CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205755Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 205755, ZYKADIA (ceritinib, LDK378)
Product Name:

PMR/PMC Description: Confirmatory trials for ceritinib (LDK378)

PMR/PMC Schedule Milestones:

Study/Trial Completion:	04/30/2019
Final Report Submission:	10/31/2019

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☒ Unmet need
   - ☒ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

Ceritinib is being approved under subpart H (accelerated approval); therefore, confirmatory trials are needed to confirm safety and efficacy in the proposed population, i.e., patients with metastatic ALK-positive non-small cell lung cancer (NSCLC). These patients have a serious and life-threatening condition with an unmet need for better therapies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

N/A

Reference ID: 3488016

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☒ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct and submit the results of (a) multicenter, randomized study or studies establishing the superiority of ceritinib over standard therapy in adult patients with ALK-rearranged (ALK-positive) metastatic NSCLC who have been previously treated with crizotinib or in adult patients with previously untreated ALK-positive metastatic NSCLC.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Reference ID: 3488016

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for NDAs)

Reference ID: 3488016

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

/s/

SEAN N KHOZIN
04/11/2014

GIDEON M BLUMENTHAL
04/11/2014

JEFFERY L SUMMERS
04/11/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 205755, ZYKADIA (Ceritinib)
Product Name:

PMR/PMC Description: Safety Trial of Ceritinib with Food

PMR/PMC Schedule Milestones

- Draft protocol submission: Jul-2014
- Final protocol submission: Sep-2014
- Interim analysis:
  - Interim analysis report submission: Jul-2016
- Final analysis:
  - Trial completion: Feb-2017
  - Final report submission: Aug-2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☒ Unmet need
   ☒ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☒ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☐ Other

   Diarrhea, nausea, vomiting, or abdominal pain occurred in 96% of 255 patients in the clinical trial including severe cases in 14% of patients when the recommended dose of ceritinib (750 mg daily) was administered under fasted condition, and resulted in dose modification in 38% of patients. The food effect study showed an increased exposure by 73% with a high-fat meal and an increased exposure by 58% with a low-fat meal as compared to a fasted state. Administration of ceritinib at the recommended dose (750 mg daily) with meals may decrease gastrointestinal (GI) toxicity, but could lead to increased exposure-related toxicities such as AST/ALT elevations, hyperglycemia, and QTc prolongation.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 3485800

The goal of the clinical trial is to determine an exposure-matched dose of ceritinib taken with meals that decreases GI toxicities without compromising efficacy.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☒ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a clinical trial to evaluate the systemic exposure and safety of 450 mg ceritinib taken with meals and 600 mg ceritinib taken with light meals as compared with that of 750 mg ceritinib taken in the fasted states in metastatic ALK-positive NSCLC patients.

Reference ID: 3485800

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☒ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for NDAs)

Reference ID: 3485800

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

/s/

RUBY LEONG
04/09/2014

HONG ZHAO
04/09/2014
I concur.

SEAN N KHOZIN
04/09/2014

GIDEON M BLUMENTHAL
04/09/2014

JEFFERY L SUMMERS
04/10/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 205755
Product Name: Certinib

PMR/PMC Description:

1. Post Marketing Commitment: Submit a revised testing monograph (TM) that will include a [redacted] (b) (4) method and specification for LDK378 drug product (capsule content) as post-approval commitment. The updated TM will be submitted by 30-April-2014.

2. Post Marketing Commitment: Submit 9 months stability data for the 3 registration stability batches (batches 1010000660, 1010000958 and 1010001326) and up to 24 months for one batch from supportive stability (batch AEUS/2012-0023). The updated stability data will be submitted by 16-May-2014.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	04/30/2014 05/16/2014
Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The Sponsor did not provide adequate amount of stability in order to grant the requested expiry dating for the product. Therefore, the sponsor has committed to provide updated and additional stability data to support the expiry dating.
Also, [redacted] (b) (4) was not included in the NDA submission. Therefore, the sponsor will develop and implement a [redacted] (b) (4) test in the NDA specification.

Reference ID: 3486368

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Not Applicable.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Not Applicable.

Reference ID: 3486368

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☐ Does the study/clinical trial meet criteria for PMRs or PMCs?
☐ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

Reference ID: 3486368

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3486368

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

/s/

ALI H AL HAKIM
04/09/2014

TEICHER N AGOSTO
04/09/2014

JEFFERY L SUMMERS
04/09/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 205755, ZYKADIA (ceritinib)
Product Name:

PMR/PMC Description: Hepatic Impairment Pharmacokinetic Trial

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	Submitted
	Study/Trial Completion:	01/31/2016
	Final Report Submission:	06/30/2016
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☒ Small subpopulation affected
   ☐ Theoretical concern
   ☐ Other

   The mass balance study suggests that hepatic elimination appears to be the major route of elimination. Patients with hepatic impairment may have higher ceritinib exposures than patients with normal hepatic function, which may lead to more toxicities.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   The goal of the clinical pharmacokinetic trial is to determine appropriate ceritinib doses in patients with moderate or severe hepatic impairment.

Reference ID: 3485722

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Complete a pharmacokinetic trial to determine the appropriate dose of ceritinib in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Reference ID: 3485722

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☒ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for NDAs)

Reference ID: 3485722

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 205755, ZYKADIA (ceritinib)
Product Name:

PMR/PMC Description: Drug-Drug Interaction Trial

PMR/PMC Schedule Milestones:

Final Protocol Submission:	09/30/2014
Study/Trial Completion:	08/31/2016
Final Report Submission:	02/28/2017
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

In vitro studies indicate that ceritinib is a time-dependent inhibitor of CYP3A4. Ceritinib may increase exposures of concomitant medications with a narrow therapeutic index that are primarily metabolized by CYP3A4, which may lead to more toxicities associated with these drugs.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the clinical trial is to determine how to dose ceritinib with regard to concomitant CYP3A4 sensitive substrates and CYP3A4 substrates with a narrow therapeutic index.

Reference ID: 3485722

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a clinical trial to evaluate the effect of repeat doses of ceritinib on the single dose pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Reference ID: 3485722

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for NDAs)

Reference ID: 3485722

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 205755, ZYKADIA (ceritinib)
Product Name:

PMR/PMC Description: Drug-Drug Interaction Trial

PMR/PMC Schedule Milestones:

Final Protocol Submission:	09/30/2014
Study/Trial Completion:	08/31/2016
Final Report Submission:	02/28/2017
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

In vitro studies indicate that ceritinib is a reversible inhibitor of CYP2C9. Ceritinib may increase exposures of concomitant medications with a narrow therapeutic index that are primarily metabolized by CYP2C9, which may lead to more toxicities associated with these drugs.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the clinical trial is to determine how to dose ceritinib with regard to concomitant CYP2C9 sensitive substrates and CYP2C9 substrates with a narrow therapeutic index.

Reference ID: 3485722

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a clinical trial to evaluate the effect of repeat doses of ceritinib on the single dose pharmacokinetics of warfarin (a sensitive CYP2C9 substrate) in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Reference ID: 3485722

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for NDAs)

Reference ID: 3485722

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 205755, ZYKADIA (ceritinib)
Product Name:

PMR/PMC Description: Drug-Drug Interaction Trial

PMR/PMC Schedule Milestones:

Final Protocol Submission:	01/31/2015
Study/Trial Completion:	08/31/2015
Final Report Submission:	02/29/2016
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Ceritinib is a weak base with pH-dependent solubility in vitro. Ceritinib is soluble in 250 mL at pH 1.0, but becomes poorly soluble as pH increases (0.0002 mg/mL at pH 6.8). Gastric acid reducing agents may decrease the solubility of ceritinib by increasing stomach pH, and therefore would change the pharmacokinetic profile of ceritinib and require dose adjustment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the clinical pharmacokinetic trial is to determine how to dose ceritinib with regard to concomitant gastric acid reducing agents.

Reference ID: 3485722

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a clinical trial to evaluate if proton pump inhibitors, H_2-receptor antagonists, and antacids alter the bioavailability of ceritinib and to determine how to dose ceritinib with regard to concomitant gastric acid reducing agents.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Reference ID: 3485722

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for NDAs)

Reference ID: 3485722

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

/s/

RUBY LEONG
04/08/2014

HONG ZHAO
04/08/2014
I concur.

JEFFERY L SUMMERS
04/08/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 28, 2014
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Quynh-Van Tran, PharmD, BCPP Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ZYKADIA (ceritinib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 205-755
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On December 24, 2013, Novartis Pharmaceuticals Corporation submitted for the Agency's review an original New Drug Application (NDA) 205-755 for ZYKADIA (ceritinib) capsules, with the proposed indication for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on January 13, 2014, and January 9, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ZYKADIA (ceritinib) capsules.

2 MATERIAL REVIEWED

- Draft ZYKADIA (ceritinib) PPI received on December 24, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 25, 2014.
- Draft ZYKADIA (ceritinib) Prescribing Information (PI) received on December 24, 2013, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on March 25, 2014.
- Approved Xalkori (crizotinib) comparator labeling dated November 20, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

SHARON R MILLS
03/28/2014

QUYNH-VAN TRAN
03/28/2014

BARBARA A FULLER
03/28/2014

LASHAWN M GRIFFITHS
03/28/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 27, 2014

To: Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)

From: Quynh-Van Tran, PharmD, BCPP
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **ZYKADIA® (ceritinib) capsules, for oral use (Zykadia)**
NDA# 205755
OPDP Review of Prescribing Information (PI) and carton/container labeling

---

Thank you for the opportunity to review and provide our comment on the proposed labeling for Zykadia. OPDP has reviewed the proposed PI (FDA version emailed to OPDP on March 25, 2014) and our comments are incorporated therein (e.g., OPDP QVT. . .).

We have no comment on the proposed container labeling for Zykadia (version submitted to the FDA on March 14, 2014).

If you have any questions, please contact Quynh-Van Tran at (301) 796-0185, or quynh-van.tran@fda.hhs.gov.

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

QUYNH-VAN TRAN
03/27/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 24 2014
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 205755
Product Name and Strength:	Zykadia (Ceritinib) Capsules, 150 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
Submission Date:	March 14, 2014
OSE RCM #:	2014-72-1
DMEPA Primary Reviewer:	Otto L. Townsend, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

Reference ID: 3476212

1. REASON FOR REVIEW

This review evaluates the revised container labels for Zykadia , NDA 205755, submitted on March 14, 2014 from Novartis for areas of vulnerability that could lead to medication errors. DMEPA previously reviewed the proposed container labels under OSE Review # 2014-72 (See DARRTS labeling review dated February 4, 2014).

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
ISMP Newsletters	C (N/A)
Previous DMEPA Reviews	D
Human Factors Study (if applicable)	E (N/A)
Other (previously reviewed container labels)	F
Container Label, Carton Labeling, and Instructions for Use or Medication Guide (if applicable)	G

N/A=not applicable for this review

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Novartis has incorporated the recommended changes into the revised container labels submitted on March 14, 2014.

4. CONCLUSION & RECOMMENDATIONS

We conclude that the revised container labels submitted on March 14, 2014 are acceptable.

Reference ID: 3476212

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ceritinib that Novartis submitted on March 14, 2014.

Table 2. Relevant Product Information for Ceritinib	
Active Ingredient	Ceritinib
Indication	Treatment of patients with (b) (4) metastatic non-small lung cancer (NSCLC) who have (b) (4)
Route of Administration	Oral
Dosage Form	Capsule
Strength	150 mg
Dose and Frequency	750 mg (5 x 150 mg capsules) once daily
How Supplied	High-density polyethylene (HDPE) bottles containing 70 capsules for commercial use (b) (4)
Storage	Store at 25°C (77°C); excursions permitted between 15°C and 30°C (59°F to 86°F).

APPENDIX D. PREVIOUS DMEPA REVIEWS

As discussed in Section 1 – Reason for Review, DMEPA previously reviewed the proposed container labels under OSE Review # 2014-72 (See DARRTS labeling review dated February 4, 2014).

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

OTTO L TOWNSEND
03/24/2014

CHI-MING TU
03/24/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: March 23, 2014

TO: Karen Boyd, Senior Regulatory Health Project Manager
Sean Khozin, M.D., Medical Officer
Division of Oncology Products 2

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205755
APPLICANT: Novartis Pharmaceuticals, Corp.

DRUG: Ceritinib (b) (4)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION(S): For the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4)

CONSULTATION REQUEST DATE: January 8, 2014
INSPECTION SUMMARY GOAL DATE: March 25, 2014
DIVISION ACTION GOAL DATE: April 17, 2014
PDUFA DATE: August 24, 2014

I. BACKGROUND:

Novartis Pharmaceuticals Corporation (Novartis), seeks approval to market LDK378 (ceritinib) for the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4) LDK378 is an orally-active, small-molecule, ATP-competitive inhibitor of ALK kinase activity. LDK378 inhibits autophosphorylation of ALK, ALK-mediated phosphorylation of downstream signaling proteins, and proliferation of ALK-dependent cancer cells.

ALK is a receptor tyrosine kinase of the insulin receptor superfamily. Genetic aberration of the ALK gene (gene re-arrangement, activating mutation, or gene amplification) resulting in constitutional, ligand-independent activation of the kinase is known to be a key oncogenic driver in several malignancies.

The first evidence that ALK-positive NSCLC responds to ALK inhibitors was seen with crizotinib, an ALK and MET inhibitor which in single arm trials was shown to induce durable responses in patients. The clinical benefit of crizotinib compared to chemotherapy in terms of median progression free survival (PFS), quality of life, and control of symptoms has been confirmed in a Phase 3 study in the second-line setting, and based on these data the FDA granted regular approval for crizotinib in November 2013. The data on crizotinib confirm that ALK rearrangements in NSCLC represent a clinically relevant target susceptible to targeted ALK inhibition. While crizotinib is effective in patients with ALK-positive NSCLC, disease progression invariably occurs, typically within 1 year, due to development of acquired drug resistance. Resistant ALK-positive NSCLC frequently conserves ALK rearrangements, but develops crizotinib resistant mutations, ALK amplification and/or alternate aberrant signaling. Patients who have failed crizotinib have very limited effective options.

The key study supporting this application is study CLDK378X2101. This study is a first in human, open-label, Phase 1 study of LDK378 conducted in adult patients with advanced tumors confirmed to have genetic abnormalities in ALK (ALK-positive). The study enrolled both ALK inhibitor naïve patients and patients previously treated with an ALK inhibitor. The study comprises a dose-escalation phase to determine the maximum tolerated dose (MTD) and recommended dose (RD), and an expansion phase to better characterize the efficacy, safety and pharmacokinetics (PK) of LDK378.

The primary evaluation of the anti-tumor activity of LDK378 in study CLDK378X2101 was based on Investigator assessment of response (ORR and DOR) per RECIST 1.0 criteria. In addition to Investigator assessment of tumor response, responses were assessed by a blinded independent review committee (BIRC) per RECIST 1.0. The BIRC function was contracted to a CRO, (b) (4)

It was planned that 40 patients would be enrolled in the dose-escalation phase including at least 6 patients treated at the MTD level. During the expansion phase, up to 310 patients could be enrolled (including all patients treated at the RD during the dose-escalation phase who were eligible for the safety set) with at least 25 and up to 100 patients in each of NSCLC arms (Arms 1A, 1B and 2), and approximately 10 patients in Arm 3. A total of 304 patients were treated with LDK378 in the study, including 59 patients from the dose-escalation phase (including 10 patients at 750 mg) and 245 patients from the expansion phase treated at LDK378 750 mg - Arm 1A (109 patients), Arm 1B (47 patients), and Arm 2 (81 patients) and Arm 3 (8 patients).

The study was conducted at 20 centers in 11 countries including Asia, Australia, Europe, and North America (US: 6 centers; Canada: 1 center). This study was conducted under IND 109272.

Three clinical sites were chosen for inspection: Site 0201 (Prof. Dongwan Kim, Seoul S. Korea), Site 0504 (Dr. Alice Shaw, Boston, Massachusetts), and Site 0505 (Dr. Ranee Mehra, Philadelphia), based on enrollment of large numbers of study subjects. The applicant, Novartis, and the blinded independent radiological review committee (BIRC, CRO (b) (4) (b) (4)) were chosen to assess overall performance of this single pivotal study.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#1: *Prof. Dongwan Kim* *Seoul National University Hospital* *Seoul Korea 110 744* *Korea, Republic of*	*Protocol: CLDK378X2101* *Site Number: 0201* *Number of Subjects: 62*	*March 17, 2014 - Ongoing*	*Pending* *Interim classification: To Be Determined*
CI#2: Dr. Alice Shaw Massachusetts General Hospital Boston MA	Protocol: CLDK378X2101 Site Number: 0504 Number of Subjects: 55	February 13-21, 2014	Pending Interim classification: NAI
CI#3: Dr. Ranee Mehra Fox Chase Cancer Center Philadelphia PA	Protocol: CLDK378X2101 Site Number: 0505 Number of Subjects: 22	January , 29, 2014 to February 25, 2014	Pending Interim classification: VAI

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
(b) (4)			
Sponsor: Novartis Pharmaceuticals Corporation One Health Plaza East Hanover, New Jersey 07936-1080	Protocol: CLDK378X2101 Site Reviewed: 0201 0504 0505 0061 0002	February 4-28, 2014	Pending Interim classification: VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **CI#1: – Prof. Dongwan Kim**
   Seoul National University
   Hospital
   Seoul Korea 110 744
   Korea, Republic of

   a. **What was inspected:** No information is available at this time. This inspection was initiated on or about March 17, 2014 and is currently ongoing.

   b. **General observations/commentary:** No information is available at this time. This inspection was initiated on or about March 17, 2014 and is currently ongoing.

   c. **Assessment of data integrity:** No information is available at this time. This inspection was initiated on or about March 17, 2014 and is currently ongoing.

   Note: This inspection was initiated on or about March 17, 2014 and is currently ongoing. The inspection is expected to be completed no later than March 28, 2014. An inspection summary addendum will be generated if preliminary inspectional findings indicate this site's data are unreliable due to significant GCP violations.

2. **CI#2: – Dr. Alice Shaw**
   Massachusetts General Hospital
   Boston, MA

a. **What was inspected:** The site screened 63 subjects, 55 subjects were enrolled, and 37 completed the study. Study records of 25 subjects were audited. The record audit was conducted in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to eCRFs and data listings submitted to NDA 205755, with particular attention paid to inclusion/exclusion criteria compliance, primary and secondary endpoints, adverse events, treatment regimens, test article accountability, protocol deviations, concomitant medications, and subject discontinuations. The FDA investigator also assessed informed consent documents, and monitoring reports.

b. **General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The source records audited at this site supported the safety and efficacy reported outcomes. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles, and drug accountability found no discrepancies. No Form FDA 483 was issued.

c. **Assessment of data integrity**: The data for Dr. Shaw's site, associated with Study CLDK378X2101 submitted to the Agency in support of NDA 205755, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

3. **CI#3: – Dr. Ranee Mehra**
   Fox Chase Cancer Center
   Philadelphia PA

a. **What was inspected:** The site screened 52 subjects, and 22 subjects were enrolled. Of the 22 enrolled subjects, all received study medication for one or more treatment cycle. At the time of this inspection there were 3 subjects continuing to receive study drug on protocol. The study records of all 22 enrolled subjects were audited. The record audit was conducted in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to eCRFs and data listings submitted to NDA 205755, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator assessed all informed consent documents, patient histories, laboratory results, drug accountability, concomitant medications, sponsor correspondence, and progress notes.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. A Form FDA 483 was issued, citing deficiencies in protocol compliance.

Observation 1: An investigation was not conducted in accordance with the investigational plan.

a) Subject #90050 did not meet entry criteria but was enrolled in the study at this site. The source documentation provided in the subject study file did not adequately confirm subject #90050 met the inclusion criteria for ALK translocation in ≥15% of tumor cells as measured by FISH.
b) The tumor response measurements and brain metastasis assessment were not entered in the eCRF for Subject #90044 following CT/MRI scans for one cycle.
c) There were no ECGs performed at required cycles/end of treatment for five subjects.
    i. Subject #90039: EOT
    ii. Subject #90042: Cycle 5
    iii. Subject #90043: Cycle 4
    iv. Subject #90044: Cycle 4 and EOT
    v. Subject #90051: EOT

OSI Reviewer Comments: *OSI reviewer Dr. Lauren Iacono-Connors discussed these inspectional observations with Medical Officer, Dr. Sean Khozin, on March 12th, 2014. While it was agreed that these are clear protocol deviations, Dr. Khozin concurred that these should not impact overall study outcomes. In addition, these observations were not systemic at this site and do not represent a trend in compliance violations for this site or the overall study. Therefore, these observations should not importantly impact study safety and efficacy assessments.*

c. Assessment of data integrity: The data for Dr. Mehra's site, associated with Study CLDK378X2101 submitted to the Agency in support of NDA 205755, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

4. **CRO:** (b) (4)
(b) (4)

   a. **What was inspected:** The CRO [BIRC] was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection included a review of the firm's organization, charters, contracts, study plans, system validation records, standard operating procedures, oncology and radiology analysis forms, and subject overall endpoints. Efficacy endpoints generated by this CRO were compared to data listings submitted to the application. A total of 294 study subjects endpoints were generated by this CRO. The FDA field investigator reviewed and verified a total of 106 study subjects endpoints from the five clinical sites noted in the table above for the identified study inspected at this CRO site.

   b. **General observations/commentary:** Records and procedures were adequate, and generally well organized. The primary efficacy endpoint data generated by this BIRC and submitted to NDA 205755 were verifiable for the clinical sites referred to above; 106 study subjects' endpoints. There were no discrepancies. Also, there was no evidence of BIRC non-compliance with the Charter. No Form FDA 483 was issued.

   c. **Assessment of data integrity:** The data generated at this site, as it pertains to Study CLDK378X2101, were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The data from this CRO submitted to the Agency in support of NDA 205755 appear reliable.

      Note: Observations noted for this CRO are based on preliminary communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

5. **Sponsor: – Novartis Pharmaceuticals Corporation**
   One Health Plaza
   East Hanover, New Jersey 07936-1080

   a. **What was inspected:** The sponsor was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection focused on adherence to protocol, and review of the firm's SOPs, monitoring reports and actions related to monitoring deficiencies. Ethics Committee/IRB approvals, completed Form FDA 1572s, and communications with the sites were also generally covered. The FDA field investigator specifically audited subject records from five clinical study sites noted in the table above, and assessed the AEs and primary efficacy endpoints.

b. General observations/commentary: Records and procedures were clear, and generally well organized. Comparison of primary efficacy endpoint data reported on the case report forms to the data listings provided with the assignment noted no discrepancies. There was evidence of underreporting AEs/SAEs by the Sponsor. This was discovered by Novartis prior to the initiation of this inspection. At the time of the inspection Novartis had already brought the discrepancy to the Review Division's attention, and corrective actions were taken.

Monitoring files were reviewed extensively for the sites identified in the assignment and selected records from other sites identified during the inspection. While monitoring appeared adequate for the listed sites, the FDA field investigator noted that several Monitoring Visit Reports (MVR) for site 0061 were never written. In addition, there were protocol deviations, specifically; protocol-specified pregnancy tests were missed. Overall the sponsor maintained adequate oversight of study conduct. A Form FDA 483 was issued citing one inspection observation.

Observation 1: Failure to ensure proper monitoring of the study.

a) The sponsor did not report the following protocol deviations in Listing 16.2.2-1.1 Protocol deviations by treatment group/arm of the Clinical Study Report submitted on 8/2/13:

Site 0504

i. Subject #90037: Pregnancy test not performed at C1D1 on 6/27/12.
ii. Subject #90047: Pregnancy test not performed at C1D1 on 11/26/12, C3D1 on 1/7/13, C4D1 on 1/28/13, and C10D1 on 6/6/13.
iii. Subject #90063: Pregnancy test not performed at C2D1 on 5/28/13.

Site 0002

iv. Subject #90006: Pregnancy test not performed at C4D1 on 3/21/13, C5D1 on 4/11/13, C6D1 on 5/2/13, C7D1 on 5/23/13, C8D1 on 6/20/13, C9D1 on 7/4/13, and C10D1 on 7/25/13.

Site 0201

v. Subject #90013: Pregnancy test not performed at C4D1 on 7/24/12.

b) There are no Monitoring Visit Reports for Visits dated 5/16/13 and 5/29/13 for Site 0061.

OSI Reviewer Comments: *The sponsor concurred with the observations and promised immediate corrective actions, and a written response. While these are clear protocol deviations the observations should not importantly impact study*

safety and efficacy outcomes. In all cases these subjects were negative for pregnancy at screening and based upon available information agreed to use protocol-specified contraception while on study.

c. Assessment of data integrity: The data generated at this site, as it pertains to Study CLDK378X2101, were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The data from this sponsor submitted to the Agency in support of NDA 205755 appear reliable.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Alice Shaw (Site 0504), Dr. Ranee Mehra (Site 0505), the Sponsor, Novartis Pharmaceuticals Corporation., and the blinded independent radiological review committee (BIRC, CRO (b) (4)) the Study CLDK378X2101data appear reliable based on available information. No preliminary inspectional findings information is available for Prof. Dongwan Kim (Site 0201) at this time. The inspection of Dr. Dongwan Kim is currently ongoing and expected to be completed no later than March 28, 2014.

The preliminary classification for clinical investigator Dr. Alice Shaw, and for CRO, (b) (4) is No Action Indicated (NAI). One clinical site inspected, Dr. Ranee Mehra (Site 0505), and the study sponsor, Novartis, were issued a Form FDA 483 citing inspectional observations and preliminary classification for each of these inspections is Voluntary Action Indicated (VAI).

Audits of the two clinical sites revealed nothing to indicate under-reporting of AEs/SAEs. In addition, the primary efficacy endpoint data were verifiable for 5 clinical sites, including the 3 clinical sites selected for clinical site inspection, via inspection of the CRO that generated key endpoint data.

The inspection of Dr. Mehra's site (0505) found that there were instances of protocol deviations, albeit relatively minor. Specifically, Subject #90050 did not meet entry criteria in that their study file did not adequately confirm inclusion criteria for ALK translocation in ≥15% of tumor cells as measured by FISH. In addition, the tumor response measurements and brain metastasis assessment were not entered in the eCRF for Subject #90044 following CT/MRI scans for one cycle. Finally, there were no ECGs performed at required cycles and/or end of treatment for 5 subjects. OSI reviewer Dr. Lauren Iacono-Connors discussed these inspectional observations with Medical Officer, Dr. Sean Khozin, on March 12th, 2014. While it was agreed that these are clear protocol deviations, Dr. Khozin concurred that these should not impact overall study outcomes. In addition, these observations were not systemic at this site and do not represent a trend in compliance violations for this site or the overall study.

Therefore, these observations should not importantly impact study safety and efficacy assessments.

Overall the sponsor maintained adequate oversight of study conduct. Monitoring files were reviewed extensively for the sites identified in the assignment and selected records from other sites identified during the inspection. While monitoring appeared adequate for the listed sites, the FDA field investigator noted that several Monitoring Visit Reports (MVR) for Site 0061 were never written. In addition, there were protocol deviations, specifically; protocol-specified pregnancy tests were occasionally missed. The sponsor concurred with the observations and promised immediate corrective actions, and a written response. While these are clear protocol deviations the observations should not importantly impact study safety and efficacy outcomes.

Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. The overall data for Study CLDK378X2101 in support of this application may be considered reliable based on available information.

Note: The observations noted above are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs. In addition, the inspection for Dr. Dongwan Kim's site (0201) is currently ongoing. This inspection was initiated on or about March 17, 2014 and is expected to be completed no later than March 28, 2014. An inspection summary addendum will be generated if preliminary inspectional findings indicate this site's data are unreliable due to significant GCP violations.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

/s/

LAUREN C IACONO-CONNORS
03/23/2014

JANICE K POHLMAN
03/24/2014

KASSA AYALEW
03/24/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Memorandum

Date: March 18, 2014

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP, Team Leader
Pediatric and Maternal Health Staff

Lynne P. Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff

To: Office of Hematology and Oncology Products (OHOP)/
Division of Oncology Products 2 (DOP2)

Drug: Zykadia (ceritinib) capsule

NDA: 205755

Applicant: Novartis Pharmaceuticals Corporation

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Proposed Ceritinib product labeling, literature provided by sponsor

Consult Question:
"New NME (breakthrough indication). This consult is primarily for Maternal Health's review of the label."

Reference ID: 3472869

INTRODUCTION

On November 27, 2013 Novartis Pharmaceuticals Corporation submitted a 505(b)(1) New Drug Application (NDA 205755) to obtain approval to market Zykadia (ceritinib) for the proposed indication of the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLS) who had (b) (4) Breakthrough designation was given to ceritinib on March 6, 2013 and orphan designation was granted on September 27, 2013.

OHOP/DOP2 consulted the Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) on January 12, 2014 to provide input for appropriate labeling of the pregnancy and nursing mothers subsections of ceritinib labeling.

BACKGROUND

Ceritinib is a kinase inhibitor. Targets of ceritinib inhibition identified in either biochemical or cellular assays at clinically relevant concentrations include anaplastic lymphoma kinase (ALK), insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROS1 (a proto-oncogene). Ceritinib inhibited autophosphorylation of ALK, ALK-mediated phosphorylation of the downstream signaling protein signal transducer and activator of transcription 3 (STAT3), and proliferation of ALK-dependent cancer cells in *in vitro* and *in vivo* assays.[1]

REVIEW OF DATA

Embryofetal toxicity was observed in animal reproduction studies with ceritinib administration. Rats and rabbits were administered ceritinib during organogenesis at maternal plasma exposures below the recommended human dose and were found to have dose-related increases in skeletal anomalies in rats and skeletal and visceral anomalies in rabbits. Pregnant rats were administered daily doses of ceritinib as low as 50mg/kg (less than 50% of the human exposure by AUC at the recommended dose) and fetuses were noted to have delayed ossification and skeletal variations. Pregnant rabbits were administered ceritinib at doses equal to or greater than 10mg/kg/day (13% of the human exposure by AUC at the recommended dose) and fetuses were found to have incomplete ossification, absent or malpositioned gallbladders and retroesophageal subclavian arteries.[2]

The pharmacology/toxicology review noted a ceritinib half-life ranging from 31 to 41 hours and recommended that effective contraception be used for up to two weeks following completion of therapy with ceritinib.

There were no studies with ceritinib done in pregnant women, and there are no data on the use of ceritinib during lactation.

[1] See DOP2 revised labeling.
[2] Brower, Margaret. Pharmacology/Toxicology Review, 2/26/2014.

DISCUSSION

PREGNANCY AND NURSING MOTHERS LABELING

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing Mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. A brief description of an available pregnancy exposure registry or pregnancy surveillance program that monitors or evaluates pregnancy outcomes with exposure of a drug during pregnancy should be placed in the pregnancy subsection. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in human milk is noted and presented in the label, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

PMHS-MHT notes that pregnancy categories will be eliminated with the publication of the PLLR and replaced with clinically relevant information to assist prescribers with benefit/risk decision making for using a drug during pregnancy.

There are no human pregnancy data for ceritinib. However, the applicant's proposed pregnancy category D classification is appropriate due to ceritinib's mechanism of action on signaling pathways relating to cell growth, cell-cycle progression, and apoptosis, as well as adverse effects observed in animal reproduction studies.

In addition, there are no clinical lactation data with ceritinib and it is not known whether the drug or its metabolites are present in human milk. The applicant has recommended against breastfeeding with maternal use of ceritinib. This proposal is appropriate due to the potential for serious adverse reactions in a nursing infant if drug is present in breastmilk. The Nursing Mothers regulatory statement (see 21 CFR 201.57(c)(9)(iii)(C)) used for ceritinib appropriately conveys the potential infant risk and advises against concurrent lactation and maternal use of ceritinib.

CONCLUSIONS

A pregnancy category D[3] is the appropriate classification for ceritinib based on its mechanism of action and findings of embryofetal toxicity observed in animal studies. The pregnancy and nursing mothers' subsections of ceritinib labeling were structured in the spirit of the proposed PLLR, while complying with current labeling regulations. Furthermore, the

[3] Pregnancy Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Reference ID: 3472869

subsection "Females and Males of Reproductive Potential" was added to ceritinib labeling to contain contraception information for females of reproductive potential due to the drug's potential embryofetal toxicity.

PMHS-MHT LABELING RECOMMENDATIONS

PMHS-MHT recommends the following revision to the Pregnancy and Nursing Mothers sections of ceritinib labeling. These recommendations were discussed at a labeling meeting with OHOP/DOP2 on March 4, 2014. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here. (See Appendix A for the applicant's proposed pregnancy and nursing mothers labeling)

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------Warnings and Precautions----------

- Embryofetal Toxicity: Advise females of reproductive potential of potential risk to a fetus (5.4, 8.1)

5 WARNINGS AND PRECAUTIONS

5.4 Embryofetal Toxicity

Based on its mechanism of action, ceritinib may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ceritinib to rats and rabbits during organogenesis at maternal plasma exposures below the recommended human dose of 750 mg daily caused dose-related increases in skeletal anomalies in rats and skeletal and visceral anomalies in rabbits. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

Reviewer comments: PMHS-MHT recommended the phrase "in animal reproduction studies." However, pharmacology/toxicology preferred using the phrase "in animal studies," which was changed in the current ceritinib label.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary

There are no data with ceritinib in pregnant women; however, based on its mechanism of action, ceritinib may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ceritinib to rats and rabbits during organogenesis at maternal plasma exposures below the recommended human dose caused dose-related increases in skeletal anomalies in rats and skeletal and visceral anomalies in rabbits. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Reviewer comments: PMHS-MHT recommended the phrase "in animal reproduction studies." However, pharmacology/toxicology preferred using the phrase "in animal studies," which was changed in the current ceritinib label.

Data

Animal data

In an embryo-fetal development study in which pregnant rats were administered daily doses of ceritinib during organogenesis, dose-related skeletal anomalies were observed at doses as low as 50 mg/kg (less than 50% of the human exposure by AUC at the recommended dose). Findings included delayed ossifications and skeletal variations.

In pregnant rabbits administered ceritinib daily during organogenesis, dose related skeletal and visceral anomalies, including incomplete ossification, absent or malpositioned gallbladder and retroesophageal subclavian cardiac artery were observed at doses equal to or greater than 10 mg/kg/day (approximately 13% of the human exposure by AUC at the recommended dose).

8.3 Nursing Mothers

It is not known whether ceritinib or its metabolites are present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from ceritinib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Reviewer comment: The statement above is standard language from the proposed PLLR when there is no lactation information available.

8.8 Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action, ceritinib may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with ceritinib and for up to 2 weeks following completion of therapy.

Reviewer Comment: Continuation of female contraception use after drug therapy is generally related to the half-life of a drug. Drugs usually clear the systemic circulation in 4 to 5 half-lives. The half-life of ceritinib was measured at 31 to 40 hours. Therefore, using a two week time period for continued contraception after therapy is a conservative approach to ensure low to no systemic drug levels.

17 PATIENT COUNSELING INFORMATION

Embryofetal Toxicity

Advise females to inform their doctor if they are pregnant. Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ceritinib and for up to 2 weeks following completion of therapy *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1, 8.8)]*.

Nursing Mothers

Advise females not to breastfeed while taking ceritinib *[see Use in Specific Populations (8.3)]*.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3472869

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

/s/

MIRIAM C DINATALE
03/19/2014

LYNNE P YAO
03/21/2014

JEANINE A BEST
03/21/2014

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	205-755
Brand Name	[redacted] (LDK378)
Generic Name	Ceritinib
Sponsor	Novartis Pharmaceuticals
Indication	Treatment of patients with [redacted] metastatic NSCLC who have [redacted]
Dosage Form	150 mg Capsule
Drug Class	ALK kinase inhibitor
Therapeutic Dosing Regimen	750 mg once daily
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	750 mg
Submission Number and Date	SDN 003/27 Dec 2013
Review Division	DOP2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 Overall Summary of Findings

Large changes (i.e., > 20 ms) in the QTc interval were detected at the steady state when LDK378 was administered at the therapeutic doses of 750 mg once daily. The mean change from baseline in QTcF was 16.5 to 19.3 ms at steady state with a sample size larger than 138 for each cycle (see Table 1). After pooling data of cycle 2 and above, a dose-dependent QT prolongation was observed (see Table 2). The sponsor did not submit positive control (moxifloxacin) arms.

This was a first-in-human, phase 1, open-label, dose-escalation and expansion study, 304 patients received LDK378 at doses ranging from 50 mg to 750 mg. An overall summary of results is provided in Table 1 and pooling data from cycle 2 and above in Table 2.

Reference ID: 3466661

Table 1: Analysis Results of ΔQTcF for LDK378 at doses of 750 mg

Treatment	Visit	Time	N	Mean	90% CI for Mean
750 mg	CYCLE 1 DAY 1	4.000	236	1.0	(-0.6, 2.6)
		8.000	215	1.5	(-0.2, 3.2)
		24.000	222	2.0	(0.3, 3.7)
	CYCLE 2 DAY 1	0.000	216	18.7	(16.7, 20.6)
	CYCLE 3 DAY 1	0.000	184	16.5	(14.1, 18.8)
	CYCLE 4 DAY 1	0.000	169	17.7	(15.3, 20.2)
	CYCLE 5 DAY 1	0.000	149	18.7	(15.9, 21.4)
	CYCLE 6 DAY 1	0.000	138	19.3	(16.5, 22.2)

Table 2: Analysis Results of ΔQTcF for LDK378 at doses of 50 mg to 750 mg (Pooling data from Cycle 2 and above)

Treatment	N	Mean (ms)	90% CI for Mean (ms)
50 mg	2	1.5	(-3.8, 6.8)
100 mg	3	-3.0	(-5.6, -0.4)
200 mg	50	-8.0	(-11.5, -4.5)
300 mg	18	13.7	(7.9, 19.4)
400 mg	91	15.3	(11.6, 19.0)
500 mg	83	18.8	(15.7, 21.8)
600 mg	60	21.2	(17.6, 24.8)
700 mg	45	16.3	(11.6, 21.0)
750 mg	955	18.2	(17.2, 19.2)

Multiple doses of the maximum tolerated dose/recommended dose of 750 mg produced a mean steady-state C_{max} of 1100 ng/mL, which was 4.2-fold higher than that of a single dose (e.g., CYCLE 1 DAY 1). Exposure-dependent increase in QTc interval was observed when LDK378 dose increased from 50 to 750 mg.

The observed concentrations did not cover the predicted worst case scenario (20% increase in C_{max} and ~200% increase in AUC when co-administered with ketoconazole). Hepatic impairment may decrease LDK378's clearance as the primary route of elimination is biliary excretion. However, exposure data in patients with hepatic impairment is not available. Renal impairment resulted in 10% increase in LDK 378 C_{max} and 20% increases in AUC, respectively. According to the concentration-QTc relationship, significant QT prolongations are expected at those scenarios.

2 PROPOSED LABEL

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3466661

(b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

LDK378 is an oral, (b) (4) inhibitor of ALK kinase activity. It is being developed by Novartis for treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4)

3.2 MARKET APPROVAL STATUS

LDK378 is not approved for marketing in any country.

(b) (4)

3.4 PREVIOUS CLINICAL EXPERIENCE

No previous clinical experience is available for LDK378. This is a first-in-human, Phase 1, open-label, study to investigate the safety, pharmacokinetics (PK), and anti-tumor activity of

Reference ID: 3466661

oral LDK378 in adult patients with advanced tumors confirmed to have genetic abnormalities in ALK (ALK-positive).

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of LDK378's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under NDA 205755. The sponsor submitted the study report CLDK378X2101 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A phase I, multicenter, open-label, dose-escalation study of LDK378, administered orally in adult patients with tumors characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK)

4.2.2 Protocol Number

CLDK378X2101

4.2.3 Study Dates

Initiation Date: 24 Jan 2011
Cut-Off Date: 02 Aug 2013

4.2.4 Objectives

Primary objective: To determine the maximum tolerated dose (MTD) of LDK378 as a single agent when administered orally to adult patients with tumors characterized by genetic abnormalities in ALK.

Secondary objectives:

- To characterize the safety and tolerability of LDK378, including both acute and chronic toxicities.
- To characterize single and multiple-dose PK of LDK378.
- To assess anti-tumor activity of LDK378 as a single agent when administered orally to adult patients with tumors characterized by genetic abnormalities in ALK at recommended dose (RD) by CT/MRI.

Exploratory objectives:

- To identify mutations in the ALK gene or other molecular abnormalities associated with clinical progression after treatment with an ALK inhibitor in tumor samples collected during the pre-screening period in cases where ALK testing was performed centrally.
- To assess overall survival (OS) in patients treated with LDK378.

Reference ID: 3466661

4.2.5 Study Description

4.2.5.1 Design

This was a first-in-human, phase 1, open-label, a dose-escalation and expansion study of oral once-daily, continuous dosing of LDK378. The dose-escalation phase enrolled patients with ALK-positive tumors to determine the MTD/RD, safety, single and multiple-dose PK, and anti-tumor activity of LDK378. The dose-escalation phase was followed by an expansion phase wherein ALK-positive patients were enrolled based on type of advanced tumor (predominantly NSCLC), and prior exposure to ALK inhibitors to further assess the safety, tolerability, PK, and anti-tumor activity of LDK378 in these patient populations at the RD.

4.2.5.2 Controls

No placebo and positive (moxifloxacin) controls arms.

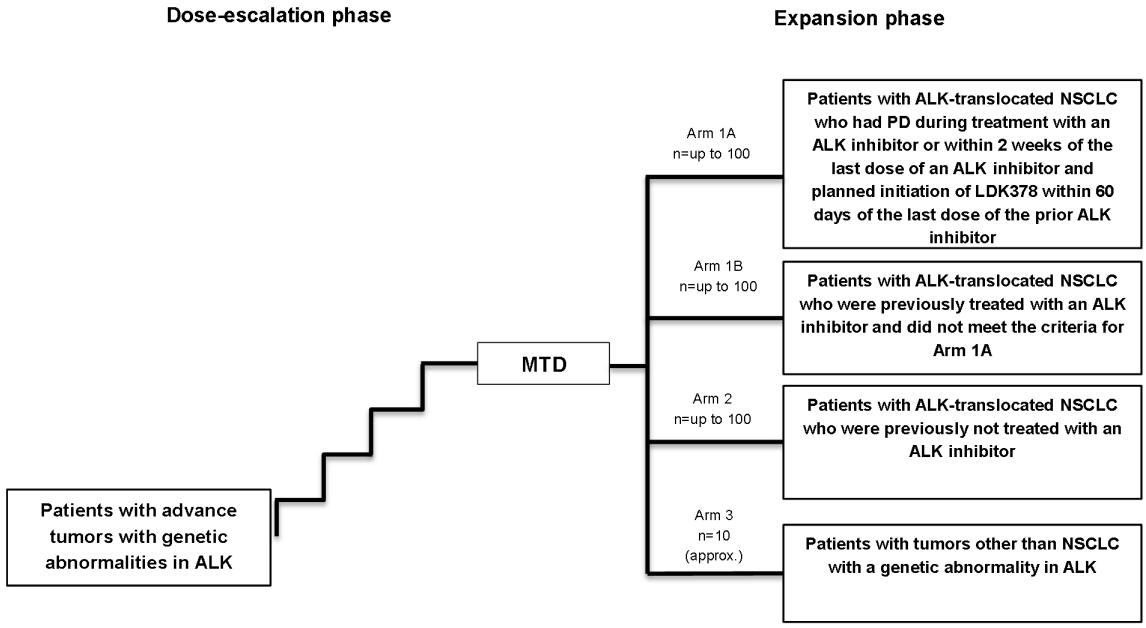
4.2.5.3 Blinding

This is an open-label, dose-escalation and expansion study.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

This study has a dose-escalation phase and an expansion phase (see figure below). Patients in the dose-escalation phase were classified into different treatment dose cohorts. Patients in the expansion phase were classified into four distinct patient populations (Arm 1A, Arm 1B, Arm 2, and Arm 3) based on type of cancer (NSCLC and others) and prior treatment with ALK inhibitors.



The starting dose for LDK378 was 50 mg administered orally, once-daily, as continuous dosing preceded by a 3-day single dose PK run-in period. Successive cohorts of patients received increasing doses of LDK378 until the MTD/RD was determined.

Reference ID: 3466661

Each cohort consisted of newly enrolled patients. Once the currently enrolling cohort was fully enrolled and before the assessment of this cohort as potential MTD/RD was done, additional cohorts of patients could be enrolled into a lower dose cohort to further characterize the safety and PK of LDK378.

Once the RD was defined in the dose-escalation phase, additional patients were enrolled into four distinct patient populations based on type of advanced tumor (predominantly NSCLC) and prior exposure to ALK inhibitor to better characterize the safety, tolerability, multipledose PK, and anti-tumor activity at this dose. These patient populations include:

- **Arm 1A**: Patients with ALK-translocated NSCLC who had disease progression during treatment with an ALK inhibitor or within 2 weeks of the last dose of an ALK inhibitor and planned initiation of LDK378 within 60 days of the last dose of the prior ALK inhibitor.
- **Arm 1B**: Patients with ALK-translocated NSCLC who were previously treated with an ALK inhibitor and did not meet the criteria for Arm 1A.
- **Arm 2**: Patients with ALK-translocated NSCLC who were previously not treated with an ALK inhibitor.
- **Arm 3**: Patients with tumors other than NSCLC with a genetic abnormality in ALK.

Enrollment was to occur in parallel for all four arms. The number of patients was increased up to 100 patients per arm for Arms 1A, 1B and 2. Further, Arm 3 explores patients with tumors other than NSCLC with a genetic abnormality in ALK (to be referred to as non-NSCLC patients).

4.2.6.2 Sponsor's Justification for Doses

This is a first-in-human phase 1, open-label, dose-escalation and expansion study to investigate the safety, PK, and anti-tumor activity of once-daily oral dosing of LDK378. In the dose-escalation phase, successive cohorts of patients received increasing doses of LDK378 (50 mg to 750 mg) until the maximum tolerated dose (MTD)/ recommended dose (RD) was determined. An adaptive Bayesian logistic regression model with 2 parameters guided by EWOC principles was used to make dose recommendations and estimate the MTD. The 750 mg daily dose was determined to be the MTD/RD.

The selection of the oral dosing schedule and initial starting dose is based on the extrapolation of *in vivo* data from preclinical models of efficacy in rat and toxicology models in rats and monkeys, respectively

Reviewer's Comment: Acceptable. The clinical experience in dose-escalation phase was reviewed and the 750-mg dose was determined to be the maximum tolerated dose in human. Further dose-escalation was not necessary due to unacceptable safety profile.

4.2.6.3 Instructions with Regard to Meals

- Patients took LDK378 once-daily at approximately the same time each day. On days that PK samples were collected, the patient took LDK378 during the clinic visit, as instructed by the study staff.

Reference ID: 3466661

- Each daily dose of LDK378 (including days which involve PK blood sampling) was taken at least 2 hours after the last meal. Furthermore, patients could not eat for at least 2 hours after LDK378 was taken.
- Each dose of LDK378 was taken with a glass of water and consumed over a short period of time (e.g. 1 capsule every 2 minutes).

Reviewer's Comment: Acceptable. LDK378 should not be taken with food because food increases drug exposure. The food effect study (Study CLDK378A2101) has indicated that, a low-fat meal increased C_{max} and AUC_{inf} following a single 500-mg oral dose of LDK378 in healthy subjects by 43% and 58%, respectively, compared to the fasted state, whereas a high-fat meal increased C_{max} and AUC_{inf} by 41% and 73%, respectively.

4.2.6.4 ECG and PK Assessments

ECG Assessments: A standard 12 lead ECG was performed at the following time points:

- Baseline/screening, single ECG within 14 days prior to first dose of LDK378
- PK run-in Day 1 in the dose-escalation phase and Cycle 1 Day 1 in expansion phase, three serial ECGs at least 5 to 10 minute apart prior to the first dose of LDK378 and single ECGs 4, 8, and 24 hours post dose
- Cycle 1 Day 8 in the dose-escalation phase, single ECG pre-dose and 4 hours post-dose
- Day 1 of Cycle 2 to Cycle 6, single ECG pre-dose
- After Cycle 6, ECGs should only be performed if clinically indicated
- End of treatment(EOT), single ECG

Pharmacokinetic assessments

Blood samples for PK assessments were collected in both dose-escalation and expansion phases.

Dose-escalation phase: Serial plasma samples were collected for the determination of LDK378 plasma concentration-time profiles in the PK run-in phase (pre-dose to 72 hours post-dose) and on Cycle 1 Day 8 (pre-dose to 24 hours post-dose). In addition, patients enrolled in the first three dose cohorts had a third PK profile (pre-dose to 24 hours post-dose) collected on Cycle 2 Day 1. Additional pre-dose trough samples were collected in all patients on Day 15 of Cycle 1 and Cycle 2; and on Day 1 of Cycle 2 and subsequent cycles.

Expansion phase: Two PK profiles were collected on Cycle 1 Day 1 (pre-dose to 24 hours post-dose) and Cycle 2 Day 1 (pre-dose to 8 hours post-dose). Additional pre-dose trough samples were collected on Day 15 of Cycle 1 and Cycle 2, and on Day 1 of Cycle 3 and Cycle 4. A 24-hour post-dose sample was also collected at Cycle 2 Day 1 for some patients enrolled in the expansion phase after Amendment 4 was implemented.

Reviewer's Comment: Acceptable. After a single dose or multiple doses of 750 mg LDK378, the median time to reach the maximum plasma concentration for LDK378 is 6 hours. The time was covered by the selected time points for ECG measurements.

Reference ID: 3466661

4.2.6.5 Baseline

The sponsor used the average of pre-dose QTc values on Day 1 as baselines.

4.2.7 ECG Collection

A standard 12 lead ECG was performed at time points as mentioned above.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 304 patients were treated at LDK378 doses ranging from 50 to 750 mg; 59 patients from the dose escalation phase (including 10 patients at 750 mg) and 245 patients from the expansion phase treated at LDK378 750 mg. They were 290 patients (95.4%) with ALK-positive NSCLC and 14 patients (4.6%) with other tumors with genetic alterations of ALK (non-NSCLC).

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The statistical reviewer could not locate the sponsor's statistical analyses.

Reviewer's Comments: We will provide our independent analysis results in Section 5.2.

4.2.8.2.2 Assay Sensitivity

There is no assay sensitivity established in this study because no positive control arm was included in the study.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc ≤450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms, and changes from baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. No subject's absolute QTc > 480 ms and ΔQTc >60 ms.

	LDK378 50-300 mg N=10 Total n %	LDK378 400-700 mg N=39 Total n %	LDK378 750 mg N=255 Total n %	All patients[1] N=304 Total n %
QT (ms)				
New > 450	9 1 (11.1)	38 5 (13.2)	246 41 (16.7)	293 47 (16.0)
New > 480	9 0 (0.0)	39 1 (2.6)	250 10 (4.0)	298 11 (3.7)
New > 500	10 1 (10.0)	39 0 (0.0)	250 3 (1.2)	299 4 (1.3)
Increase from baseline > 30	10 3 (30.0)	39 31 (79.5)	250 165 (66.0)	299 199 (66.6)
Increase from baseline > 60	10 0 (0.0)	39 15 (38.5)	250 64 (25.6)	299 79 (26.4)
QTcP (ms)				
New > 450	7 2 (28.6)	37 13 (35.1)	245 75 (30.6)	289 90 (31.1)
New > 480	10 1 (10.0)	39 1 (2.6)	250 8 (3.2)	299 10 (3.3)
New > 500	10 0 (0.0)	39 1 (2.6)	250 0 (0.0)	299 1 (0.3)
Increase from baseline > 30	10 2 (20.0)	39 20 (51.3)	250 97 (38.8)	299 119 (39.8)
Increase from baseline > 60	10 0 (0.0)	39 3 (7.7)	250 4 (1.6)	299 7 (2.3)
HR (bpm)				
Decrease > 25% and to < 50	10 0 (0.0)	39 1 (2.6)	250 8 (3.2)	299 9 (3.0)
Increase > 25% and to > 100	10 2 (20.0)	39 2 (5.1)	250 14 (5.6)	299 18 (6.0)
PR (ms)				
Increase > 25% and to > 200	10 0 (0.0)	38 0 (0.0)	250 0 (0.0)	298 0 (0.0)

Reference ID: 3466661

New PR >200 and ≤ 220	10 0 (0.0)	38 1 (2.6)	250 17 (6.8)	298 18 (6.0)
New PR >220	10 0 (0.0)	38 0 (0.0)	250 5 (2.0)	298 5 (1.7)
QRS (ms)				
Increase > 25% and to > 110	10 0 (0.0)	39 0 (0.0)	250 0 (0.0)	299 0 (0.0)
New QRS >110 and ≤ 120	10 0 (0.0)	39 0 (0.0)	250 4 (1.6)	299 4 (1.3)
New QRS > 120	10 0 (0.0)	39 0 (0.0)	250 0 (0.0)	299 0 (0.0)

This table presents data for all patients (NSCLC and non-NSCLC) treated with at least one dose of LDK378 (Safety set).
[1] All patients include 14 non-NSCLC patients (50-300 mg: 2 patients, 400-700 mg: 3 patients, and 750 mg: 9 patients).
Total is the number of patients at risk for a specific category. For new abnormality post baseline values, this is the number of patients with both baseline and post baseline, and baseline not meeting the criteria. For abnormal change from baseline, this is the number of patients with both baseline and post baseline evaluations.

4.2.8.3 Safety Analysis

In the 304 patients (NSCLC and non-NSCLC) treated with any dose of LDK378, 99.3% of the patients reported at least one AE during the study. The most frequently reported AEs (≥25%) were GI disorders (diarrhea, nausea, vomiting, and constipation) and increased transaminases (ALT and AST), fatigue, abdominal pain, and decreased appetite. The most frequently reported grade 3-4 AEs (≥ 5%) were increases in transaminase (ALT and AST), and diarrhea.

Serious adverse events were reported in 114 patients (37.5%). The frequently reported (≥2%) SAEs were: pneumonia, convulsion, dyspnea, pneumonitis, hyperglycemia, and respiratory failure.

The AEs of special interest identified with LDK378 are hepatotoxicity, ILD/pneumonitis, and QT interval prolongation.

Forty on-treatment deaths were reported (defined as deaths that occurred during treatment or within 28 days of the last dose of LDK378): 29 deaths due to study indication and 11 deaths reported as "other" were due to a variety of other reasons generally in the context of progression of underlying cancer, and were assessed as not related to LKD378 by the Investigator.

In the ECG data, a modest, dose-dependent potential to cause QT prolongation has been shown for LDK378. The estimated QTcP increase was 13.6 ms, and at concentrations as high as the 75% percentile of Cmax, the upper bound of the 90% CI for mean QTcP change from baseline was < 20 ms indicating a moderate risk for severe QT prolongation events. QT prolongation AEs were reported in 5.9% of patients at 750 mg, most commonly QT interval prolonged. Four cases of syncope were not suspected to be related to the study drug. Two SAEs were reported that occurred in the setting of disease progression. None of the patients discontinued the study due to QT prolongation events. While in the rest events resolved either spontaneously, with dose adjustment or interruption (4 patients), or following appropriate medical management.

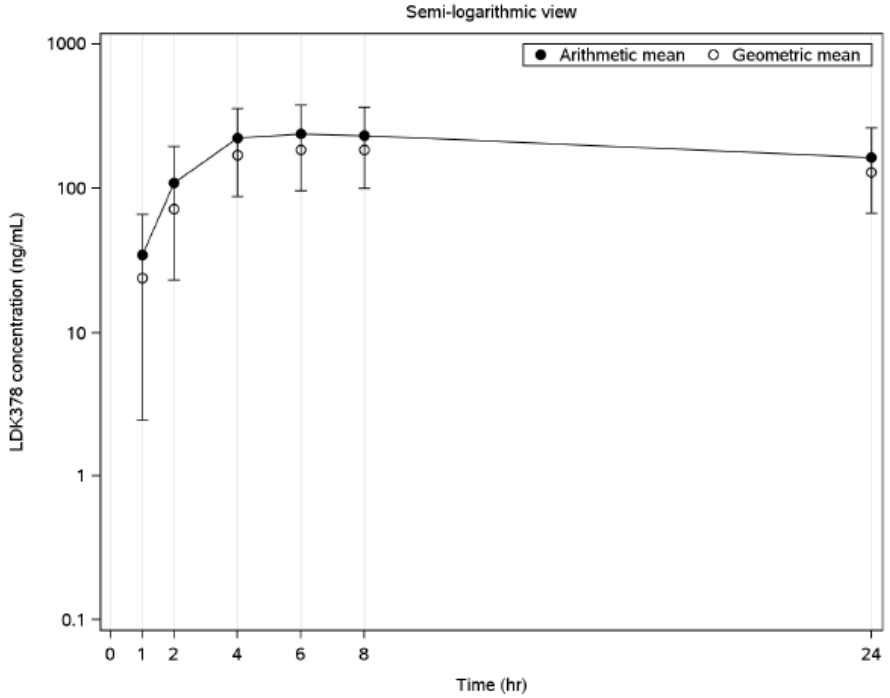
4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

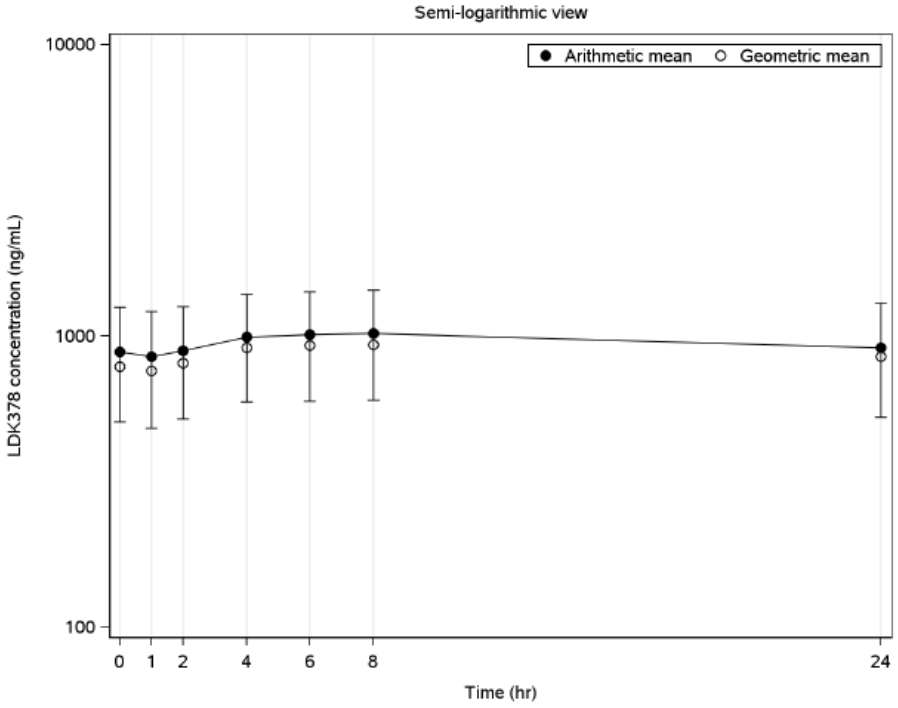
The PK results are presented in Table 3 (LDK678) and demonstrated in Figure 1. The steady state C_{max} values following administration of multiple 750-mg doses of LDK378 were 4.2-fold those following a single 750-mg dose.

Figure 1: Geometric mean and arithmetic mean (SD) concentration-time profiles for LDK378 750 mg group in the expansion phase (PAS)

Profile day: Cycle 1 Day 1



Profile day: Cycle 2 Day 1



Source: Figure 11-11 on page 199 of the sponsor's report

Table 3: Summary of Primary PK parameters for LDK378

Profile Day: Cycle 1 Day 1 and Cycle 2 Day 1 at 750 mg of Dose-escalation and Expansion phases

Study Day	Statistics	AUClast (ng*h/mL)	AUC0-24h (ng*h/mL)	Cmax (ng/mL)	Cmin (ng/mL)	Tmax (h)
Cycle 1 Day 1	n	208	73	208	N/A	208
	Mean (SD)	3320 (2700)	4430 (2740)	262 (153)		
	CV% mean	81.3	61.8	58.4		
	Geo-mean	2040	3340	203		
	CV% geo-mean	175.4	111.9	100.9		
	Median	2640	4410	264		6.00
	[Min; Max]	[48.0;13000]	[278;13000]	[13.8;767]		[1.13;24.0]
Cycle 2 Day 1	n	133	23	133	169	133
	Mean (SD)	11200 (8350)	23800 (7050)	1100 (441)	910 (376)	
	CV% mean	74.3	29.6	40.1	41.3	
	Geo-mean	8900	22600	1010	828	
	CV% geo-mean	76.1	37.1	44.8	48.4	
	Median	8670	24500	1100	859	6.00
	[Min; Max]	[1760;40500]	[8880;33600]	[261;3360]	[199;2260]	[0;22.6]

n: number of patients with non-missing values.
CV% = coefficient of variation (%) = sd/mean*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100
Not all PK parameters are available on all days.
Source: Table 14.2-3.1a

Source: Table 11-27 on page 193 of the sponsor's report

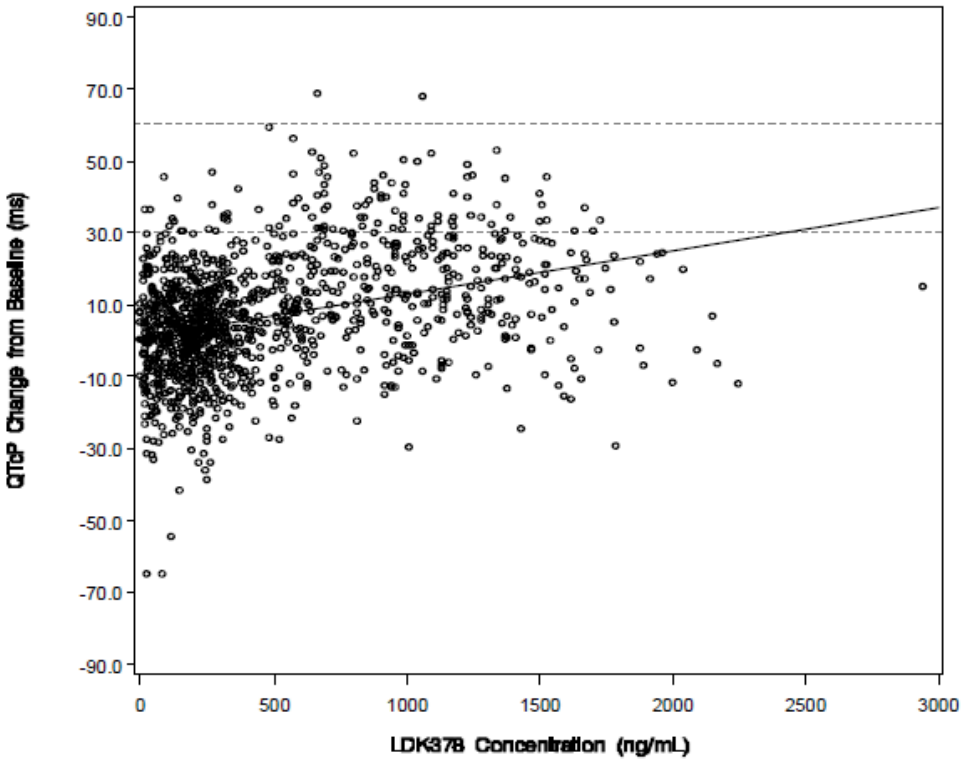
4.2.8.4.2 Exposure-Response Analysis

The sponsor plotted QTcP change from baseline versus time-matched LDK378 plasma concentration, with an evident exposure-response relationship observed

Reference ID: 3466661

BEST AVAILABLE COPY)

Figure 12-2 QTcP change from baseline versus time-matched LDK378 plasma concentrations (Safety Set)



Source: Figure 12-2 on page 253 of the sponsor's report

Reviewer's Analysis: A plot of ΔQTcF vs. LDK378 concentrations by the reviewer is presented in Figure 3.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHODU

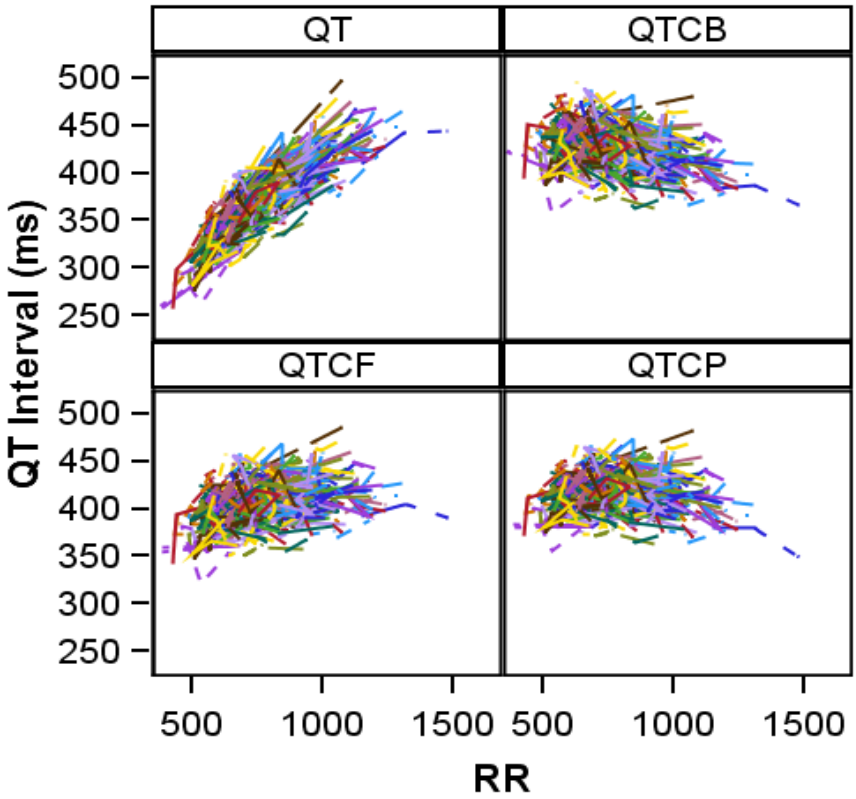
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 4, it appears that QTcP is better than QTcB, QTcF and QTLP. To be consistent with the sponsor's analyses, we choose to present QTcF results.

Table 4: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method							
	QTLP		QTcB		QTcF		QTcP	
	N	MSSS	N	MSSS	N	MSSS	N	MSSS
50 mg	2	0.0054	2	0.0146	2	0.0001	2	0.0011
100 mg	2	0.1576	2	0.2055	2	0.1139	2	0.1046
200 mg	3	0.9802	3	1.0162	3	0.8022	3	0.6043
300 mg	3	0.0071	3	0.0053	3	0.0120	3	0.0097
400 mg	14	0.4017	14	0.4236	14	0.3727	14	0.2261
500 mg	10	0.0205	10	0.0283	10	0.0163	10	0.0163
600 mg	10	0.0295	10	0.0272	10	0.0346	10	0.0249
700 mg	5	0.0290	5	0.0380	5	0.0295	5	0.0211
750 mg	252	0.0235	252	0.0277	252	0.0238	252	0.0183
All	301	0.0514	301	0.0570	301	0.0483	301	0.0344

The QT-RR interval relationship is presented in Figure 2 together with the Bazett's (QTcB), Fridericia (QTcF), linear regression (QTcP), and log-linear regression (QTcLogP) corrections.

Figure 2: QT, QTcB, QTcF, QTcP an vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 (STAT) STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The primary endpoint is the change from the baseline of QTcF. The descriptive statistics are listed in Table 5. The largest upper bound of the 2-sided 90% CI for the mean difference between LDK378 200 mg and placebo is 280.7 ms. This reviewer performs analysis pooling data for each dose for cycle 2 and above. The largest upper bound of the 2-sided 90% CI for the mean difference between LDK378 600 mg and placebo is 24.8 ms (see Table 6) for Cycle 2 and above. Large changes (i.e., > 20 ms) in the QTc interval were detected when LDK378 was administered at doses of 50 mg to 750 mg.

Reference ID: 3466661

Table 5: Analysis Results of ΔQTcF for LDK378 at doses of 50 mg to 750 mg

Treatment	Visit	Time	N	Mean	Std Dev	90% CI for Mean
50 mg	CYCLE 1 DAY 8	0.000	2	-3.0	3.8	(-19.8, 13.8)
		4.000	2	0.0	3.8	(-16.8, 16.8)
100 mg	CYCLE 1 DAY 8	0.000	2	-28.7	69.3	(-338, 280.7)
		4.000	2	-1.2	41.7	(-187, 185.1)
200 mg	CYCLE 1 DAY 8	0.000	3	9.6	22.0	(-27.5, 46.6)
		4.000	3	12.6	20.0	(-21.2, 46.3)
300 mg	CYCLE 1 DAY 8	0.000	3	12.5	11.5	(-6.8, 31.9)
		4.000	3	3.9	13.2	(-18.3, 26.0)
400 mg	CYCLE 1 DAY 8	0.000	14	8.3	19.2	(-0.8, 17.4)
		4.000	14	13.1	18.4	(4.4, 21.8)
500 mg	CYCLE 1 DAY 8	0.000	9	14.8	12.8	(6.9, 22.7)
		4.000	9	18.8	10.4	(12.4, 25.2)
600 mg	CYCLE 1 DAY 8	0.000	9	22.1	22.6	(8.1, 36.1)
		4.000	9	20.0	12.4	(12.3, 27.7)
700 mg	CYCLE 1 DAY 8	0.000	4	40.8	31.2	(4.1, 77.5)
		4.000	5	35.0	21.5	(14.5, 55.5)
750 mg	CYCLE 1 DAY 1	0.000	4	-7.5	19.9	(-30.9, 15.9)
		4.000	236	1.0	14.8	(-0.6, 2.6)
		8.000	215	1.5	14.8	(-0.2, 3.2)
		24.000	222	2.0	15.2	(0.3, 3.7)
	CYCLE 1 DAY 8	0.000	9	5.3	11.0	(-1.5, 12.2)
		4.000	8	12.4	17.4	(0.7, 24.0)
	CYCLE 2 DAY 1	0.000	216	18.7	17.1	(16.7, 20.6)
	CYCLE 3 DAY 1	0.000	184	16.5	18.9	(14.1, 18.8)
	CYCLE 4 DAY 1	0.000	169	17.7	19.4	(15.3, 20.2)
	CYCLE 5 DAY 1	0.000	149	18.7	20.3	(15.9, 21.4)
	CYCLE 6 DAY 1	0.000	138	19.3	20.4	(16.5, 22.2)
	CYCLE 7 DAY 1	0.000	26	18.6	18.9	(12.3, 24.9)
	CYCLE 8 DAY 1	0.000	14	17.5	22.6	(6.8, 28.2)
	CYCLE 9 DAY 1	0.000	14	18.4	25.1	(6.5, 30.3)
	CYCLE 10 DAY 1	0.000	10	27.6	21.3	(15.3, 39.9)
	CYCLE 11 DAY 1	0.000	6	20.8	17.7	(6.3, 35.3)
	CYCLE 12 DAY 1	0.000	7	24.2	13.6	(14.3, 34.2)
	CYCLE 13 DAY 1	0.000	7	13.7	16.5	(1.6, 25.8)
	CYCLE 14 DAY 1	0.000	5	17.0	16.8	(1.0, 33.0)
	CYCLE 15 DAY 1	0.000	4	26.9	8.7	(16.6, 37.2)

Table 6: Analysis Results of ΔQTcF for LDK378 at doses of 50 mg to 750 mg (Pooling data from Cycle 2 and above)

Treatment	N	Mean	Std Dev	90% CI for Mean
50 mg	2	1.5	1.2	(-3.8, 6.8)
100 mg	3	-3.0	1.5	(-5.6, -0.4)
200 mg	50	-8.0	14.7	(-11.5, -4.5)
300 mg	18	13.7	14.0	(7.9, 19.4)
400 mg	91	15.3	21.2	(11.6, 19.0)
500 mg	83	18.8	16.9	(15.7, 21.8)
600 mg	60	21.2	16.6	(17.6, 24.8)
700 mg	45	16.3	18.8	(11.6, 21.0)
750 mg	955	18.2	19.1	(17.2, 19.2)

5.2.1.2 Assay Sensitivity Analysis

No assay sensitivity analysis performed in this study because there was no positive control arm.

5.2.1.3 Categorical Analysis

Table 7 and Table 8 list the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms. No subject's QTcF was above 480 ms in Cycle 1 (see Table 7). However, one subject was above 480 ms in Cycle 2 (see Table 8).

Table 7: Categorical Analysis for QTcF in Cycle 1

Treatment	Total N	Value<=450 ms	450 ms<Value<=480 ms	480 ms<Value<=500 ms	Value>500 ms
750 mg	239	227 (95%)	12 (17.1%)	3 (5.0%)	0 (0.0%)

Reference ID: 3466661

Table 8: Categorical Analysis for QTcF in Cycle 2 and above

Treatment	Total N	Value<=450 ms	450 ms<Value<=480 ms	480 ms<Value<=500 ms	Value>500 ms
50 mg	2	2 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
100 mg	3	1 (34%)	2 (67%)	0 (0.0%)	0 (0.0%)
200 mg	3	2 (6.7%)	0 (0.0%)	1 (33.3%)	0 (0.0%)
300 mg	14	10 (71.4%)	4 (28.6%)	0 (0.0%)	0 (0.0%)
400 mg	2	2 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
500 mg	9	7 (77.8%)	2 (22.2%)	0 (0.0%)	0 (0.0%)
600 mg	9	5 (55.6%)	4 (44.4%)	0 (0.0%)	0 (0.0%)
700 mg	5	2 (40%)	2 (40%)	0 (0.0%)	1 (20%)
750 mg	251	186 (81.7%)	40 (17.5%)	3 (1.3%)	0 (0.0%)

Table 9 and Table 10 list the number of subjects whose changes from baseline QTc ≤30 ms, between 30 and 60 ms and >60 ms. No subject's change from baseline was above 60 ms in Cycle 1. However, sixteen subjects were above 60 ms in Cycle 2 (see Table 10).

Table 9: Categorical Analysis for ΔQTcF in Cycle 1

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms	Value>60 ms
750 mg	239	228 (95.4%)	11 (4.6%)	0 (0.0%)

Table 10: Categorical Analysis for ΔQTcF in Cycle 2 and above

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms	Value>60 ms
50 mg	2	2 (100%)	0 (0.0%)	0 (0.0%)
100 mg	2	2 (100%)	0 (0.0%)	0 (0.0%)
200 mg	3	2 (66.7%)	1 (33.3%)	0 (0.0%)
300 mg	3	2 (66.7%)	1 (33.3%)	0 (0.0%)
400 mg	14	7 (50%)	6 (42.8%)	1 (7.1%)
500 mg	9	3 (33.3%)	6 (66.7%)	0 (0.0%)
600 mg	9	1 (11.1%)	7 (77.8%)	1 (11.1%)
700 mg	5	1 (20.0%)	2 (40.0%)	2 (40.0%)
750 mg	228	120 (52.6%)	96 (42.1.8%)	12 (5.3%)

5.2.2 HR Analysis

The primary endpoint is the change from the baseline of HR. The descriptive statistics are listed in Table 11. The largest upper bound of the 2-sided 90% CI for the mean difference between LDK378 400 mg and placebo is 73.8 bpm. This reviewer performs analysis pooling data for each dose for cycle 2 and above. After pooling data of cycle 2 above, the largest upper bound of the 2-sided 90% CI for the mean difference between LDK378 100 mg and

Reference ID: 3466661

placebo is 44.0 bpm (see Table 12). Large changes (i.e., > 20 ms) in the HR interval were detected when LDK378 was administered at doses of 50 mg to 750 mg. Table 13 presents the categorical analysis of HR. Sixty-two subjects who experienced HR interval greater than 100 bpm are in LDK378 750-mg group.

Table 11: Primary Analysis Results of ΔHR for LDK378 at doses of 50 mg to 750 mg

Treatment	Visit	Time	N	Mean	Std Dev	90% CI for Mean
50 mg	CYCLE 1 DAY 8	0.000	2	-3.8	3.1	(-17.5, 9.8)
		4.000	2	-1.8	11.1	(-51.3, 47.6)
100 mg	CYCLE 1 DAY 8	0.000	2	15.3	6.6	(-14.1, 44.8)
		4.000	2	4.8	11.5	(-46.7, 56.4)
200 mg	CYCLE 1 DAY 8	0.000	3	1.1	2.4	(-2.9, 5.1)
		4.000	3	-0.2	1.8	(-3.3, 2.9)
300 mg	CYCLE 1 DAY 8	0.000	3	-0.7	8.6	(-15.2, 13.8)
		4.000	3	3.9	9.4	(-11.9, 19.8)
400 mg	CYCLE 1 DAY 8	0.000	14	-11.8	18.5	(-20.5, -3.0)
		4.000	14	-9.0	17.6	(-17.3, -0.7)
500 mg	CYCLE 1 DAY 8	0.000	9	-9.9	12.6	(-17.7, -2.0)
		4.000	9	-11.2	13.3	(-19.5, -2.9)
600 mg	CYCLE 1 DAY 8	0.000	9	-7.9	7.6	(-12.6, -3.1)
		4.000	9	-6.6	9.6	(-12.6, -0.6)
700 mg	CYCLE 1 DAY 8	0.000	4	-12.7	13.7	(-28.8, 3.5)
		4.000	5	-11.5	11.4	(-22.4, -0.6)
750 mg	CYCLE 1 DAY 1	0.000	6	10.3	3.7	(7.3, 13.4)
		4.000	236	4.4	8.3	(3.5, 5.3)
		8.000	217	1.2	8.8	(0.3, 2.2)
		24.000	222	-1.7	8.2	(-2.6, -0.8)
	CYCLE 1 DAY 8	0.000	9	-13.7	12.1	(-21.2, -6.2)
		4.000	8	-9.8	17.0	(-21.1, 1.6)
	CYCLE 2 DAY 1	0.000	216	-9.1	12.4	(-10.5, -7.8)
	CYCLE 3 DAY 1	0.000	185	-6.4	17.0	(-8.5, -4.3)
	CYCLE 4 DAY 1	0.000	169	-8.0	15.4	(-10.0, -6.1)
	CYCLE 5 DAY 1	0.000	150	-6.9	15.8	(-9.0, -4.7)
	CYCLE 6 DAY 1	0.000	138	-7.7	15.8	(-9.9, -5.4)
	CYCLE 7 DAY 1	0.000	26	-8.0	13.8	(-12.6, -3.4)
	CYCLE 8 DAY 1	0.000	14	-11.2	9.8	(-15.8, -6.5)
	CYCLE 9 DAY 1	0.000	14	-10.7	12.7	(-16.8, -4.7)
	CYCLE 10 DAY 1	0.000	10	-13.9	10.1	(-19.7, -8.0)
	CYCLE 11 DAY 1	0.000	6	-9.7	6.9	(-15.3, -4.0)
	CYCLE 12 DAY 1	0.000	7	-9.9	9.2	(-16.6, -3.1)

Treatment	Visit	Time	N	Mean	Std Dev	90% CI for Mean
	CYCLE 13 DAY 1	0.000	7	-5.4	7.4	(-10.9, -0.0)
	CYCLE 14 DAY 1	0.000	5	-7.5	11.0	(-18.0, 3.0)
	CYCLE 15 DAY 1	0.000	4	-6.1	10.8	(-18.9, 6.6)
	CYCLE 16 DAY 1	0.000	2	-13.5	19.6	(-101, 73.8)
	CYCLE 17 DAY 1	0.000	2	-10.8	2.2	(-20.5, -1.1)

Table 12: Analysis Results of ΔHR for LDK378 at doses of 50 mg to 750 mg (Pooling data from Cycle 2 and above)

Treatment	N	Mean	Std Dev	90% CI for Mean
50 mg	2	-4.8	4.0	(-22.7, 13.1)
100 mg	3	17.7	15.6	(-8.7, 44.0)
200 mg	50	9.7	9.5	(7.4, 12.0)
300 mg	18	5.2	8.6	(1.7, 8.7)
400 mg	91	-13.9	18.4	(-17.1, -10.7)
500 mg	83	-11.1	13.6	(-13.6, -8.6)
600 mg	60	-10.0	15.9	(-13.4, -6.5)
700 mg	45	-5.7	15.0	(-9.4, -1.9)
750 mg	957	-7.9	14.8	(-8.7, -7.1)

Table 13: Categorical Analysis for HR

Treatment Group	Total N	HR < 100 bpm	HR >=100 bpm
50 mg	2	2 (100%)	0 (0.0%)
100 mg	2	1 (50.0%)	1 (50.0%)
200 mg	3	2 (66.7%)	1 (33.3%)
300 mg	3	1 (33.3%)	2 (66.7%)
400 mg	14	9 (64.3%)	5 (35.7%)
500 mg	10	7 (70.0%)	3 (30.0%)
600 mg	10	8 (80.0%)	2 (20.0%)
700 mg	5	5 (100%)	0 (0.0%)
750 mg	249	187 (75.1%)	62 (24.9%)

5.2.3 PR Analysis

The primary endpoint is the change from the baseline of PR. The descriptive statistics are listed in Table 14. The largest upper bound of the 2-sided 90% CI for the mean difference between LDK378 50 mg and placebo is 70.5 ms. This reviewer performs analysis pooling data for each dose for cycle 2 and above. After pooling data of cycle 2 above, the largest upper bound of the 2-sided 90% CI for the mean difference between LDK378 50 mg and placebo is 36.3 ms (see Table 15). Large changes (i.e., > 20 ms) in the PR interval were detected when LDK378 was administered at doses of 50 mg to 750 mg. Table 16 presents the categorical analysis of PR. Twelve subjects who experienced PR interval greater than 200 ms are in LDK378 750-mg group.

Table 14: Primary Analysis Results of ΔPR for LDK at doses of 50 mg to 750 mg

Treatment	Visit	Time	N	Mean	Std Dev	90% CI for Mean
50 mg	CYCLE 1 DAY 8	0.000	2	-2.2	11.1	(-51.6, 47.3)
		4.000	2	-4.7	14.6	(-69.9, 60.6)
100 mg	CYCLE 1 DAY 8	0.000	2	0.7	1.4	(-5.6, 7.0)
		4.000	2	5.2	3.5	(-10.6, 21.0)
200 mg	CYCLE 1 DAY 8	0.000	3	1.9	9.7	(-14.4, 18.2)
		4.000	3	-4.1	6.2	(-14.6, 6.3)
500 mg	CYCLE 1 DAY 8	0.000	8	7.2	8.8	(1.3, 13.1)
		4.000	8	-0.6	16.2	(-11.4, 10.3)
600 mg	CYCLE 1 DAY 8	0.000	9	2.9	15.0	(-6.5, 12.2)
		4.000	9	1.9	9.7	(-4.2, 7.9)
700 mg	CYCLE 1 DAY 8	0.000	4	-6.3	15.7	(-24.7, 12.1)
		4.000	5	-11.8	12.6	(-23.8, 0.2)
750 mg	CYCLE 1 DAY 1	0.000	6	-8.2	8.0	(-14.7, -1.6)
		4.000	234	-0.3	9.8	(-1.4, 0.7)

Treatment	Visit	Time	N	Mean	Std Dev	90% CI for Mean
		8.000	216	0.3	10.8	(-0.9, 1.5)
		24.000	221	-0.1	10.3	(-1.3, 1.0)
	CYCLE 1 DAY 8	0.000	9	-3.3	8.2	(-8.3, 1.8)
		4.000	8	-0.3	9.2	(-6.4, 5.9)
	CYCLE 2 DAY 1	0.000	216	3.9	12.3	(2.5, 5.3)
	CYCLE 3 DAY 1	0.000	184	0.3	13.5	(-1.3, 2.0)
	CYCLE 4 DAY 1	0.000	169	0.8	13.1	(-0.8, 2.5)
	CYCLE 5 DAY 1	0.000	149	1.5	13.7	(-0.4, 3.3)
	CYCLE 6 DAY 1	0.000	138	1.6	14.1	(-0.4, 3.6)
	CYCLE 7 DAY 1	0.000	26	0.4	16.6	(-5.1, 6.0)
	CYCLE 8 DAY 1	0.000	14	1.9	16.8	(-6.0, 9.9)
	CYCLE 9 DAY 1	0.000	14	6.5	14.8	(-0.4, 13.5)
	CYCLE 10 DAY 1	0.000	10	1.5	21.8	(-11.2, 14.1)
	CYCLE 11 DAY 1	0.000	6	-0.3	17.0	(-14.3, 13.6)
	CYCLE 12 DAY 1	0.000	7	0.2	15.7	(-11.3, 11.7)
	CYCLE 13 DAY 1	0.000	7	-4.8	8.9	(-11.3, 1.7)
	CYCLE 14 DAY 1	0.000	5	-10.1	16.8	(-26.1, 5.9)
	CYCLE 15 DAY 1	0.000	4	-5.4	20.6	(-29.6, 18.9)
	CYCLE 16 DAY 1	0.000	2	1.5	15.3	(-66.9, 69.9)
	CYCLE 17 DAY 1	0.000	2	10.8	13.4	(-48.9, 70.5)

Table 15: Analysis Results of ΔPR for LDK at doses of 50 mg to 750 mg (Pooling data from Cycle 2 and above)

Treatment	N	Mean	Std Dev	90% CI for Mean
50 mg	2	-3.7	9.0	(-43.7, 36.3)
100 mg	3	-3.7	11.8	(-23.6, 16.3)
200 mg	50	-6.0	8.5	(-8.0, -4.0)
300 mg	18	-3.4	12.9	(-8.7, 1.9)
400 mg	91	2.2	13.7	(-0.2, 4.6)
500 mg	76	3.8	10.3	(1.8, 5.7)
600 mg	60	0.3	12.9	(-2.5, 3.1)
700 mg	45	-10.4	16.9	(-14.6, -6.2)
750 mg	955	1.6	13.6	(0.9, 2.3)

Table 16: Categorical Analysis for PR

Treatment Group	Total N	PR < 200 ms	PR >=200 ms
50 mg	2	2 (100%)	0 (0.0%)
100 mg	3	3 (100%)	0 (0.0%)
200 mg	3	3 (100%)	0 (0.0%)
300 mg	14	14 (100%)	0 (0.0%)
400 mg	2	2 (100%)	0 (0.0%)
500 mg	10	10 (100%)	0 (0.0%)
600 mg	10	10 (100%)	0 (0.0%)
700 mg	5	5 (100%)	0 (0.0%)
750 mg	248	236 (95.2%)	12 (4.8%)

5.2.4 QRS Analysis

The primary endpoint is the change from the baseline of QRS. The descriptive statistics are listed in Table 17. The largest upper bound of the 2-sided 90% CI for the mean difference between LDK378 50 mg and placebo is 41.2 ms. This reviewer performs secondary analysis pooling data for each dose for cycle 2 and above. After pooling data of cycle 2 above, the largest upper bound of the 2-sided 90% CI for the mean difference between LDK378 50 mg and placebo is 19.3 ms (see Table 18). Table 19 presents the categorical analysis of QRS. Four subjects who experienced QRS interval greater than 110 ms are in LDK378 750-mg group.

Table 17: Analysis Results of ΔQRS for LDK378 at doses of 50 mg to 750 mg

Treatment	Visit	Time	N	Mean	Std Dev	90% CI for Mean
50 mg	CYCLE 1 DAY 8	0.000	2	6.5	7.8	(-28.2, 41.2)
100 mg	CYCLE 1 DAY 8	0.000	2	-2.5	6.4	(-30.9, 25.9)
		4.000	2	2.5	4.9	(-19.6, 24.6)
200 mg	CYCLE 1 DAY 8	0.000	3	-3.7	4.4	(-11.1, 3.8)
		4.000	3	-1.3	4.3	(-8.6, 6.0)
300 mg	CYCLE 1 DAY 8	0.000	3	-1.2	1.6	(-3.9, 1.5)
		4.000	3	-0.2	1.9	(-3.4, 3.0)
400 mg	CYCLE 1 DAY 8	0.000	14	3.5	5.6	(0.9, 6.2)
		4.000	14	1.6	5.8	(-1.1, 4.4)
500 mg	CYCLE 1 DAY 8	0.000	9	0.7	6.0	(-3.0, 4.5)
		4.000	9	2.6	3.2	(0.7, 4.6)
600 mg	CYCLE 1 DAY 8	0.000	9	6.4	4.9	(3.4, 9.4)
		4.000	9	4.3	6.3	(0.4, 8.2)
700 mg	CYCLE 1 DAY 8	0.000	4	2.1	3.6	(-2.1, 6.3)
		4.000	5	1.3	4.6	(-3.0, 5.7)

Treatment	Visit	Time	N	Mean	Std Dev	90% CI for Mean
750 mg	CYCLE 1 DAY 1	0.000	15	-2.4	6.7	(-5.5, 0.6)
		4.000	244	0.8	5.9	(0.2, 1.5)
		8.000	217	0.7	6.0	(-0.0, 1.3)
		24.000	222	1.0	6.1	(0.4, 1.7)
	CYCLE 1 DAY 8	0.000	9	1.0	5.7	(-2.6, 4.5)
		4.000	8	4.1	5.9	(0.1, 8.0)
	CYCLE 2 DAY 1	0.000	216	1.2	6.9	(0.5, 2.0)
	CYCLE 3 DAY 1	0.000	185	1.1	6.3	(0.4, 1.9)
	CYCLE 4 DAY 1	0.000	169	1.0	6.9	(0.1, 1.8)
	CYCLE 5 DAY 1	0.000	150	0.6	6.8	(-0.3, 1.5)
	CYCLE 6 DAY 1	0.000	138	1.0	7.0	(0.0, 2.0)
	CYCLE 7 DAY 1	0.000	26	1.0	7.8	(-1.6, 3.7)
	CYCLE 8 DAY 1	0.000	14	-1.6	6.6	(-4.7, 1.5)
	CYCLE 9 DAY 1	0.000	14	1.7	8.5	(-2.3, 5.7)
	CYCLE 10 DAY 1	0.000	10	3.8	7.1	(-0.3, 7.9)
	CYCLE 11 DAY 1	0.000	6	4.3	10.7	(-4.6, 13.1)
	CYCLE 12 DAY 1	0.000	7	2.5	2.7	(0.6, 4.5)
	CYCLE 13 DAY 1	0.000	7	1.2	6.7	(-3.7, 6.2)
	CYCLE 14 DAY 1	0.000	5	3.1	5.2	(-1.9, 8.0)
	CYCLE 15 DAY 1	0.000	4	5.9	10.5	(-6.5, 18.3)
	CYCLE 16 DAY 1	0.000	2	-3.2	5.4	(-27.4, 21.0)
	CYCLE 17 DAY 1	0.000	2	7.1	3.0	(-6.3, 20.5)

Table 18: Secondary Analysis Results of ΔQRS for LDK378 at doses of 50 mg to 750 mg (Pooling data from Cycle 2 and above)

Treatment	N	Mean	Std Dev	90% CI for Mean
50 mg	2	3.5	3.5	(-12.3, 19.3)
100 mg	3	3.0	5.0	(-5.4, 11.4)
200 mg	50	2.2	5.8	(0.8, 3.6)
300 mg	18	-2.3	2.6	(-3.4, -1.2)
400 mg	91	3.1	5.6	(2.1, 4.1)
500 mg	83	1.2	6.3	(0.0, 2.3)
600 mg	60	2.7	5.8	(1.4, 3.9)
700 mg	45	-3.0	7.7	(-5.0, -1.1)
750 mg	957	1.1	6.8	(0.7, 1.4)

Table 19: Categorical Analysis for QRS

Treatment Group	Total N	QRS < 110 ms	QRS >= 110 ms
50 mg	2	2 (100%)	0 (0.0%)
100 mg	2	2 (100%)	0 (0.0%)
200 mg	3	2 (66.7%)	1 (33.3%)
300 mg	3	3 (100%)	0 (0.0%)
400 mg	14	14 (100%)	0 (0.0%)
500 mg	10	10 (100%)	0 (0.0%)
600 mg	10	10 (100%)	0 (0.0%)
700 mg	5	5 (100%)	0 (0.0%)
750 mg	249	245 (98.4%)	4 (1.6%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

5.3.1 LDK378 Concentration-QTcF Analysis

The relationship between ΔQTcF and LDK378 concentrations was investigated by mixed-effects modeling. The following models were considered:

- Model 1 is a linear model with an intercept;
- Model 2 is a linear/ model with mean intercept fixed to 0 (with variability);
- Model 3 is a linear model with no intercept.
- Model 4 is a nonlinear Emax model

The relationship between Δ QTcF and LDK378 concentrations is visualized in Figure 3 with evident exposure-response relationship. The goodness-of-fit for Model 1 showed the observed (top) and median-quantile concentrations (bottom) and associated mean ΔQTcF (90% CI) together with the mean (90% CI) model- predicted ΔQTcF (black line with shaded grey area). Observed and model-predicted changes in ΔQTcF with the Emax model are shown in Figure 4.

Figure 3: ΔQTcF vs. LDK378 concentration (Linear Model)

BEST AVAILABLE COPY

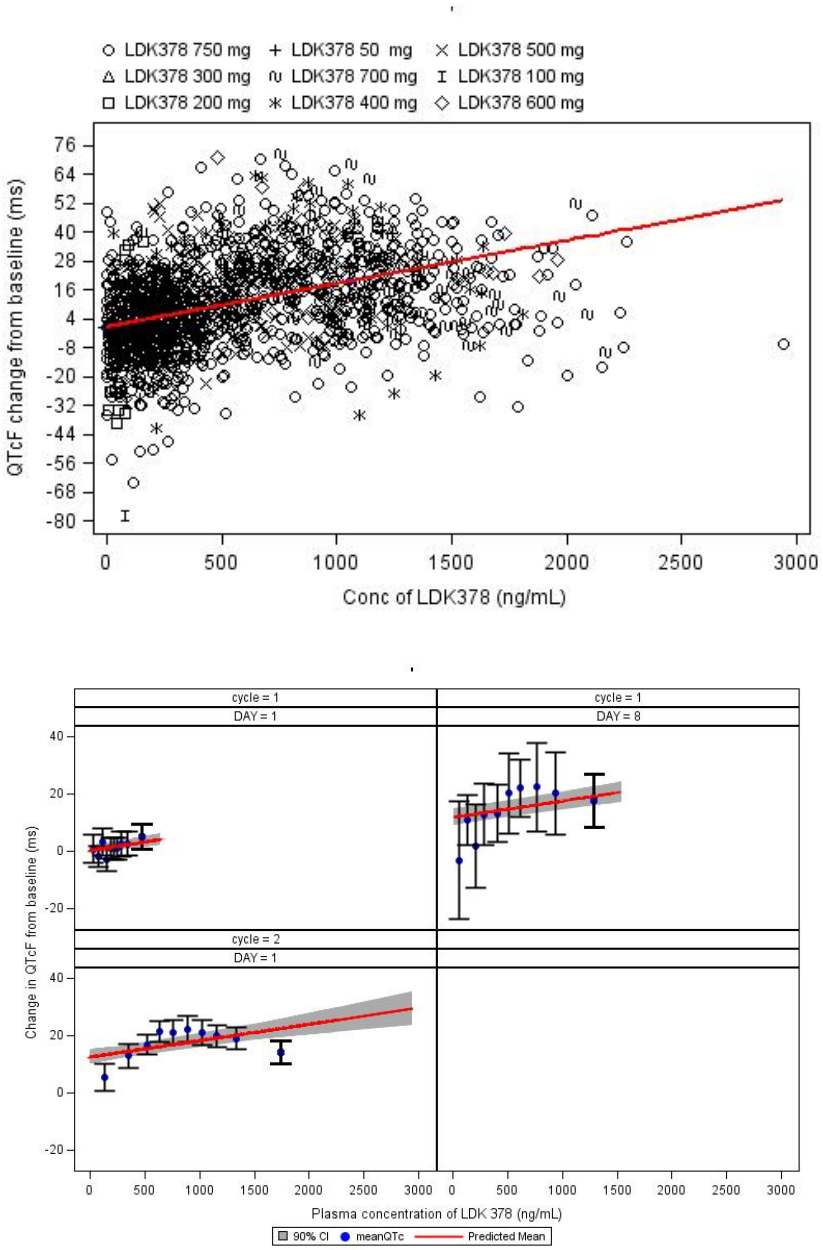
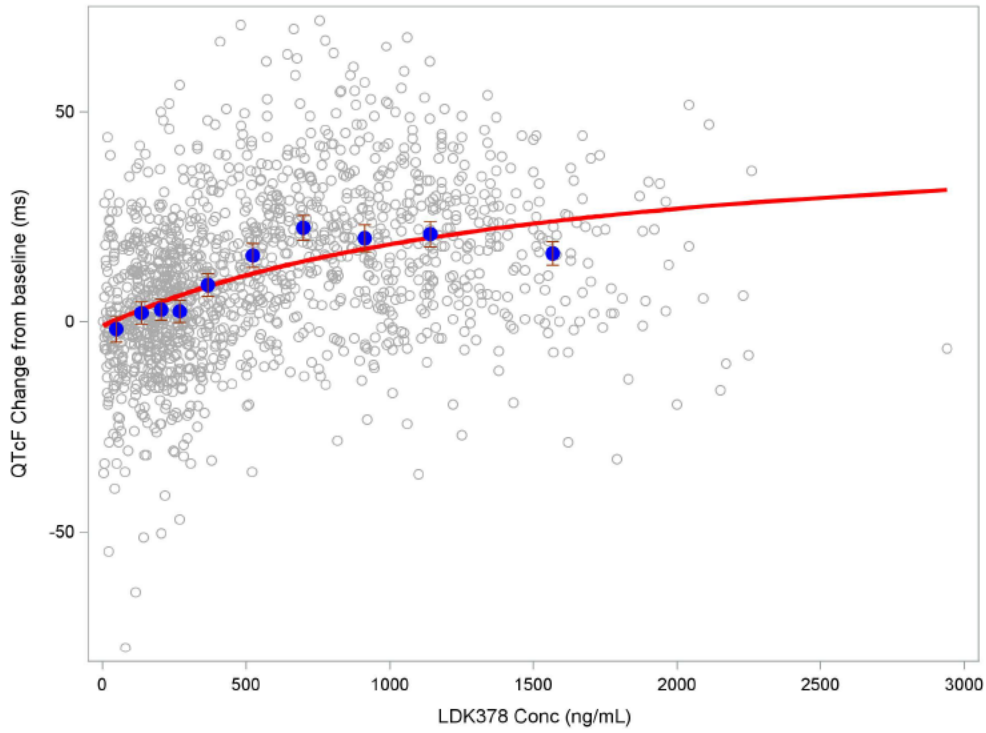


Figure 4: ΔQTcF vs. LDK378 Concentration (Nonlinear Emax model)



Reference ID: 3466661

Table 20 summarizes the results of the LDK378 concentration - QTcF analyses. Model 1 was used for further analysis since the model with intercept was found to fit the data best among the three linear models. Alternatively, a nonlinear Emax model (Model 4) was used to fit the data and to compare results with model 1 because of the appeared plateau at the high exposure end. The predicted ΔQTcF at mean peak LDK378 concentration can be found in Table 21, indicating a QTcF prolongation of approximate 20 ms around the C_{max} at the steady state.

Reference ID: 3466661

Table 20. **Exposure-Response Analysis of LDK378 associated ΔQTcF Prolongation**.

	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: ΔQTcF = Intercept + Cycle+ Day+slope * LDK378 Concentration		
Intercept (ms)	24.0 (19.6, 28.4) <0.0001	10.63
Cycle 1	-12.16(-14.28, -10.04) <0.0001	-
Day 1	-11.46 (-14.3, -8.58) <0.0001	-
Slope (ms per ng/mL)	0.00572 (0.00316; 0.00829) .0003	0.0083
Residual Variability (ms)	12.41	-
Model 4: ΔQTcF = E0 + Emax*+ * LDK378 Concentration/(ec50+ LDK378 *Concentration)		
E0	-1.14 (-1.69,-0.59) 0.0007	
Emax	49.0	-
EC50	1493.9	-

Table 21: Predicted Change of ΔQTcF Interval at Mean Peak LDK368 Concentration using Model 1 and Model 4.

Dose Group	Predicted change in Δ QTcF interval (ms)	
	Model 1 (Linear Model)	Model 4 (Emax Model)
	Mean (90% CI)	Mean (90% CI)
LDK368 750 mg Cycle 1 Day 1		
Mean C_{max} (262 ng/mL)	1.9 (0.4, 3.4)	6.2(5.2; 7.1)
LDK368 750 mg Cycle 1 Day 8		
Mean C_{max} (780 ng/mL)	16.3(13.7; 19.0)	15.7 (14.9; 16.4)
LDK368 750 mg Cycle 2 Day 1		
Mean C_{max} (1100 ng/mL)	18.8 (17.1; 20.6)	19.6(18.5; 20.8)

Reference ID: 3466661

5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

Nevertheless, this drug produces substantial QT prolongation. See our recommended labeling.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics—of the ECGs were annotated in the primary lead--, with less than—of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

This drug prolongs PR and QRS somewhat, but these effects are less clinically relevant than are its effects on QT.

Reference ID: 3466661

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	750 mg daily (taken orally)	
Maximum tolerated dose	750 mg (studied dose)	
Principal adverse events	The most common adverse events (AEs) associated with ceritinib treatment are those related to GI toxicity (nausea, diarrhea, vomiting, decreased appetite, constipation), increases in transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), and fatigue. The majority of AEs were grade 1-2, and AEs were managed with study drug adjustment and/or interruption.	
Maximum dose tested	Single dose	750 mg
	Multiple dose	750 mg daily
Exposures achieved at maximum tested dose	Single dose	Geometric mean (%CV): • Cmax: 186 ng/mL (127%) in patients • AUClast (Tlast is 72 h): 7870 ng*h/mL (127%) in patients
	Multiple dose	Geometric mean (%CV): • Cmax: 1010 ng/mL (44.8%) in patients at steady-state (Cycle 2 Day 1) • AUCtau (tau is 24 h): 22600 ng*h/mL (37.1%) in patients at steady-state (Cycle 2 Day 1)
Range of linear PK	After a single dose in patients, Cmax and AUClast increased dose-proportionally across the full dose range (50 mg to 750 mg) with an estimated slope of 0.97 (90% CI: 0.65–1.29) for Cmax, 1.11 (90% CI: 0.77-1.45) for AUClast, and 0.99 (90% CI: 0.68-1.30) for AUCtau. After multiple doses, pre-dose Cmin on Cycle 2 Day 1 appeared to increase in a greater than dose-proportional manner, with an estimated slope of 1.47 (90% CI: 1.10–1.84).	
Accumulation at steady state	Geometric mean (%CV): 6.20 (58.5%); 750 mg daily in patients	
Metabolites	A total of eleven metabolites were found circulating in plasma at low levels following a single oral dose of 750 mg (mean contribution to the radioactivity AUC was ≤2.3% for each metabolite). Additionally, no single metabolite contributed greater than 5.8% to the plasma radioactivity AUC of any individual subject in the study. By comparison, unchanged ceritinib had a mean contribution of 82% to	

Reference ID: 3466661

	the plasma radioactivity AUC. Due to their low levels in circulation relative to unchanged ceritinib, the metabolites were not tested for pharmacological activity.	
Absorption	Absolute/relative bioavailability	The absolute bioavailability of ceritinib was not determined in clinical studies, but was estimated to be about 40% to 60% in various preclinical species when administered as a solution or suspension under fasted conditions. The lower limit for the extent of ceritinib oral absorption is estimated to be approximately 25% in humans based on the percentage of metabolites recovered in feces.
	Tmax	• Median (range) for parent: 6 h (individual range: 4 to 24 h) at 750 mg after a single-dose in patients; 6 h (individual range: 0 to 23 h) at 750 mg at steady-state (Cycle 2 Day 1) in patients. • Median (range) for metabolites: Not determined as metabolite levels were too low.
Distribution	Vd/F or Vd	Geometric mean (%CV): Vd/F: 4230 L (164%) at 750 mg after a single dose in patients.
	% bound	Mean (%CV): 97.2% (1.75%) bound to plasma protein.
Elimination	Route	• Primary route: The primary route of elimination of ceritinib is via the feces (mean: 91% of an oral dose) with 68% being excreted as unchanged ceritinib and the remainder eliminated as metabolites. Evidence from preclinical studies suggests that hepatic metabolism and potentially biliary excretion and gastrointestinal secretion may all contribute to the fecal elimination of ceritinib. • Other routes: Only 1.3% of the single administered oral dose is recovered in the urine.
	Terminal t1/2	• Geometric mean (%CV) for parent: 40.6 h (34.7%) at 750 mg after a single dose in patients. • Geometric mean (%CV) for metabolites: Not determined as metabolite levels were too low.
	CL/F or CL	Geometric mean (%CV): CL/F: 88.5 L/h (162.5%) at 750 mg after a single dose in patients; 33.2 L/h (37.1%) at 750 mg at steady-state (Cycle 2 Day 1) in patients.
Intrinsic factors	Age	The Cmax and AUCtau at steady state in patients ≥65 years were estimated to be 1.04-fold higher than in the reference population (age <65 years). The age effect was not considered to be clinically relevant.

	Sex	The Cmax and AUCtau at steady state in female patients were estimated to be 1.14-fold higher than in male patients. The gender effect was not considered to be clinically relevant.
	Race	The Cmax and AUC at steady state in Asian patients were estimated to be 1.1-fold higher than in non-Asian patients. The race effect was not considered to be clinically relevant.
	Hepatic and renal impairment	• Hepatic impairment: The Cmax and AUCtau at steady state in patients with mild hepatic impairment (classified based on the NCI-ODWG criteria) were estimated to be similar to those in patients with normal hepatic function (mean fold change: 0.99). However, it should be noted that the population PK analysis was limited by the fact that no data were available for patients with moderate or severe hepatic impairment. Study CLDK378A2110 was initiated to assess the effect of hepatic impairment on the PK of ceritinib in non-cancer patients with varying degrees of impaired hepatic function (mild, moderate, and severe dysfunction) and matched normal hepatic function subjects. • Renal impairment: Patients with mild and moderate renal impairment had a modest, but clinically unimportant increase in systemic exposure of ceritinib as baseline CLcr decreased. The Cmax and AUCtau at steady state in patients with mild or moderate renal impairment were estimated to be 1.10-fold and 1.20-fold higher, respectively, than those in patients with normal renal function.
Extrinsic factors	Drug interactions	CYP3A was identified as the major CYP isozyme responsible for the metabolism of ceritinib. • An inhibition drug-drug interaction (DDI) study conducted in healthy volunteers indicated that ketoconazole (200 mg bid for 14 days), a strong CYP3A inhibitor, increased the Cmax and AUCinf of a single 450 mg oral dose of ceritinib by 1.2-fold and 2.9-fold, respectively, compared with ceritinib alone (Study CLDK378A2104). • An induction DDI study conducted in healthy volunteers indicated that rifampin (600 mg daily for 14 days), a strong CYP3A inducer, decreased the Cmax and AUCinf of a single 750 mg oral dose of ceritinib by 44% and 70%, respectively, compared with ceritinib alone (Study CLDK378A2106).

	Food effects	Compared to the fasted state, a low-fat meal increased Cmax and AUCinf following a single 500 mg oral dose of ceritinib in healthy subjects by 43% and 58%, respectively, whereas a high-fat meal increased Cmax and AUCinf by 41% and 73%, respectively (Study CLDK378A2101).
Expected high clinical exposure scenario	In vitro metabolism studies revealed that ceritinib is a reversible and time dependent inhibitor of CYP3A, and is metabolized mainly by CYP3A. Based on the results of an inhibition DDI study, a strong CYP3A inhibitor, ketoconazole, increased the Cmax and AUCinf of a single 450 mg oral dose of ceritinib by 1.2-fold and 2.9-fold, respectively, compared with ceritinib alone. These results demonstrated that concurrent use of strong CYP3A inhibitors may markedly increase ceritinib exposure and should be avoided. The recommended dose for ceritinib tested in the expansion phase of registration Study CLDK378X2101 was determined to be 750 mg, which is the maximum tolerated dose (MTD) and the highest dose evaluated in clinical studies thus far.	

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

/s/

FANG LI
03/07/2014

JIANG LIU
03/07/2014

MOH JEE NG
03/07/2014

QIANYU DANG
03/07/2014

NORMAN L STOCKBRIDGE
03/08/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 7, 2014

From: Karen Boyd, M.S., DOP2/OHOP/CDER

Subject: NDA 205755: FDA proposed changes to the container labeling

---

Dear Nina,

Please refer to your November 27, 2013, December 12, 2013, and December 24, 2013 rolling submission regarding New Drug Application (NDA) 205755. Please also refer to your December 24, 2013 and February 21, 2014, submissions, which contained your proposed and updated, respectively, commercial supply and physician sample container labels.

FDA requests that you make the following changes to the commercial supply and physician sample container labels:

1. Revise the presentation of the proprietary name so only the first letter in the proprietary name is capitalized. Words written in all-capital letters are less legible than words written in mixed case letters.
2. Relocate the net quantity statement (i.e., 70 capsules) away from the strength statement, such as to the upper right corner or the lower one-third portion of the principal display panel. As currently presented, this statement appears too close to the strength statement and competes in prominence.
3. Increase the font size of the strength statement (i.e., 150 mg) to that same font size of the established name and dosage form to increase the prominence of the strength statement.
4. Revise the storage statement so it matches the wording in the prescribing information "Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F)."

Please submit three versions of the commercial supply container label (one with each of your proposed proprietary names) [redacted] (b) (4) with the requested changes by COB EST on Friday, March 14, 2014, followed by a formal submission to your NDA.

If you have any questions, please let me know.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration

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
03/07/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 205755 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Proposed name unacceptable; new proposed name under review. Established/Proper Name: ceritinib Dosage Form: capsules Strengths: 150 mg		
Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable): N/A		
Date of Application: 12/24/13 Date of Receipt: 12/24/13 Date clock started after UN: N/A		
PDUFA Goal Date: 8/24/14	Action Goal Date (if different): 4/17/14	
Filing Date: 2/22/14	Date of Filing Meeting: 1/21/14	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1 NME		
Proposed indication(s)/Proposed change(s): Treatment of patients with [redacted] (b) (4) metastatic non-small cell lung cancer (NSCLC) who have [redacted] (b) (4) [redacted]		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.*** .		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? No. ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

Reference ID: 3458975

☐ Fast Track Designation ☒ Breakthrough Therapy Designation ☒ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): N/A	
List referenced IND Number(s): IND 109272, (b) (4)	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		Yes, it is included in the 11/27/13 submission

Reference ID: 3458975

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	☐	☒	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐	☒	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

Reference ID: 3458975

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	Yes, they claim marketing exclusivity but do not mention the number of years requested.
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☒	☐	KB confirmed with CMC.
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Kendra Stewart.***	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

Reference ID: 3458975

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		Only 96.06% of clinical investigators responded (122 out of a total of 127) for Study CLDK378X2101 (US). For Study CLDK378X2101 (Non-US) and CLDK378X1101 (Non-US), 100% of the clinical investigators responded. An IR was sent January 22, 2014 requesting

				documentation of due diligence to obtain the missing disclosures and a response from Novartis was received on 1/29/14.
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☐	☒		Form is included but Yanina Gutman, sponsor representative, did not sign this form. It was signed on behalf of Ms. Gutman by a person who is not an authorized official. Request for properly signed form included in the filing letter issued on February 21, 2014.
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	Novartis did include a field copy certification even though it is an electronic submission.
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**

Reference ID: 3458975

For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? Orphan designation. ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☐	☒		Orphan designation
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☐	☒	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☐	☐	☒	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☐	☐	☒	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted?	☐	☐		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

Reference ID: 3458975

If no, request in 74-day letter.				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	QT IRT, OSI, OSE, Pediatric and Maternal Health, OPDP, Patient Labeling, and SEALD consults requested.
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 5/15/13 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 11/22/13, 8/14/13 (content and format WRO Type C meeting) ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

Reference ID: 3458975

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1/21/14

BLA/NDA/Supp #: NDA 205755

PROPRIETARY NAME: Not established yet

ESTABLISHED/PROPER NAME: ceritinib

DOSAGE FORM/STRENGTH: capsules/150 mg

APPLICANT: Novartis Pharmaceuticals Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4)

BACKGROUND: Novartis Pharmaceuticals Corporation submitted their NME application for ceritinib (LDK378) on December 24, 2013 with the following indication statement: treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4) The company requested priority review and approval under subpart H, accelerated approval. NDA 205755 references IND 109272 (b) (4). The majority of the drug development work and background information for this application is referenced under IND 109272. The application was granted Breakthrough Therapy designation on March 6, 2013 and orphan designation on September 27, 2013.

On May 13, 2013, preliminary comments were issued to Novartis in response to Novartis' March 18, 2013 meeting request to obtain FDA guidance on drug substance starting materials and drug substance and drug product stability data for the NDA submission for the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4) crizotinib. After receipt of FDA's comments, Novartis elected to cancel the meeting.

On May 15, 2013, an End-of-Phase 2 meeting was held to discuss the clinical development program of LDK378 in previously untreated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive. The protocols discussed during the meeting was Protocol CLDK378A2301, an open-label, randomized, active-controlled, multi-center, active-controlled, phase III trial in 348 previously untreated adult patients with ALK-positive, stage IIIB or IV, non-squamous NSCLC and Protocol CLDK378A2304, an open-label, randomized, active-controlled, multi-center, phase III study comparing the efficacy and safety of single-agent LDK378 versus crizotinib.

On May 20, 2013, FDA issued Written Responses to Novartis in response to Novartis' February 22, 2013 meeting request. The purpose of the meeting was to discuss the content and format of the NDA submission for LDK378 in the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4)

Reference ID: 3458975

crizotinib.

On November 22, 2013, a pre-NDA meeting was held with Novartis Pharmaceuticals Corporation to discuss the content of the NDA and content and format of the Safety and Efficacy Update. As a result of this meeting, Novartis agreed to submit a safety and efficacy update, which includes data up to the October 31, 2013 cut-off date and an updated version of the PI, within 60 days of the submission date. This application was submitted as a rolling review. Part 1 submitted November 27, 2013 contained pharmacology written summary and tabular reports in module 2, all module 4 documents with the exception of three embryo-fetal development reports, and reports of hepatic metabolism and drug interaction studies in module 5. Part 2 submitted December 12, 2013 contained three embryo-fetal development reports and Office of Scientific Investigation general study-related information, comprehensive clinical investigator information, and subject level data listings by site. Part 3 submitted December 24, 2013 completed the submission and started the review clock.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Karen Boyd	Y
	CPMS/TL:	Karen Jones	Y
Cross-Discipline Team Leader (CDTL)	Gideon Blumenthal		Y
Clinical	Reviewer:	Sean Khozin	Y
	TL:	Gideon Blumenthal	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Reference ID: 3458975

Clinical Pharmacology	Reviewer:	Ruby Leong	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:	Lijun Zhang	Y
	TL:	Shenghui Tang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Margaret Brower Emily Fox	Y Y
	TL:	Whitney Helms	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Jean Tang, Drug Product Donghao Lu, Drug Safety	Y Y
	TL:	Liang Zhou	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Jessica Cole	Y
	TL:	Bryan Riley	Y
CMC Labeling Review	Reviewer:	Jean Tang Donghao Lu	Y Y
	TL:	Liang Zhou	Y
Facility Review/Inspection	Reviewer:	Robert Wittorf	Y
	TL:	Mahesh Ramanadham	N
OSE/DMEPA (proprietary name)	Reviewer:	Otto Townsend	Y
	TL:	Alice Tu	Y
OSE/DRISK (REMS)	Reviewer:	Naomi Redd	Y
	TL:	Cynthia LaCivita	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Reference ID: 3458975

Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connor	Y
	TL:	Janice Pohlman	Y
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers Biopharmaceutics Pharmacometrics Pharmacometrics (TL) OPDP Maternal Health Patient Labeling OSE-Safety RPM ONDQA—Quality RPM		Okpo Eradiri Pengfei Song Qi Liu Quynh-Van Tran Miriam Dinatale Morgan Walker Kevin Wright Jewell Martin	Y Y Y Y Y Y Y Y
Other attendees		Richard Pazdur Patricia Keegan Joseph Gootenberg Ali Al Hakim Kate Gelperin Afrouz Nayernama Peter Waldron Tracy Salaam Rosane Charlab-Orbach	Y Y Y Y Y Y Y Y Y

FILING MEETING DISCUSSION:

GENERAL	
• 505(b)(2) filing issues:	☒ Not Applicable
o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☐ YES ☐ NO
Describe the scientific bridge (e.g., BA/BE studies):	
• Per reviewers, are all parts in English or English translation?	☒ YES ☐ NO

Reference ID: 3458975

If no, explain:	
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: • This drug is not first in its class. • The clinical study design was acceptable
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE

Reference ID: 3458975

Comments:	☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 7 4-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products)	☐ Not Applicable

Reference ID: 3458975

• Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☒ YES ☐ NO ☒ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	As agreed in the pre-NDA meeting, the safety and efficacy updates will arrive by February 25, 2014.

Reference ID: 3458975

• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Richard Pazdur, MD

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): February 25, 2014

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product

Reference ID: 3458975

	classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Reference ID: 3458975

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
02/21/2014

KAREN D JONES
02/21/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 205755

Application Type: New NDA

Name of Drug/Dosage Form: ceritinib capsules, 150 mg

Applicant: Novartis Pharmaceuticals Corporation

Receipt Date: 12/24/13

Goal Date: 8/24/14

1. Regulatory History and Applicant's Main Proposals

Novartis Pharmaceuticals Corporation submitted their NME application for ceritinib (LDK378) on December 24, 2013 with the following indication statement: treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4) The company requested priority review and approval under subpart H, accelerated approval. NDA 205755 references IND 109272 (b) (4). The majority of the drug development work and background information for this application is referenced under IND 109272. The application was granted Breakthrough Therapy designation on March 6, 2013 and orphan designation on September 27, 2013.

On May 13, 2013, preliminary comments were issued to Novartis in response to Novartis' March 18, 2013 meeting request to obtain FDA guidance on drug substance starting materials and drug substance and drug product stability data for the NDA submission for the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4) crizotinib. After receipt of FDA's comments, Novartis elected to cancel the meeting.

On May 15, 2013, an End-of-Phase 2 meeting was held to discuss the clinical development program of LDK378 in previously untreated patients with (b) (4) metastatic nonsmall cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive. The protocols discussed during the meeting was Protocol CLDK378A2301, an open-label, randomized, active-controlled, multi-center, active-controlled, phase III trial in 348 previously untreated adult patients with ALK-positive, stage IIIB or IV, non-squamous NSCLC and Protocol CLDK378A2304, an open-label, randomized, active-controlled, multi-center, phase III study comparing the efficacy and safety of single-agent LDK378 versus crizotinib.

On May 20, 2013, FDA issued Written Responses to Novartis in response to Novartis' February 22, 2013 meeting request. The purpose of the meeting was to discuss the content and format of the NDA submission for LDK378 in the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4) crizotinib.

On November 22, 2013, a pre-NDA meeting was held with Novartis Pharmaceuticals Corporation to discuss the content of the NDA and content and format of the Safety and Efficacy Update. As a result of this meeting, Novartis agreed to submit a safety and efficacy update, which includes data up to the October 31, 2013 cut-off date and an updated version of the PI, within 60 days of the submission date. This application was

submitted as a rolling review. Part 1 submitted November 27, 2013 contained pharmacology written summary and tabular reports in module 2, all module 4 documents with the exception of three embryo-fetal development reports, and reports of hepatic metabolism and drug interaction studies in module 5. Part 2 submitted December 12, 2013 contained three embryo-fetal development reports and office of scientific investigation general study-related information and comprehensive clinical investigator information and subject level data listings by site. Part 3 submitted December 24, 2013 completed the submission and started the review clock.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI were conveyed to the applicant in the January 31, 2014, FDA correspondence with the sponsor that included initial FDA edits to Novartis' proposed labeling. The applicant was asked to correct these deficiencies and resubmit the PI in Word format by February 19, 2014. The resubmitted PI will be used for further labeling review.

Reference ID: 3448629

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

NO 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *Headings bolded but the horizontal line does not extend the width of the column.*

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between

Reference ID: 3448629

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *There is white space between the HL Heading and HL Limitation Statement*

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Reference ID: 3448629

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES

Reference ID: 3448629

19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

NO 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *Drug interactions (7.1, 7.2, 7.3) --first letter of prepositions (that, may, be, by) are capitalized.*

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Reference ID: 3448629

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment:

Reference ID: 3448629

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Reference ID: 3448629

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

Reference ID: 3448629

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
02/05/2014

KAREN D JONES
02/07/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 4, 2014
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 205755
Product Name and Strength:	Ceritinib Capsules, 150 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
Submission Date:	December 24, 2013
OSE RCM #:	2014-72
DMEPA Primary Reviewer:	Otto L. Townsend, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

Reference ID: 3447594

1. REASON FOR REVIEW

This review is written in response to a consult from DOP2 requesting DMEPA to assess the proposed prescribing information and container labels for areas of vulnerability that could lead to medication errors.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
ISMP Newsletters	C (N/A)
Previous DMEPA Reviews	D (N/A)
Human Factors Study (if applicable)	E (N/A)
Other (if applicable)	F (N/A)
Container Label, Carton Labeling, and Instructions for Use or Medication Guide (if applicable)	G

N/A=not applicable for this review

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We identified the following areas of vulnerability to error:

- The use of all capital letters to present the proprietary name decreases readability.
- Close proximity of the net quantity statement (i.e., (b) (4) and 70 capsules) to the strength statement (i.e., 150 mg).
- Use of the phrases, (b) (4)

Reference ID: 3447594

4. CONCLUSION & RECOMMENDATIONS

We conclude that the proposed labels can be improved to increase readability and prominence of important information on the label to promote the safe use of the product and to clarify information.

4.1 COMMENTS TO THE DIVISION

Prescribing Information:

1. In the Dosing and Administration Section's Dose Modification Table (Table 1), replace all instances of the statement, [redacted] with the statement, [redacted] 150 mg' and replace all instances of the statement, [redacted] to [redacted] 300 mg'. This more clearly guides the prescriber in dose reduction.

4.2 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR

Please note that the proposed proprietary name [redacted] has not been granted, but our recommendations below are still applicable to the display of the proprietary name.

Commercial supply [redacted] container labels:

1. Revise the presentation of the proprietary name so only the first letter in the proprietary name is capitalized. Words written in all-capital letters are less legible than words written in mixed case letters.[1]

2. Relocate the net quantity statement (i.e., 70 capsules) away from the strength statement, such as to the upper right corner or the lower one-third portion of the principal display panel. As currently presented, this statement appears too close to the strength statement and competes in prominence.

3. Increase the font size of the strength statement (i.e., 150 mg) to that same font size of the established name and dosage form to increase the prominence of the strength statement.

4. Revise the storage statement so it matches the wording in the prescribing information "Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F)."

[1] Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance). April 2013.

Reference ID: 3447594

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ceritinib that Novartis submitted on December 24, 2013.

Table 2. Relevant Product Information for Ceritinib	
Active Ingredient	Ceritinib
Indication	Treatment of patients with (b) (4) metastatic non-small lung cancer (NSCLC) who have (b) (4)
Route of Administration	Oral
Dosage Form	Capsule
Strength	150 mg
Dose and Frequency	750 mg (5 x 150 mg capsules) once daily
How Supplied	High-density polyethylene (HDPE) bottles containing 70 capsules for commercial use and (b) (4)
Storage	Store at 25°C (77°C); excursions permitted between 15°C and 30°C (59°F to 86°F).

APPENDIX G. CONTAINER LABEL, CARTON LABELING, INSTRUCTIONS FOR USE, MEDICATION GUIDE

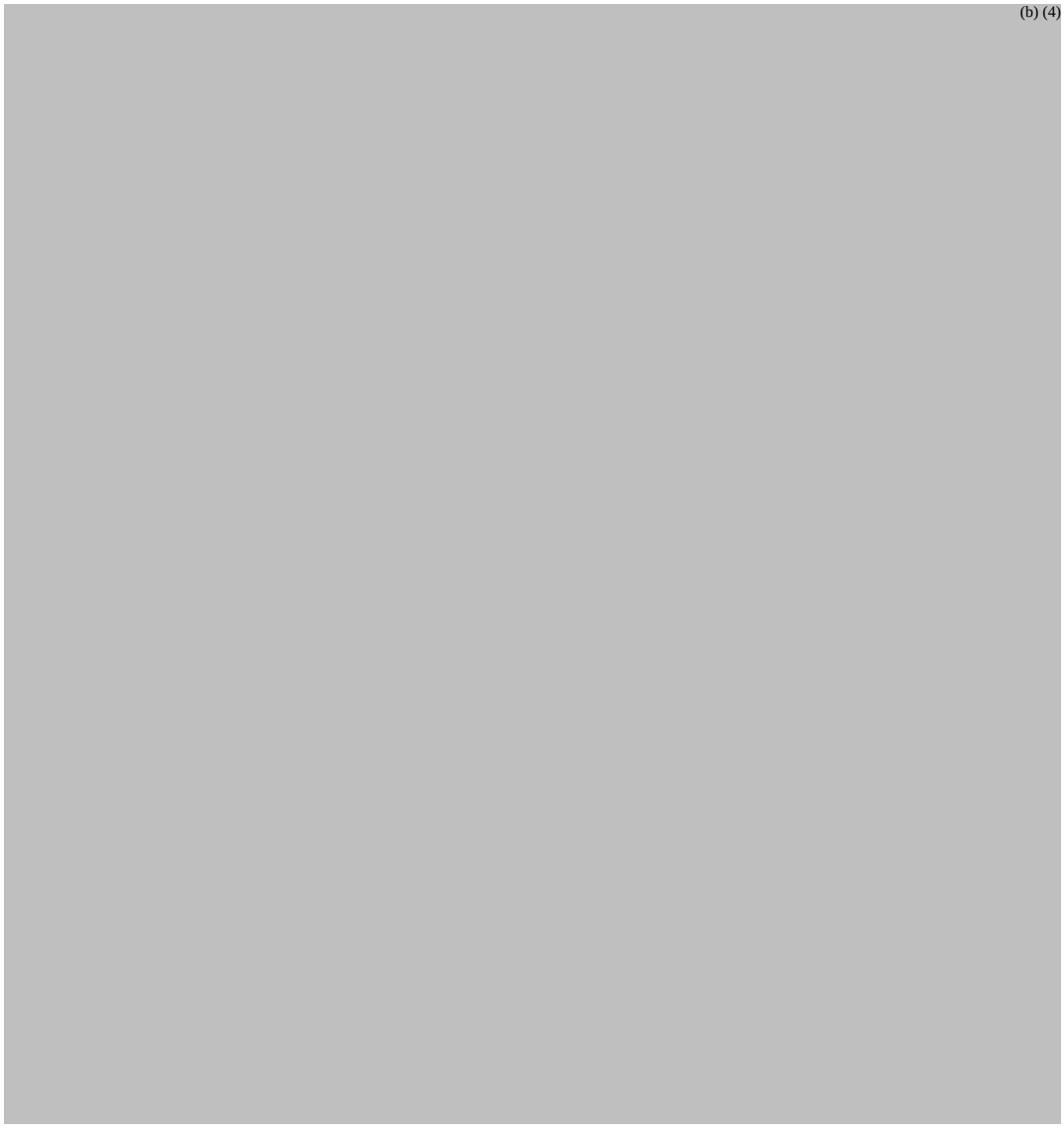
G.1 List of Label and Labeling Reviewed

We reviewed the following Ceritinib labels and labeling submitted by Novartis on December 24, 2013.

- Container labels
- Full Prescribing Information

G.2 Label and Labeling Images

(b) (4)



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

/s/

OTTO L TOWNSEND
02/04/2014

CHI-MING TU
02/04/2014