

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210868Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 118296

MEETING MINUTES

Pfizer, Inc.
Attn: Ann Carey
Senior Director, Worldwide Safety and Regulatory
235 East 42nd Street
New York, NY 10017

Dear Ms. Carey:

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

We also refer to the meeting between representatives of your firm and the FDA on August 30, 2017. The purpose of the meeting was to discuss and reach agreement on the content and format of a New Drug Application (NDA) for lorlatinib for the proposed indication of treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC), previously treated with one or more ALK tyrosine kinase inhibitors..

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

If you have any questions, call me at (301) 796-7910.

Sincerely,

{See appended electronic signature page}

Shubhangi (Gina) Mehta, PharmD
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: pre-NDA

Meeting Date and Time: August 30, 2017, 2:00 pm to 3:00 pm
Meeting Location: White Oak Building 22, Room 1309

Application Number: 118296
Product Name: Lorlatinib
Indication: Treatment of patients with anaplastic lymphoma kinase (ALK)-metastatic non-small cell lung cancer (NSCLC), previously treated with one or more ALK tyrosine kinase inhibitors (TKIs)

Sponsor/Applicant Name: Pfizer, Inc.

FDA ATTENDEES (tentative)

Patricia Keegan	Division Director
Erin Larkins	Clinical Team Lead
Nicole Drezner	Clinical Reviewer
Whitney Helms	Nonclinical Team Lead
Dubravka Kufrin	Nonclinical Reviewer
Jeanne Fourie Zirkelbach	Clinical Pharmacology Team Lead
Edwin Chow	Clinical Pharmacology Reviewer
Manasi Sheth –Chandra	Statistics Reviewer
Ingrid N. Chapman	DRISK Reviewer
Janine Stewart	DMEPA Reviewer
Ana Nunes	Rotating Fellow/Clinical
Rosane Charlab Orbach	Genomics Reviewer
Shubhangi (Gina) Mehta	Regulatory Health Project Manager
Leah Her	Regulatory Health Project Manager
Maryam Khazraee	Regulatory Health Project Manager

PFIZER ATTENDEES

Lee James, MD PhD	Asset Team Lead
Holger Thurm, MD MSc	Global Clinical Lead
Gerson Peltz, MD	Safety Risk Lead
Jean-Francois Martini, PhD	Translational Oncology Lead
Yazdi Pithavala	Clinical Pharmacology Lead
Nasir Khan	Vice President, Drug Safety R&D

Betsy Stone
Ann Carey

US Regulatory Lead
Global Regulatory Lead

BACKGROUND

Proposed Indication

Lorlatinib is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) previously treated with one or more ALK tyrosine kinase inhibitors (TKIs).

Regulatory

On June 30, 2017, Pfizer, Inc. (Pfizer) requested a Type B, pre-NDA (multidisciplinary) meeting to discuss and reach agreement on the content and format of a New Drug Application (NDA) for lorlatinib in the above proposed indication under the accelerated approval pathway (21 CFR Subpart H). FDA granted this meeting request on July 18, 2017. The meeting package, containing results from Study B7461001 (Study 1001) based on a data cut-off date of March 15, 2017, was received on July 26, 2017.

Key Regulatory Interactions

- June 18, 2013 – Pre-IND / Written Response Only (WRO) meeting responses regarding the development of lorlatinib and design of the proposed initial open-label, multicenter, multiple-dose study in advanced NSCLC that is ALK mutation- or ROS1 mutation-positive
- September 13, 2013 – New IND containing Protocol B7461001, entitled “A Phase 1/2 Study of PF-06463922 (An ALK/ROS1 Tyrosine Kinase Inhibitor) in Patients with Advanced Non-Small Cell Lung Cancer Harboring Specific Molecular Alterations,” allowed to proceed
- June 23, 2015 – Orphan Drug Designation granted for lorlatinib for the treatment of ALK-positive or ROS1 positive NSCLC (Designation No.: 15-4810)
- December 18, 2015 – End-of-Phase 1 / Pre-Phase 3 meeting held to discuss the lorlatinib clinical development program, including adequacy of the existing data to support a Breakthrough Therapy Designation (BTD), adequacy of data intended to support a future accelerated approval for treatment of patients with ALK-positive metastatic NSCLC with disease progression following crizotinib, proposed revisions to Protocol B7461001 and advice on design of the proposed confirmatory trial in treatment-naïve patients with ALK-positive metastatic NSCLC intended to verify the clinical benefit of lorlatinib
- April 26, 2017 – BTD granted for lorlatinib for the treatment of patients with ALK-positive metastatic NSCLC previously treated with one or more ALK inhibitors
- April 27, 2017 – New protocol B7461020, entitled “An Expanded Access Protocol for Lorlatinib for Treatment of Patients with Advanced Non-Small Cell Lung Cancer Harboring Specific Molecular Alterations,” submitted and is pending activation

There are 10 studies that have been completed or are planned to characterize the clinical pharmacology and pharmacokinetics of lorlatinib under IND 118296.

On June 14, 2017, Pfizer submitted the proposed proprietary name of (b) (4) to the Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE). The target goal date for FDA's response is on or before December 11, 2017.

Pfizer planned to meet with FDA on August 29, 2017, for a Type B, pre-NDA (CMC-only) meeting. After review of FDA's Preliminary Responses dated August 18, 2017, Pfizer submitted a request to cancel the CMC meeting. FDA acknowledged Pfizer's request to cancel the meeting on August 24, 2017.

Proposed NDA Submission

According to Pfizer, submission of an NDA is planned for November 2017. The NDA will contain safety and efficacy data from Study 1001 and safety and PK data from the following supportive clinical pharmacology studies in healthy volunteers: Studies B7461004, B7461005, B7461007, B7461008, B7461011, B7461012 and B7461016.

Pfizer intends to submit a 120-day safety update using a data cutoff date of September 15, 2017, to provide an additional 6 months of safety data from Study 1001. Pfizer also notes that formal renal impairment and hepatic impairment studies are being planned; protocols will be submitted for FDA review prior to the initiation of such studies.

FDA sent Preliminary Comments to Pfizer on August 28, 2017.

Chemistry, Manufacturing, and Controls

Lorlatinib is a small molecule new molecular entity with the molecular formula of $C_{21}H_{19}FN_6O$ and molecular weight of 406.41 Daltons. The drug substance is isolated as anhydrous form 7. Lorlatinib Form 7 is a white to (b) (4) powder that is a (b) (4) solid. The drug substance will be formulated into an immediate release tablet for oral administration. Lorlatinib will be marketed in 25 mg and 100 mg strengths. The proposed commercial image for the 25 mg tablet is a round, tan colored tablet, debossed with "Pfizer" on one side and "25" and "LLN" on the other. The 100 mg tablet is an oval, lavender colored tablet, debossed with "Pfizer" on one side and "LLN 100" on the other.

Nonclinical

Lorlatinib is a kinase inhibitor targeting ALK and cRos. Pfizer states that the nonclinical development program for lorlatinib includes pharmacology, pharmacodynamics, safety pharmacology, ADME, and pharmacokinetic studies, as well as repeat-dose toxicity studies of up to 13 weeks in rats and dogs. In addition, Pfizer states that they have conducted preliminary embryo-fetal development studies in rats and rabbits. The results of all of these studies will be provided in the NDA.

Clinical

The proposed NDA will contain the results of the Study 1001 with a clinical cut-off date of March 15, 2017, as the primary efficacy and safety data in support of a request for accelerated

approval for lorlatinib for the proposed indication of “the treatment of patients with ALK-positive metastatic NSCLC previously treated with one or more ALK tyrosine kinase inhibitors (TKIs). To confirm the clinical benefit of lorlatinib, Pfizer is conducting a randomized, open-label study of lorlatinib versus crizotinib in treatment-naïve patients with advanced ALK-positive NSCLC (Study B7461006); the protocol was submitted on November 29, 2016, first subject first visit occurred on April 14, 2017, and first subject first dose occurred on May 12, 2017.

Study 1001 is an open-label, multicenter, multiple-dose, dose-escalation, safety, PK, and activity-estimating trial of lorlatinib as a single agent in patients with advanced ALK-positive or ROS1-positive NSCLC. The dose-escalation portion of the study was designed to estimate the maximum tolerated dose (MTD) for lorlatinib administered as a single agent over a dose range of 10 mg to 200 mg and to select the recommended phase 2 dose (RP2D) in patients with ALK-positive or ROS1-positive NSCLC with or without asymptomatic central nervous system (CNS) metastases who had received at least one prior ALK tyrosine kinase inhibitor (TKI). The activity-estimating portion of the study is ongoing but has completed patient recruitment and is evaluating the antitumor activity of lorlatinib in expansion cohorts of patients with ALK-positive and ROS1-positive NSCLC at the RP2D of 100 mg daily. The cohorts being evaluated in the activity-estimating portion of the study are defined by the number and type of prior treatment(s) as follows:

	Expansion cohorts	Safety analysis set	ITT analysis set
Total		275	274 ^a
EXP-1	Treatment-naïve	30	30
EXP-2	Prior crizotinib only	27	27
EXP-3A	Prior crizotinib + chemotherapy	60 ^a	32
EXP-3B	1 prior non-crizotinib ALK TKI ± chemotherapy		27
EXP-4	2 prior ALK TKIs ± chemotherapy	65	65
EXP-5	3 or more prior ALK TKIs ± chemotherapy	46	46
EXP-6	ROS-1 positive, any prior line of therapy	47	47

a: 1 patient enrolled in EXP-3 had no documentation of ALK positivity and was removed from the ITT analysis set

The primary endpoint for the dose escalation phase was cycle 1 dose-limiting-toxicities (DLTs), and the secondary endpoints were determination of MTD and RP2D. The primary endpoint for the activity-estimating phase is objective response rate (ORR), overall and intracranial (IC), as assessed by RECIST v1.1 by Independent Central Review (ICR). Key secondary endpoints are duration of response (DOR) and progression-free survival (PFS).

In the proposed NDA submission, Pfizer plans to present efficacy data based on ICR and investigators only for patients with ALK-positive NSCLC who have been previously treated with an ALK TKI. Pfizer plans to present efficacy data based on investigator assessment separately for the dose escalation and dose expansion portions of Study 1001 in the Summary of Clinical Efficacy (SCE). Pfizer plans to present safety data from Study 1001 separately for the dose escalation and dose expansion portions of the trial. The dose expansion safety data will contain

pooled data from cohorts EXP-1 to EXP-6 since this population reflects all patients in the expansion cohorts treated at the RP2D.

Study 1001 Results

A total of 329 patients (54 in dose-escalation phase and 275 across the 6 expansion cohorts) have received lorlatinib in Study 1001. Patient enrollment began in October 2015 and ended in October 2016. As of the data cutoff date of March 15, 2017, treatment was ongoing for 157 of 275 patients (57.1%) in the expansion cohorts with a median duration of treatment of 8.3 months (range <0.1, 17.8). Key demographic and baseline characteristics are presented as pooled data across the six expansion cohorts (n=275). The mean age was 53.6 years (range 19, 85). 57% of patients were female, 48% were white and 38% were Asian, 96% had an ECOG performance status of 0 or 1, and 60% had brain metastases present at baseline.

Summary efficacy results for Study 1001 are presented in the following table:

Efficacy parameter	EXP-2:EXP-5 1 or more prior ALK TKIs	EXP-2:EXP-3A Prior crizotinib ± chemo only	EXP-4:EXP-5 2-3 prior ALK TKIs	EXP-3B Prior non- crizotinib ALK TKI
Evaluable for ORR by ICR, n ^a	197	59	111	27
ORR, % 95% CI	47% (40, 54)	70% (56, 81)	39% (30, 49)	33% (17, 54)
Duration of response	(n=93)			
% of responders with DOR ≥ 6 mos	43%	Not provided	Not provided	Not provided
Evaluable for IC ORR by ICR, n	132	37	83	12
IC ORR, % 95% CI	53% (44, 62)	68% (50, 82)	48% (37, 59)	42% (15, 72)
% of responders with DOR ≥ 6 mos	Not provided	Not provided	Not provided	Not provided

a: 1 patient enrolled in EXP-3 had no documentation of ALK positivity and was removed from the ITT analysis set

The meeting package does not include efficacy results for patients treated in the dose escalation phase of Study 1001.

Safety results for patients in the expansion cohorts (cohorts 1-6) are provided in the tables below; Pfizer reports that these results are consistent with those from the dose escalation phase of the study. All but one patient experienced an adverse event (AE), while grade 3-4 AEs were reported in 145 patients (53%).

Adverse events (n=275)	All-causality AEs, %	Treatment-related AEs, %
Patients with AEs	99.6	95
Patients with serious AEs	32	7
Grade 3-4 AEs	63	42
Grade 5 AEs	11	0
Permanently discontinued treatment due to AE	7.6	2.5
Treatment held due to AE	46	30
Dose reduced due to AE	23	22

AEs occurring in $\geq 20\%$ of patients regardless of causality

Adverse event (n=275)	All grades (%)	Grades 3-4 (%)
Hypercholesterolemia*	82	16
Hypertriglyceridemia*	61	16
Edema*	51	2.5
Peripheral neuropathy*	43	2.5
Dyspnea	23	4.4
Cognitive effects*	23	1.5
Fatigue*	22	0.4
Mood effects*	22	1.5
Weight increased	21	2.2
Arthralgia	20	0

There were 30 Grade 5 AEs reported, with 22 attributed categorized as disease progression. Disease progression was to be reported as an AE if it was fatal (i.e., Grade 5) and occurred during the treatment period or within 28 days of the last dose of lorlatinib. Pfizer reports that 4 patients had disease progression occurring greater than 28 days from the last dose reported as a Grade 5 AE even though it was not required per reporting guidelines, leading to a discrepancy between the number of patients with Grade 5 AEs (n = 30) and the number of deaths within 28 days of last dose (n = 26). The following fatal AEs were reported in 1 patient each: pneumonia, lung infection, acute pulmonary edema, embolism, general physical health deterioration, myocardial infarction, peripheral artery occlusion, and respiratory distress. No deaths were assessed by investigators as related to treatment.

Treatment-emergent AEs resulted in permanent discontinuation of lorlatinib in 21 patients (7.6%). Most AEs leading to discontinuation occurred in only a single patient, except for acute respiratory failure, dyspnea, and respiratory failure, which led to discontinuation of lorlatinib in 2 patients each.

Serious adverse events (SAEs), regardless of causality, and adverse events of special interest are presented in the tables below. SAEs occurred in 89 patients (32%), with grade 3-4 SAEs reported in 43 patients (16%).

Treatment-emergent serious AEs (SAEs) occurring in $\geq 1\%$ of patients

Preferred term (n=275)	All grades (%)	Grades 3-4 (%)
Disease progression	8	0
Dyspnea	2.2	2.2
Pyrexia	2.2	0.7
Pneumonia	1.8	1.1
Mental status changes	1.1	1.1
Pericardial effusion	1.1	0.7
Pulmonary embolism	1.1	1.1

Adverse events of special interest

Preferred term (n=275)	All-causality	Grades 3-4 all-causality	Treatment-related	Grades 3-4 treatment-related
Hyperlipidemia ^a	86%	22%	85%	25%
Edema ^b	51%	2.5%	43%	2.2%
Peripheral neuropathy ^c	43%	2.5%	30%	1.8%
Cognitive effects ^d	23%	1.5%	18%	1.1%
Mood effects ^e	22%	1.5%	15%	0.7%
Speech effects ^f	8.4%	0.4%	7%	0
Weight gain	21%	2.2%	18%	1.8%
Vision disorder ^g	12%	0.4%	7%	0
Liver tests increased ^h	24%	2.2%	21%	1.1%
QT prolonged	7%	0.4%	6%	0
ILD/pneumonitis	1.5%	1.1%	0.7%	0.4%
Atrioventricular block	0.7%	0.4%	0.7%	0
Pancreatitis	0.4%	0.4%	0.4%	0.4%

a: Includes hypertriglyceridemia, hypercholesterolemia, blood cholesterol increased

b: Includes edema peripheral, edema, peripheral swelling

c: Includes paresthesia, neuropathy peripheral, peripheral sensory neuropathy, muscular weakness

d: Includes memory impairment, cognitive disorder, amnesia

e: Includes irritability, anxiety, depression, affect lability, personality change, mood swings

f: Includes dysarthria, slow speech, speech disorder

g: Includes vision blurred, visual impairment, diplopia, visual acuity reduced

h: Includes AST increased, ALT increased, hepatic function abnormal, blood bilirubin increased, hepatic enzyme increased, liver function test increased, cholecystitis

SPONSOR QUESTIONS AND FDA ANSWERS

1. *ALK-positive metastatic NSCLC patients previously treated with one or more ALK TKIs represent a group of patients with unmet medical need. Despite the availability of ALK TKIs, ALK-positive metastatic NSCLC remains an incurable disease, and thus, additional treatment options are still needed. The clinical data from the Phase 1 and Phase 2 studies indicate that lorlatinib has a favorable benefit-risk profile and provides substantial and meaningful clinical benefit as evidenced by rapid, deep, and durable responses, and by clinically significant IC antitumor activity, beyond that provided by the standard-of-care*

for patients with ALK-positive NSCLC who have been previously treated with one or more ALK inhibitors.

Does the Agency agree that an NDA submission filed under the accelerated approval (Subpart H) regulations for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with one or more ALK TKIs would be accepted for review based on the unmet medical need and the favorable benefit-risk profile?

FDA Response:

FDA agrees that the study results proposed for inclusion in an NDA submitted under the provisions of 21 CFR 314 Subpart H (accelerated approval) may provide sufficient clinical evidence to characterize the benefit and risks of lorlatinib in patients with ALK-positive metastatic NSCLC previously treated with one or more ALK TKIs. However, the adequacy of the data to support accelerated approval will be determined during the review of the NDA.

Pfizer August 29, 2017 Email Response:

Pfizer acknowledged FDA's response and stated that no additional discussion was necessary.

Discussion During August 30, 2017 Meeting:

No discussion occurred.

2. *Patients with ALK-positive metastatic NSCLC previously treated with one or more ALK TKIs represent a group of NSCLC patients with unmet medical need. Lorlatinib addresses this unmet medical need as evidenced by the efficacy and safety results of Study 1001. The Sponsor plans to present efficacy data only for patients with ALK-positive NSCLC to support the NDA, separately for the Phase 1 and Phase 2 portions of Study B7461001 in the SCE. The efficacy information for the Phase 2 portion of this study will contain pooled data for the following cohorts: EXP-2 through EXP-5 corresponding to patients with ALK-positive metastatic NSCLC previously treated with one or more ALK TKIs, which is the proposed indication population, EXP-4 and EXP-5 representing patients treated with 2 or 3 prior ALK TKIs, and EXP-2 and EXP-3A, which are patients treated with only prior crizotinib or with prior crizotinib and chemotherapy. Cohort EXP-3B will be presented separately, as these are patients treated with a prior non-crizotinib ALK TKI, with or without prior chemotherapy. Assessments based on ICR will comprise the primary analysis in the SCE, while investigator assessments will be referenced as supportive analyses. The Sponsor plans to present safety data to support the NDA in the SCS, including separate information for the Phase 1 and Phase 2 portions of Study B7461001. The safety information in Phase 1 and Phase 2 portions of this study will contain both ALK-positive NSCLC and ROS1-positive NSCLC populations. The Phase 2 portion will contain pooled data from cohorts EXP-1 to EXP-6, since this population reflects all Phase 2 patients treated at the RP2D.*

Does the Agency agree with the format and content of the submission package to support an NDA for the treatment of adult patients with ALK-positive metastatic NSCLC previously treated with one or more ALK TKIs?

Specifically:

- a. **Does the Agency agree that the single-arm Phase 2 data and results from Study B7461001 could potentially support accelerated approval for the treatment of adult patients with ALK-positive metastatic NSCLC previously treated with one or more ALK TKIs?**

FDA Response:

See FDA response to Question 1.

Pfizer August 29, 2017 Email Response:

Pfizer acknowledged FDA's response and stated that no additional discussion was necessary.

Discussion During August 30, 2017 Meeting:

No discussion occurred.

- b. **Does the Agency agree that the proposed safety population is sufficient to adequately characterize the lorlatinib safety profile to support an NDA submission and adequate benefit/risk assessment in the proposed indication?**

FDA Response:

FDA does not agree with the proposed safety population; in addition to the 275 patients treated in the dose expansion portion of the study, the safety population should also include all 54 patients from the dose escalation portion of Study 1001. Separate safety analyses should be performed and provided for the 292 patients, across both parts of Study 1001, who received lorlatinib at the RPD2 of 100 mg daily.

Pfizer August 29, 2017 Email Response:

The Sponsor agrees that the safety population will include the 275 patients treated in the dose expansion portion of the study (Phase 2) and the 54 patients from the dose escalation portion of the study (Phase 1). The Sponsor proposes to present this information from both parts of the study separately, not in a pooled fashion. In addition the Sponsor will provide separate safety summaries for the 292 patients, across both phases of the study, who received lorlatinib at the RP2D of 100 mg daily.

Discussion During August 30, 2017 Meeting:

FDA stated this was acceptable.

c. Does the Agency agree with the presentation of study data in the Summary of Clinical Efficacy (SCE)?

FDA Response:

FDA does not agree with the proposed ITT population, which excludes one patient enrolled in EXP-3 for whom ALK positivity was not confirmed. The ITT population should include all patients in expansion cohorts 2-5 who received at least one dose of lorlatinib (n=198).

FDA does not object to Pfizer's plan to present efficacy data for the dose escalation portion of the study and the dose expansion portion of the study separately in the SCE; however, the SCE should also present pooled efficacy data based on ICR assessment for all patients with ALK-positive NSCLC who have received previous treatment with an ALK TKI treated at the RP2D, including patients from the dose escalation portion of the study.

Pfizer August 29, 2017 Email Response:

As specified in the SAP "the ITT analysis set includes all enrolled patients with documented ALK or ROS1 rearrangement who receive at least one dose of PF-06463922 (including Day-7 Lead-in dose). Patients without documentation of ALK or ROS1 rearrangement are excluded from the ITT analysis sets". This patient was excluded from the ITT because the ALK status is unknown. In light of this clarification, the Sponsor would like to ask the Agency to reconsider this request.

The Sponsor agrees to provide additional sensitivity analyses in the SCE for pooled efficacy data based on ICR assessment for all patients with ALK-positive NSCLC who have received previous treatment with an ALK TKI treated at the RP2D, including patients from the dose escalation portion of the study.

Discussion During August 30, 2017 Meeting:

FDA and Pfizer agreed to provide analyses of ORR and DOR in the following populations: all patients with documented ALK mutation enrolled in the phase 2 portion of study, all patients with documented ALK mutation receiving 100 mg lorlatinib across the entire study, all patients enrolled in the Phase 2 portion of the study purported to be ALK positive and received prior treatment, and all patients receiving 100 mg lorlatinib across the entire study purported to be ALK positive and received prior treatment. The analysis to be presented in product labeling will be determined during review of the application. The dataset will contain the appropriate flags to allow identification of subgroups as described above.

d. Does the Agency agree with the presentation of study data in the Summary of Clinical Safety (SCS)?

FDA Response:

FDA does not object to Pfizer's plan to present safety data for the dose escalation portion of the study and the dose expansion portion of the study separately in the

SCS; however, the SCS should also include presentation of pooled safety data for all patients in Study 1001 treated at the RP2D, including patients from the dose escalation portion of the study.

Pfizer August 29, 2017 Email Response:

The SCS will include 54 patients from Phase 1 and 275 patients from Phase 2, separately. The Sponsor agrees to provide an additional presentation in the SCS for the 292 patients, across Phase 1 (17 patients) and Phase 2 (275 patient), who received lorlatinib at the RP2D of 100 mg daily.

Discussion During August 30, 2017 Meeting:

No discussion occurred.

3. *The Sponsor plans to follow the Guidance for Industry entitled, “Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document” dated April 2009, Section V. D. – Example 4, for the SCE and the SCS to meet the requirements of the ISE and the ISS, respectively. The mapping ISE will provide the locations within the Common Technical Document (CTD) of the components of the ISE. The mapping ISS will provide the locations within the CTD of the components of the ISS.*

Does the Agency agree with the proposal for the Integrated Summary of Efficacy (ISE) and the Integrated Summary of Safety (ISS) mapping documents?

FDA Response:

The proposal to follow the Guidance document cited above is acceptable; however, insufficient information is provided in the meeting package to provide agreement with the proposed content and format of the ISS and ISE. Additional information should be provided by Pfizer at the pre-NDA meeting, (e.g., a proposed Table of Contents for each module of the NDA and a description of the content planned for inclusion in the ISS and ISE) to permit sufficient information for FDA to discuss whether there is agreement on the content and format of these sections of the planned NDA.

Pfizer August 29, 2017 Email Response:

The Sponsor believes that the proposed SCE and SCS are sufficiently detailed to meet the summary requirements of the ISE and ISS, as outlined in 21 CFR 314.50(d)(5)(vi)(a) and that separate ISE and ISS documents are not required. The SCE and SCS, along with the SBS and SCP, will be within the recommended page limits for the clinical summary section (i.e., 2.7 of the CTD). The Sponsor proposes to provide mapping documents in the NDA, which will provide the locations in the eCTD of the relevant information. Draft mapping ISE and mapping ISS documents are provided in Table 1 and Table 2 (see attachment: Pfizer Response document).

For the ISE, the mapping document will include locations for each of the following:

- textual summary of the clinical efficacy data
- results of statistical analyses of the efficacy data (tables)
- efficacy data split by age, race, gender

- case report forms (CRFs) and CRF tabulations

For the ISS, the mapping document will include locations for each of the following:

- textual summary of the clinical safety data
- safety data tables
- safety data split by age, race, gender
- CRFs and CRF tabulations
- patient narratives
- adverse event data sets

Discussion During August 30, 2017 Meeting:

FDA acknowledged the proposal, but needs additional time to research the acceptability of the proposed approach. Pfizer will provide examples of previously submitted applications that use this approach. FDA will provide comments on the proposed approach within 2 to 4 weeks of this meeting.

4. *The Sponsor plans to include narratives in the NDA for:*
- o *Deaths on treatment and within 28 days of the last dose of study drug*
 - o *Permanent discontinuations due to AEs*
 - o *SAEs*

The narratives for deaths and SAEs will be provided as auto-generated Council for International Organizations of Medical Sciences (CIOMS) reports, and the narratives for the permanent discontinuations due to AEs will be provided in prose format.

Does the Agency agree with the proposed plan regarding inclusion of patient narratives in the NDA? Does the Agency agree with the proposed narrative format?

FDA Response:

No, FDA does not agree. Case report forms (CRFs) and narratives should be provided for all patients who died, dropped out or permanently discontinued study treatment, experienced serious adverse events, experienced selected adverse events of interest (i.e., hypercholesterolemia, edema, etc.), or became or were pregnant from all trials across the clinical development program, including clinical pharmacology studies, studies in healthy volunteers, and the ongoing randomized trial, Study B7461006.

Pfizer August 29, 2017 Email Response:

The Sponsor agrees to provide Case report forms (CRFs) and narratives for all patients who specifically:

- dropped out (i.e. permanently discontinued study treatment due to withdrawal of consent) (Prose)
- permanently discontinued study treatment due to AEs (Prose)
- experienced serious adverse events (CIOMS)

- experienced selected adverse events of interest (Prose or CIOMS)
- became or were pregnant (CIOMS)

from all trials across the clinical development program, including clinical pharmacology studies, studies in healthy volunteers.

CRFs will be provided for all patients who died. Please note that CIOMSs are available for patients who died within 28 days of the last dose of study drug, however CIOMSs are not available for all patients who died after that unless the death was attributed to study drug.

No patients were enrolled in the ongoing randomized trial B7461006 at the March 15, 2017 data cut-off date.

Narratives for selected AEs of interest are outlined in the safety narrative plan for cases of all causality a) all grades pneumonitis, QTc prolongation, and AV block; b) grade 2 or higher cognitive effects, mood effects, speech effects, vision disorder, pancreatitis, and edema; and c) grade 3 or higher peripheral neuropathy, and liver tests increased. Please note that the safety narrative plan does not include cases of hyperlipidemia, because these clinically present as laboratory abnormalities only.

Please note that CRFs will be provided but narratives are not available for permanent discontinuations in all of the healthy volunteer studies.

Discussion During August 30, 2017 Meeting:

FDA agrees with the proposed approach for providing safety information across the clinical development program, acknowledging that no patients were enrolled in B7461006 as of the data cutoff date.

5. *In accordance with 21 CFR 314.50 (f) (2), the Sponsor plans to submit copies of individual CRFs for each patient who died during a clinical study, had an SAE, or who was permanently discontinued because of an AE, in order to support information provided in safety narrative. As such, the Sponsor does not plan to submit copies of other CRFs or of CRFs from healthy volunteer studies or clinical pharmacology studies, as these are unlikely to provide additional relevant information.*

Does the Agency concur with Sponsor's proposal regarding inclusion of copies of individual case report forms (CRFs)?

FDA Response:

See FDA response to Question 4.

Pfizer August 29, 2017 Email Response:

Pfizer acknowledged FDA's response and stated that no additional discussion was necessary.

Discussion During August 30, 2017 Meeting:

No discussion occurred.

6. *Per the FDA Guidance for Industry: Cancer Drug and Biological Products Clinical Data in Marketing Applications (issued October 2001), the Sponsor understands that tumor images do not need to be submitted with the NDA. Therefore, the Sponsor proposes that tumor images will be made available to FDA “upon request” during review of the NDA.*

Does the Agency agree with the Sponsor’s proposal not to submit radiographic images from the IRC at the time of NDA submission, but make them available upon request during the NDA review process?

FDA Response:

Yes, FDA agrees.

Pfizer August 29, 2017 Email Response:

Pfizer acknowledged FDA’s response and stated that no additional discussion was necessary.

Discussion During August 30, 2017 Meeting:

No discussion occurred.

7. *Pfizer proposes to provide the following with the NDA submission:*
- o *Statistical analysis system (SAS) Datasets for clinical study reports (CSRs) provided in legacy (non-Clinical Data Interchange Standards Consortium [CDISC]) format including analysis datasets (which include raw collected data) as .xpt files, define.pdf, and annotated CRF (where available);*
 - o *Dataset Guide detailing the datasets being provided with the submission;*
 - o *SAS programming codes used to generate the primary and key secondary efficacy analyses in Study 1001 CSR, as well as simplified SAS codes to replicate the key efficacy analysis results;*
 - o *Text (.txt), documentation (*.pdf files), input datasets (.xpt files), define.pdf for PK modeling and simulation output.*

Does the Agency agree with the proposal for submission of the datasets?

FDA Response:

The proposal for the submission of datasets is acceptable. Also, refer to additional clinical pharmacology comments.

Pfizer August 29, 2017 Email Response:

Pfizer acknowledged FDA’s response and stated that no additional discussion was necessary.

Discussion During August 30, 2017 Meeting:

No discussion occurred.

8. *The Sponsor plans to have the studies itemized in Table 10 completed and included with the initial NDA submission. Formal hepatic and renal impairment studies are currently being planned. In addition, the Sponsor intends to submit the following 4 population PK/PK-PD reports with the initial NDA submission:*
- i. *Pooled population PK analysis*
 - ii. *Population PK-PD analysis for key efficacy endpoints*
 - iii. *Population PK-PD analysis for key safety endpoints*
 - iv. *Population PK-PD analysis for electrocardiogram (ECG) endpoints (QTc, partial response [PR], etc.)*

Does the Agency agree with the Sponsor's plan for the biopharmaceutics, and for the clinical pharmacology studies and PK/PK-PD reports?

FDA Response:

Pfizer Inc.'s proposed plan for the clinical pharmacology studies and PK/PK-PD reports to be submitted in the initial NDA appears acceptable with exception of the failure to provide an adequate response to Question #10 captured in the minutes for the EOP1/Pre-Phase 3 Meeting held on Dec 18, 2015. In the response to Question #10, FDA stated that additional pharmacokinetic studies to determine the appropriate dose of lorlatinib, when it is coadministered with inducers or inhibitors of CYP2C8, 2C19, 3A4 and UGT1A4, may be warranted if these enzymes are responsible for $\geq 25\%$ of lorlatinib's total metabolism. At the time of the pre-NDA meeting, provide information regarding the metabolism of lorlatinib (and major active metabolites) by CYP2C8, 2C19, 3A4 and UGT1A4, including justification that risk/benefit assessments for lorlatinib can be made in the absence of these data and describe potential clinical pharmacokinetic studies planned to assess such effects. If this information is not provided, FDA and Pfizer may not be able to reach an agreement on the contents of a complete application.

Pfizer August 29, 2017 Email Response:

Based on in vitro studies with the human hepatocyte relay assay with mechanism based chemical inhibitors, results indicated that total CYP contributions to lorlatinib metabolism was $\sim 67\%$ and that $\sim 33\%$ of the in vitro metabolism was via non-CYP mediated pathway(s). CYP3A was estimated to contribute $\sim 37\%$ of the in vitro metabolism of lorlatinib, with minor contributions from CYP2C8 and CYP2C19.

A clinical study has been conducted with the strong CYP3A4 inducer rifampin (B7461011), which also induces CYP2C8, CYP2C19, and UGT1A4. Thus, the overall effect of a strong inducer of the relevant metabolic enzymes for lorlatinib has been evaluated; however the effect of rifampin-mediated induction on individual CYP enzymes is unknown. Results from this study will be included in the NDA submission.

For CYP3A4, a clinical study with a strong inhibitor, itraconazole have been completed, and results from this study B7461012 will be included in the NDA submission.

Since CYP2C8 and CYP2C19 have minor contributions (<25%) to the overall metabolism of lorlatinib, studies with inhibitors have not been initiated. In addition, pharmacogenomics analysis with CYP2C19 will be evaluated to confirm the potential role of its contribution to the overall clearance of lorlatinib.

For UGT1A4, a selective, strong inhibitor that can be clinically used has been difficult to identify. Ketoconazole and paclitaxel have been noted in the literature as being inhibitors of UGT1A4 in vitro, but the use of either drug in healthy volunteers is not feasible.

The major circulating metabolite of lorlatinib in human plasma, as identified from the mass balance study, is PF-06895751 (also referred to as M8), which is a pharmacologically inactive metabolite. The formation of this metabolite likely involves multiple metabolic steps. No active human metabolites of lorlatinib have been identified.

Discussion During August 30, 2017 Meeting:

Pfizer's response appears acceptable, and final determination will be made during NDA review.

9. *Appendix 2 lists the nonclinical study reports including nonclinical toxicology studies that the Sponsor proposes to include in Module 4 of the eCTD.*

Does the Agency concur that the proposed content of Module 4, as described in Section 9.5 and Appendix 2 is adequate to support the proposed indication for registration?

FDA Response:

In general, the proposed nonclinical package appears sufficient to support the submission of an NDA for the treatment of patients with advanced cancer; however, the package contains insufficient details of results of the embryo-fetal development studies to determine whether they are sufficient to support an NDA submission. If there are clear signs of embryofetal lethality or teratogenicity then the preliminary studies in rats in rabbits along with the exploratory studies in zebrafish and murine embryonic stem cells may be sufficient to support the marketing application. In addition, if there are any metabolites that are only present in humans or occur at extremely disproportionate levels in humans compared to animals, then additional short term toxicology studies may be warranted. At the time of the pre-NDA meeting, please provide a summary of this information, which is lacking in the meeting package. If this information is not provided, FDA and Pfizer may not be able to reach agreement on the contents of a complete application.

Pfizer August 29, 2017 Email Response:

Clear signs of embryofetal lethality and teratogenicity have been observed in rats and rabbits after administration of lorlatinib. In embryo-fetal development studies,

developmental toxicity consisting of lower embryo-fetal viability, lower fetal body weights, and malformations were observed in rats and rabbits.

There are no lorlatinib oxidative metabolites that are only present in humans or that occur at extremely disproportionate levels in humans compared to animals. However there is an inactive benzoic acid major human circulating metabolite, which does appear at higher levels in humans than in animals (M8, PF-06895751; 21% of circulating radioactivity and 5% of total dose in humans), that was identified in plasma of rats, dogs, and humans. The unbound plasma AUC of PF-06895751 in rats and dogs following oral administration of lorlatinib in the 13-week toxicity studies were <4% of that observed in human plasma. PF-06895751 was not considered to be pharmacologically active as it did not inhibit ALK phosphorylation (on-target effect) and had no activity on other pharmacologically important receptors (off-target effects). PF-06895751 was not mutagenic in the bacterial reverse mutation and induced weak (11.8%) inhibition in a hERG assay with an IC50 estimated to be greater than 300 μ M (55,260 ng/mL). Therefore, the Sponsor does not intend to conduct a short term in vivo toxicity study with PF-06895751.

Discussion During August 30, 2017 Meeting:

FDA stated that based on the summary description of the EFD assessment, the proposed approach appears acceptable.

10. *For the 120-day safety update, the Sponsor proposes a data cutoff date of 15 September 2017, providing an additional 6 months of data from Study B7461001 beyond that included in the NDA for which the data cutoff date is 15 March 2017. The Sponsor is planning to include targeted safety data comprised of the following: deaths, SAEs, all-causality and treatment-related AEs, laboratory abnormalities, ADRs, and AEs of special interest. Narratives for deaths and SAEs (in CIOMS format) and narratives for permanent discontinuation due to AEs (in prose format) will be provided for newly reported events. In addition, updates to previously provided safety case narratives will also be included, as applicable. The Sponsor will also provide SAE and Grade 5 AE information from other ongoing studies of single-agent lorlatinib, including investigator-initiated research studies and compassionate use.*

Does the Agency agree with the proposal for the 120-day safety update?

FDA Response:

FDA agrees with the proposal for a 120-day safety update using a data cutoff date of September 15, 2017. In addition to the “targeted safety data” proposed by Pfizer, the 120-day safety update should also include updated information for patients who dropped out or permanently discontinued study treatment. FDA agrees with Pfizer’s plan to provide narratives for deaths, SAEs, and permanent discontinuation due to AEs for newly reported events; however, rather than only including events occurring through September 15, 2017, Pfizer should submit narratives for all such events using a data cut-off date of 1 month prior to the submission of the NDA.

Pfizer August 29, 2017 Email Response:

The Sponsor agrees to include information for patients who dropped out (withdrawal of consent) or permanently discontinued study treatment in the 120-day safety update. The Sponsor proposes to provide narratives in CIOMS format for all SAEs reported one month prior to the NDA submission date. The sponsor proposes to provide all other narrative types from the information collected through the data cut-off date of September 15, 2017.

Discussion During August 30, 2017 Meeting:

FDA agreed to the proposal to provide narratives for all on-study deaths and SAEs reported one month prior to NDA submission date and to provide narratives for all permanent discontinuations through the data cutoff of September 15, 2017, as proposed.

ADDITIONAL COMMENTS

Clinical Pharmacology

11. Address the following questions in the Summary of Clinical Pharmacology:
- What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
 - What are the exposure-response relationships for efficacy, safety and biomarkers?
 - What is the effect of lorlatinib on the QT/QTc interval?
 - What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
 - What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.
 - How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

Pfizer August 29, 2017 Email Response:

Pfizer acknowledged FDA's comment and stated that no additional discussion was necessary.

Discussion During August 30, 2017 Meeting:

No discussion occurred.

12. Apply the following advice in preparing the clinical pharmacology sections of the original submission:

- a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
- b. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean $\pm$ standard deviation) and median with minimum and maximum values as appropriate.
- c. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
 - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.
- d. Submit the following for the population pharmacokinetic analysis reports:
 - Standard model diagnostic plots
 - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
 - Model parameter names and units in tables.
 - Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.
- e. Submit the following information and data to support the population pharmacokinetic analysis:
 - SAS transport files (*.xpt) for all datasets used for model development and validation
 - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
 - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

- f. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> for population PK, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf> for exposure-response relationships, and <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm> for pharmacometric data and models submission guidelines.

Pfizer August 29, 2017 Email Response:

Pfizer acknowledged FDA's comment and stated that no additional discussion was necessary.

Discussion During August 30, 2017 Meeting:

No discussion occurred.

Submit to QT IRT Group

13. Include the following items when you submit your QT study report:
- Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
 - Electronic copy of the study report
 - Electronic or hard copy of the clinical protocol
 - Electronic or hard copy of the Investigator's Brochure
 - Annotated CRF
 - A data definition file which describes the contents of the electronic data sets
 - Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
 - Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
 - Data set whose QT/QTc values are the average of the above replicates at each nominal time point

- j. Narrative summaries and case report forms for any:
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation
 - iv. Episodes of syncope
 - v. Episodes of seizure
 - vi. Adverse events resulting in the subject discontinuing from the study
- k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- l. A completed Highlights of Clinical Pharmacology Table

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

Pfizer August 29, 2017 Email Response:

Pfizer acknowledged FDA's comment and stated that no additional discussion was necessary.

Discussion During August 30, 2017 Meeting:

No discussion occurred.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The agreements reached regarding the content of a complete application are summarized in the meeting minutes for the August 30, 2017 meeting. Since the August 29, 2017, CMC meeting was cancelled, Pfizer commits to providing a complete application of the CMC components. FDA refers Pfizer to the August 18, 2017, correspondence containing preliminary meeting responses and the August 24, 2017, correspondence acknowledging the meeting cancellation.
- Pfizer stated that the application will be complete at the time of submission and there are no plans for late submission of minor components. There are no agreements for late submission of application components.
- Pfizer confirmed that the NDA will include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion on the need for a REMS was held and it was concluded that while a REMS will not be required for filing the NDA. However, at this time the Office

of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and, if it is necessary, what the required elements will be. FDA will determine the need for REMS during the review of the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. Pfizer confirmed their intent to submit a complete application.

PREA REQUIREMENTS

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

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

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

SUBMISSION FORMAT REQUIREMENTS

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

SECURE EMAIL COMMUNICATIONS

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

MANUFACTURING FACILITIES

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

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

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided

in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

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

Corresponding names and titles of onsite contact:

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

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

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

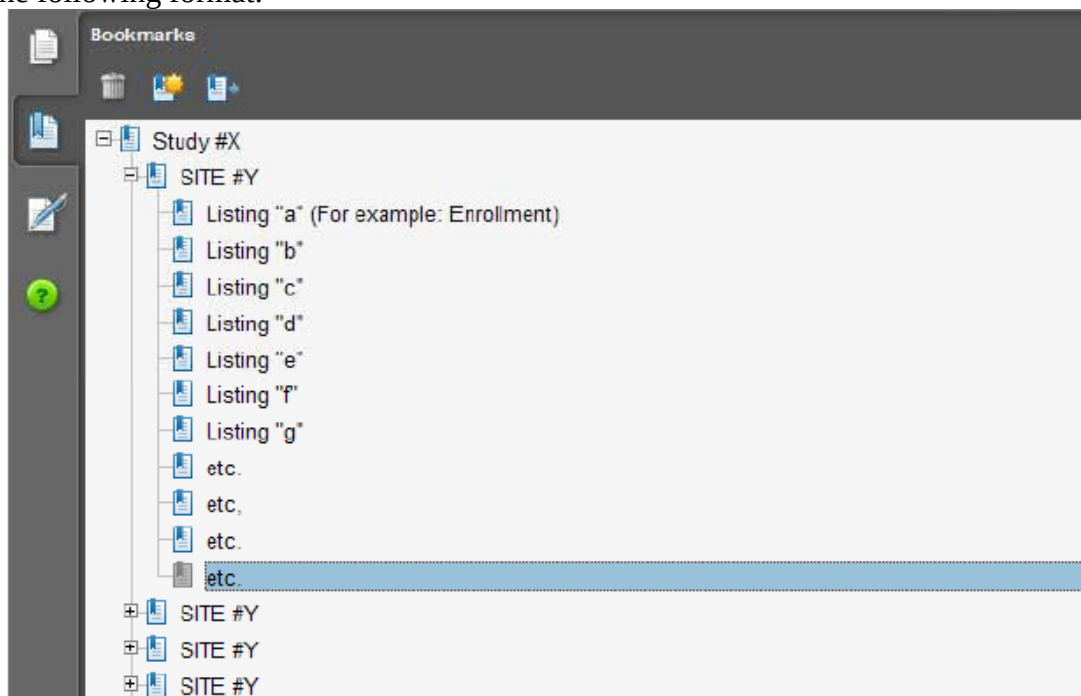
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number

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

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)

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



III. Request for Site Level Dataset:

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

Attachment 1

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

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

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

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



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

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

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

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

/s/

SHUBHANGI H MEHTA
09/15/2017

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	118,296
Request Receipt Date	March 2, 2017
Product	Lorlatinib
Indication	Metastatic NSCLC previously treated with 1 or more ALK TKIs
Drug Class/Mechanism of Action	ALK/ROS1 tyrosine kinase inhibitor (TKI)
Sponsor	Pfizer, Inc
ODE/Division	DOP2
Breakthrough Therapy Request Goal Date (within <u>60</u> days of receipt)	May 1, 2017

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (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.

- 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):**
Lorlatinib is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) previously treated with one or more ALK inhibitors.
- Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐ YES ☒ NO

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

3. Consideration of Breakthrough Therapy Criteria:

- Is the condition serious/life-threatening¹? ☒ YES ☐ NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

- 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):
 - Only animal/nonclinical data submitted as evidence ☐
 - Insufficient clinical data provided to evaluate the BTDR

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>

- (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 therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

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

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

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

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

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

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

Lorlatinib is an oral, macrocyclic, adenosine triphosphate (ATP)-competitive small-molecule inhibitor of ALK and c-ros oncogene 1 (ROS1) receptor tyrosine kinases. It is being developed for the treatment of ALK-positive (b) (4). In preclinical studies, lorlatinib demonstrated inhibitory activity against ALK or ROS1 translocations and most known acquired crizotinib-resistant ALK or ROS1 mutations (1). It was also capable of penetrating the blood-brain barrier in preclinical animal models (2). The ALK fusion oncogene is one of the newer molecular targets identified in NSCLC. ALK-positive NSCLC has a prevalence of approximately 4.4% with 10,000 to 15,000 new cases per year, typically occurs in younger patients who are never/light smokers, and is of predominantly adenocarcinoma histology. Crizotinib, a small molecule inhibitor of ALK, MET, and ROS1 kinases, received regular approval from the FDA for the first-line treatment of advanced ALK-positive NSCLC in November 2013. However, some patients with ALK-positive NSCLC will not derive any benefit from crizotinib, and other patients who initially experience benefit will later develop resistance. In vitro, lorlatinib inhibited catalytic activities of wild-type ALK and 15 different ALK mutant kinases, including those with crizotinib-resistant mutations, in recombinant enzyme and cell-based assays. Lorlatinib also achieved brain exposure of 20-30% of plasma levels in mice and rats; the brain has been reported as the single site of disease progression in 15-46% of patients following crizotinib treatment.

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>

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

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

The clinical data to support the breakthrough therapy designation request is from Study B7461001, an open-label, multicenter, dose-escalation (phase I) and activity-estimating (phase II) study in patients with ALK-positive or ROS1-positive NSCLC. The primary endpoint for the dose escalation phase was cycle 1 dose-limiting-toxicities (DLTs), and the secondary endpoints were determination of maximum tolerated dose (MTD) and recommended phase II dose (RP2D). The primary endpoint for the activity-estimating phase is objective response rate (ORR), as assessed by RECIST v1.1; ORR is considered a surrogate endpoint for NSCLC. Adverse events, graded by NCI CTCAE v4.03, are a secondary endpoint for both phases. Time-to-event endpoints e.g. duration of response (DOR), progression-free survival (PFS), and overall survival (OS) are secondary endpoints in the activity-estimating phase.

- 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:**

Endpoints accepted as clinically significant outcome measures for patients with metastatic NSCLC and considered adequate to support traditional approval include an improvement in OS or a large, clinically meaningful improvement in PFS. ORR, the primary endpoint of the activity-estimating portion of the study, of large magnitude and long duration is considered a surrogate endpoint reasonably likely to predict clinical benefit in NSCLC and has been considered adequate to support accelerated approval for the treatment of patients with NSCLC (3).

- 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.**

N/A

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

Table 1: Available therapies for advanced ALK+ NSCLC (5)

	Chemotherapy (pemetrexed or docetaxel) n=174	Ceritinib n=163	Alectinib Study 1: n=87 Study 2: n=138	Brigatinib n=110
Intended population	ALK+ NSCLC who received 1 prior platinum-based regimen	ALK+ NSCLC who received prior crizotinib	ALK+ NSCLC who received prior crizotinib	ALK+ NSCLC who received prior crizotinib
Approval	Regular	Accelerated	Accelerated	BTDR (In house for AA)
ORR (95% Confidence Interval [CI])	20% , (14, 26)	44% , (36, 52)	Study 1: 38% (28, 49) Study 2: 44% (36, 53)	54% (44, 63)

Median DOR, mths (95% CI)	Median PFS: 3.0 (2.6, 4.3)	7.1, (5.6, NE)	11.2, (9.6, NE)	Median PFS: 11.1
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BTDR=breakthrough therapy designation, AA= accelerated approval

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

Crizotinib was the first ALK TKI approved by the FDA for patients with ALK-positive NSCLC, with a reported ORR of approximately 70%. However, disease progression often occurs within the first 12 months of treatment with the central nervous system (CNS) being one of the most common first sites of progression. The emergence of acquired crizotinib-resistance mutations, including the “gate-keeper” L1196M and G1202R mutations, are the main cause of crizotinib-resistant disease (4). Given these limitations, several second-generation and third-generation ALK TKIs have been developed for patients who experienced progression on or were intolerant to crizotinib, including ceritinib, alectinib, and brigatinib. All received breakthrough therapy designation for the treatment of ALK-positive NSCLC after progression on or intolerance to crizotinib. Ceritinib was the first drug to receive accelerated approval from the FDA (June 2014) for patients who have experienced progression on or are intolerant to crizotinib and has shown objective response rates of approximately 60% across its ASCEND development program. Alectinib has also received accelerated approval from the FDA (December 2015) and is currently accruing data from a randomized, controlled trial comparing alectinib to crizotinib in the first-line setting (ALEX). Brigatinib received breakthrough designation status in 2014 and has an NDA under review for accelerated approval for the treatment of patients with ALK-positive NSCLC who are resistant to crizotinib.

10. Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.**

Study ID	Trial Design	# of Patients	Treatment Group	Primary Endpoint
B7461001	Open label, single arm, multicenter, dose-escalating and activity-estimating trial	~200 (planned)	Patients with advanced, ALK-positive NSCLC who are either treatment naïve in the advanced setting or have had disease progression after 1 or 2 previous ALK inhibitor therapies, as the last therapy given	Ph I: Cycle 1 DLTs
Phase I		Ph I: 54 (complete)		Ph II: ORR
Phase II		Ph II: 116 (ongoing)		Ph I ORR: 37% (95% CI 22, 53)
				Ph II ORR (EXP:2-5): 33% (95% CI 23, 44)

Study B7461001 is the main source of data to support the BTDR. The study is an open-label, multicenter, single arm, dose-escalation (phase I) and activity-estimating (phase II) study in patients with ALK-positive or ROS1-

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.

positive advanced NSCLC. The dose escalation portion enrolled 54 patients at dose levels ranging from 10 mg daily to 200 mg daily and established the RP2D of 100 mg daily; patients in the activity-estimating portion received lorlatinib 100 mg daily in multiple expansion cohorts. ALK-positive NSCLC patients must either be treatment naïve in the advanced setting or have had disease progression after 1 or 2 previous ALK inhibitors as the last therapy given. The primary endpoint for the dose escalation phase is cycle 1 DLTs and the key secondary endpoints are MTD, RP2D, and adverse events (AEs), DOR, PFS, and OS. The primary endpoint for the activity-estimating phase is ORR, and the key secondary endpoints are AEs, DOR, PFS, and OS. The dose escalation portion of the study is complete, with a total accrual of 54 patients, of whom 41 patients had ALK-positive NSCLC. The ORR was 37% (95% CI: 22, 53), with a median DOR of 14 months (95% CI: 2.8-26.5). In the fifteen patients treated at the RP2D of 100 mg daily, the ORR was 27% (95% CI: 4.8, 55) with a duration of response ranging from 2.8 to 19.3 months. The total accrual to date of the ongoing activity-estimating portion of the study is 116 patients, which includes all patients enrolled in the six expansion cohorts (see Table 2); this is the safety analysis set being used in support of the BTDR. The data cutoff date was August 15, 2016, and includes patients enrolled from September 2015 (start of Phase II) through March 2016. The efficacy analysis set includes 83 patients enrolled in expansion cohorts 2 through 5; this excludes treatment-naïve patients (EXP-1) and ROS1-positive patients (EXP-6). The ORR for the pooled EXP-2:EXP-5 cohorts (at least one prior ALK TKI) is 33% (95% CI: 23, 44). The ORR for the 57 patients in the pooled EXP-4:EXP-5 cohorts (≥ 2 prior ALK TKIs $\pm$ chemo) is 26% (95% CI: 16, 40). Of the 27 EXP-2:EXP-5 patients with objective responses, 9 patients have had progression with a duration of response range from 2.6-4.2 months for these 9 patients. For patients with measurable CNS metastases at baseline, the intracranial (IC) ORR for the dose escalation portion (n=20) was 35% (95% CI: 15, 59) and was 51% for the pooled EXP-2:EXP-5 from the activity-estimating portion (n=35), for an overall IC ORR of 46% (95% CI: 32, 59).

Table 2: Expansion Cohorts

	Cohorts	Safety analysis set	Efficacy analysis set
Total		116	83
EXP-1	Treatment naïve	10	N/A
EXP-2	Prior crizotinib	7	7
EXP-3A	Prior crizotinib + 1-2 chemo regimens	9	9
EXP-3B	1 prior ALK TKI $\pm$ chemo	9	9
EXP-4	2 prior ALK TKIs $\pm$ chemo	45	45
EXP-5	3 prior ALK TKIs $\pm$ chemo	13	13
EXP-6	ROS1-positive	23	N/A

b. Include any additional relevant information.

The data provided for lorlatinib should be considered preliminary clinical evidence of a substantial improvement over available therapies in terms of durability of response. There are no currently available therapies that have regular approval for ALK-positive NSCLC after progression on one more more ALK TKIs. Ceritinib and alectinib have accelerated approval for the treatment of patients with ALK-positive NSCLC with progression on or intolerance to crizotinib. Among patients in EXP2:EXP5, 77% had received prior treatment with platinum-containing chemotherapy. In a study of patients with ALK-positive NSCLC comparing crizotinib to chemotherapy after progression of disease following platinum-based chemotherapy, ORR was 20% (14, 26) for chemotherapy; median DOR was not reported but median PFS was 3.0 months (95% CI: 2.6-4.3) (5).

The AEs reported for lorlatinib were generally manageable with most treatment-related AEs being Grade 1 or 2 in severity. In the dose escalation phase, the most common treatment-related AEs in decreasing frequency were hypercholesterolemia (72%), hypertriglyceridemia (39%), peripheral neuropathy (39%), and peripheral edema

(39%). In the activity-estimating phase, the most common treatment-related AEs in decreasing frequency were hypercholesterolemia (90%), hypertriglyceridemia (72%), peripheral edema (33%), and peripheral neuropathy (28%). In the dose escalation portion of the study, the only treatment-emergent Grade 5 AEs were disease progression (8 events all-causality and 0 events treatment-related). In the activity-estimating portion of the study, the only treatment emergent Grade 5 AEs were disease progression (6 events all-causality) and pneumonia (1 event all-causality). There were no treatment-related Grade 5 AEs. In the dose escalation portion of the study (N = 54), the treatment-emergent CNS AEs in each category greater than 5%, are as follows: MOOD EFFECTS: affect lability 5 (9.3%), anxiety 4 (7.4%), and irritability 3 (5.6%); SPEECH EFFECTS: slow speech 6 (11.1%), speech disorder 5 (9.3%), and dysarthria 3 (5.6%); COGNITIVE EFFECTS: cognitive disorder 8 (14.8%), confusional state 5 (9.3%), and memory impairment 4 (7.4%). When considering Grade 3 and higher adverse events across all 3 categories, there were 2 patients with a Grade 3 COGNITIVE EFFECTS and 1 patient with a Grade 4 MOOD EFFECTS. The CNS effects were evaluated in greater detail in the activity-estimating portion of the study, including specific tests for cognition, mood, and suicidality.

In the activity-estimating portion of the study (N = 116), the treatment-emergent CNS AEs in each category reported at >5% incidence were MOOD EFFECTS: anxiety 9 (7.8%); COGNITIVE EFFECTS: memory impairment 10 (8.6%), amnesia 7 (6.0%), and cognitive disorder 6 (5.2%). When considering Grade ≥ 3 AEs across all 3 categories, there was 1 patient with a Grade 3 MOOD EFFECTS, 1 patient with a Grade 3 SPEECH EFFECTS, and 2 patients with Grade 3 COGNITIVE EFFECTS. There were no patients with any events of Grade 4 or 5 in severity. In the dose escalation phase, 7% of patients had treatment permanently discontinued due to AEs, 24% of patients had dose reductions due to AEs, and 48% of patients had a temporary discontinuation of treatment due to AEs. In the activity-estimating phase, 7% of patients had treatment permanently discontinued due to AEs, 21% of patients had dose reductions due to AEs, and 41% of patients had temporary discontinuation of treatment due to AEs.

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

☒ GRANT :

Provide brief summary of rationale for granting:

DOP2 recommends granting breakthrough designation status for lorlatinib for the treatment of patients with ALK-positive metastatic NSCLC who have received treatment with one or more prior ALK inhibitors. ALK-positive metastatic NSCLC is a serious and life-threatening condition with an unmet medical need. The results of Study B7461001, demonstrating a clinically meaningful improvement in durability of response compared to second-line chemotherapy represents a substantial improvement over available therapy.

☐ DENY:

Provide brief summary of rationale for denial:

12. 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):**

Study B7461001 is ongoing and is expected to enroll a total of 240 patients across the six cohorts. The global clinical trial, "A Phase 3, Randomized, Open-label Study Of Lorlatinib (Pf-06463922) Monotherapy Versus Crizotinib Monotherapy In The First-line Treatment Of Patients With Advanced Alk-positive Non-small Cell Lung Cancer," intended to support the approval of lorlatinib for the first-line treatment of NSCLC, will begin enrollment in April 2017.

- 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:

13. List references, if any:

- 1) Johnson TW et al, J Med Chem, 2014, 57:4720-4744.
- 2) Zou HY et al, Cancer Cell, 2015, 28:70-81.
- 3) Blumenthal GM et al, J Clin Oncol, 2015, 33:1008-1014.
- 4) Sullivan I and Planchard D, J Thoracic Dis, 2016, 8:1287-1292.
- 5) Shaw AT et al, N Engl J Med, 2013, 368:2385-2394.

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



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

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

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

Revised 1/15/16/M. Raggio

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

/s/

KAYLA J GARVIN
05/15/2017

PATRICIA KEEGAN
05/17/2017



IND 118296

MEETING MINUTES

Pfizer Inc.
Attention: Ann Carey
Senior Director, Worldwide Regulatory Strategy
235 East 42nd Street
New York, NY 10017-7555

Dear Ms. Carey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for lorlatinib (PF-06463922).

We also refer to the meeting between representatives of your firm and the FDA on December 18, 2015. The purpose of the meeting was to discuss the clinical development program for lorlatinib. Specifically, you sought preliminary advice on the clinical evidence that would support a request for Breakthrough Therapy Designation, advice on the proposed revisions to an ongoing trial, B7461001, to provide data intended to support a request for accelerated approval of lorlatinib for the and treatment of patients with ALK-positive metastatic NSCLC with disease progression following crizotinib, and advice on the general design of a proposed trial intended to verify the clinical benefit of lorlatinib in the first-line treatment of patients with ALK-positive metastatic NSCLC.

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

If you have any questions, call me at (301) 796-7032.

Sincerely,

{See appended electronic signature page}

Karen C. Boyd, MS, PMP
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 1/Pre-Phase 3

Meeting Date and Time: December 18, 2015, 11:00AM to 12:00 PM
Meeting Location: White Oak 22, Room 1311

Application Number: IND 118296
Product Name: lorlatinib (PF-06463922)
Indication: Treatment of ALK-positive metastatic NSCLC
Sponsor Name: Pfizer, Inc.

Meeting Chair: Gideon Blumenthal, MD
Meeting Recorder: Karen Boyd, MS

FDA ATTENDEES

Patricia Keegan, M.D., Director, OHOP/DOP2
Gideon Blumenthal, M.D., Clinical Team Leader, OHOP/DOP2
Dickran Kazandjian, M.D., Clinical Reviewer, OHOP/DOP2
Melanie Pierce, Chief, Project Management Staff, OHOP/DOP2
Karen Boyd, M.S., Senior Regulatory Project Manager, OHOP/DOP2
Kun He, Ph.D., Biostatistics Team Leader, OB/DBV
Whitney Helms, Ph.D., Nonclinical Team Leader, OHOP/DHOT
Dubravka Kufrin, Ph.D., Nonclinical Reviewer, OHOP/DHOT
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader, OCP/DCPV
Stacy Shord, Pharm.D., Clinical Pharmacology Reviewer, OCP/DCPV
Reena Philip, Ph.D., Branch Chief, CDRH/OIR/DMGP
Soma Ghosh, Ph.D., Device reviewer, CDRH/OIR/DMGP

SPONSOR ATTENDEES

Pfizer, Inc.

Jennifer Tursi, MsC – Development Team Lead
Lee James, MD, PhD – Clinical
Dimitry Nuyten, MD, PhD – Clinical
Antonello Abbattista, BS – Statistics
Dmitri Pavlov, PhD – Statistics
Karen Klammer, PharmD - Clinical Pharmacology
Joseph Heissler, PharmD – Safety
Wenyue Hu, PhD – Nonclinical Toxicology

Omar Perez, PhD -- Diagnostics
Melissa McMahon, MS - Regulatory Strategy
Ann Carey, MS - Regulatory Strategy
Geraldine Taber, PhD - Pharmaceutical Sciences
Joe Heissler, Pharm D - Safety
Allan Safferman, MD - Group Head Oncology Drug Safety
Grace Vandal - Project Manager

Regulatory History:

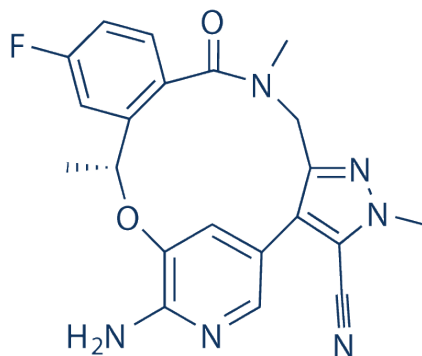
On October 15, 2015, Pfizer submitted a Type B meeting request to discuss the clinical development program for lorlatinib for the treatment of anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC). Specifically, Pfizer seeks preliminary advice on the clinical evidence that would support a request for Breakthrough Therapy Designation, advice on the proposed revisions to an ongoing trial, B7461001, to provide data intended to support a request for accelerated approval of lorlatinib for the treatment of patients with ALK-positive metastatic NSCLC with disease progression following crizotinib, and advice on the general design of a proposed trial intended to verify the clinical benefit of lorlatinib in the first-line treatment of patients with ALK-positive metastatic NSCLC.

The original IND was submitted on August 15, 2013 with the protocol entitled, "Phase 1/2 Study of PF-06463922 (an ALK/ROS1 tyrosine kinase inhibitor) in patients with advanced non-small cell lung cancer harboring specific molecular alterations." The study was allowed to proceed on September 13, 2013.

Pfizer submitted a meeting package on November 16, 2015. Meeting preliminary comments were sent to Pfizer on December 18, 2015.

Chemistry, Manufacturing and Controls:

PF-06463922 (lorlatinib) is small molecule inhibitor of anaplastic lymphoma kinase (ALK) and ROS1 (c-ROS oncogene 1) receptor tyrosine kinases. This macrocyclic, orally bioavailable molecule is a white to (b) (4) powder and has a molecular weight of 406.41 g/mol and molecular formula of $C_{21}H_{19}FN_6O_2$. The drug product is available as 25 mg tablets, labeled on the basis of the free base.



Clinical

Study B7461001 is the ongoing multicenter, two-stage, sequential dose-escalation (Phase 1 portion) and activity-estimating (Phase 2 portion), study conducted by Pfizer for lorlatinib. The completed first portion of the study evaluated safety and tolerability to determine the recommended phase 2 dose (RP2D) to be utilized in the second portion, activity-estimating portion of the trial in 4 disease-specific cohorts. The ten dosage regimens tested were lorlatinib at doses of 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, and 200 mg once daily (QD) and lorlatinib at doses of 35 mg BID, 75 mg BID, and 100 mg BID twice daily (BID). Pfizer determined RP2D was 100 mg QD based on the observation of Grade 2 dose-limiting neurologic toxicity as summarized in the next paragraph.

Preliminary safety data from the Phase 1 portion of Protocol B7461001:

The most commonly occurring treatment-related adverse events across all of the doses tested in were hypercholesterolemia (64%), CNS effects (36%), edema peripheral (32%), peripheral neuropathy (28%), and hypertriglyceridemia (26%). The most frequently occurring treatment-related Grade ≥ 3 adverse events were hypercholesterolemia (10%) and blood triglycerides increased (4%).

There were 5 patients with treatment-related serious adverse events; 3 had CNS effects events that included

- grade 2 hallucinations and grade 2 seizure in 1 patient (grade 2 hallucinations occurred while receiving 150 mg qd and grade 2 seizure occurred while receiving 100 mg qd);
- grade 2 seizure in a second patient (receiving 75 mg BID),
- and mental status changes in a third patient (receiving 150 mg QD).
- In addition, 1 patient (receiving 150 mg QD) had Grade 3 dermatomyositis,
- and 1 patient (receiving 100 mg QD) had Grade 3 lipase increased.

Preliminary efficacy data from the Phase 1 portion of Protocol B7461001:

The Phase 1 portion enrolled patients with ALK-positive NSCLC who must have been either treatment naïve in the advanced setting or have had disease progression after at least 1 previous ALK inhibitor therapy(ies). ROS1-positive NSCLC patients must have been either treatment naïve in the advanced setting or have had disease progression after at least 1 previous ROS1 inhibitor therapy(ies). Among the 50 total patients enrolled in the Phase 1 portion, 43 patients were considered evaluable by Pfizer for efficacy as of the data cutoff date of June 2015, the ORR was 37% comprising 1 confirmed CR (2%) and 15 (35%) confirmed PRs. Further, 10 (23%) patients had SD as their best overall response. The response rate appeared similar whether patients had 1 or 2 prior TKIs. Of the 16 patients with a confirmed response, 3 patients (18.8%) have progressed after response. The duration of response for those three patients ranged from 2.6 to 2.8 months. The remaining 13 patients (81.3%) had ongoing responses at the time of analysis: the duration was less than 6 months in 7 patients, from at least 6 months to less than 9 months in 2 patients, and at least 9 months in 4 patients. Thirty-four (69%) patients had CNS metastases at study entry. Of the 30 patients evaluable for intracranial response at the time of the data cut-off, 4 (13%) patients had a confirmed intracranial CR and 5 (17%) patients had a confirmed intracranial PR. Further, 10 (33%) patients had intracranial SD as their best CNS response.

Current Study Design for the Phase 2 portion of Study B7461001

The Phase 2 portion of the study contains 6 parallel arm expansion cohorts for the purpose of estimating activity in disease-specific cohorts outlined in the table below.

Cohort	Indication
1	Treatment-naïve patients with advanced ALK-positive NSCLC with or without asymptomatic CNS metastases. No prior chemotherapy is allowed in the metastatic setting.
2	Patients with advanced ALK-positive NSCLC with or without asymptomatic CNS metastases relapsing after only crizotinib therapy. No prior chemotherapy is allowed in the metastatic setting.
3	Patients with advanced ALK-positive NSCLC with or without asymptomatic CNS metastases relapsing after crizotinib therapy and 1 or 2 prior regimens of chemotherapy given before or after crizotinib therapy OR patients with advanced ALK-positive NSCLC with or without asymptomatic CNS metastases relapsing after 1 ALK inhibitor therapy other than crizotinib with or without any number of prior chemotherapy regimens in any disease setting.
4	Patients with advanced ALK-positive NSCLC with or without asymptomatic CNS metastases relapsing after 2 prior lines of ALK inhibitor therapies. Patients may have had any number of prior chemotherapy regimens in any disease setting.
5	Patients with advanced ALK-positive NSCLC with or without asymptomatic CNS metastases relapsing after 3 prior lines of ALK inhibitor therapies. Patients may have had any number of prior chemotherapy regimens in any disease setting.
6	Patients with advanced ROS1-positive NSCLC who are treatment-naïve or have had any number of prior therapies (chemotherapy or TKI). Patients may or may not have asymptomatic CNS metastases. In those countries where standard of care does not allow for ROS1-positive NSCLC treatment-naïve patients to receive PF-06463922 in the first-line treatment setting, patients will not be enrolled in Cohort-6 treatment-naïve subgroup.

According to the current version of the protocol, for subpopulations in cohorts 1-5 the goal of the primary analysis of objective response will be to estimate the Objective Response Rates (ORR) and their exact 95% confidence intervals (Clopper-Pearson). Table 17 from the protocol below shows possible estimated ORR and 95% CIs for different level of responses in populations of 40 patients.

Table 17. Estimated ORRs and Related 95% Confidence Intervals

Responses/Cohort Sample Size	ORR (Estimated 95% CI)
16/40	40% (24.9-56.7)
20/40	50% (33.8-66.2)
24/40	60% (43.3-75.1)
28/40	70% (53.5-83.4)

For cohort 6, the group-sequential two-stage design using an O'Brien-Fleming non-binding stopping boundary for futility to test the null hypothesis that the response rate $P \leq 0.30$ versus the alternative that $P \geq 0.50$ has an expected sample size of 31 and a probability of early termination of 0.40 under the null hypothesis. This is based on a target 1-sided type I error rate of 0.10 and power of 0.90. After testing the drug on 20 patients in the first stage, the trial will be terminated if ≤ 5 patients respond. If the trial proceeds to the second stage, a total of 39 patients will be studied. If the total number of responding patients is ≥ 16 for this subpopulation, then the null hypothesis will be rejected.

Proposed Revisions to the Phase 2 Portion of Study B7461001 to Obtain Data Intended to Support a Request for Accelerated Approval:

Pfizer proposes to use the data from Cohorts 2-5 to characterize the anti-tumor activity of lorlatinib in approximately 160 patients with ALK-positive NSCLC who have received prior ALK inhibitors. As of amendment 4 of the protocol, the tumor assessments obtained on study will be independently reviewed by an external vendor for determination of response or progression. This will consist of both a determination of intracranial response and overall (intra- and extra-cranial) response. In patients who have relapsed or are refractory to prior ALK inhibitors, the primary analysis of ORR will be made according to investigator assessment and the secondary analysis according to independent radiology assessment.

The analysis plan will provide descriptive statistics (rate and 95% confidence intervals) for investigator-assessed and IRC-assessed ORR. The primary analysis will be performed in the "Response Evaluable" population enrolled in Cohorts 2-5 as determined by investigators. Analyses will be performed in "evaluable" patients, defined as all patients who receive study treatment, have a baseline tumor assessment, and at least one on-study tumor assessment and patients who are treated but removed from study prior to on-study tumor assessment because of disease progression.

A secondary endpoint will be the determination of intracranial ORR and will be assessed in the CNS Metastases Response population enrolled in Cohorts 1-5. The analysis population (CNS Metastasis Response) is defined as the subset of "Response Evaluable" population (defined above) with CNS metastases at study entry.

Pooled intracranial ORR is defined as the percent of patients with intracranial objective response relative to the above mentioned pool of patients evaluable for CNS metastases, and will be provided along with the corresponding 95% confidence interval. By obtaining brain Magnetic Resonance Imaging at every assessment including baseline in patients without CNS metastases, time to intracranial-progression can also be determined.

(b) (4)

(b) (4)



Companion Diagnostic:

In Study B7461001, evidence of histologically or cytologically confirmed diagnosis of metastatic NSCLC harboring an ALK rearrangement, as determined by an FDA-approved FISH assay (Abbott Molecular Inc) or by IHC (Ventana Inc).

(b) (4)



Clinical Pharmacology

Pfizer has completed one study to evaluate the effect of lorlatinib on the pharmacokinetics (PK) of midazolam and another pilot study to evaluate the effect of food on the PK of lorlatinib following administration of the (b) (4) tablets formulation. Lorlatinib appears to be a moderate inducer of CYP3A4 in humans and food does not appear to affect bioavailability of lorlatinib (b) (4) tablets formulation.

The following table provided in the briefing package lists the studies Pfizer has completed or plans to conduct in support of the original NDA submission.

Table 9. Clinical Pharmacology Plan for PF-06463922

Anticipated status at submission	Protocol Number	Protocol Design	Estimated Number to Receive PF-06463922	
			Subjects	Oncology Patients
Completed	B7461005	Relative Bioavailability	19	
Completed	B7461004	Mass Balance	6	
Completed	B7461008	Effect of acid-reducing agents and food; exploratory effect of particle size and oral solution	24	
Completed	B7461007	Absolute bioavailability	18	
Completed	B7461012	DDI – Itraconazole	18	
Completed	B7461011	DDI – Rifampin	18	
Ongoing	B7461009	Hepatic Impairment	30 ^a	^c
Ongoing	B7461010	Renal Impairment	20 ^b	^c
Ongoing	(b) (4)			
Ongoing	(b) (4)			

a. 8 mild, 8 moderate, 6 severe hepatic impairment and 8 normal hepatic function

b. 6 moderate and 6 severe renal impairment and 8 normal renal function

c. if multiple doses are needed or major potent metabolite identified than study will be conducted in oncology patients rather than healthy volunteers

(b) (4)

DISCUSSION

CLINICAL:

- Sponsor Question 1:** Although most patients with ALK-positive NSCLC derive substantial clinical benefit from crizotinib, some ALK-positive NSCLC patients will not derive any benefit (intrinsic resistance) while other patients who initially derive benefit may later develop resistance (acquired resistance). (b) (4)

For patients who progress on ALK inhibitor therapy, there are few treatment options. PF-06463922 was designed to address the mutations that have been identified to cause resistance to crizotinib and to other ALK inhibitors. In the phase 1 portion of study, promising activity was seen that appeared to be similar in patients who had received only one prior ALK inhibitor and those that had received more than one prior ALK inhibitor. Does the Agency agree that the Phase 1 data is supportive of a request for Breakthrough Therapy Designation for a potential indication for the treatment of patients with ALK-positive metastatic NSCLC with (b) (4) prior ALK inhibitor therapy?

FDA Response: FDA agrees that an IRC-assessed, confirmed ORR of 37% (corresponding 95% CI: 23, 51) in the intent-to-treat population (all patients enrolled and

receiving at least one dose of lorlatinib), with adequate durability of response may support a breakthrough designation request for the treatment of patients who have progressed on (b) (4) crizotinib. However, FDA recommends that Pfizer initially submit an informal request for FDA feedback that contains the following:

- Updated ORR and response duration for the subset of all patients who have completed 12 weeks of follow-up on study or who discontinued treatment for disease progression or toxicity; (include graphic representations, e.g., swimmers and spider plots).
- Clear delineation of individual patients with confirmed responses, as defined by RECIST 1.1, from those with unconfirmed responses.
- Detailed listing of prior therapies and the basis for determining “intolerance to crizotinib,” as applicable.
- The number of patients in the intent-to-treat population with CNS metastasis across Cohorts 1-5 and the ORR in the CNS as determined by an IRC.
- Details of the genetic alterations in tumors of patients evaluated for ORR, which support statements in the briefing document regarding heterogeneity.

Discussion during the meeting: Pfizer acknowledged FDA’s response and no further discussion occurred during the meeting.

2. **Sponsor Question 2:** Phase 2 of Study B7461001 includes four cohorts of patients with ALK-positive NSCLC who have been treated with prior ALK inhibitor therapy (prior crizotinib without prior chemotherapy, one prior ALK inhibitor and prior chemotherapy, two prior ALK inhibitors, and 3 prior ALK inhibitors, the latter two cohorts also permitting prior chemotherapies). Does the Agency agree that data could be pooled from these four cohorts to support an application for accelerated approval, if the data demonstrate a positive benefit/risk for patients relative to the standard of care for each of the individual cohorts? This application would be based on a surrogate endpoint of objective response rate based on investigator assessment (primary analysis) and independent central radiology review (secondary analysis). Data on the durability of responses will also be provided. The intended indication would be treatment of patients with ALK-positive NSCLC who have (b) (4) prior ALK inhibitor therapy.

FDA Response: FDA agrees that demonstration of an ORR that is clinically meaningful in magnitude and durability in approximately 160 patients with disease progression following treatment with crizotinib, with or without prior chemotherapy or other ALK inhibitors, in a pooled analysis of patients enrolled cohorts 2-5 of Study B7461001, could potentially support an accelerated approval for the indication of treatment of patients with ALK-positive NSCLC with disease progression following crizotinib, provided that there are no available therapies for this indication or lorlatinib has demonstrated significant improvement over these available therapies. However, the determination will be made at the pre-NDA meeting on whether the data is robust enough to support an application. Furthermore, the specific indication will depend on the patient characteristics of the enrolled population.

Discussion during the meeting: Pfizer asked for clarification [REDACTED] (b) (4)

would create a space that would allow approval of lorlatinib for patients who have progressed following prior ALK inhibitor therapy. [REDACTED] (b) (4)

[REDACTED] FDA recommended that Pfizer consider providing data in populations not covered by these drugs such as those who received more than one prior ALK inhibitor or specific ALK mutations where lorlatinib may have superior efficacy. FDA agreed that a subset of 80 patients with two or more prior lines of ALK inhibitor prior therapy could represent the primary analysis population supported by results from 160 patients. FDA expects that the analysis of ORR would be conducted in the intent to treat population based on IRC assessment using RECIST 1.1.

3. **Sponsor Question 3:** Does the Agency agree with the proposal for analyzing the intracranial efficacy of PF-06463922 in patients with brain metastases at study entry in Study B7461001? Could this analysis support a statement in the product labeling?

FDA Response: Analyses to estimated intracranial ORR and DOR per RECIST v1.1, as determined by independent radiology assessment, in a subgroup of patients with CNS metastases at baseline across cohorts 1-5, pooling data across these cohorts, as outlined in the briefing document may support an inclusion of CNS ORR results in product labeling. However, this will depend on the robustness of the data. The statistical plan must be prespecified. Finally, the significance of a “time to intracranial-progression” endpoint cannot be interpreted in a single arm study and will not be included in product labeling.

Discussion during the meeting: Pfizer acknowledged FDA’s response and no further discussion occurred during the meeting.

4. **Sponsor Question 4:** With respect to the proposed [REDACTED] (b) (4)

FDA Response: [REDACTED] (b) (4)

Discussion during the meeting: Pfizer acknowledged FDA’s response and no further discussion occurred during the meeting.

5. **Sponsor Question 5:** With respect to the proposed [REDACTED] (b) (4)

(b) (4)

FDA Response: No, FDA disagrees. The current analysis plan is not designed to test the hypothesis (b) (4)

Discussion during the meeting: FDA stated that there are two scenarios of concern with regard to the analysis of the proposed trial. (b) (4)

6. **Sponsor Question 6:** If single-agent PF-06463922 receives approval under the accelerated approval provisions for (b) (4) ALK-positive NSCLC indication, based on Phase 2 data from Study B7461001, could the results from the proposed (b) (4) Phase 3 study conducted in treatment-naïve ALK-positive NSCLC patients be used as the (b) (4)

FDA Response: Yes. See response to question 5.

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

7. **Sponsor Question 7:** (b) (4)

FDA Response:

(b) (4)

See response to question 5.

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

COMPANION DIAGNOSTIC:

8. **Sponsor Question 8:** In cases where the ALK status of patients has been determined locally using the FDA-approved, commercially available Ventana ALK (D5F3) CDx Assay, does the Agency agree that the local test result may be used to determine eligibility for enrollment of patients in the proposed Phase 3 study, and that it is not necessary to confirm the local test result by central lab testing using the same Ventana ALK (D5F3) CDx Assay?

FDA Response: Based on the information provided, FDA's understanding is that the local test results, using the FDA-approved commercially available Ventana ALK (D5F3) CDx Assay will be identical (with regard to the protocol, reagents, scoring algorithm, data analysis, etc.) to the central lab test using the same assay. If this is so, then the local test results may be used to determine eligibility for enrollment in the proposed trial and it is not necessary to confirm the local test result by central lab testing using the same Ventana ALK (D5F3) CDx Assay. However, if there is any deviation from the FDA-approved protocol at any of the local sites, then re-testing samples at the central lab using the FDA-approved Ventana ALK (D5F3) CDx assay may be necessary for the appropriate efficacy analysis to be performed.

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

9. **Sponsor Question 9:** In cases where the ALK status of patients has been determined locally using the FDA-approved, commercially available Vysis ALK Break Apart FISH Probe Kit, does the Agency agree that the local test result may be used to determine eligibility for enrollment of patients in the proposed Phase 3 study, and that it is not necessary to confirm the local test result by central lab testing using the Ventana ALK (D5F3) CDx Assay, given the data supporting concordance of the two tests previously submitted by Ventana in support of the Ventana ALK (D5F3) CDx Assay approval?

FDA Response: If the ALK status of patients is determined locally using the FDA-approved, commercially available Vysis ALK Break Apart FISH Probe Kit, and the central lab testing is utilizing the Ventana ALK (D5F3) CDx Assay, then patients can be enrolled based on the Vysis ALK Break Apart FISH test. However, it is strongly recommended that any patients enrolled using Vysis ALK Break Apart FISH assay should be confirmed using the central lab Ventana ALK (D5F3) CDx Assay to support the efficacy analysis for a future marketing application.

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

CLINICAL PHARMACOLOGY:

10. **Sponsor Question 10:** Pfizer plans to have the following studies either completed or ongoing at the time of initial NDA submission, if the submission is based on Phase 2 data. Does the Agency agree with the Sponsor's plan including timelines for the following biopharmaceutics and clinical pharmacology studies in healthy volunteers, if an accelerated approval NDA is pursued?

FDA Response: Yes, FDA agrees with the list of the proposed studies found in table 9 of the meeting package to be included in the original NDA submission. Also, FDA expects inclusion of population pharmacokinetic analyses and exposure-response analyses for safety and activity in the original NDA submission.

Additional pharmacokinetic studies to determine an appropriate dose of lorlatinib when it is coadministered with inducers or inhibitors of CYP2C8, 2C19, 3A4 or UGT1A4 may be warranted if these enzymes are responsible for $\geq 25\%$ of lorlatinib's total metabolism.

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

11. **Sponsor Question 11:** In the current Phase 2 study, patients are instructed to have a 2 hour fast before and after each dose. If the fed-fast study shows no PK difference then the food restriction in Phase 2 may be lifted. Does the Agency agree that having no PK difference in the fed-fast study and a mix of fed-fast conditions in the Phase 2 study would allow the label to state that PF-06463922 can be taken irrespective of food?

FDA Response: In general, FDA agrees with this approach; however, the labeling statement regarding the food intake will be dependent on review of the data included in the original NDA submission.

FDA recommends that Pfizer define a fasted state as one hour before or two hours after a meal in accordance with the FDA Guidance for Industry entitled "Food-Effect Bioavailability and Fed Bioequivalence Studies" found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070241.pdf>.

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

ADDITIONAL COMMENTS:

CLINICAL:

Study (b) (4)

12.

(b) (4)

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

Study B7461001

13. There are many proposed analyses for different subpopulations in which Pfizer references type 1 error. Please note that the proposed analyses are not hypothesis testing, and, therefore, no type 1 error should be assigned.

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

NONCLINICAL:

14. In support of continued development of lorlatinib, results from GLP-compliant repeat-dose toxicology studies of at least 3 months duration following the intended clinical schedule and route of administration are expected to be available for review prior to initiation of clinical trials intended to support a marketing application. For additional information please refer to ICH S9 Guidance for Industry entitled "Nonclinical Evaluation for Anticancer Pharmaceuticals" available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf>

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

CLINICAL PHAMACOLOGY:

15.

(b) (4)

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

COMPANION DIAGNOSTIC:

16. Please ensure that the ROS-1 Laboratory Developed Tests (LDTs), such as ROS1 FISH and ROS1 RT-PCR tests, are fully specified and analytically validated prior to their use for patient enrollment in the proposed trial.

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

17. FDA recommends that a pre-submission is submitted to CDRH to discuss the development plans for the devices to be used in the proposed trials.

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

18. Please plan to submit a formal study risk determination pre-submission to CDRH to determine if the proposed trials are significant risk or non-significant risk studies.

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

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within **60 days of this meeting**. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

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

development, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

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

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

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

Office of Scientific Investigations (OSI) Requests

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

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

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

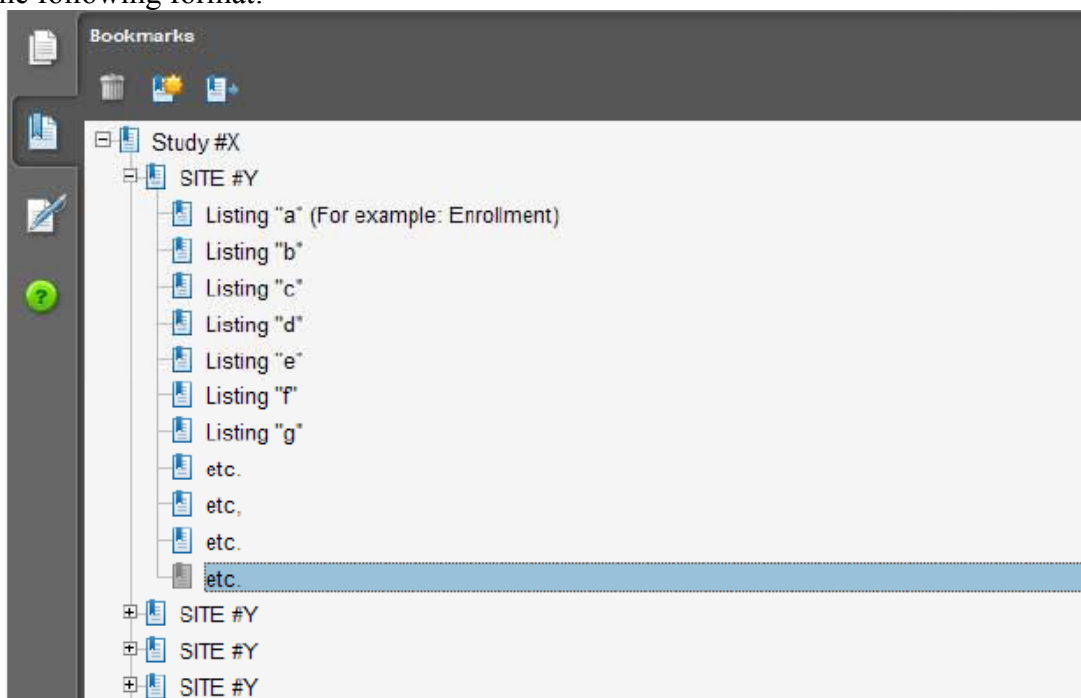
- I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

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

II. Request for Subject Level Data Listings by Site

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

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



III. Request for Site Level Dataset:

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

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

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

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

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



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

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

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

FDA eCTD web page

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

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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

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

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

KAREN C BOYD
01/08/2016