CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208772Orig1s000

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 # 208772, ALUNBRIG (brigatinib)
Product Name:

PMR/PMC Description: Hepatic Impairment Pharmacokinetic Study

PMR/PMC Schedule Milestones:

Final Protocol Submission:	Submitted
Study/Trial Completion:	03/31/2017
Final Report Submission:	09/30/2017
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

The mass balance study suggests that hepatic elimination is the major route of elimination for brigatinib. Patients with hepatic impairment may have higher brigatinib systemic exposures than patients with normal hepatic function, which may lead to more toxicities. We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of excessive drug toxicity from impaired hepatic function on the pharmacokinetics of brigatinib.

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 an appropriate brigatinib dose in patients with moderate to severe hepatic impairment.

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 clinical pharmacokinetic trial to determine an appropriate dose of brigatinib to minimize toxicity in patients with hepatic impairment. Design and conduct the trial 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)

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.*

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(signature line for NDAs)

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 # 208772, ALUNBRIG (brigatinib)
Product Name:

PMR/PMC Description: Renal Impairment Pharmacokinetic Study

PMR/PMC Schedule Milestones:

Final Protocol Submission:	Submitted
Study/Trial Completion:	09/30/2017
Final Report Submission:	06/30/2018
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 renal excretion is an important route of elimination for brigatinib. Patients with severe renal impairment may have higher brigatinib systemic exposures than patients with normal renal function, which may lead to more toxicities. We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of excessive drug toxicity from impaired renal function on the pharmacokinetics of brigatinib.

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 an appropriate brigatinib dose in patients with severe renal impairment.

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 clinical pharmacokinetic trial to determine an appropriate dose of brigatinib to minimize toxicity in patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal 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)

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.*

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(signature line for NDAs)

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 # 208772, ALUNBRIG (brigatinib)
Product Name:

PMR/PMC Description: Drug-Drug Interaction Trial

PMR/PMC Schedule Milestones:

Final Protocol Submission:	12/31/2017
Study/Trial Completion:	12/31/2019
Final Report Submission:	06/30/2020
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

Brigatinib may induce CYP3A at clinically relevant concentrations based on the human hepatocytes and PXR activation in vitro studies. Brigatinib may decrease exposures of concomitant CYP3A4 sensitive substrates and CYP3A4 substrates with a narrow therapeutic index.

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 brigatinib with regards to concomitant CYP3A4 sensitive substrates and CYP3A4 substrates with a narrow therapeutic index.

3. If the study/clinical trial is a **PMR**, check the applicable regulation. (Not applicable, **PMC**)
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 brigatinib on the single dose pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) to assess the magnitude of decreased drug exposures of a sensitive CYP3A4 substrate and to determine appropriate dosing recommendations. Design and conduct the trial 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)

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.*

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(signature line for NDAs)

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 # 208772, ALUNBRIG (brigatinib)
Product Name:

PMR/PMC Description: Drug-Drug Interaction Assessment

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	06/30/2017
	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

Coadministration of a strong CYP3A4 inhibitor increased brigatinib exposure by two-fold. Given the magnitude of change with a strong CYP3A4 inhibitor, a moderate CYP3A4 inhibitor may also increase brigatinib systemic exposures and 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 drug-drug interaction assessment is to determine how to dose brigatinib in patients requiring concomitant use of a moderate CYP3A4 inhibitor.

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 physiologically-based pharmacokinetic modeling study to evaluate the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose pharmacokinetics of brigatinib to address the potential for excessive drug toxicity.

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.*

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(signature line for NDAs)

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 # 208772, ALUNBRIG (brigatinib)
Product Name:

PMR/PMC Description: Drug-Drug Interaction Assessment

PMR/PMC Schedule Milestones:

Final Protocol Submission:	N/A
Study/Trial Completion:	N/A
Final Report Submission:	06/30/2017
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

Coadministration of a strong CYP3A4 inducer decreased brigatinib exposure by 80%. Given the magnitude of change with a strong CYP3A4 inducer, a moderate CYP3A4 inducer may also decrease brigatinib systemic exposures and therefore requires 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 drug-drug interaction assessment is to determine how to dose brigatinib in patients requiring concomitant use of a moderate CYP3A4 inducer.

3. If the study/clinical trial is a **PMR**, check the applicable regulation. (Not applicable, **PMC**)
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 physiologically-based pharmacokinetic modeling study to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of brigatinib to assess the magnitude of decreased drug exposure and to determine appropriate dosing 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)

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.*

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(signature line for NDAs)

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
04/27/2017

HONG ZHAO
04/27/2017
I concur.

JEFFERY L SUMMERS
04/27/2017

PMR/PMC Development Template

NDA/BLA # NDA 208772
Product Name: Brigatinib

PMR/PMC Description: Conduct and submit the results of at least one multicenter, randomized clinical trial that verifies and describes the clinical benefit of brigatinib in patients with metastatic anaplastic lymphoma kinase positive non-small cell lung cancer (NSCLC).

PMR/PMC Schedule Milestones:

Final Protocol Submission:	11/15/2015
Study/Trial Completion:	3/31/2020
Final Report Submission:	12/31/2020
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

Brigatinib is being approved under the accelerated approval program for the treatment of ALK-positive NSCLC and thus the confirmatory randomized trial is not required for the initial approval. This PMR consists of the confirmatory randomized clinical trial.

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 purpose of the randomized clinical trial is to verify and describe the clinical benefit of brigatinib in patients with ALK-positive NSCLC. This is not a FDAAA PMR.

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

Which regulation?

- [x] 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.

5. The purpose of the randomized clinical trial is to verify and describe the clinical benefit of brigatinib to demonstrate the superiority of brigatinib over available therapy in patients with ALK-positive NSCLC. The study is currently ongoing and may serve as the basis to seek traditional approval.

Required

- [ ] Observational pharmacoepidemiologic study
- [ ] Registry studies
- [x] 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

_____

6. 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

---

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.*

_____

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/s/

MARGIT N HORIBA
03/30/2017

STEVEN J LEMERY
03/30/2017

JEFFERY L SUMMERS
04/07/2017

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 # NDA 208772
Product Name: Brigatinib

PMR/PMC Description: Submit the final analysis of intracranial response duration based upon independent radiology reviewer assessment of imaging data collected for two years following the date of enrollment of the last patient in Study AP26113-13-201.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	n/a
Study/Trial Completion:	9/30/2017
Final Report Submission:	3/31/18
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

Brigatinib is being approved under the accelerated approval program for the treatment of ALK-positive NSCLC. Intracranial response is a secondary endpoint of a clinical trial which is ongoing.

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."

Long-term follow-up of the applicant's ongoing trial will permit better characterization of the intracranial duration of response.

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.

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

Longer follow-up will permit a better characterization of the duration of response.

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

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.*

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/s/

LEAH S HER
03/13/2017

MARGIT N HORIBA
03/21/2017

STEVEN J LEMERY
03/21/2017

JEFFERY L SUMMERS
03/21/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	February 15, 2017
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 208772
Product Name and Strength:	Alunbrig (brigatinib) Tablets, 30 mg and 90 mg
Submission Date:	January 27, 2017
Applicant/Sponsor Name:	Ariad Pharmaceuticals Inc.
OSE RCM #:	2016-1965-1
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Oncology Product 2 (DOP2) requested that we review the revised container labels and carton labeling for Alunbrig (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling for Alunbrig are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Stewart J. Label and Labeling Review for Alunbrig (NDA 208772). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 JAN 06. 14 p. OSE RCM No.: 2016-1965.

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/s/

JANINE A STEWART
02/15/2017

CHI-MING TU
02/15/2017

Clinical Inspection Summary

Date	February 7, 2017
From	Lauren Iacono-Connors, Reviewer Division of Clinical Compliance Evaluation (DCCE) Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H, Branch Chief
To	Leah Her, Regulatory Project Manager M. Naomi Horiba, Clinical Reviewer Division of Oncology Products 2
NDA #	208772
Applicant	Ariad Pharmaceuticals, Inc.
Drug	Alunbrig™ (Brigatinib)
NME	Yes
Therapeutic Classification	Priority
Proposed Indication	Alunbrig™ is a kinase inhibitor indicated 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.
Consultation Request Date	September 15, 2016
Summary Goal Date	Extended to February 10, 2017 (original due date: January 27, 2017)
Action Goal Date	April 28, 2017
PDUFA Date	April 29, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study AP26113-13-201 were submitted to the Agency in support of NDA 208772. Four clinical sites, Dr. David Ross Camidge (Site 15), Dr. Karen Reckamp (Site 9), Dr. Dong-Wan Kim (Site 915), Dr. Sang-We Kim (Site 917), the study sponsor, Ariad Pharmaceuticals, Inc., and one CRO [(b) (4).], who performed the independent radiology central (IRC) review for confirmation of Objective Response (OR), were selected for audit.

The primary efficacy endpoint, objective response rate (ORR) as determined by the clinical investigators, was verified with the source records generated at the inspected clinical sites. There were no significant inspectional findings for clinical investigators Dr. David Ross Camidge, Dr. Karen Reckamp, Dr. Dong-Wan Kim, Dr. Sang-We Kim, and the study sponsor Ariad Pharmaceuticals, Inc. The primary efficacy endpoint, objective response rate (ORR) as determined by the IRC review vendor, (b) (4) could not be verified because a substantial amount of the study data timepoints were re-read/changed (1055 out of a total of 2663 reads) by the radiology readers to previously signed and locked imaging

assessments for Study AP26113-13-201. OSI cannot make a recommendation on data reliability from this vendor and suggests that the review division request the sponsor, Ariad, submit additional information on the data time point re-reads and/or changes so that a determination can be made regarding the impact of those changes on study outcomes.

II. BACKGROUND

Ariad seeks approval of Brigatinib (AP26113) 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 request is based on the results from primarily Study AP26113-13-201.

(b) (4) the IRC vendor, was contracted by Ariad, to perform time-point imaging assessments, per RECIST 1.1, in accordance with Study AP26113-13-201 pre-specified efficacy outcome measures including objective response; achievement of Complete Response (CR) or Partial Response (PR). Key services/responsibilities for the IRC vendor included but were not limited to development and distribution of a Site Procedural Manual to all clinical sites, clinical site evaluation to determine capability with protocol, equipment, software, and personnel qualifications, to collect and perform quality assurance (QA) for all subject time points for both RESCIST 1.1 and Brain MRI assessments, to use validated computerized systems compliant with 21 CFR Part 11 for image handling and assessments, and to support radiology reviewer training. (b) (4) also developed a protocol-specific Charter for imaging services and an Independent Review Manual (IRM) for the independent reviewers. (b) (4) was to archive imaging data to a unique and protocol-specific clinical image management data repository that is 21 CFR Part II compliant. (b) (4) was to develop a database to manage and archive image data for Study AP26113-13-201.

Study AP26113-13-201 is a Phase 2, open-label, randomized, multicenter, international study entitled, "A Randomized Phase 2 Study of AP26113 in Patients with ALK-positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated with Crizotinib." The study randomized 222 subjects at 71 clinical centers in North America, Europe, Australia and Asia.

Study Period: Study initiation date (first subject randomized): June 4, 2014
Date of last subject randomized: September 21, 2015
Data cut-off date for analysis (data extraction date): February 29, 2016
IRC-assessed data (data extraction date): May 31, 2016

Primary efficacy endpoint: objective response rate (ORR); the proportion of subjects with a best response of Complete Response (CR) or Partial Response (PR) using RECIST v1.1 as assessed by the Investigator and the IRC, (b) (4) as confirmatory.

Objectives of Inspections:

a. Verify best confirmed response of CR or PR as assessed by the investigator using RECIST Version 1.1.
b. Identification, documentation, and reporting of adverse events (AEs) for a sample of enrolled subjects.
c. General compliance with the investigational plan.

III. RESULTS (by site):

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI#1: David Ross Camidge (Site 15) University of Colorado Cancer Center 1665 Aurora Court, Room 3200 Aurora, CO 80045	Protocol: AP26113-13-201 Subjects: 11	October 20-24, 2016	Preliminary Classification NAI
CI#2: Karen Reckamp (Site 9) City of Hope 1500 E. Duarte Rd. Duarte, CA 91010	Protocol: AP26113-13-201 Subjects: 7	November 9-18, 2016	Preliminary Classification NAI
CI#3: Dong-Wan Kim (Site 915) Seoul National University Hospital/Department of Internal Medicine 101 Daehang-ro, Jongno-gu Seoul, NA 110-744 Korea	Protocol: AP26113-13-201 Subjects: 24	November 14-18, 2016	Preliminary Classification VAI
CI#4: Sang-We Kim (Site 917) Asan Medical Center, Department of Oncology 88, Olympic-ro, 43-gil, Songpa-gu Seoul, NA 138-736 Korea	Protocol: AP26113-13-201 Subjects: 7	November 7-11, 2016	Preliminary Classification NAI
Sponsor: Ariad Pharmaceuticals, Inc. 26 Landsdowne St. Cambridge MA 02139	Protocol: AP26113-13-201 Site Numbers: 9, 15, 915, and 917	November 29, 2016 – December 2, 2016	Preliminary Classification NAI
(b) (4)	Protocol: AP26113-13-201 Site Numbers: 9, 15, 915 and 917	(b) (4)	Preliminary Classification VAI

Key to Compliance 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. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. David Ross Camidge, M.D. (Site 15)

The site screened and enrolled 11 subjects. A complete record review was done for all subjects. Study subject source documents/records were compared to the eCRF and data listings submitted to NDA 208772, focusing on inclusion/exclusion criteria compliance, adverse events, randomization, and efficacy endpoint verification. The primary efficacy endpoint, ORR per the investigator, was verifiable. There was no evidence of under-reporting AEs; however, there were a few instances where the site did not report the AEs within the protocol-specified timeframe. This was discussed with the site during the inspection and no Form FDA 483 was issued. The discussion item should not importantly impact study outcomes or have placed the subjects at undue risk.

The data from Site 15, associated with Study AP26113-13-201 appear reliable.

2. Dr. Karen Reckamp, M.D. (Site 9)

The site screened eight subjects and enrolled seven subjects. At the time of this inspection three subjects had completed the study. A complete record review was done for all enrolled subjects.

The inspection revealed no significant deficiencies. With one exception, the primary efficacy endpoint, confirmed ORR per the investigator, was verifiable with the source records generated at the site. Briefly, there was a discrepancy between the data listings submitted to the application to support the conduct of clinical inspections and the source documents at the site for one subject. Subject 009007 had a confirmed PR as recorded in the source document and the eCRF. However, the datalistings submitted to the application to support clinical site inspections indicate the confirmed Best Response was Stable Disease (SD).

OSI Reviewer Note: It appears that the subject datalistings by site, entitled, "BIMO SUBJECT LEVEL LINE LISTING - BY SITE (AP26113-13-201)", submitted, as part of the OSI/BIMO program request, was incomplete and incorrect for this subject. There were no other study-related datalisting discrepancies for Subject 009007 or any other subject enrolled at this site. It should be noted that the datalistings included in the Clinical Study Report, Appendix 16.2.6, Individual Efficacy Response Data, includes both the Individual Investigator-assessed and the IRC-Assessed systemic efficacy response for this subject; both of which recorded Subject 009007 Best Response as PR. The datalistings included in the CSR are consistent with Subject 009007 source documents and eCRF reviewed at this clinical site. The inspectional observation does not impact study outcomes or subject safety.

There was no evidence of under-reporting of AEs.

The data from Site 9, associated with Study AP26113-13-201, appear reliable.

3. Dr. Dong-Wan Kim (Site 915)

The site screened 27 subjects and enrolled 24 subjects. At the time of this inspection nine subjects had completed the study. A complete record review was done for 12 subjects. The inspection included assessments of primary efficacy data, adverse events, serious adverse events, IRB approval, IRB continuing review, monitoring, test article accountability, randomization, test article administration, delegation of authority, informed consent form utilization, subject follow-up, and Quality of Life (QoL) survey.

The inspection revealed no significant deficiencies. The primary efficacy endpoint, confirmed ORR per the investigator, was verifiable with the source records generated at the site. However, there were several inspectional observations and a Form FDA 483 was issued. The FDA field investigator noted that the delegation of authority log was not always followed by the study team in the conduct of the study. For example, based upon the documentation of AE evaluation and entry criteria it appeared that a study coordinator completed these tasks instead of Dr. Kim (PI) or one of the sub-investigators (sub-PI) assigned to this task. In a written response to the Form FDA 483 inspectional observations, dated December 2, 2016, Dr. Kim stated that all medical evaluations and decisions on AEs and entry criteria were performed by either the PI or a sub-PI and that the study coordinator's role was limited to describing basic study information, such as a laboratory test value, concomitant medications and to write down the dictation of the PI/sub-PIs evaluation onto a visit worksheet. Dr. Kim also stated that the content of the study visit worksheet was reviewed and confirmed by the PI/sub-PI by signing off on the worksheet. Dr. Kim committed to making process improvements to documentation procedures to minimize misinterpretations of study information sources moving forward.

Not all AEs found in the source documents were accurately reported in the case report forms. For example, Subject 003 reported on their patient diary card (PDC), pain in the hand on September 25, 2015 and on October 2, 2015, and pain in the arm on October 9 and 16, 2015. These AEs were not documented in the subjects EMR or eCRF. Dr. Kim stated, in his written response dated December 2, 2016, that during the study visit the subject told a sub-PI that the hand pain was "very subtle" but that the leg and feet pain were "bothersome". The sub-PI assessed the hand pain as not clinically significant (NCS) and did not document it as an AE, but instead documented the leg and foot pain appropriately as AEs (parenthesis in both leg and foot) in both the visit worksheet and the eCRF. Dr. Kim has since updated the eCRF for this subject to reflect these AEs, and has revised their processes for reviewing information documented in the patient diary cards to be properly documented. These unreported AEs should not importantly impact overall study outcomes or have placed the subject at risk.

Finally, the FDA field investigator was not able to copy Electronic Medical Records (EMR) in audit trail mode. The current EMR system used at the site is designed to access the audit trail only on screen/PC monitor, and is not able to copy and/or print the medical records' audit trail as hard copy. This was listed as an inspectional observation, specifically; failure to

permit an authorized office or employee of FDA to copy records or reports. The audit trail in the EMR was accessible and reviewed during the inspection. The issue was that the system did not support printing or copying records viewed in audit trail mode. This inspectional observation should not have any impact on study outcome or subject safety. Dr. Kim informed in his written response to the Form FDA 483, that the hospital is in the process of improving the EMR system to be able to copy/print EMRs with audit trails on demand.

The data from Site 915, associated with Study AP26113-13-201, appear reliable.

4. Dr. Sang-We Kim (Site 917)

The site screened and enrolled seven subjects. At the time of this inspection six subjects had completed the study. A complete record review was done for all seven subjects. The inspection included assessments of primary efficacy data, adverse events, serious adverse events, IRB approval, IRB continuing review, monitoring, test article accountability, randomization, test article administration, delegation of authority, informed consent form utilization, subject follow-up, and Quality of Life (QoL) survey.

The inspection revealed no significant deficiencies. The primary efficacy endpoint, ORR per the investigator, was verifiable. There was no evidence of under-reporting AEs.

The data from Site 917, associated with Study AP26113-13-201 appear reliable.

5. CRO: (b) (4) (Independent Review Center for Image assessment)

This inspection was issued to review the conduct of one clinical study (AP26113-13-201), performed in support of NDA 208772. The inspection covered quality assurance, quality control, blinding of reviewers, process flows, organizational responsibilities, operating procedures for imaging, training, system validations, correspondence between CRO, sponsor, clinical sites, subject data points, protocol deviations, storage of data, work orders and service agreements, and compliance with the Imaging Service Review Charter [charter]. The inspection specifically assessed tumor response per RECIST1.1 criteria per the CRO, secondary efficacy endpoints, and overall tumor response for four sites totaling 52 subjects.

There was evidence that the CRO did not always comply with the charter. The inspection found that out of 2663 timepoints reviewed by the readers, there have been 1055 (40% of all time point reads) rereads and/or changes made by the readers to previously signed imaging assessments. The CRO used a commercially available software package, initially Core Lab in a Box (CLIB), then switched to Mint Lesion software after the study initiated, to support imaging acquisition, management and assessments via web based portal. Although the charter contains acceptable circumstances for data changes, the reasons for the data changes in the audit trail were vague and not attributable or accurate. The audit trail did not include the origin of the requesting entity for data point changes/rereads or date of the change request or the

charter-pre-specified reasons for the changes. All data changes were categorized as "erroneous or incomplete lesion classification, measurement or diagnosis" in the software system. The charter specifies the reasons why data changes may be necessary to previously signed off readings. The charter, "Section 5.9, Additional Review Post-Review", states that instances may occur where the CRO may need to re-review cases where an independent reviewer already conducted an initial independent review. Also, quality assurance checks for incoming data/media from clinical sites were required by the charter to be conducted within 2 days of receiving the data. Of the 2663 timepoints reviewed by the CRO/readers, 774 time point media/imaging were quality reviewed five or more days after receipt. Training was also a concern as two of the four readers did not have documented training for the Mint Lesion software. Finally, the CRO used a third party software platform for the independent radiology review function that was not consistent with the charter-specified requirements for timepoint reads and re-reads and for the selection of the short axis measurement of lymph node target lesions instead of the long axis measurement, as is used for non-nodal target lesions, when calculating the sum of target lesion diameters.

All 52 reviewed subjects' image timepoint readings performed by the CRO radiologists were verified against the data listings submitted to the application. There were no discrepancies. A one item Form FDA 483, inspectional observations, was issued to the CRO for failure to ensure the study is conducted in accordance with the investigational plan. The key inspectional observations are summarized below.

1. The CRO used oncology clinical trial software (Mint Lesion software provided by a third party vendor, Mint Medical GmbH) for image management, reading the images submitted by clinical sites for protocol AP26113-13-201 and data control, prior to validating the system software as specified in the charter or confirmation that the system software was Part 11 compliant.

   Specifically,

   a. The CRO approved the vendor software (Mint Lesion software version 2.4) for use on 4/21/2014, though the vendor had disclosed that the Mint Lesion software was not 21 CFR Part 11 compliant. It was not until January 2016, that (b) (4) performed a 21 CFR Part 11 System Compliance evaluation of the Mint Lesion Software. However, it could not be determined what version(s) of the software was evaluated for Part 11 compliance.

   b. The validation for the Mint Lesion software version 2.6 was conducted on August 22, 2014 by the CRO without testing it to ensure that the software properly measures and reads radiographic target lesions per the charter, specifically regarding using the short axis measurement of lymph node target lesions. Charter, Section 5.4, for the target lesion measurement requirements states that, "Radiographic target lesions must be measured in at least one dimension (Longest Diameter [LD] axis in the plane of

measurement is to be recorded) for non-lymph node lesions. If the lesion is a lymph node lesion measurement will use the short axis."

On 3/23/2016, a complaint from the Sponsor, Ariad, to the CRO revealed lymph nodes identified as target lesions by radiology readers were not appropriately calculating in the Mint Lesion software as a lymph node target lesion per the protocol and charter. Mint Lesion software was calculating the lymph nodes as simple target lesions which resulted in the system calculating the long axis of the organ instead of the short axis which was study specific to protocol AP26113-13-201. This calculation error affected 126 subject reads, and required the readers to re-read the images. Re-reading was conducted to ensure all data was calculated the same. The re-reading required an electronic signature by the assigned Radiologist.

OSI Reviewer Note: The Mint Lesion software version(s) used by the CRO/readers for radiology reads could not produce a detailed audit trail for re-reads and/or data changes made after the reader had previously signed imaging assessments, thus not 21 CFR Part 11 compliant. While this is a regulatory violation, it is unclear the extent to which this may have impacted data integrity.

With respect to item 1.b., the miscalculation of lymph node measurements for this study were identified by the sponsor and corrected by the CRO. A detailed review of the incident report (Ariad Complaint), and the CRO-proposed corrective action plan (CAPA) dated March 24, 2016, found that the Mint Lesion vendor was to update the software to calculate organs per the charter, the CRO would then enable readers to update imaging reviews for affected subjects' imaging and that this work would be completed on or before April 29. 2016.

Additional CAPA objectives included identification and assessment of all other Mint Lesion studies that utilized a customized organ list to ensure proper classification was configured. The CAPA was completed on April 19, 2016. The data cut-off date for the IRC-assessed data (data extraction date) was May 31, 2016 and should include the corrected lesion measurements for lymph nodes. While the CRO failed to validate the Mint Lesion software to properly measure and read radiographic target lesions per the charter the implementation of the CAPA should have corrected all affected subject outcomes and should mitigate these inspectional observations moving forward.

2. The CRO did not conduct variability testing, as was specified in the charter, for the radiology readers. Section 4.5, Inter/Intra-Reader Variability [readers], specifies that "the CRO will re-introduce a randomly-selected 2% of the cases read during the study to each independent reader to determine their intra-reader variability. Appropriate masking/blinding will be performed so the reader does not know the subject is a re-test. The variable to be tested for concordance will be the same as the adjudication variable, namely overall response at a time point. The CRO will complete 50% of the re-test cases per reader once the first stage of the study is complete and read. The remaining 50% of subjects will be read towards the end of

the study so that the results will be available at the time of data lock."
The CRO Variability Testing SOP IMG-SP-079.000, specifies, in part, that (b) (4) will provide a detailed methodology specific to the clinical study. The Project Manager then submits a Data Management Work Request to Application Development to include both requests for variability reporting and setting up alerts for when variability should be conducted within the study. The Project Manager was required to request a reader variability assessment by informing Application Development of the required sample size and the study data subset to draw from. Application Development then randomly selects the required sample and provides it to the Project Manager for variability preparation. Application Development was to provide the original read data as well as the variability data to Scientific Affairs for analysis.

However, the CRO Variability Testing SOP IMG-SP-079.000 was not followed in that the variability testing process for this protocol appeared to be managed solely by the Project Manager. There was no Data Management Work Request and no involvement from Application Development or Scientific Affairs. The Project Manager stated [he] created three "dummy" subjects, selected 14 data points from these three subjects, and re-submitted to the readers. The variability testing for each of the four readers was conducted in October 2016. There was no variability testing conducted "for 50% of the re-test cases per reader once the first stage of the study is complete and read", only at the end of the study.

OSI Reviewer Notes: The CRO failed to follow the charter; specifically to complete 50% of the re-test cases per reader once the first stage of the study was complete and read. The remaining 50% of subjects were to be read towards the end of the study so that the results will be available at the time of data lock. When questioned as to why the variability testing was not conducted after the first stage of the study, the Project Manager stated that [he] did not know when the "first stage of the study was completed". The Project Manager informed that he did all (2%) the variability testing at one time (October 2016). The CRO also failed to follow their own Variability Testing SOP IMG-SP-079.000, which describes a more robust approach to the conduct of variability testing for independent radiology readers, including prespecified roles for Scientific Affairs, the Project Manager and Application Development.

While this is a regulatory violation, it is unclear what, if any, impact the events had on the efficacy endpoint data generated by the CRO. However, since there was only variability testing conducted near the end of the study, October 2016, there was no opportunity to identify a reader(s) with intra-variability reads outside of acceptable limits as specified in the charter and to take corrective actions such retrain the reader. It is unclear if the missed intra-variability testing had a substantial impact on study outcomes based upon the CRO generated efficacy data.

3. The audit trails relating to data changes made after the reader had previously signed imaging assessments were inadequate. There have been 1055 (40% of all

timepoints read) data changes made by the readers to previously signed imaging assessments for this study. All data changes were categorized as "erroneous or incomplete lesion classification, measurement or diagnosis" in the software system. The charter specifies the reasons why data changes may be necessary to previously signed off readings. The charter, "Section 5.9, Additional Review Post-Review", states that instances may occur where the CRO may need to re-review cases where an independent reviewer already conducted an initial independent review. The CRO may trigger re-reviews or they may be requested by the sponsor. The imaging charter specified at least ten scenarios for justification to trigger a re-review. The charter also specifies that "in the event that [the CRO] conducts additional reviews of post-review data, [the CRO] will document the rationale for performing the re-review and maintain the documentation on file. The [CRO] will also maintain the original assessment output along with the previously mentioned audit trail."

When the CRO Project Manager unlocked data in the Mint Lesion software needing revision or re-read they had to select one of three options from a drop-down menu as to why the data must be unlocked and revised; 1) Erroneous or incomplete measurement of diagnosis; 2) Late retrieval or additional DICOM studies; and 3) Confirmation of new lesions recorded as equivocal. Once selection has been made the Project Manager is able to send the data/images to the individual readers. The Project Manager stated during the inspection that he only used the first option (erroneous or incomplete measurement of diagnosis) and that he did not know what the other two options meant. The justification options as prespecified in the charter, for data change, are not represented in the drop down menu selection for the Mint Lesion software. Because the justification for data changes is not attributable or verifiable in the software system, the reliability of the data changes could not be verified.

OSI Reviewer notes: Software validation by the CRO prior to implementation should have identified the software inconsistencies with the charter and the software vendor could have made appropriate modifications to satisfy the charter requirements. However, this was not addressed and corrected by the CRO prior to implementation. The audit trail maintained by the CRO only documents changes to data as a 'true' or 'false' value. If the data has been changed, the audit trail reveals a 'false' timepoint revision. In addition, the revision field shows how many times the same data was changed. There were no data change form requests, or any other formal procedure or source document that could define when and why data was changed.

It should be noted that in November 2015, during the conduct of the study, the CRO changed software for this protocol from Clinical Laboratory in a Box (CLIB) to Mint Lesion. At that time the readers had signed off on a combined total of 153 time points and 12 cases had been adjudicated for Study AP26113-13-201. Moreover, the CRO decided to send all of the previously read and signed-off-on cases back to the readers in Mint Lesion "to maintain consistency with the data". It is unclear why the CRO changed vendor software in the middle of the study, and why the CRO wanted to have

all locked reads, re-read using the new Mint Lesion software. The 153 "readings" are documented as data changes and show a 'false' revision in the firm's audit trail correctly, but included only the 'erroneous or incomplete measurement of diagnosis" selection to unlock the data. A 're-read due to change in software' was not an option for the firm to include to justify the data change.

The CRO also had to revalidate the software to reconfigure the measurements for the lymph nodes. As a result, 126 subject reads had to be re-read, and required the readers to re-read the images, 14 of which had a different time point response with the new configuration. Again, 'lymph node reconfiguration measurement' was not an option to justify the data change.

The basis for all data changes could not be verified based upon the source documents at the CRO. There were no data change form requests, or any other formal procedure or source document that could validate when and why data was changed. The data changes made in the Mint Lesion system could not be verified.

4. Quality assurance checks for incoming data/media from clinical sites were required per charter to be conducted within two days of receiving the data. Of the 2663 timepoints reviewed by the CRO/readers, 774 time points were quality reviewed five or more days after receipt.

OSI Reviewer notes: All 2663 timepoints were reviewed by the CRO/readers and documented in the database prior to IRC database lock on May 31, 2016. This inspectional observation should not impact overall study outcomes or have placed subjects at undue risk.

The totality of the inspectional observations indicates that the CRO did not adequately provide oversight and control of the execution of the investigational plan as specified in the charter. Failure of CRO (b) (4) to validate the software used for the conduct of the blinded imaging review, for all subject timepoints for Study AP26113-13-201, resulted in the software selecting the wrong axis measurement for lymph node target lesions, and the inability to validate, through source documentation or audit trails in the Mint Lesion system, the majority of data changes (40% [1055 out of a total of 2663 reads]) made by the readers to previously signed imaging assessments for this Study AP26113-13-201. The CRO could not produce 1) source documentation that identifies the specific reason for a substantial number of re-reads, and/or database changes, and 2) the source of the request to conduct re-reads, and/or database changes. For this reason, the data from this CRO that has a history of one or more re-reads and/or data point changes could not be verified.

The reliability of a significant proportion of the data from this CRO, associated with Study AP26113-13-201 could not be verified.

6. Sponsor: Ariad Pharmaceuticals, Inc.

The inspection focused on the sponsor's control, oversight, and management of Study AP26113-13-201. Monitoring records were reviewed from six clinical sites. There were no non-compliant clinical sites. Contract agreements and sponsor responsibility transfer agreements were reviewed as appropriate. Reporting practices for AEs and SAEs were also reviewed. The primary efficacy endpoint, ORR, per RECIST1.1, as determined by the clinical investigators and AEs found in the study clinical database was assessed for four clinical sites. There were no major issues. With respect to CROs, there were specific issues/concerns identified by the sponsor regarding (b) (4) error in measuring lymph nodes as target lesions. The sponsor identified the measurement errors very quickly and immediately contacted the (b) (4) to institute appropriate corrective actions. In 2014 the firm implemented a more robust vendor monitoring program. Ariad maintained adequate oversight over the study.

With the exception of the primary efficacy endpoint, ORR per IRC, the data from this sponsor submitted to the Agency associated with Study AP26113-13-201 appear reliable based on available information.

{See appended electronic signature page}

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CC:
Central Doc. Rm. NDA #208772
DOP2/Division Director/Patricia Keegan
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DOP2/Project Manager/ Leah Her
DOP2/Medical Officer/M. Naomi Horiba
OSI/Office Director (Acting)/David Burrow
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OSI/DCCE/Branch Chief/Kassa Ayalew
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OSI/DCCE/GCP Reviewer/Lauren Iacono-Connors
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

LAUREN C IACONO-CONNORS
02/09/2017

SUSAN D THOMPSON
02/10/2017

KASSA AYALEW
02/14/2017

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

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

Memorandum

Date: February 10, 2017

To: Leah S. Her, MS
Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products

From: Nazia Fatima, PharmD, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **Alunbrig™ (brigatinib) tablets, for oral use**
NDA 208772

Office of Prescription Drug Promotion comments on proposed carton/container labeling

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Office of Prescription Drug Promotion (OPDP) has reviewed the carton/container labeling for Alunbrig™ (brigatinib) tablets, for oral use (Alunbrig) as requested by Division of Oncology Products (DOP2) in the consult dated September 14, 2016.

OPDP's review of the proposed carton/container labeling is based on the drafts of carton/container labeling accessed via EDR link that was send by electronic mail on February 7, 2017 to OPDP (Nazia Fatima) from DOP2 (Leah Her). OPDP has reviewed the draft carton/container labeling and has no comments.

Combined OPDP and Division of Medical Policy Programs (DMPP) comments on the proposed Patient Package Insert (PPI) were provided under a separate cover on February 09, 2017. OPDP comments on draft package insert (PI) were provided under a separate cover on February 10, 2017.

If you have any questions, please feel free to contact, Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov. OPDP appreciates the opportunity to provide comments on this PI. Thank you!

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/s/

NAZIA FATIMA
02/10/2017

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

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

Memorandum

Date: February 10, 2017

To: Leah S. Her, MS
Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products

From: Nazia Fatima, PharmD, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **Alunbrig™ (brigatinib) tablets, for oral use**
NDA 208772

Office of Prescription Drug Promotion comments on proposed prescribing information (PI)

Office of Prescription Drug Promotion (OPDP) has reviewed the draft prescribing information (PI) for Alunbrig™ (brigatinib) tablets, for oral use (Alunbrig) as requested by Division of Oncology Products (DOP2) in the consult dated September 14, 2016.

OPDP's review of the proposed PI is based on the draft PI titled, "012717 FDA Comments to 112116 brigatinib" send by electronic mail on January 27, 2017 to OPDP (Nazia Fatima) from DOP2 (Leah Her). OPDP comments are listed on the attached PI.

Combined OPDP and Division of Medical Policy Programs (DMPP) comments on the proposed Patient Package Insert (PPI) were provided under a separate cover on February 09, 2017. OPDP's comments on Carton/Container Labeling will be provided under a separate cover.

If you have any questions, please feel free to contact, Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov. OPDP appreciates the opportunity to provide comments on this PI. Thank you!

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/s/

NAZIA FATIMA
02/10/2017

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: February 10, 2017

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Leah Her, RPM
DOP2

Subject: QT-IRT Consult to NDA 208772

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

This memo responds to your consult to us dated 01/13/2017 regarding the labeling statement related to heart rate in the sponsor's proposed label. The QT-IRT received and reviewed the following materials:

- Your consult;
- The sponsor's currently proposed label in NDA 208772 under Sequence 0019;
- Previous QT-IRT review under IND 110935 (dated 09/08/2015 in DARRTS); and
- Dataset submitted to IND 110935 under Sequence 0143

The Division has asked for QT-IRT's feedback about the following statement in the sponsor's proposed label under Section 5.3 (Bradycardia) and under Section 12.2 (Pharmacodynamics): "(b) (4)".

QT-IRT Comments for DOP2

We evaluated the heart rate and PK data from Cycle 2 Day 1 visit (after multiple QD dosing in Cycle 1 followed by first dose in Cycle 2) in Study AP26113-11-101 which had doses ranging from 30 mg QD to 240 mg QD, but with no placebo control. Our analysis of this dataset suggests that there is inconclusive evidence about the association of decrease in heart rate with increasing brigatinib plasma concentrations. The proposed labeling (b) (4) is not supported by the data from Study AP26113-11-101.

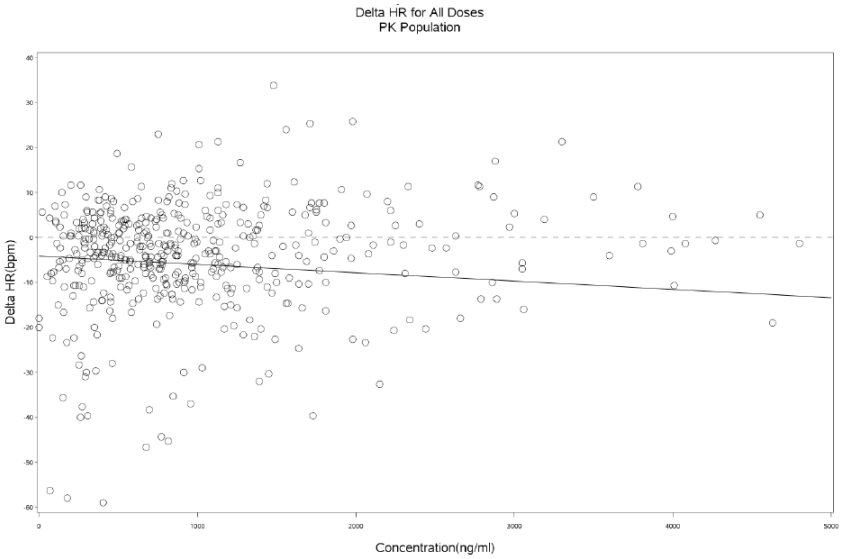
BACKGROUND

Brigatinib is a tyrosine kinase inhibitor that targets ALK, ROS1, and insulin-like growth factor-1 receptor (IGF-1R). The proposed indication for this drug is 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. The proposed dosing is initial dose of 90 mg orally once daily for the first 7 days, then 180 mg orally once daily, with or without food.

The data and analysis based on [redacted] (b) (4) heart rate [redacted] (b) (4) by the sponsor is described below:

An exploratory PK-PD analysis was performed using a linear mixed effects model for the 108 patients (a total of 468 observations) in the ECG PK Population in Study AP26113-11-101 (data from Cycle 2 Day 1 after multiple QD dosing in Cycle 1 followed by first dose in Cycle 2; refer to Table 2 for dose levels in this study). Figure 1 shows the relationship for plasma concentration of brigatinib (AP26113) and the ΔHR (change from baseline for heart rate) and Table 1 provides the slope estimate. The relationship between plasma concentration of AP26113 and the change from baseline for heart rate showed a statistically significant negative slope, which is consistent with the central tendency analysis for the change in heart rate. 1.6% of patients met the bradycardic outlier criteria without relationship to AP26113 dosage. The time point analysis averaging all dose groups revealed a small effect on heart rate on Cycle 2 Day 1, with a decline in heart rate of 4-6 bpm (compared with Cycle 2 Day 1 pre-dose) at 1 hour and 2 hours, but return to baseline by 4 hours (Figure 2). There was no clear signal of a clinically significant effect of brigatinib on heart rate at other time points.

Figure 1: Relationship of ΔHR vs. plasma concentration of brigatinib (AP26113)



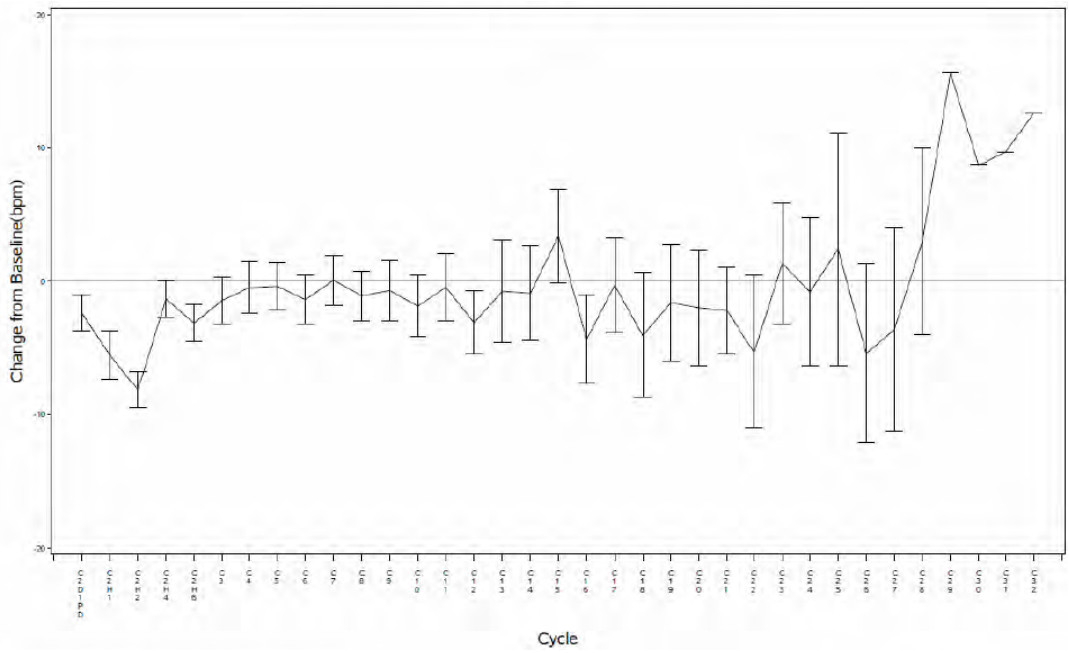
Source: Figure 3-9 in CSR AP26113-11-101, page 32

Table 1: Change from baseline versus the brigatinib (AP26113) plasma concentration; estimates from linear mixed model

QT Parameter	Slope of Plasma Conc. Effect on Δ QTc	p-value	Predicted Δ QTc at Max Concentration 4800 ng/mL	One-sided Upper 95% Confidence Bound of Predicted Δ QTc
QTcF (ms)	-0.00520	<0.0001	-18.4	-4.7
QTcB (ms)	-0.00603	0.0035	--26.4	-11.5
HR (bpm)	-0.00239	0.0001	-13.4	-17.6 (1)

(1) Lower 95% 1-sided confidence interval for HR (bpm)
Source: Table 3-3 in CSR AP26113-11-101, page 29

Figure 2: Change from baseline in heart rate (ΔHR; bpm) with means and 90% CI in ECG population across different cycles (including different time points in Cycle 2)



Source: Figure 3-2 in CSR AP26113-11-101, page 24

REVIEWER'S ANALYSIS

In order to assess the heart rate effects and its association to concentration and time, the reviewer analyzed the data from Study AP26113-11-101. The dose level analysis of heart rate in previous QT-IRT review did show decreased heart rate upon treatment, with peak effect at 2 h across doses in general, but there did not appear to be a consistent dose-response relationship for mean level decrease in heart rate (Table 2) or categorical analysis of percentage of subjects with heart rate ≤50 bpm post-dose in Cycle 2 (Table 3). Also there was inconsistent concentration-response relationship for decrease in heart rate. e.g.,

1. With the proposed dosing regimen of 90 mg/180 mg QD (n=27), the mean drug and metabolite concentrations at 2 and 4 h post-dose are similar (profile with pink symbols in Figure 3), while the mean ΔHR are -5.3 and 1.5 bpm respectively (Table 2).
2. Also with the 180 mg QD dosing regimen (n~33-35), the mean drug and metabolite concentrations at 2 and 4 h post-dose are similar (profile with olive colored symbols in Figure 3), while the mean ΔHR are -6.6 and -1.1 bpm respectively (Table 2).

The pooled data across all dose levels, suggest that there is a time component to the heart rate response with maximum decrease in heart rate at 2 h post-dose, and the mean effect being dissimilar despite similar mean level concentrations at 2 and 4 h (Figure 4).

Because of this observation of time component to the response, a concentration-ΔHR linear mixed effects model including the following terms was evaluated: drug concentration, nominal time postdose (categorical) and random effect of subject on the intercept and slope. The model showed statistically significant effect of time at 1, 2 and 4 h post-dose, while the effect of concentration was not statistically significant (Table 4).

Overall, our analysis based on dose-response and exposure-response relationships suggests that there is inconclusive evidence about the association of decrease in heart rate with increasing brigatinib plasma concentrations (b) (4)

Table 2: Analysis results of ΔHR for brigatinib treatment (Cycle 2 Day 1)

Treatment	Cycle/Day/Time	N	Mean	Std Dev	90% CI for Mean
30 mg QD	Cycle 2 Day 1 (Predose)	2	-9.2	0.7	(-12.3, -6.0)
	Cycle 2 Day 1 (2 h Post Dose)	2	-9.3	1.9	(-17.8, -0.9)
	Cycle 2 Day 1 (4 h Post Dose)	2	-8.2	4.0	(-26.1, 9.7)
	Cycle 2 Day 1 (6 h Post Dose)	2	-6.3	1.9	(-14.8, 2.1)
60 mg QD	Cycle 2 Day 1 (Predose)	3	-23.4	29.6	(-73.3, 26.4)
	Cycle 2 Day 1 (2 h Post Dose)	3	-24.9	30.6	(-76.4, 26.6)
	Cycle 2 Day 1 (4 h Post Dose)	3	-11.7	25.9	(-55.3, 31.9)
	Cycle 2 Day 1 (6 h Post Dose)	3	-23.8	30.3	(-74.9, 27.3)
60 mg BID	Cycle 2 Day 1 (Predose)	7	-0.5	4.4	(-3.7, 2.8)
	Cycle 2 Day 1 (1 h Post Dose)	5	-6.0	5.7	(-11.4, -0.6)
	Cycle 2 Day 1 (2 h Post Dose)	7	-4.9	7.1	(-10.1, 0.3)
	Cycle 2 Day 1 (4 h Post Dose)	7	1.6	7.9	(-4.2, 7.4)
	Cycle 2 Day 1 (6 h Post Dose)	7	0.6	5.9	(-3.7, 5.0)
90 mg QD	Cycle 2 Day 1 (Predose)	13	-10.9	16.7	(-19.1, -2.6)
	Cycle 2 Day 1 (1 h Post Dose)	9	-12.8	16.3	(-22.9, -2.7)
	Cycle 2 Day 1 (2 h Post Dose)	14	-13.4	15.1	(-20.6, -6.3)
	Cycle 2 Day 1 (4 h Post Dose)	13	-6.3	15.9	(-14.1, 1.5)
	Cycle 2 Day 1 (6 h Post Dose)	13	-6.9	11.4	(-12.5, -1.3)
90 mg BID	Cycle 2 Day 1 (Predose)	3	4.2	7.0	(-7.6, 16.1)
	Cycle 2 Day 1 (1 h Post Dose)	3	-6.9	12.7	(-28.2, 14.5)
	Cycle 2 Day 1 (2 h Post Dose)	4	-9.3	10.7	(-21.8, 3.3)
	Cycle 2 Day 1 (4 h Post Dose)	4	2.3	12.9	(-12.9, 17.4)
	Cycle 2 Day 1 (6 h Post Dose)	4	-1.8	11.7	(-15.5, 12.0)
90 mg/180 mg	Cycle 2 Day 1 (Predose)	24	0.1	7.5	(-2.5, 2.7)
	Cycle 2 Day 1 (1 h Post Dose)	21	-4.2	8.9	(-7.6, -0.9)
	Cycle 2 Day 1 (2 h Post Dose)	27	-5.3	12.5	(-9.4, -1.2)
	Cycle 2 Day 1 (4 h Post Dose)	27	1.5	12.1	(-2.5, 5.5)
	Cycle 2 Day 1 (6 h Post Dose)	26	-0.4	12.3	(-4.5, 3.7)

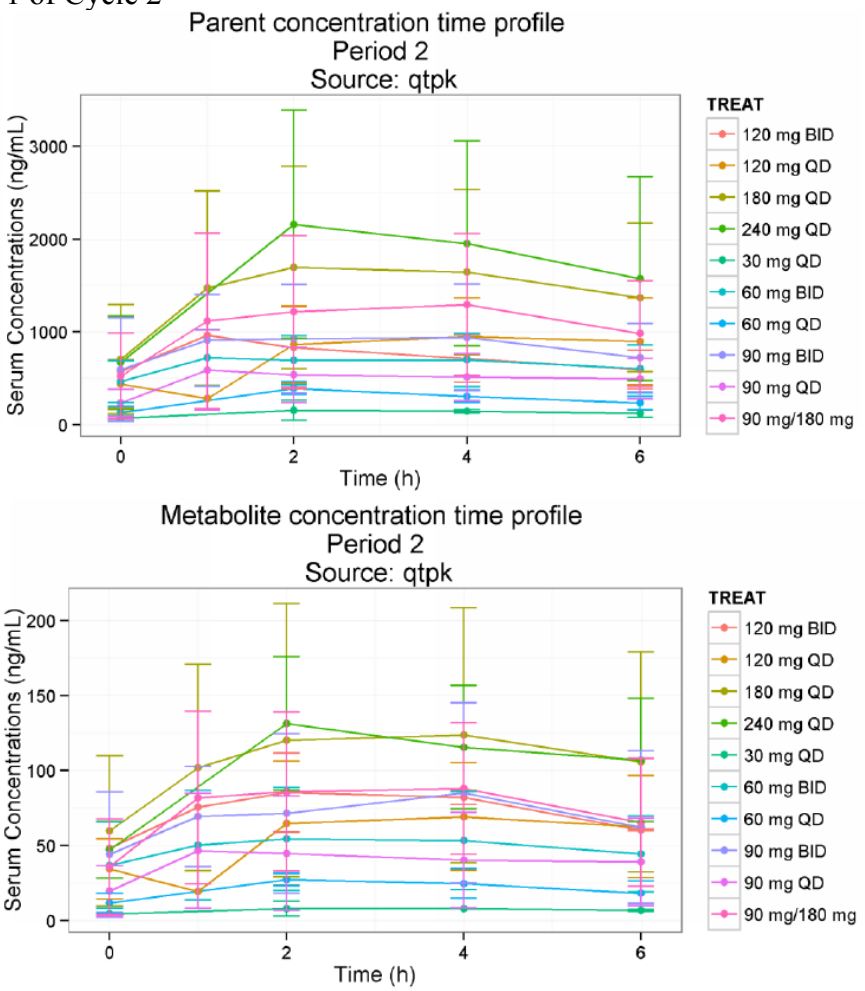
120 mg QD	Cycle 2 Day 1 (Predose)	9	-3.6	8.0	(-8.6, 1.4)
	Cycle 2 Day 1 (2 h Post Dose)	9	-6.0	5.3	(-9.3, -2.7)
	Cycle 2 Day 1 (4 h Post Dose)	9	-0.6	3.0	(-2.4, 1.3)
	Cycle 2 Day 1 (6 h Post Dose)	9	-3.5	5.4	(-6.8, -0.1)
120 mg BID	Cycle 2 Day 1 (Predose)	2	-1.0	5.7	(-26.3, 24.3)
	Cycle 2 Day 1 (2 h Post Dose)	2	-4.2	0.2	(-5.2, -3.1)
	Cycle 2 Day 1 (4 h Post Dose)	2	4.0	0.5	(1.9, 6.1)
	Cycle 2 Day 1 (6 h Post Dose)	2	1.2	4.0	(-16.7, 19.1)
180 mg QD	Cycle 2 Day 1 (Predose)	35	0.6	10.6	(-2.4, 3.7)
	Cycle 2 Day 1 (1 h Post Dose)	15	-2.8	12.7	(-8.5, 3.0)
	Cycle 2 Day 1 (2 h Post Dose)	35	-6.6	11.3	(-9.8, -3.4)
	Cycle 2 Day 1 (4 h Post Dose)	33	-1.1	11.2	(-4.4, 2.2)
	Cycle 2 Day 1 (6 h Post Dose)	35	-1.9	11.8	(-5.3, 1.5)
240 mg QD	Cycle 2 Day 1 (Predose)	8	-2.7	14.1	(-12.2, 6.7)
	Cycle 2 Day 1 (2 h Post Dose)	7	-15.8	12.3	(-24.9, -6.8)
	Cycle 2 Day 1 (4 h Post Dose)	7	-5.9	14.7	(-16.7, 4.9)
	Cycle 2 Day 1 (6 h Post Dose)	7	-8.4	11.7	(-17.0, 0.2)

Source: Table 6 in Previous QT-IRT review under IND 110935 (dated 09/08/2015 in DARRTS)

Table 3: Categorical analysis for HR≤50 bpm occurring at any time post-dose (1 to 6 h; Cycle 2 Day 1)

	# Subjects	
Treatment	HR≤50 bpm	HR>50 bpm
30 mg QD	1 (50%)	1
60 mg QD	0 (0%)	3
60 mg BID	2 (29%)	5
90 mg QD	3 (21%)	11
90 mg BID	1 (25%)	3
120 mg QD	0 (0%)	9
120 mg BID	0 (0%)	2
90 mg/180 mg QD	3 (11%)	25
180 mg QD	3 (9%)	32
240 mg QD	1 (14%)	6

Figure 3: Mean (±SD) AP26113 (Top) and AP26113-Metabolite (Bottom) concentration-time profiles at Day 1 of Cycle 2



Source: Figure 5 in Previous QT-IRT review under IND 110935 (dated 09/08/2015 in DARRTS)

Figure 4: Drug concentration, metabolite concentration, and change in heart rate (ΔHR) plotted on the same time axis; Mean ± SD for concentrations and Mean ± 90% CI for ΔHR

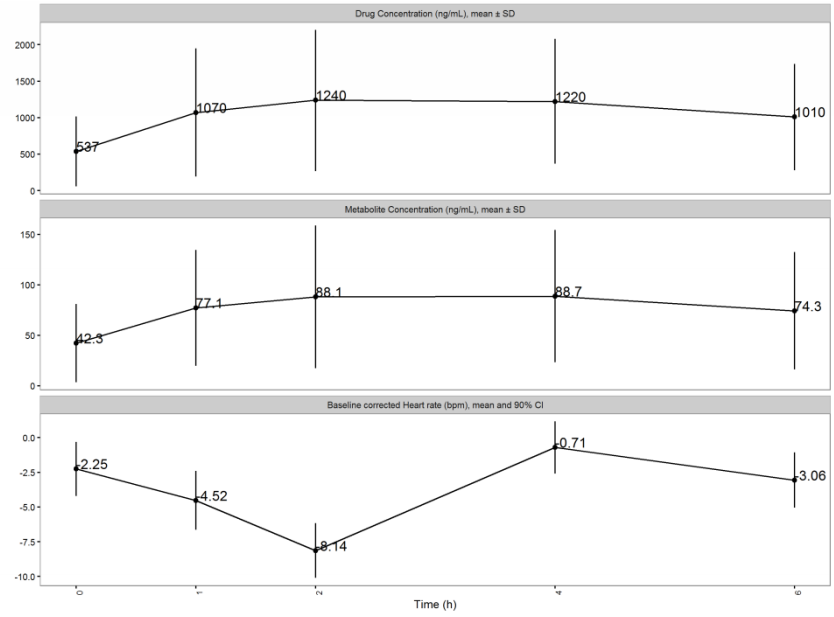


Table 4: Concentration-ΔHR relationship fixed effects parameter estimates and their associated precision, based on Kenward-Roger approximation

Fixed effect parameter	Estimate	Lower 95% CI	Upper 95% CI	RSE (%)	p-value
Intercept (bpm)	-1.50	-3.97	0.97	-83.17	0.233
CONC (bpm/µg/mL)	-1.42	-2.98	0.15	-55.03	0.0829
TIME1	-5.06	-6.77	-3.34	-17.25	<0.001
TIME2	-4.71	-6.24	-3.19	-16.43	<0.001
TIME4	2.44	0.94	3.95	31.34	0.00168
TIME6	-0.23	-1.57	1.12	-298.29	0.739

Thank you for requesting our input into the development of this product under NDA 208772. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

DHANANJAY D MARATHE
02/10/2017

CHRISTINE E GARNETT
02/10/2017

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:	February 9, 2017
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)** Shawna Hutchins, MPH, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Rowell Medina, PharmD, BCPS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nazia Fatima, PharmD, MBA, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ALUNBRIG (brigatinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 208772
Applicant:	ARIAD Pharmaceuticals, Inc.

1 INTRODUCTION

On August 29, 2016, ARIAD Pharmaceuticals, Inc. submitted for the Agency's review the third and final part of a rolling submission for New Drug Application (NDA) 208772 for ALUNBRIG (brigatinib) tablets. The proposed indication for ALUNBRIG (brigatinib) tablets is 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 September 14, 2016 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ALUNBRIG (brigatinib) tablets.

2 MATERIAL REVIEWED

- Draft ALUNBRIG (brigatinib) tablets PPI received on August 29, 2016 and received by DMPP and OPDP on January 27, 2017.
- Draft ALUNBRIG (brigatinib) tablets Prescribing Information (PI) received on August 29, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 27, 2017.
- Approved ALECENSA (alectinib) comparator labeling dated November 4, 2016.

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 reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- 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

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/s/

ROWELL MEDINA
02/09/2017

NAZIA FATIMA
02/09/2017

SHAWNA L HUTCHINS
02/09/2017

LASHAWN M GRIFFITHS
02/09/2017

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 # 208772, ALUNBRIG (brigatinib)
Product Name:

PMR/PMC Description: Hepatic Impairment Pharmacokinetic Study

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	Submitted
	Study/Trial Completion:	03/31/2017
	Final Report Submission:	09/30/2017
	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

   The mass balance study suggests that hepatic elimination is the major route of elimination for brigatinib. Patients with hepatic impairment may have higher brigatinib systemic exposures than patients with normal hepatic function, which may lead to more toxicities. We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of excessive drug toxicity from impaired hepatic function on the pharmacokinetics of brigatinib.

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 an appropriate brigatinib dose in patients with moderate to severe hepatic impairment.

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 clinical pharmacokinetic trial to determine an appropriate dose of brigatinib to minimize toxicity in patients with hepatic impairment. Design and conduct the trial 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)

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)

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 # 208772, ALUNBRIG (brigatinib)
Product Name:

PMR/PMC Description: Renal Impairment Pharmacokinetic Study

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	Submitted
	Study/Trial Completion:	09/30/2017
	Final Report Submission:	06/30/2018
	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 renal excretion is an important route of elimination for brigatinib. Patients with severe renal impairment may have higher brigatinib systemic exposures than patients with normal renal function, which may lead to more toxicities. We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of excessive drug toxicity from impaired renal function on the pharmacokinetics of brigatinib.

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 an appropriate brigatinib dose in patients with severe renal impairment.

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 clinical pharmacokinetic trial to determine an appropriate dose of brigatinib to minimize toxicity in patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal 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)

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.*

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(signature line for NDAs)

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 # 208772, ALUNBRIG (brigatinib)
Product Name:

PMR/PMC Description: Drug-Drug Interaction Trial

PMR/PMC Schedule Milestones:

Final Protocol Submission:	12/31/2017
Study/Trial Completion:	12/31/2019
Final Report Submission:	06/30/2020
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

Brigatinib may induce CYP3A at clinically relevant concentrations based on the human hepatocytes and PXR activation in vitro studies. Brigatinib may decrease exposures of concomitant CYP3A4 sensitive substrates and CYP3A4 substrates with a narrow therapeutic index.

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 brigatinib with regards to concomitant CYP3A4 sensitive substrates and CYP3A4 substrates with a narrow therapeutic index.

3. If the study/clinical trial is a **PMR**, check the applicable regulation. (Not applicable, **PMC**)
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 brigatinib on the single dose pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) to assess the magnitude of decreased drug exposures of a sensitive CYP3A4 substrate and to determine appropriate dosing recommendations. Design and conduct the trial 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)
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)

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 # 208772, ALUNBRIG (brigatinib)
Product Name:

PMR/PMC Description: Drug-Drug Interaction Assessment

PMR/PMC Schedule Milestones:

Final Protocol Submission:	N/A
Study/Trial Completion:	N/A
Final Report Submission:	06/30/2017
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

Coadministration of a strong CYP3A4 inhibitor increased brigatinib exposure by two-fold. Given the magnitude of change with a strong CYP3A4 inhibitor, a moderate CYP3A4 inhibitor may also increase brigatinib systemic exposures and 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 drug-drug interaction assessment is to determine how to dose brigatinib in patients requiring concomitant use of a moderate CYP3A4 inhibitor.

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 pharmacokinetic trial to evaluate the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose pharmacokinetics of brigatinib to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations." Alternatively, use of a physiologically-based pharmacokinetic modeling approach to address the potential for excessive drug toxicity may be acceptable.

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
Physiologically-based pharmacokinetic modeling to address the potential for excessive drug toxicity may be an acceptable alternative approach.

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)

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 # 208772, ALUNBRIG (brigatinib)
Product Name:

PMR/PMC Description: Drug-Drug Interaction Assessment

PMR/PMC Schedule Milestones:

Final Protocol Submission:	N/A
Study/Trial Completion:	N/A
Final Report Submission:	06/30/2017
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

Coadministration of a strong CYP3A4 inducer decreased brigatinib exposure by 80%. Given the magnitude of change with a strong CYP3A4 inducer, a moderate CYP3A4 inducer may also decrease brigatinib systemic exposures and therefore requires 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 drug-drug interaction assessment is to determine how to dose brigatinib in patients requiring concomitant use of a moderate CYP3A4 inducer.

3. If the study/clinical trial is a **PMR**, check the applicable regulation. (Not applicable, **PMC**)
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 pharmacokinetic trial to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of brigatinib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations." Alternatively, use of a physiologically-based pharmacokinetic modeling approach to address the potential for decreased drug exposure may be acceptable.

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
Physiologically-based pharmacokinetic modeling to address the potential for decreased drug exposure may be an acceptable alternative approach.

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)

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
01/24/2017

HONG ZHAO
01/24/2017
I concur.

JEFFERY L SUMMERS
01/24/2017

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:	January 6, 2017
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 208772
Product Name and Strength:	Alunbrig (brigatinib) Tablets, 30 mg and 90 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Ariad Pharmaceuticals Inc.
Submission Date:	November 18, 2016, November 21, 2016, and December 14, 2016
OSE RCM #:	2016-1965
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of the review of this new molecular entity under NDA 208772, Alunbrig (brigatinib) Tablets, this review evaluates the proposed container labels, carton labeling, and Prescribing Information (PI) for areas of vulnerability that can lead to medication errors. This review is in response to a request from the Division of Oncology Products 2 (DOP2).

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
Previous DMEPA Reviews	B- N/A
Human Factors Study	C- N/A
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed container labels, carton labeling, and Prescribing Information (PI) to identify deficiencies that may lead to medication errors and areas for improvement.

The Applicant proposed bottle count sizes of 21, (b) (4) and 180 tablets for the 30 mg tablets and 7 and 30 tablets for the 90 mg tablets; all packaged in bottles with a desiccant. The proposed dosing schedule for Alunbrig is 90 mg daily for the first 7 days, then 180 mg once daily continuously. Dose modifications for adverse reactions include dose reductions to 120 mg, 90 mg, and 60 mg. However, the language proposed in Section 16 of the PI states (b) (4) ” Based on the proposed count sizes, it is not feasible to dispense a 30 day supply for most dosing schedule in the original containers without dispensing excess quantities of tablets. However, because physicians usually prescribe a specific quantity on the prescription, pharmacies would not be able to dispense excess tablets. We anticipate pharmacists would inadvertently open the original

container and re-package the tablets in a pharmacy bottle to dispense the exact prescribed quantity. In communication with OPQ, an Information Request (IR) was sent to the Applicant regarding [redacted] and that the proposed bottle count sizes do not support quantities needed to dispense most dosing schedule. In the Applicant's response to IR, they provided data that demonstrated the stability of 30 mg and 90mg Alunbrig tablets in non-desiccated containers for 6 to 12 months and provided support for repackaging Alunbrig using non-desiccated pharmacy bottles.[a]

Also in the Applicant's response, they announced they no longer intend to market the [redacted] count bottle that they originally proposed and they provided justification for the remaining proposed bottle count sizes. However, they acknowledge that the proposed packaging configurations do not naturally conform to a provision for a one-month supply. Given there is data to support repackaging Alunbrig into pharmacy bottles, we find the proposed configurations to be acceptable.

We noted the container labels and carton labeling include placeholders for linear bar codes, lot numbers and expiration dates. In addition, we also noted the drug product will be manufactured by Penn Pharmaceutical Services Ltd (Penn) (30 mg and 90 mg tablets) or [redacted] finished packaging and labeling for all strengths and configurations will occur at Penn.

We note the font color chosen to highlight the strength of the 90 mg tablets [redacted] color of the proprietary name for both the 30 mg and 90 mg strengths which minimizes the visual difference between the strengths and can lead to selection errors. Further, the strength expressions lack prominence when compared to the "Rx only [redacted] statement on the principal display panel (PDP). In addition, the storage temperature information is inconsistently expressed between the PI, the container label and the carton labeling. Therefore, we provide recommendations in Section 4 in order to promote the safe use of this product.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed Alunbrig container labels, carton labeling and PI can be improved to provide important product information and to increase readability and the prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. In section 16: How Supplied/ Storage and Handling, remove the statement, "[redacted]."

[a] See DARRTS NDA 208772, Quality/Response to Information Request submitted 12/14/2016.

4.2 RECOMMENDATIONS FOR ARIAD PHARMACEUTICALS INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments

1. Revise the storage temperature language for consistency including order of information between the PI, the container labels and the carton labeling. As currently presented, the PI states "Store at room temperature 68°F to 77°F (20°C to 25°C). [redacted] (b) (4)." versus the container labels and carton labeling state "Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursion permitted between 15 to 30°C (59° to 86°F) (See USP)."

B. Container Labels and Carton Labeling

1. Revise the font color of the proprietary name [redacted] (b) (4) or revise the color scheme of the 90 mg strength [redacted] (b) (4) so both the strength and the proprietary name appear in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths. The use of the same [redacted] (b) (4) color font for the proprietary name and one of the product's strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors.

2. The strength expression lacks prominence when compared to the highlighted "Rx only [redacted] (b) (4) statement on the principal display panel (PDP). Consider using a color block and/or larger font size or bolding to increase the prominence of the strength of the product.

3. Decrease the prominence of the "Rx Only" statement as this information appears more prominent than the strength expression on the PDP. Consider removing the color block from the "Rx Only" statement to make it appear less prominent, and relocate it to another line on the PDP or to another panel.

4. The [redacted] (b) (4) is not required to appear in the PDP. Consider removing the [redacted] (b) (4) statement from the PDP to reduce crowding of information and to improve readability.

5. Revise the "[redacted] (b) (4)" statement on the side panel to read: "Usual Dose: See prescribing information".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Alunbrig that Ariad Pharmaceuticals. Inc. submitted on November 21, 2016.

Table 2. Relevant Product Information for Alunbrig	
Initial Approval Date	N/A
Active Ingredient	brigatinib
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.
Route of Administration	Oral
Dosage Form	Tablets
Strength	30 mg and 90 mg
Dose and Frequency	90 mg orally once daily for 7 days, followed by 180 mg once daily (continuously). Dose modifications to 60 mg once daily are permitted for management of adverse reactions.
How Supplied	30 mg- • 21 count bottles • 180 count bottles 90 mg- • 7 count bottles • 30 count bottles
Storage	Store at room temperature 68°F to 77°F (20°C to 25°C); [see USP Controlled Room Temperature]. (b) (4) [redacted] (b) (4) [redacted]
Container Closure	60 cc wide mouth, round, white high density polyethylene (HDPE) bottle with a 33 mm (b) (4) [redacted] cap with foiled induction seal liner and a 1 g molecular sieve desiccant in canister

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

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

/s/

JANINE A STEWART
01/06/2017

CHI-MING TU
01/06/2017

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

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

Application: NDA 208772

Application Type: New NDA

Drug Name(s)/Dosage Form(s): ALUNBRIG (brigatinib) Tablets, 30 and 90 mg.

Applicant: ARIAD Pharmaceuticals Inc.

Receipt Date: 8/29/16

Goal Date: April 29, 2017

1. Regulatory History and Applicant's Main Proposals

On August 29, 2016, ARIAD Pharmaceuticals Inc (ARIAD) submitted a New Drug Application (NDA) for brigatinib (proposed as ALUNBRIG (brigatinib) Tablets, for oral use) for the proposed indication of "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." ARIAD is seeking Priority Review Designation, and a 5-year and a 7-year marketing and orphan drug exclusivities, respectively.

ARIAD states that the NDA will primarily be supported by efficacy and safety data from the following two studies:

- Study AP26113-13-101, entitled "Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral ALK/EGFR Inhibitor"

- Study AP26113-13-201, entitled "A Randomized Phase 2 Study of AP26113 in Patients with ALK-Positive, Non-Small Cell Lung Cancer (NSCLC) Previously Treated with Crizotinib"

The development of brigatinib has been under IND 110935. Brigatinib has been granted Breakthrough Therapy Designation for treatment of patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) whose tumors are resistant to crizotinib (October 1, 2014) and Orphan Drug Designation for treatment of ALK positive or c-ros 1 oncogene positive (ROS1+) or epidermal growth factor receptor (EGFR)-positive NSCLC (August 28, 2016).

A pre-NDA / CMC-only meeting and a pre-NDA / multi-disciplinary meeting were held on March 2, 2016 and April 15, 2016, respectively, and a rolling review was granted on May 25, 2016.

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 of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by November 18, 2016. The resubmitted PI will be used for further labeling review.

---

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-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 for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

NO 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: *HL section has 1-inch margins on all sides and less than 1/2 inch margin in between columns.*

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *HL section is more than one-half page.This will be addressed during labeling review.*

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment: *No comments*

NO 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment: *The headings are not presented in the center of a horizontal line.*

YES 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 the product title and Initial U.S. Approval. See Appendix for HL format.

Comment: *No comments*

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: *No comments*

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

Heading	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **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 five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment: *No comments*

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment: *No comments*

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: *No comments*

Product Title in Highlights

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

Comment: *No comments*

Initial U.S. Approval in Highlights

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

Comment: *No comments*

Boxed Warning (BW) in Highlights

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

Comment: *No Boxed Warning section was provided in the Applicant's proposed label.*

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term

"**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment: *No Boxed Warning section was provided in the Applicant's proposed label.*

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

Comment: *No Boxed Warning section was provided in the Applicant's proposed label.*

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

Comment: *No Boxed Warning section was provided in the Applicant's proposed label.*

Recent Major Changes (RMC) in Highlights

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

Comment: *This is an original label.*

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) --- 8/2015."

Comment: *This is an original label.*

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment: *This is an original label.*

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment: *There is only tablet form in the Applicant's proposed label.*

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment: *No comments*

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

NO 21. 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 which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment: *Verbatim statement not used as it contains the Applicant's webpage.*

Patient Counseling Information Statement in Highlights

YES 22. 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 (or will have)** 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: *No comments*

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment: *No comments*

Contents: Table of Contents (TOC)

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

YES 24. The TOC should be in a two-column format.

Comment: *No comments*

NO 25. 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: *The title is missing the colon between "Information" and "Contents."*

N/A 26. The same title 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: *No Boxed Warning section was provided in the Applicant's proposed label.*

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment: *No comments*

YES 28. 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 (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment: *No comments*

NO 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment: *The Table of Contents contains sections 6.2 and 8.8 which are not in the Full Prescribing Information.*

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment: *No comments*

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. 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 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**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: *No comments*

YES 32. 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)]."*

Comment: *No comments*

N/A

33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment: *This is an original label.*

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment: *No comments*

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment: *No Boxed Warning section was provided in the Applicant's proposed label.*

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment: *No Boxed Warning section was provided in the Applicant's proposed label*

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state "None."

Comment: *No comments*

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "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: *No comments*

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), 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: *No Postmarketing Experience section was included in the Applicant's proposed label.*

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment: *No comments*

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) 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: *Submitted as a separate document.*

Appendix: Highlights and Table of Contents Format

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

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

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

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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

/s/

LEAH S HER
11/07/2016

MONICA L HUGHES
11/08/2016

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 # 208772	NDA Supplement #: S- NA; this is an original NDA	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Alunbrig (conditional approval) Established/Proper Name: brigatinib Dosage Form: Tablet, for oral use Strengths: 30 and 90 mg		
Applicant: ARIAD Pharmaceuticals Inc. Agent for Applicant (if applicable): NA		
Date of Application: August 29, 2016 Date of Receipt: August 29, 2016 Date clock started after Unacceptable for Filing (UN): NA		
PDUFA/BsUFA Goal Date: April 29, 2017	Action Goal Date (if different): April 29, 2017	
Filing Date: October 28, 2016	Date of Filing Meeting: October 3, 2016	
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): ALUNBRIG™ is a kinase inhibitor indicated 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.		
Type of Original NDA: AND (if applicable)		☒ 505(b)(1) ☐ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☐ 505(b)(2)

APPEARS THIS WAY ON ORIGINAL

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***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)

☐ Fast Track Designation ☒ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☒ 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 (FDCA Section 505B) ☐ 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*): NA	
List referenced IND Number(s): 110935	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☐	☒		Verified 9/27/16
Are the established/proper and applicant names correct in electronic archive? ***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 electronic***	☒	☐		Verified 9/1/16

archive.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***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.***	☒	☐	☐	Verified 9/27/16
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***	☐	☒		Verified 9/1/16
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		Verified 9/1/16; Orphan Designation was granted on April 28, 2016 for this product in this indication.

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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☐ 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. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**

Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☐	☒		
• 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 bulleted 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 for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same 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 another listed drug product containing the same active moiety, 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 orphan or 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 Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		Verified 9/2/16
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***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 5 years	☒	☐	☐	Verified 9/1/16

Note: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	Verified 9/1/16
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 the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	This is an original NDA.

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).	☒	☐	☐	Verified 9/1/16
Index: Does the submission contain an accurate comprehensive index?	☒	☐		Verified 9/1/16
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:	☒	☐		Verified 9/1/16; Note: final portion of rolling submission reviewer guide did

[1] http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				not contain hyperlinks
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	This is an original NDA.

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 (3397/3792), 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)].***	☒	☐		Verified 9/1/16 & 9/6/16
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	Verified 9/1/16
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)?	☒	☐	☐	Verified 9/1/16
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.*	☒	☐		Verified 9/1/16
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."***	☒	☐		Verified 9/1/16

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
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, <u>both</u> 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…"*	☒	☐	☐	Verified 9/2/16; Note: Applicant's debarment certification statement did not use exact language in FD&C Act Section 306(k)(1).
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.***	☒	☐	☐	Verified 9/2/16
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> 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:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]***	☐	☒		Orphan Designation was granted 4/28/16 for this product in this indication.

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMatern

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), 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.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: 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."***	☒	☐	☐	Verified 9/2/16
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	Verified on 9/2/16; A REMS was not submitted; however, a risk management plan was submitted
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		Verified 9/2/16

alHealthStaff/ucm027829.htm

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

If no, request applicant to submit SPL before the filing date.				
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		Verified 9/2/16
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.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☐	☐ ☒	☐ ☐	Verified on 9/2/16
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR 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 PLLR format before the filing date.***	☐	☐	☒	Please refer to section above.
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	Uploaded 9/14/16
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	Uploaded 9/14/16
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	Uploaded 9/14/16
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			

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

	☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***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 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 – uploaded 9/14/16 OSI – uploaded 9/14/16 DMPP – uploaded 9/14/16	☒	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** June 30, 2015	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** April 15, 2016	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 3, 2016

BACKGROUND: On August 29, 2016, ARIAD Pharmaceuticals Inc (ARIAD) submitted a New Drug Application (NDA) for brigatinib (proposed as ALUNBRIG (brigatinib) Tablets, for oral use) for the proposed indication of "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." ARIAD is seeking an Accelerated Approval under a Priority Review Designation, and a 5-year and 7-year marketing and orphan drug exclusivities, respectively.

ARIAD states that the NDA will primarily be supported by efficacy and safety data from the following two studies:

- Study AP26113-13-101, entitled "Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral ALK/EGFR Inhibitor"
- Study AP26113-13-201, entitled "A Randomized Phase 2 Study of AP26113 in Patients with ALK-Positive, Non-Small Cell Lung Cancer (NSCLC) Previously Treated with Crizotinib"

Brigatinib was granted Breakthrough Therapy Designation on October 1, 2014 for treatment of patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) whose tumors are resistant to crizotinib; (b) (4) Brigatinib received Orphan Drug Designation on August 28, 2016 for treatment of ALK positive or c-ros 1 oncogene positive (ROS1+) or EGFR positive NSCLC. The proposed proprietary name of ALUNBRIG was granted conditional approval on November 16, 2015.

The clinical development of brigatinib has been under IND 110935. On May 24, 2011, a pre-IND meeting was held to discuss the first-in-human (FIH) trial, Protocol AP26113-11-01, and the overall development plan of brigatinib for treatment of cancer patients with ALK rearrangements or EGFR mutations. On June 28, 2011, an IND was filed with Protocol AP26113-11-01 and allowed to proceed on July 26, 2011. On March 18, 2013, an End-of-Phase 1 meeting was held to discuss the development program for brigatinib that would support an NDA for treatment of patients with (b) (4) metastatic ALK-positive NSCLC (b) (4) intolerant to crizotinib. On August 8, 2013, Protocol AP26113-13-201 was submitted. On October 22, 2013, preliminary comments issued for a Pre-Phase 3 meeting to discuss Protocol AP26113-13-201 was considered acceptable by ARIAD, and the meeting request was withdrawn. On June 30, 2015, an Initial Multidisciplinary Breakthrough Therapy meeting was held to discuss the brigatinib development program.

A pre-NDA / CMC-only meeting and a pre-NDA / multi-disciplinary meeting were held on March 2, 2016 and April 15, 2016, respectively, to discuss the content and data to support a

proposed NDA for the proposed indication in ALK-positive NSCLC in patients who have progressed on or are intolerant to crizotinib:

- FDA agreed to the following two clinical pharmacology components as post-marketing requirements: 1) Hepatic Impairment Study AP26113-15-107 and 2) Renal Impairment Study AP26113-15-108
- FDA agreed to a minor component that includes updated stability data for the drug substance and drug product within 30 days of the submission of the final component of the rolling submission.

A rolling review for the NDA was granted on May 25, 2016. On June 16, 2016, the 1st portion of the rolling submission containing nonclinical information, priority name request and majority of module 1 (except the labeling and risk management plan), was received. On July 28, 2016, the 2nd portion of the rolling submission containing CMC information, establishment and clinical site information, clinical site dataset, letters of authorization, and environmental analysis, was received. On August 29, 2016, the 3rd and final portion of the rolling submission, containing clinical information, risk management plan, and labeling, was received.

A NDA planning meeting was held on September 19, 2016. The summary of the planning meeting was uploaded in DARRTS on September 20, 2016. Key decisions made during the planning meeting are as follow:

- The application will be under a priority review (8-month clock).
- The application will be under the shared review pilot.
- Consults filed for OPDP, DMPP, OSI, OSE and QT-IRT. The Team determined that a DPMH consult was not needed at this point in time. SGEs will be consulted.
- ODAC is not needed at this point in time.
- Internal monthly team meetings will be scheduled; no standing tcons with the Applicant is needed at this point in time.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Leah Her	Y
	CPMS/TL:	Monica Hughes	Y
Cross-Discipline Team Leader (CDTL)	Steven Lemery		Y
Division Director/Deputy	Martha Donoghue (Associate Acting Director, covering this application in place of the Division Director)		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Margit Horiba	Y
	TL:	Steven Lemery	Y
Clinical Pharmacology	Reviewer:	Ruby Leong	Y
	TL:	Hong Zhao	Y

• Genomics	Reviewer:	Not assigned	NA
	TL:	Rosane Charlab Orbach	N
• Pharmacometrics	Reviewer:	Hongshan Li	Y
	TL:	Jiang Liu	N
Biostatistics	Reviewer:	Thomas Ly	Y
	TL:	Kun He	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Anwar Goheer	Y
	TL:	Whitney Helms	Y
Product Quality (CMC) Review Team:	ATL:	Anamitro Banerjee	N
	RBPM:	Steven Kinsley	Y
• Drug Substance	Reviewer:	Katherine Windsor	Y
	TL:	Kasturi Srinivasachar	N
• Drug Product	Reviewer:	Olen Stephens	Y
	TL:	Joyce Crich	Y
• Process and Microbiology	Reviewer:	Ying Zhang	N
	TL:	Rakhi Shah	N
• Facility	Reviewer:	Thuy Nguyen/Ruth Moore	Y/N
	TL:	Zhihao (Peter) Qiu	N
• Biopharmaceutics	Reviewer:	Joan (Zhuojun) Zhao	Y
	TL:	Okpo Eradiri	N
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Rowe Medina	Y
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Nazia Fatima	Y
	TL:	Jessica Cleck Derenick	N
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Janine Stewart	Y
	TL:	Chi-Ming (Alice) Tu	N
OSE/DRISK (REMS)	Reviewer:	Elizabeth Everhart	N
	TL:	Naomi Redd	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Lauren Iacono-Connor	Y
	TL:	Susan Thompson	N

Other attendees	Anuradha Ramamoorthy	Y
	Jennie Chang	Y
	Edwin Chow	Y
	Jeanne Fourie Zirkelbach	Y
	Emily Fox	Y

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

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: The Team determined that the application did not raise significant safety or efficacy issues at this point in time.
• 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
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ 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
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	 ☒ YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ 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?	Updated stability data for drug substance and product submitted on September 27, 2016
• 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 **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): November 29, 2016 **Comments**: Filing Meeting Notes: 1 The Review Team determined that the application is sufficiently complete to permit a substantive review; therefore, is acceptable to be considered filed 60 days after the date of the application receipt. 2 The Review Team confirmed that the application will be under a priority review (8-month clock). The review timelines were discussed, with a target action date of April 28, 2017. 3 The Review Team determined that a Day 60 letter will be issued. Since no review issues, a Day 74 letter will not be necessary; however, any comments will be sent as information requests or via an advice letter as needed. 4 The Review Team discussed the timelines for the labeling meetings in December 2016. RPM will review the dates and reschedule as needed based on reviewers' availability for January 2017 timeframe. 5 The Review Team discussed the status of the manufacturing facilities' inspections. Some sites are already cleared and some sites are scheduled to be inspected by end of 2016. A drug substance (DS) manufacturing site's inspection date was noted as being scheduled for before February 2017. As primary reviews are due by end of January 2017, the CMC Review Team will follow up on whether the final determination of the DS facility inspection will be available by end of January 2017.

	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. Review Classification: ☐ Standard Review ☒ Priority Review

	ACTION ITEMS
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM

☐	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.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	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 applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

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

/s/

LEAH S HER
11/07/2016

MONICA L HUGHES
11/08/2016

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: October 6, 2016

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Leah Her, RPM
DOP2

Subject: QT-IRT Consult to NDA 208772

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

This memo responds to your consult to us dated 9/14/2016 regarding the sponsor's proposed QT-related labeling language for brigatinib. The QT-IRT received and reviewed the following materials:

- Your consult;
- QT-IRT's previous review for study report AP26113-11-101 (dated 9/8/2015); and
- The proposed draft label for brigatinib.

QT-IRT Comments for DOP2

The following is the sponsor's proposed labeling language related to QT.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4) the QT interval prolongation potential of ALUNBRIG was assessed in 123 patients (b) (4) following once daily ALUNBRIG doses of 30 mg to 240 mg. (b) (4)

Reviewer's Comment: We don't agree with the sponsor's proposal because the study is not designed to (b) (4). *Therefore, we suggest the following labeling language. We defer final labeling decisions to the Division.*

12.2 Pharmacodynamics

Cardiac Electrophysiology

In the phase 1/2 study, the QT interval prolongation potential of ALUNBRIG was assessed in 123 patients with advanced malignancies following once daily ALUNBRIG doses of 30 mg to 240 mg. No large changes in the mean QT interval (i.e., >20 ms) were detected in the study. An exposure-QT analysis suggested no concentration-dependent QTc interval prolongation.

BACKGROUND

Brigatinib is a kinase inhibitor indicated 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.

QT-IRT's previously reviewed the sponsor's QT-assessment based on Study AP26113-11-101 and concluded that no large changes (i.e., > 20 ms) in the QTcF interval were detected at the potential therapeutic doses 90 mg daily and 90 mg daily for 7 days followed by 180 mg daily. No significant positive relationship between brigatinib concentration and QTcF change from baseline was observed.

Thank you for requesting our input into the development of this product under NDA 208772. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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

/s/

JIANG LIU
10/06/2016

CHRISTINE E GARNETT
10/07/2016