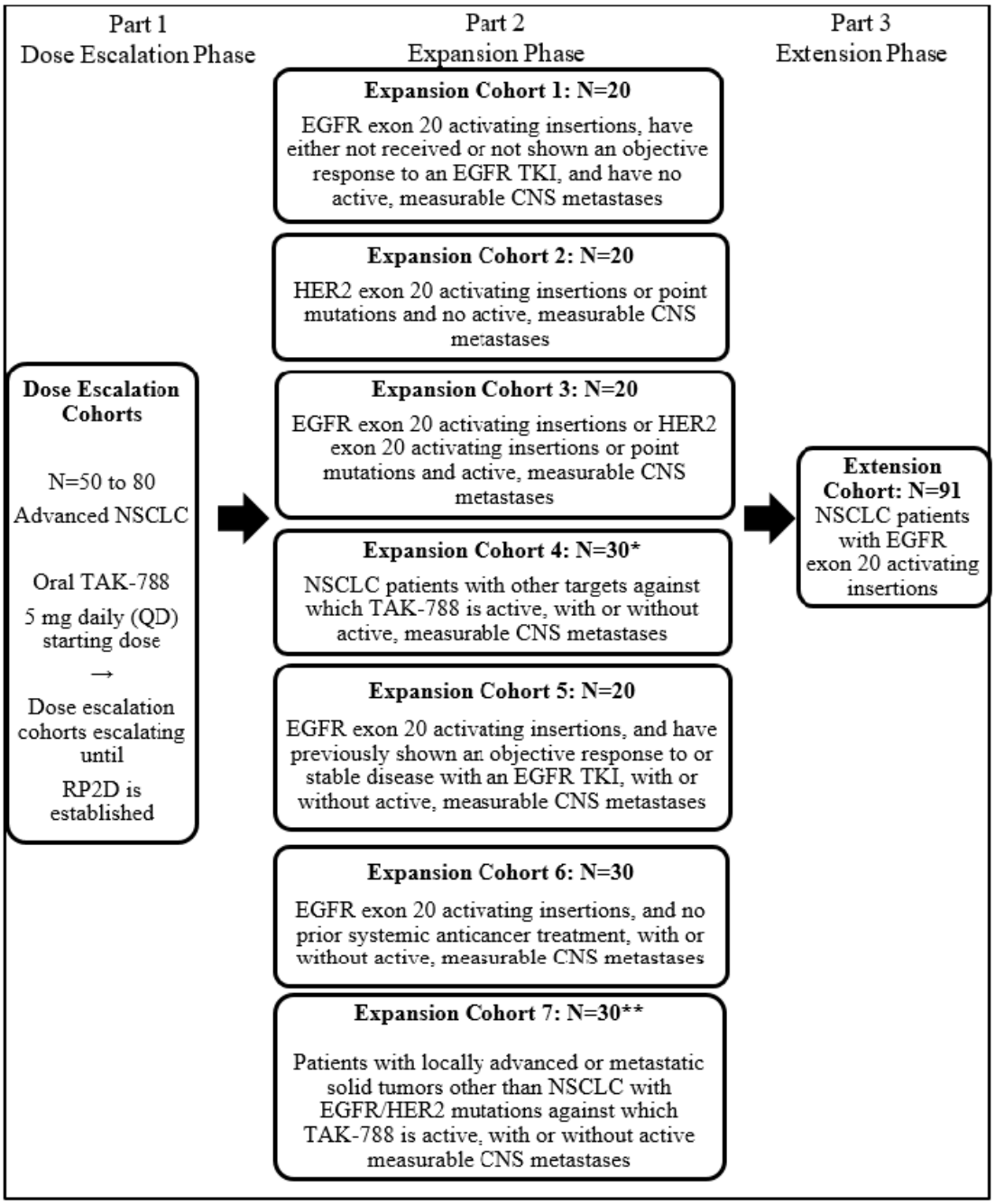
The TAK-788-1001 study also evaluated the comparative bioavailability of a test (b) (4) 20 mg) drug-in-capsule formulation relative to a reference ((b) (4) 20 mg) drug-in-capsule formulation. The results of this assessment have not been provided in this meeting package. Additionally, Millennium has indicated in the EOP1 meeting package that a commercial formulation is under development; no updates have been provided in this meeting package. The protocol synopsis does not clearly indicate the formulation that will be used in the planned randomized study TAK-788-3001.

Clinical

Study AP32788-15-101

Study AP32788-15-101 is an ongoing first-in-human, open-label, multi-center, dose escalation (3+3 design), dose expansion, and dose extension study designed to determine the recommended phase 2 dose (RP2D), evaluate the anti-tumor activity, and identify the safety profile of single agent TAK-788 in patients with metastatic NSCLC and other solid tumors. The protocol has been amended several times since its initiation. The current study design is presented in Figure 1 below, abstracted from the meeting briefing package. Enrollment began in June 2016, dose expansion cohorts opened in mid-January 2018, and enrollment in the dose extension phase began in February 2019.

Figure 1: Study AP32788-15-101 Schema
(Adapted from Millennium Package, Page 36)



The primary objective of the dose expansion portion is to determine the overall response rate (ORR) as assessed by investigator per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) in each cohort. The dose extension portion is enrolling patients with metastatic NSCLC whose tumors harbor EGFR exon 20 insertion

mutations and who have received at least one prior line of therapy for locally advanced or metastatic disease and no more than two regimens of systemic anticancer chemotherapies. According to the Millennium, EGFR exon 20 insertion mutations will be retrospectively confirmed in all patients' tumor specimens using an analytically validated central test. The confirmed ORR as assessed by Independent Review Committee (IRC) per RECISTv1.1 is the primary endpoint for the extension cohort.

Preliminary Results from Study AP32788-15-101

Based on the results of the dose escalation and dose expansion portion of study AP32788-15-101, the RP2D was determined to be 160mg once daily. As of the safety data cutoff date of September 14, 2018, 101 patients have received TAK-788 in Study AP32788-15-101, including 46 patients at the 160 mg daily dose level. The most common adverse events (≥ 20%) across all doses were: diarrhea, nausea, decreased appetite, rash, vomiting, and fatigue. The most common adverse events (occurring in ≥ 20%) of patients treated with TAK-788 160 mg QD were: diarrhea (85%), rash (43%) nausea (41%), vomiting (30%), decreased appetite (28%), and stomatitis (22%).

As of September 14, 2018, 22 patients had been treated in cohort 1, which is comprised of patients with NSCLC harboring exon 20 insertion mutations who have received at least one prior line of systemic anticancer therapy. Six patients treated at the RP2D of 160 mg daily in the dose escalation portion of the study met these same criteria. Millennium presents pooled ORR data for 26 of these 28 patients who had or were due for at least one post-baseline disease assessment at the time of data cut-off. Among these 26 patients, the confirmed ORR is 27% (95% CI:12, 48).

Proposed Clinical Trial: Study TAK-788-3001

Study TAK-788-3001 is an open-label, multicenter, randomized study of TAK-788 in patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations who have not previously received systemic treatment with the exception that prior neoadjuvant or adjuvant chemotherapy or combined modality chemotherapy/radiation is allowed if completed > 6 months before the development of metastatic disease.

Determination of EGFR mutation status for enrollment will be based on a documentation of EGFR in-frame exon 20 insertion by a local laboratory test (LLT);confirmation by central testing is not required before randomization. Formalin-fixed paraffin embedded (FFPE) tumor samples, collected either from an archival or recent biopsy specimen as part of the standard of care, will be requested at enrollment and retrospectively tested in a central laboratory for the presence of EGFR exon 20 insertion mutations by the candidate companion diagnostic (CDx), Thermo Fisher Scientific Oncomine Dx Target Test CDx assay (ODxT Test), an investigational use only (IUO) assay analytically validated for the detection of EGFR exon 20 mutation variants. Patients must have measurable disease per RECIST v1.1 and ECOG performance status of 0 or 1.

Randomization will be stratified by the presence of central nervous system (CNS) metastases at baseline (yes versus no) and race (Asian versus non-Asian). An estimated 318 patients (159 per arm) will be randomized at approximately 150 sites. Eligible patients will be randomly assigned (1:1) to receive:

- Experimental (Arm A): TAK-788 at 160 mg daily (orally) on a 21-day cycle or

- Control (Arm B): Platinum-based chemotherapy— investigator's choice of either pemetrexed/cisplatin or pemetrexed/carboplatin every 3 weeks (Q3W) for 4 cycles followed by maintenance treatment with pemetrexed Q3W

Disease assessment, including brain imaging for patients with baseline CNS metastases, will be performed every 6 weeks through cycle 18 then every 12 weeks thereafter, until documentation of progression disease. Brain imaging is required at screening for all patients but will only be repeated post-baseline for patients with baseline CNS metastases. Patients in the control arm who experience disease progression will be offered TAK-788 at the time of disease progression. Patients will be treated until they experience progressive disease (PD) assessed by the blinded independent review committee (IRC), intolerable toxicity, or another discontinuation criterion. Continuation of study drug beyond PD is permitted, at the investigator's discretion, if the investigator believes there is evidence of continued clinical benefit.

The primary efficacy endpoint for this study is progression-free survival (PFS) assessed by blinded IRC according to RECIST version 1.1. The primary analysis of PFS will be a stratified log rank test. Key secondary endpoints are confirmed ORR as assessed by IRC per RECIST v1.1 and overall survival (OS). Additional secondary endpoints are duration of response as assessed by IRC, time to response, disease control rate, and change from baseline scores across different time points in overall global qualify of life (the Global Health Status/QoL Scale) and fatigue with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and time to deterioration in the dyspnea, cough, and chest pain scales based on the EORTC lung cancer module (QLQ-LC13).

Study TAK-788-3001 will use an adaptive event-size reassessment approach for the primary endpoint and a sequential testing procedure for type I error control. One interim analysis is planned for futility, sample-size re-estimation, or efficacy after approximately 70% of the minimum total expected PFS events (159 of 227 events) have been observed. An O'Brien-Fleming Lan-DeMets alpha spending function will be used to control the overall two-sided alpha level at 0.05. If the interim analysis is statistically significant per the pre-specified alpha boundary, the study will be stopped for efficacy. If the interim analysis is not statistically significant per the pre-specified alpha boundary, the study will either be stopped for futility (if the futility criteria are met) or the total event size for the final analysis will be re-estimated using a conditional power approach, with an event cap of 270, if the results of the interim analysis fall in a "promising zone". The Cui-Hung-

Wang (CHW) testing procedure will be applied at the final analysis to control type I error for event size re-estimation. The adaptation rule will be prepared by an independent design statistician who is not directly involved in the study conduct and will adopt an asymmetric step function for event size increase to further improve treatment effect size confidentiality.

Assuming the median PFS for platinum-doublet chemotherapy is 6.5 months and the median PFS for TAK-788 is 10 months,159 events will provide approximately 61% power to detect a hazard ratio of 0.65 given the alpha allocated to the interim analysis (alpha level at approximately 0.0082). The minimal detectable HR at the interim analysis will be approximately 0.68, which corresponds to an approximately 3-month improvement in median PFS. If the analysis of the primary endpoint demonstrates a statistically significantly longer PFS for TAK-788 compared with platinum-based chemotherapy at the interim analysis, key secondary endpoints will be tested sequentially at the two-sided 0.05 level.

SPONSOR SUBITTED QUESTIONS AND FDA RESPONSES

1. The Sponsor is planning to conduct a randomized phase 3 study (Study TAK-788-3001) to evaluate the efficacy and safety of TAK-788, compared with platinum-doublet chemotherapy, in patients with locally advanced or metastatic NSCLC harboring *EGFR* exon 20 insertion mutations who have not previously received systemic treatment. The study is intended to support approval for TAK-788 as a first-line treatment for patients with NSCLC with *EGFR* exon 20 insertion mutations. The criteria defining the study population are described in the inclusion and exclusion criteria in the protocol synopsis (Appendix 1).

   Does the Agency agree that the planned study population is adequately defined to support approval for the proposed indication?

   FDA Response: The planned study population appears adequately defined to support a risk:benefit assessment for the proposed indication.

   Millennium's May 29, 2019, response: The Sponsor acknowledges the Agency's feedback. The proposed phase 3 study (Study TAK-788-3001) is planned to enroll patients in North America, Europe, and Asia. The Sponsor would like to obtain the Agency's advice on relative proportions of Asian vs non-Asian patients enrolled in TAK-788 clinical studies.

   Discussion during the meeting: Millennium requested further clarification regarding the percentage of non-Asian patients to be enrolled in Study TAK-788-3001 to support extrapolation of the results to the U.S. population. FDA stated that there is no specified proportion and that FDA requires that data be provided

in the NDA which would support extrapolation of the clinical results to the U.S. population based upon natural history of the disease and standard of care across regions. If the disease is not different across regions, real world data could be provided to support the extrapolation in lieu of substantial amount of clinical trials data.

2. Does the Agency agree that platinum-based chemotherapy is an acceptable comparator for this phase 3 trial (Study TAK-788-3001) to evaluate the clinical benefit of TAK-788 as first-line treatment in patients with NSCLC with *EGFR* exon 20 insertion mutations?

FDA Response: Platinum-based chemotherapy, with or without pembrolizumab, is an acceptable comparator for Study TAK-788-3001. Millennium should collect all available data regarding the natural history and responsiveness to anti-PD-1/PD-L1 antibodies of NSCLC harboring EGFR exon 20 insertion mutations, since such data will be necessary to support the review of a marketing application for the proposed first-line indication. If the available data do not support the assertion that anti-PD-1/PD-L1 antibodies are likely to be ineffective in the treatment of NSCLC harboring EGFR exon 20 insertion mutations, FDA would consider anti-PD-1/PD-L1 antibodies FDA-approved for the first-line treatment of NSCLC, either alone or in combination with platinum-based chemotherapy, as available therapies when assessing risk:benefit during review of a marketing application.

Millennium's May 29, 2019, response: The Sponsor acknowledged the Agency's advice. We propose to use platinum-based chemotherapy without pembrolizumab as the comparable for Study TAK-788-3001.

We are exploring the options to collect all available data (e.g., real world evidence etc.) regarding the natural history and responsiveness to anti-PD-1/PD-L1 antibodies either alone or in combination with chemotherapy of NSCLC harboring EGFR exon 20 insertion mutations to support future marketing application.

Can the agency please comment on the acceptability of such data collection options?

Discussion during the meeting: FDA stated that the proposed comparator was acceptable. If real world data are available regarding the effectiveness of anti-PD-(L)1 antibodies for the treatment of patients with EGFR exon 20 insertion mutation-positive NSCLC, FDA stated that these data should also be provided in a future marketing application.

3. Does the Agency agree with the proposed primary and secondary endpoints to assess the clinical benefit of TAK-788 in this study population?

FDA Response: FDA does not object to the proposed primary and secondary endpoints for Study TAK-788-3001. Regarding the proposed exploratory endpoints intended to assess efficacy in the CNS, please see Additional Comments.

Millennium's May 29, 2019, response: The Sponsor acknowledges the Agency's feedback. No further discussion pertaining to the primary and secondary endpoints is required at the May 29, 2019 meeting.

Regarding the proposed exploratory endpoints to assess efficacy in the CNS, the Sponsor agrees to the Agency's advice to use the incidence of progression in the CNS as first site of disease progression (alone or with concurrent systemic progression) instead of intracranial PFS to evaluate CNS benefit. Please refer to our response to the "Additional Comment 9" pertaining to the exploratory endpoints intended to assess efficacy in the CNS in Study TAK-788-3001.

Discussion during the meeting: Millennium acknowledged FDA's response to question # 3 and no further discussion occurred. However, discussion regarding the proposed endpoint to assess the efficacy in CNS was captured under additional comment # 9.

4. Can the Agency comment on suitability of the patient-reported outcome (PRO) instruments selected for the proposed phase 3 trial to assess patient-reported HRQoL, symptom, and adverse event (AE) impact of TAK-788 in the trial population?

FDA Response: There is inadequate information included in the meeting package for FDA to comment on the suitability of the patient-reported outcome (PRO) instruments proposed for use in Study TAK-788-3001 (e.g., details regarding specific items to be used, magnitude of change that would be considered clinically meaningful, statistical analysis plan for PRO endpoints).

FDA recommends that Millennium submit a meeting request to obtain FDA's feedback regarding assessment of PRO endpoints in Study TAK-788-301 once details regarding Millennium's plan to evaluate these endpoints are available.

Millennium's May 29, 2019, response: The Sponsor acknowledges the Agency's advice. We will submit a meeting request to obtain Agency's feedback regarding PRO endpoints in Study TAK-788-3001, and we welcome an early opportunity to discuss and concur with the Agency on the proposed plan for PRO assessment.

Below is a high level summary on the work we have done and continue working on to inform our PRO strategy in Study TAK-788-3001. Given the patient-focused work we have conducted to date and our efforts to finalize the protocol of Study TAK-788-3001 in July/Aug-2019, the Sponsor has defined the PRO instruments and data collection schedule to be incorporated into the protocol as outlined below. We appreciate any guidance from the Agency at the May 29, 2019, meeting for us to better prepare the separate meeting focusing on PRO assessment.

Proposed PRO Instruments:
A patient-focused evidence generation plan has been implemented for the evaluation of relevant patient-reported outcome (PRO) concepts in the clinical program for TAK-788 by engagement and partnership with Exon 20 Group at ICAN® (International Cancer Advocacy Network). Patient-centered qualitative research was undertaken to support the conceptualization of treatment benefit and confirm the selection of appropriate PRO measures. Patients living with EGFR Exon 20 mutation NSCLC were interviewed using a 1:1 interviewing approach with a semi-structured guide (concept elicitation and cognitive debriefing interviews). Our patient-focused work has led to PRO instruments selection of EORTC QLQ-C30, the lung cancer module QLQ-LC13, EQ-5D-5L and selected items from the PRO-CTCAE. Specifically, for PRO-CTCAE which allows for the inclusion of the patient voice in symptomatic adverse event reporting alongside the traditional clinician-reported CTCAE, our work has shown that the most relevant symptomatic AEs from PRO-CTCAE for this population include decreased appetite, nausea, vomiting, constipation, diarrhea, fatigue, rash, skin dryness, mouth/throat sores, general pain, numbness & tingling, and chills.

Proposed Data Collection Schedule:

- EORTC QLQ-C30, LC13 and EQ-5D-5L: Day 1 every cycle up to Cycle 19, Day 1 every 4 cycles starting from Cycle 23, end of treatment, and 30 days after last dose. Only EQ-5D-5L will be collected during post-treatment and survival follow-up periods.
- PRO-CTCAE: Day 1 Cycle 1, weekly for the first 4 cycles, Day 7 every cycle up to Cycle 19, Day 7 every 4 cycles starting from Cycle 23, end of treatment, and 30 days after last dose.

In addition to the work informing PRO instrument selection, the Sponsor has been working on establishing clinical meaningfulness and the statistical analysis plan for PRO endpoints to inform data analysis and interpretation in Study TAK-788-3001. Further details will be discussed during future separate meeting for PRO.

Discussion during the meeting: FDA acknowledged Millennium's response but stated that there was insufficient time to review Millennium's response prior to the

meeting. FDA agreed with Millennium's approach to seek a separate meeting with the COA team and encouraged Millennium to provide as much description as possible in the meeting package.

5. Does the agency agree with the TAK-788 dose of 160 mg QD for the proposed phase 3 trial TAK-788-3001?

FDA Response: The proposed dose of TAK-788 of 160 mg QD for Study TAK-788-3001 may be acceptable depending upon the formulation to be used in the study. It is unclear from the information included in the meeting package if the drug-in-capsule formulation used in Study AP32788-15-101 is the same as that to be used in the proposed trial, Study TAK-788-3001, or if an alternative formulation will be used in Study TAK-788-3001 ((b) (4) or a different planned commercial formulation). Millennium has not provided any information regarding the comparative bioavailability of the formulation used in Study AP32788-15-101 (b) (4) based on the results of Study TAK-788-1001. Additionally, plans for bridging to the commercial formulation have not been provided. Include formulation-related information at the time of full protocol submission to enable assessment of the acceptability of the proposed dosage regimen.

Millennium's May 29, 2019, response: The Sponsor acknowledges the FDA's comments and is hereby providing an overview of the formulations used for the TAK-788 development program (Table 1). No further discussion with the Agency is required at the May 29, 2019 meeting.

The formulations used for the TAK-788 clinical program have been a drug-in-capsule (DiC) with no additional excipients using three drug substance processes (b) (4). The formulation currently being used in the ongoing Phase 1/2 Study AP32788-15-101 (Part 3: pivotal extension) is a 40 mg DiC formulation (b) (4). The same formulation will be used in the proposed Phase 3 clinical trial, TAK-788-3001, and is being considered as the commercial formulation.

Table 1: Formulation Overview for TAK-788

Strength by Study	Drug Substance Process
Study TAK-788-1001	
20 mg	Process (b) (4)
40mg	Process
Study AP32788-15-101 (Part 1: Dose Escalation, Part 2: Expansion Cohorts)	
20 mg	Process (b) (4)
	Process
40 mg	Process

Strength by Study	Drug Substance Process
Study AP32788-15-101 (Part 3: Pivotal Extension)	
40 mg	Process (b) (4)
Study TAK-788-3001	
40 mg	Process (b) (4)
Proposed Commercial Formulation (Under Development)	
40 mg	Process (b) (4)

As outlined in Table 1, the DiC formulation (b) (4) have been used in TAK-788 clinical studies including Part 1 and Part 2 of Study AP32788-15-101. An amendment to the IND submitted on 13 December 2018 (Serial No. 092) provided CMC information for the addition of DiC formulation using drug substance (b) (4) before its introduction to the Part 3 Pivotal Extension Phase of AP32788-15-101.

The transition of the drug substance (b) (4)

Results from the relative bioavailability study in healthy subjects (Study TAK-788-1001 Part 3) demonstrated that (b) (4) DiC is bioequivalent to (b) (4) DiC (see Table 2), indicating that the changes to the drug substance synthetic process do not impact bioavailability of TAK-788 in humans**.**

Table 2. ANOVA Result of Oral Bioavailability of TAK-788 (b) (4) DiC Relative to (b) (4) DiC in Study TAK-788-1001

TAK-788 Dose (Number of Subjects)	Comparison (Test : Reference)	C_{max} %GMR (90% CI)	AUC_{∞} %GMR (90% CI)
160 mg (N = 12)	**DiC B versus DiC A**	**93.2 (84.6-103)**	**96.0 (88.6-104)**

Source: data on file.
AUC_{∞}: area under the plasma concentration-time curve from time 0 to infinity; C_{max}: maximum observed serum concentration; GMR: geometric mean ratio.

The commercial formulation is still under evaluation by the sponsor with the leading candidate (b) (4) DiC formulation similar to the clinical formulation currently used in the Pivotal Extension cohort of Study TAK-788-15-101 (Part 3) with improved scale of capsule production. The sponsor will seek the FDA's advice regarding our CMC development strategy to bridge the pivotal and commercial formulation in the future as needed.

Discussion during the meeting: Millennium acknowledged FDA's response and no further discussion occurred**.**

6. Does the Agency agree that the proposed statistical approach for the phase 3 trial TAK-788-3001 is appropriate to evaluate the efficacy of TAK-788 in treatment-naïve patients with NSCLC harboring EGFR exon 20 insertion mutations? Specifically, can the Agency comment on the proposed sample size and adaptive design (particularly the interim analysis plan) to support approval for the proposed indication?

FDA Response: The statistical analysis plan, including the adaptive design and interim analysis plan, appear acceptable. However, the magnitude of the proposed treatment effect, which corresponds to a 3.0- to 3.5-month improvement in median PFS, may not demonstrate substantial evidence of effectiveness unless it is supported by an effect of overall survival or the treatment effect of PFS is underestimated by the difference in medians (e.g., hazard ratio < 0.5).

While, in general, a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive and has an acceptable risk-benefit profile may be adequate to support a marketing application, Millennium should be aware that PFS is subject to ascertainment bias and the results of the analysis may be influenced by any imbalance in assessment dates or missing data between treatment arms. Therefore, an interim PFS analysis may not provide an accurate or reproducible estimate of the treatment effect size due to inadequate follow-up, missing assessments, and/or disagreements between investigator and independent assessments.

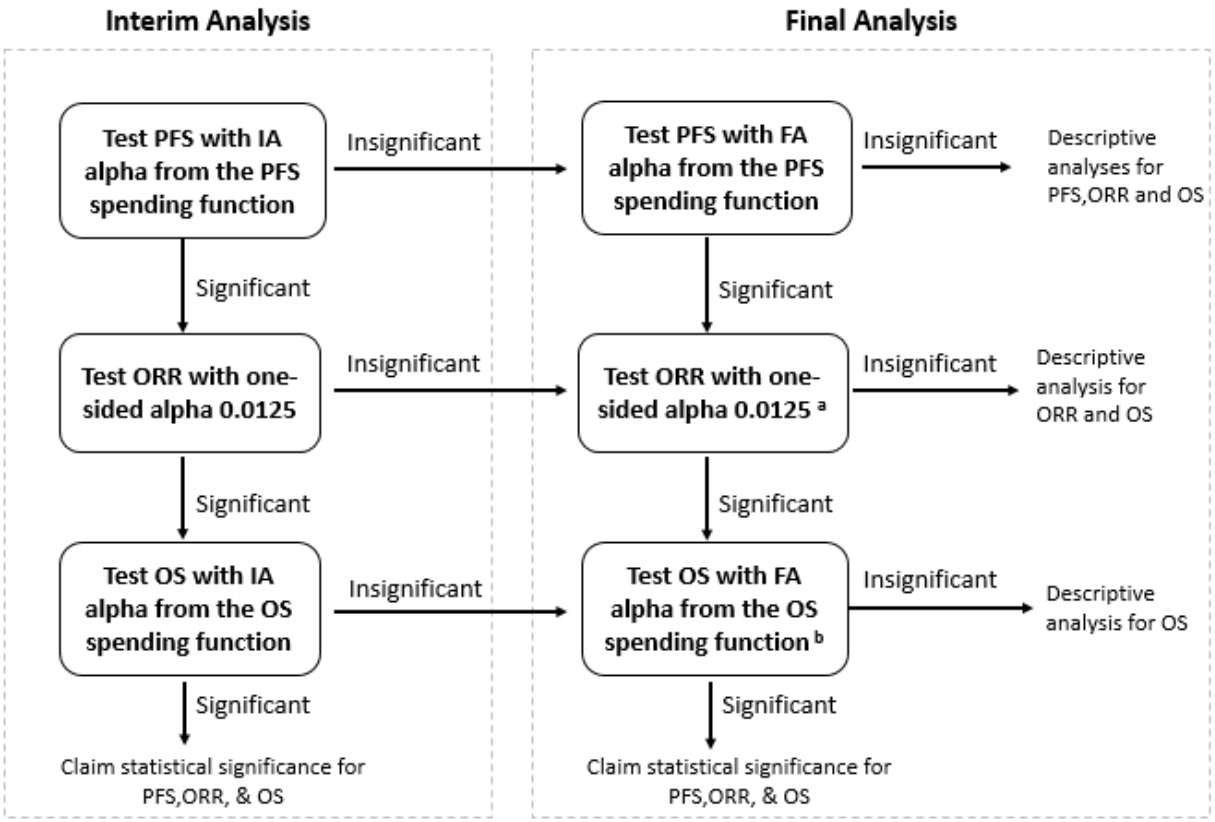
Please provide a statistical analysis plan for OS including the difference to be detected, power, the number of deaths for the final OS analysis, and the number of deaths for an interim OS analysis to be conducted at the time of the final PFS analysis.

Millennium's May 29, 2019, response: The Sponsor acknowledges the Agency's advice. We are hereby providing the statistical analysis plan for OS as requested and would like to discuss and concur with the Agency at the May 29, 2019 meeting.

For the key secondary endpoints including OS, the Sponsor will follow Tang and Geller (1994), Hung et al (2007) and Glimm et al (2010) in order to strongly control the family-wise type I error. Separate alpha allocation and alpha spending function will be used for testing the confirmed ORR per IRC assessment using RECIST v1.1 and OS, respectively. Specifically, strategy 3 from Hung et al (2010) will be used for ORR, i.e., one-sided alpha 0.025 will be split between the IA and FA. Following Tang and Geller (1994) and Glimm et al (2010) for OS, the

Sponsor will use an O'Brien-Fleming Lan-DeMets alpha spending function to allocate one-sided alpha 0.025 between OS IA and OS FA. Figure 1 includes the statistical analysis schema for testing the primary and key secondary endpoints.

Figure 1. Statistical analysis schema for testing the primary and key secondary endpoints



[a] If PFS is not significant at the IA, ORR will be tested after PFS reaches significance at PFS FA. If PFS is significant at the IA and ORR is not significant at the IA, ORR will be tested at the ORR/OS FA when approximately 148 deaths are observed.

[b] Testing procedure for OS FA:

- If PFS and ORR are significant at the IA but OS is not significant at the IA (OS alpha at the IA will be determined based on the observed number of deaths at the IA and projected 148 deaths at the OS FA), OS FA will be conducted when approximately 148 deaths are observed. The OS FA critical value will be determined based on the observed number of deaths at the IA and OS FA and actual alpha spent at the OS IA;
- If PFS is significant at the IA but ORR is not significant at the IA, ORR/OS FA will be conducted when approximately 148 deaths are observed. The OS FA critical value will be determined based on the observed number of deaths at the IA and FA;
- If PFS is not significant at the IA and the study continues without FA PFS event size increase, the OS FA critical value will be determined based on the observed number of deaths at the IA and FA;
- If PFS is not significant at the IA and the FA PFS event size is increased, after PFS and ORR reach significance at the FA, the information fraction and the OS FA critical value will be determined based on the observed number of deaths IA and the observed number of deaths when the minimally planned PFS FA event size (227 PFS events) is observed. CHW test statistic will be used for OS FA.

Assuming that the median OS for platinum-doublet chemotherapy is 15 months and the median OS for TAK-788 is 20 months, it is projected that 93 deaths will be observed at the interim analysis. If the interim analysis for PFS is not significant (and neither the sample size nor the event size for the final analysis is increased), it is projected that 148 deaths will be observed at the final analysis.

- If PFS and ORR achieve statistical significance at the IA, OS will be tested using the IA alpha allocated from the OS alpha spending function. Given the projected number of OS events at the IA and FA, the planned information fraction for OS analysis at the IA is 93/148=63%, and the power for OS analysis is 13% (with minimum detectable HR 0.59) at the IA. The probability of observing a positive OS trend (i.e. OS HR<1) is 92% at the IA, and the probability of observing an OS HR<0.9 is 81% at the IA.
- If the interim analysis for PFS is not significant (and neither the sample size nor the event size for the final analysis is increased), or if PFS is significant but OS is not significant at the IA, the power for OS analysis (based on projected or planned OS events) is 40% (with minimum detectable HR 0.72) at the FA. For this case, the probability of observing a positive OS trend (i.e. OS HR<1) is 96% at the FA, and the probability of observing an OS HR<0.9 is 87% at the FA.
- In addition, the Sponsor will conduct sensitivity analyses of OS accounting for the crossover design, using methods including but not limited to Rank Preserving Structure Failure Time (RPSFT, Robins 1989) and Inverse Probability of Censoring Weighting (IPCW, Robins and Finkelstein 2000). When appropriate, RWE may also be used to further evaluate the OS benefit.

References:

- Glimm E., Maurer W., and Bretz F., “Hierarchical testing of multiple endpoints in group-sequential trials”, 2010; 29 (2): 219-228
- Hung H.M., Wang S.J., and O'Neill R., “Statistical considerations for testing multiple endpoints in group sequential or adaptive clinical trials.” J Biopharm Stat. 2007; 17(6): 1201-10.
- Tang DI, Geller NL. “Closed testing procedures for group sequential clinical trials with multiple endpoints.” Biometrics 1994; 55: 1188--1192.
- Robins JM, Finkelstein DM. “Correcting for noncompliance and dependent censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests. Biometrics” 2000;56(3):779-88.
- Robins JM. “The Analysis of Randomized and Non-Randomized AIDS Treatment Trials Using a New Approach to Causal Inference in Longitudinal Studies. In: Health Service Research Methodology: A Focus on AIDS. Eds: Sechrest L., Freeman H., Mulley A. Washington, D. C.: US Public Health Service, National Center for Health Services Research (1989), pp. 113-159

Discussion during the meeting: FDA stated that they will provide an assessment of the statistical analysis plan as an addendum to the final meeting minutes.

Post-Meeting Addendum

FDA requests that Millennium provide a more detailed description of the plan to control Type I error for the proposed study as a formal amendment to the statistical analysis plan. The statistical analysis plan should have strong overall

control for Type I error at a level of no more than 0.025 (1-sided) for all endpoints of interest.

7. Does the Agency (CDER and CDRH) agree that the proposed testing strategy and the use of ODxT Test in this phase 3 study can be exempt from investigational device exemption (IDE) regulations?

FDA Response: FDA will discuss this question in detail at the May 29, 2019, meeting with Millennium.

Millennium's May 29, 2019, response: The Sponsor looks forward to the Agency's advice at the May 29, 2019 meeting.

Discussion during the meeting: FDA conveyed the following comments to Millennium during the meeting:

a. The main inclusion/exclusion criteria for Study TAK-788-3001 did not specify whether patients who potentially qualify for enrollment may be forgoing effective therapies based on the identification of other EGFR activating mutations (e.g., EGFR Ex. 19 deletions, L858R, T790M, etc.) which are approved for selection of patients for treatment with FDA-approved EGFR tyrosine kinase inhibitors (EGFR TKIs). If patients forgo other therapies known to be effective based on other actionable EGFR mutations identified in their tumor specimens in order to enroll into Study TAK-788-3001, the study would be considered a significant risk trial and would require the submission and approval of an Investigational Device Exemption (IDE) prior to the start of enrollment of patients in the planned study.

b. Millennium plans to enroll patients to Study TAK-788-3001 based on local test results and then retrospectively test for EGFR exon 20 insertion mutation in a central laboratory using the candidate CDx test. FDA recommends that Millennium utilize the candidate CDx assay to enroll patients into the study, as discussed in (c) below. If patients will be enrolled based on central testing using the candidate CDx, Thermo Fisher Scientific should submit an IDE to CDRH for approval prior to enrolling patients into the study.

c. While the proposed local tests may identify the presence of EGFR exon 20 insertions, the performance of the different assays may not be comparable due to differences in the assays, platforms, or specimen types tested. Also, the different local tests and methodologies may not be adequately validated to detect the different exon 20 insertions. As such, if different tests are utilized at the clinical sites, the different tests may not identify the same populations. Therefore, FDA recommends that Millennium use the same testing procedures (including specimen type, test method, NGS platform and bioinformatics pipeline etc.) to enroll all patients. If Millennium is able to

successfully address the inclusion/exclusion criterion concern outlined in (a) above and choose to proceed with the currently proposed enrollment strategy, at a minimum, Millennium should attempt to obtain information regarding the test(s) used to identify the mutations for enrollment as well as information regarding the analytical and clinical performance characteristics (e.g., limit of detection, analytical sensitivity, cut-offs, etc.) of the test(s). In addition, FDA recommends that Millennium verify and use test results from sites whose tests are fully specified and have cutoffs that are locked down.

d. Based on the design of the Study TAK-788-3001, FDA considers that a device would be essential for the safe and effective use of TAK-788, and, therefore, a companion diagnostic test would be required, and a regulatory submission would be needed to establish the performance of the test with the drug. If results from Study TAK-788-3001 are used to support drug approval and the final device (the companion diagnostic which is intended to be marketed) will not be used for testing, Millennium should bank all specimens from the patients enrolled/screened (mutation positives and a random subset of mutation-negatives from local/central testing laboratories) into the trial for a bridging study to test the companion diagnostic which is intended to be marketed. FDA recommends that Millennium contact CDRH regarding the analytical and clinical study (bridging study) to support test approval.

Millennium stated that Thermo Fisher is the companion diagnostic partner for this development program. However, Millennium clarified that patients with EGFR exon 20 insertion mutation-positive NSCLC will be enrolled in the proposed study based upon local tests. CDRH staff stated that the Thermo Fisher test for detection of EGFR exon 20 insertion mutation-positive NSCLC can be evaluated under abbreviated IDE requirements with the analytical and clinical data submitted to the IND. Millennium stated that analytical validations and clinical validations are under way; clinical validations will be performed Study AP32788-15-101 among the subgroup of patients with NSCLC.

Millennium further stated that evaluation of the performance characteristics of local laboratory tests acceptable for determination of patient eligibility in Study TAK-788-3001 will be based upon evaluation of the test methodology rather than by the individual test.

Millennium agreed to revise Study TAK-788-3001 to specify how patients with discordant results between local and central testing will be handled with regard to: 1) continuing protocol-assigned treatment, 2) inclusion in efficacy analyses, and 3) how data from patients with discordant results will be handled in the clinical validation studies for the Thermo Fisher test.

8. The Sponsor intends to use clinical results from the ongoing phase 1/2 Study AP32788-15-101 in patients with NSCLC with EGFR exon 20 insertion mutations

as the primary basis to support an initial NDA submission for TAK-788 in the US. The proposed phase 3 Study TAK-788-3001 can be used to confirm clinical benefit of TAK-788 observed from Study AP32788-15-101 as a post-approval requirement if the initial NDA is granted under accelerated approval.

Can the Agency please comment on the proposed registration plans?

FDA Response: Based on the confirmed overall response rate of 27% (95% CI:12, 48) among the 26 patients receiving TAK-788 at 160 mg daily, the preliminary clinical results would not support accelerated approval.

If the final results from Study AP32788-15-01 are adequate to support a marketing application under the provisions of accelerated approval, then Study TAK-788-3001 would be acceptable as a clinical trial intended to verify the clinical benefit of TAK-788 for the treatment of patients with NSCLC with EGFR exon 20 insertion mutation-positive NSCLC.

Millennium's May 29, 2019, response: The Sponsor has provided the updated clinical data for TAK-788 to be presented at the upcoming ASCO meeting. Please refer to the Sponsor's email to the FDA dated May 24, 2019 (Attachment 1). Based on the March 1, 2019 data cut-off, the confirmed overall response rate (ORR) is 43% (95% CI: 24.5, 62.8) among the 28 patients receiving TAK-788 at 160 mg daily and all confirmed responders having follow-up of at least 6 months. At the May 29, 2019 meeting, we would like to clarify and seek the Agency's advice on the overall registration plan for TAK-788. We look forward to the Agency's guidance on the possibility of obtaining Breakthrough Therapy Designation (BTD) in refractory setting based on the updated ASCO data.

Discussion during the meeting: FDA recommended that Millennium submit a request for preliminary BTD advice. The request should include a tabular listing summarizing the prior therapy, date of first dose of TAK-788, date of onset of response, date of progression or last follow-up if remaining in response for the 28 patients who received TAK-788 after progression on platinum-based chemotherapy. FDA stated that all patients should have at least 6 months follow-up from the onset of response.

ADDITIONAL COMMENTS

Clinical

9. FDA has the following comments regarding the exploratory endpoints intended to assess efficacy in the CNS in Study TAK-788-3001:

   a. In order to perform a valid assessment of progression in the CNS, CNS imaging at baseline and at all post-baseline tumor assessment timepoints

would be required, as opposed to the current proposal to obtain post-baseline brain imaging only for patients with baseline CNS metastases.

Millennium's May 29, 2019, comment: The sponsor appreciates the Agency's feedback on the CNS specific endpoint and recommended brain imaging schedules. Per the Agency's advice, the CNS exploratory endpoints in phase 3 study will be modified to only include the incidence of brain progression as the first site of disease progression alone or in combination with concurrent systemic progression.

Based on the preliminary data obtained from 28 patients with EGFR exon 20 insertion mutations treated at 160 mg QD of TAK-788 (please refer to ASCO oral presentation) and direct feedback from investigators, it appears that TAK-788 has only limited CNS activity, particularly in patients with active brain metastases at baseline.

Given these early observations, the current design of the clinical study would require brain imaging on all patients at baseline. For patients with brain metastases at baseline, brain imaging will be repeated post-baseline. Brain imaging will also be recommended at any time if clinically indicated for patients who have no brain metastases at baseline.

The sponsor recognizes that not completing brain imaging on all patients could limit our ability to detect CNS brain metastases at the earliest time point. However, given the burden of frequent brain imaging on patients without brain metastases, the sponsor proposes to keep the schedule as currently outlined in the synopsis.

A similar approach has been implemented in the Pivotal Extension cohort (Part 3) of ongoing phase 1/2 study (AP32788-15-101), and inclusion/exclusion criteria had been modified to limit enrollment to patients without active brain metastases and the CNS endpoints was included as exploratory.

Discussion during the meeting: FDA stated that if evaluation of effects on CNS disease are conducted as exploratory endpoints, FDA has no objection.

b. FDA discourages use of intracranial PFS as an endpoint, since this endpoint primarily captures effects on tumor in only one organ site in the setting of a systemic disease. CNS PFS results may be difficult to interpret due to censoring of patients with systemic progression. A more appropriate way to convey information regarding the potential benefit of efficacy in the CNS is to assess the incidence of progression in the CNS as first site of disease progression, alone or with concurrent systemic progression.

Millennium's May 29, 2019, comment: The Sponsor agrees to the Agency's advice to use the incidence of progression in the CNS as first site of disease progression (alone or with concurrent systemic progression) instead of intracranial PFS to evaluate CNS benefit. No further discussion is required at the May 29, 2019 meeting.

Discussion during the meeting: Millennium acknowledged FDA's additional comment and no discussion occurred.

c. Assessment of responses in the CNS may be an exploratory endpoint in order to assess the anti-tumor activity of TAK-788 in the CNS.

Millennium's May 29, 2019, comment: The Sponsor agrees to the Agency's advice, which is consistent with the current protocol design as shown in the synopsis (see below).

"Exploratory: – To evaluate and compare the efficacy in the CNS of TAK-788 to that of platinum-based chemotherapy, as evidenced by intracranial PFS, time to CNS progression, and incidence of CNS progression." No further discussion with the Agency is required at the May 29, 2019 meeting**.**

Discussion during the meeting: Millennium acknowledged FDA's additional comment and no discussion occurred**.**

10. FDA reminds Millennium that FDA expects submission of reports from the 13-week toxicology studies prior to initiation of clinical trials intended to support a marketing application. Please refer to the discussion included in the June 11, 2018, meeting minutes for additional information on the adequacy of the nonclinical development plan.

Millennium's May 29, 2019, comment: The chronic 13-week dog and rat studies with 4-week recovery have been completed and the final reports will be submitted to the IND in June 2019. No further discussion is required at the May 29, 2019 meeting.

Please note that the prior agreement during the 11 June 2018 EOP1 meeting is to submit the aforementioned reports to the Agency prior to "*enrollment of more than 50 patients in the extension phase (Part 3)*" of the ongoing Ph1/2 Study AP32788-15-101, instead of prior to "*initiation of clinical trials*". Please refer to page 9 of the FDA EOP1 Meeting minutes, dated 19 June 2018. As of May 28, 2019, a total of 8 treatment naïve patients was enrolled in the expansion cohort of Part 2 in Study TAK-788-15-101.

Discussion during the meeting: Millennium acknowledged FDA's additional comment and no discussion occurred.

Clinical Pharmacology

Regarding Study TAK-788-3001:

11. At the time of full protocol submission, provide justification for the proposed revision of renal function-related inclusion criteria from creatinine clearance ≥ 30 mL/min in Study AP32788-15-101 to ≥45mL/min in Study TAK-788-3001.

    Millennium's May 29, 2019, comment: The Sponsor acknowledges the Agency's comment and will continue to assess the possibility to broaden the inclusion criteria of renal function beyond the label limitation on pemetrexed (Renal function: Do not administer when CrCl <45 mL/min) from creatinine clearance >=45 mL/min to >=30 mL/min and potential impact on efficacy and safety profile assuming there are some imbalance distribution of renal function between TAK-788 and control arm.

    We look forward to the Agency's advice on broadening the inclusion criteria of renal function, in light of the limitation associated with comparator in Study TAK-788-3001.

    Discussion during the meeting: In light of the limitations imposed by the control arm, FDA stated that it is acceptable to maintain the currently proposed renal function inclusion criterion (creatinine clearance greater than or equal to 45 mL/min) in Study TAK-788-3001.

12. In the full study protocol, clearly indicate that on-treatment ECGs will be collected around estimated post-dose T_{max} of TAK-788.

    Millennium's May 29, 2019, comment: The Sponsor agrees to the Agency's advice to collect the single on-treatment ECG around $T_{max.}$ No further discussion is required at the May 29, 2019 meeting**.**

    Discussion during the meeting: Millennium acknowledged FDA's additional comment and no discussion occurred.

13. Millennium states that administration with food is hypothesized to mitigate GI TEAEs, and a low-fat meal had no clinically meaningful effect of TAK-788 exposure. Therefore, clarify the rationale for permitting administration both with food and without food in Study TAK-788-3001, as this may lead to differential GI toxicity profiles in patients taking TAK-788 under fasted vs. fed conditions. If Millennium plans to recommend dosing under both fed and fasted conditions for potential approval, FDA encourages Millennium to adequately characterize the effect of food on GI AEs in the ongoing/planned studies to inform potential labeling language regarding the effect of food on TAK-788 mediated GI AEs and the optimal dosing of TAK-788 with regard to food. FDA recommends that

Millennium consider whether it is feasible for this characterization to include a pre-specified sub-group analysis (TAK-788 administered with or without a low-fat meal) with patient-reported outcomes (using the GI-associated adverse event subset of questions of the PRO-CTCAE) as an endpoint in Study TAK-788-3001 or another sub-study. Collect time-matched PK data to characterize the potential exposure-response relationship with GI TEAEs.

Millennium's May 29, 2019, comment: The Sponsor acknowledges the Agency's comments and will make efforts to characterize the effect of food on GI AEs in the ongoing/planned studies as appropriate. No further discussion is required at the May 29, 2019 meeting.

Further details may be discussed with the Agency regarding capturing food condition in the PRO-CTCAE questionnaire in a future meeting related to PRO.

Discussion during the meeting: Millennium acknowledged FDA's additional comment and no discussion occurred.

As drug development proceeds:

14. As it is not known whether a high fat meal could have clinically significant effect on the systemic exposure of TAK-788, provide an assessment of the effect of high-fat food on the exposure of TAK-788 at the time of initial NDA submission. This is needed to inform labeling language on clinical dosing of TAK-788 with regard to food.

    Millennium's May 29, 2019, comment: The Sponsor plans to conduct study to assess effect of high fat meal on TAK-788 exposure and results will be included in the initial NDA submission. No further discussion is required at the May 29, 2019 meeting.

    Discussion during the meeting: Millennium acknowledged FDA's additional comment and no discussion occurred.

15. Within 30 days of current submission:

    a. Submit the QT assessment plan to be included in the initial NDA submission for FDA review.

       Millennium's May 29, 2019, comment: The Sponsor will submit the QT risk assessment plan in first half of 2020 for Agency's review. No further discussion is required at the May 29, 2019 meeting.

       Discussion during the meeting: Millennium acknowledged FDA's additional comment and no discussion occurred.

b. Submit the exposure-response and population PK analysis plan to be included in the initial NDA submission for FDA review. The population PK analysis plan should include detailed information on the proposed approach for assessing the effect of renal and hepatic impairment of TAK-788 exposure. This is to inform labeling language around the recommended TAK-788 dosage in these populations.

Millennium's May 29, 2019, comment: The Sponsor will submit the exposure-response and population PK analysis plan in first half of 2020 for Agency's review. No further discussion is required at the May 29, 2019 meeting.

Discussion during the meeting: Millennium acknowledged FDA's additional comment and no discussion occurred.

16. Submit the high-fat food effect, hepatic and renal impairment study protocols for FDA review prior to their initiation.

Millennium's May 29, 2019, comment: The Sponsor will submit the protocols of high-fat food effect, hepatic and renal impairment studies for FDA review prior to study initiation. No further discussion is required at the May 29, 2019 meeting.

Discussion during the meeting: Millennium acknowledged FDA's additional comment and no discussion occurred.

17. Based on the information provided in the EOP1 meeting package, Millennium proposes to assess the effect of mild to moderate renal and mild hepatic impairment on TAK-788 PK with population PK analysis. In this case, the proposed eligibility criteria for Study TAK-788-3001 should allow inclusion of patients with varying degrees of renal (CLcr 30 to 60 mL/min) or hepatic impairment and adequate PK sampling should be performed. Pre-plan the statistical analysis and power the study to get precise estimates (relative standard error ≤ 20%) of the mean clearance parameter in renal or hepatic impaired patients. Refer to FDA guidance documents:

a. Population Pharmacokinetics

b. Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling

c. Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling

Millennium's May 29, 2019, comment**:** The Sponsor acknowledges the Agency's comments and will refer to FDA guidance documents to assess the effect of mild

to moderate renal and mild hepatic impairment on TAK-788 PK using population PK analysis. No further discussion is required at the May 29, 2019 meeting**.**

Discussion during the meeting: Millennium acknowledged FDA's additional comments and no discussion occurred.

18. Submit the clinical DDI study protocols for FDA review prior to their initiation. As current clinical PK data indicates that TAK-788 induces CYP3A, FDA has the following recommendations regarding the clinical DDI victim study (TAK-788-1006):

    a. Study the effect of strong index CYP3A inhibitors and inducers on both single and multiple dose PK of TAK-788. This would necessitate that this study be conducted in patients and not healthy subjects to allow for multiple dosing of TAK-788. Alternatively address the effect of strong index CYP3A inhibitors or inducers using a single dose study in healthy volunteers, in addition to PBPK modeling to address the effect of strong CYP3A inhibitors and inducers on the multiple dose PK of TAK-788.

    b. Conduct the study with a strong index inhibitor that is not a substrate of CYP3A, e.g.: ketoconazole

    Millennium's May 29, 2019, comment: The Sponsor acknowledges the Agency's comments.

    Sponsor plans to address the effect of strong index CYP3A inhibitor (itraconazole) or inducer (rifampin) using a single dose study in healthy volunteers, in addition to PBPK modeling to address the effect of strong CYP3A inhibitors and inducers on the multiple dose PK of TAK-788. Note that, clinical pharmacology studies TAK-788-1004 and TAK-788-1006, as listed below, have been submitted to IND 126,721 on April 30, 2019 (eCTD Sequence No. 0113).

    - TAK-788-1004: *"A Phase 1, Open-Label, Multicenter, Drug-Drug Interaction Study of TAK-788 and Midazolam, a Sensitive CYP3A Substrate, in Patients With Advanced Non-Small Cell Lung Cell Cancer.".*

    - TAK-788-1006: *"A Phase 1 Study of Oral TAK-788 to Evaluate the Drug-Drug Interaction with Itraconazole and Rifampin in Healthy Adult Subjects."*

    No further discussion is required at the May 29, 2019 meeting.

    Discussion during the meeting: Millennium acknowledged FDA's comments and no discussion occurred.

19. Given the auto-induction of CYP3A metabolism by TAK-788, address how the effect of moderate CYP3A inhibitors or inducers on multiple dose TAK-788 PK will be evaluated. If the effects will be addressed using modeling and simulation as indicated in the EOP1 meeting package, submit the PBPK plan for FDA review within 30 days of the current submission.

Millennium's May 29, 2019, comment: The Sponsor plans to assess effect of moderate CYP3A inhibitors or inducers on multiple dose TAK-788 PK using a PBPK approach. Sponsor will submit PBPK plan for FDA review in first half of 2020._No further discussion is required at the May 29, 2019 meeting.

Discussion during the meeting: Millennium acknowledged FDA's additional comment and no discussion occurred.

20. As antiemetics/antidiarrheal medications are expected to be co-administered with TAK-788 for the management of GI TEAEs, in the initial NDA submission provide an assessment of potential DDIs with such medications. Clarify how these concomitant drugs will be administered in the clinical trials designed to demonstrate efficacy and safety (i.e., prophylactically, or as needed).

Millennium's May 29, 2019, comment: The Sponsor acknowledges the Agency's comment and the concomitant drugs including antiemetics/antidiarrheal medications will be collected in eCRF throughout the study. Sponsor will collect information on concomitant drugs including antiemetics/antidiarrheals. However, commonly used antiemetics/antidiarrheals are not known to be CYP3A inhibitors/inducers.

Sponsor may assess risk of potential DDI using population PK approach, as appropriate, to further clarify antiemetics/antidiarrheal medications used in this study. No further discussion is required at the May 29, 2019 meeting.

Discussion during the meeting: Millennium acknowledged FDA's additional comment and no discussion occurred.

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 two weeks of this meeting**. 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 the latest version of the molecular target list, please refer to FDA.gov.[1]

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*.

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.[2]

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[1] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm5 44641.htm

[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

Millennium's May 29, 2019, comment: The Sponsor plans to submit iPSP by end of 2019 or sooner, prior to the completion of our Phase 1/2 Study AP32788-101f, as advised by the Agency per email dated Aug 7, 2018, within which, the Agency has advised the Sponsor to submit a pediatric study plan prior to completion of our phase 2 study or sooner.

Discussion during the meeting: No discussion occurred.

Post-meeting Addendum: In accordance with section 505B(e)(2)(A)(i) of the FD&C Act, an applicant must reach agreement on the iPSP no later than 210 days prior to submission of a planned NDA. Given the potential to seek accelerated approval based on the results of Study AP32788-101, the proposed plan to submit the iPSP "by the end of 2019" is not acceptable. Millennium should submit the iPSP as soon as possible, considering the need for up to 180 days of potential negotiation with FDA to reach agreement on the iPSP and the timing of submission of the planned NDA. As noted above, if the NDA is submitted after August 20, 2020, the NDA will be subject to the requirements of Title V of the FDA Reauthorization Act of 2017 (FDARA), section 505B(a)(1)(B). Millennium should provide a plan for submission of the iPSP based upon the planned timing of submission of an NDA.

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.[3]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[4] 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 started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study

[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[4] http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

Data Standards Resources web page[5] 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 started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[6] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[7] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[8] When submitting sample data sets, clearly

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[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

[6] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/Electro nicSubmissions/ucm174459.htm

[7] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

[8] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission. Additional information can be found at FDA.gov.[9]

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.

[9] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[10] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[11]

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.[12]

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 *for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[13]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email

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[10] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

[11] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf

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

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

request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[14]

[14] 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.

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/

GINA M DAVIS
06/13/2019 02:40:51 PM