

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209606Orig1s000

OTHER REVIEW(S)

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: July 13, 2017
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 209606
Product Name and Strength: Idhifa (enasidenib) Tablets
50 mg, 100 mg
Applicant/Sponsor Name: Celgene
Submission Date: June 06, 2017
OSE RCM #: 2017-17-1
DMEPA Primary Reviewer: Leeza Rahimi, Pharm.D.
DMEPA Team Leader: Hina Mehta, Pharm.D.

1 PURPOSE OF MEMO

Division of Hematology Products (DHP) requested that we review the revised container labels for Idhifa (enasidenib) Tablets (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 Sponsor has accepted most of our previous recommendations for the container labels. However, we identified additional areas in the container labels that can be improved to increase the readability and clarity of information to promote the safe use of the product. We note that the net quantity statement is in close proximity of the statement for product strength. We provide letter-ready recommendations for the Applicant in Section 3 of this review.

2 CONCLUSION

DMEPA concludes that the container labels can be improved to increase the clarity of information to promote the safe use of the product. Please see recommendations for the Applicant in Section 3 below:

^a Rahimi, L. Label and Labeling Review for Idhifa (enasidenib) Tablets (NDA 209606). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 APR 07. RCM No.: 2017-17.

3 RECOMMENDATIONS FOR CELGENE

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

1. Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and the net quantity increases when the net quantity statement is located in close proximity to the strength statement.

APPENDIX A. LABEL AND LABELING SUBMITTED ON JUNE 6, 2017

Container labels



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

/s/

LEEZA RAHIMI
07/13/2017

HINA S MEHTA
07/13/2017

PMR/PMC Development Template

NDA # 209606
Product Idhifa (enasidenib)
Set # 3240

PMR Description: Conduct a meta-analysis to characterize enasidenib- (b) (4) differentiation syndrome, specifically incidence, appropriate diagnostic criteria, and effective treatment based on patient-level data and pooled analyses for on-going trials in patients with acute myeloid leukemia: AG221-C-001, AG-120-221-C-001, AG-221-AML-004, and AG-221-AML-005. Submit the study report and analysis data set.

Schedule Milestones: Preliminary Protocol Submission: 10/2017
Final Protocol Submission: 01/2018
Study Completion: 02/2020
Final Report Submission: 12/2020

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

Relapsed or refractory acute myeloid leukemia (AML) is a life-threatening disease with limited treatment options. Based on the extreme unmet need in this population and the apparent clinical benefit from enasidenib in relapsed/refractory IDH2+ AML observed on a single-arm trial, it is appropriate to obtain additional needed safety information in a post-marketing trial.

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

Enasidenib caused a differentiation-like syndrome in 10-20% of patients with AML who received the drug on study AG-221-C-001. However, as understanding of the adverse event improved over the course of the study, which resulted in changes in recognition and management over time, the true incidence of differentiation syndrome, its component signs and symptoms, the timing with respect to initiation of enasidenib, its severity, and the effectiveness of the management guidelines recommended in the product label are still not clear. Diagnostic criteria need to be established, and the effectiveness of the proposed management guidelines must be demonstrated.

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

- 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.

The study will analyze pooled data from trials of enasidenib in AML (AG-221-C-001, C-001, AAML-004, and AML-005).

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
- 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 or 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.

PMR/PMC Development Template

PMR Description: Characterize the long-term safety of enasidenib in patients with relapsed or refractory acute myeloid leukemia (AML). Submit the final study report and dataset with three years of follow-up from ongoing Study AG221-C-001, *A phase 1/2, multi-center, open-label, dose-escalation and expansion, safety, pharmacokinetic, pharmacodynamics, and clinical activity study of orally administered AG-221 in subjects with advanced hematologic malignancies with an IDH2 mutation*. Include data from approximately 280 patients with relapsed or refractory AML.

Schedule Milestones: [Final Protocol Submitted: 10/2015]
Trial Completion: 05/2019
Final Report Submission: 03/2020

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

Relapsed or refractory acute myeloid leukemia (AML) is a life-threatening disease with limited treatment options. Based on the extreme unmet need in this population and the apparent clinical benefit from enasidenib in relapsed/refractory IDH2+ AML observed on a single-arm trial, it is appropriate to obtain additional needed safety information in a post-marketing trial.

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

The approval of enasidenib is based on durable CR/CRh and improvements in transfusion requirements in relapsed/refractory IDH2+ AML, but enasidenib has been tested in only a limited number of clinically heterogeneous patients over a relatively short duration of time with short follow-up, and there is concern that the toxicity profile may not be fully understood. While the primary analysis on this study (submitted for NDA review) was performed at a minimum follow-up time of 6 months for all patients, the study is still ongoing, and the final study report is planned when all subjects have a minimum follow-up time of 12 months. Longer follow-up time will provide a better understanding of safety.

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

- 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.

A phase 1/2, open-label, (b) (4) study of enasidenib in subjects with relapsed or refractory hematologic malignancies harboring an IDH2 mutation.

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
- 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 or 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.

PMR/PMC Development Template

PMR Description: Conduct a trial to provide evidence sufficient to characterize the long-term safety of enasidenib compared to conventional care regimens in patients with acute myeloid leukemia (AML). Submit the final study report and dataset with three years of follow-up from Study AG-221-AML-004, *A phase 3, multicenter, open-label, randomized study comparing the efficacy and safety of AG-221 versus conventional care regimens in older subjects with late stage acute myeloid leukemia harboring an isocitrate dehydrogenase 2 mutation*. Include data from approximately 140 patients with relapsed or refractory AML.

Schedule Milestones: [Final Protocol Submitted: 08/2015]
Trial Completion: 09/2022
Final Report Submission: 07/2023

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

Relapsed or refractory acute myeloid leukemia (AML) is a life-threatening disease with limited treatment options. Based on the extreme unmet need in this population and the apparent clinical benefit from enasidenib in relapsed/refractory IDH2+ AML observed on a single-arm trial, it is appropriate to obtain additional needed safety information in a post-marketing trial.

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

The approval of enasidenib is based on durable CR/CRh and improvements in transfusion requirements in relapsed/refractory IDH2+ AML, but enasidenib has been tested in only a limited number of clinically heterogeneous patients over a relatively short duration of time, and there is concern that the toxicity profile may not be fully understood. A study conducted in a randomized fashion against conventional care regimens will provide a better understanding of safety (including survival) compared to that of supportive care and other available options.

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

- 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.

A phase 3, randomized, open-label, multi-center study comparing enasidenib to conventional care regimens in subjects with IDH2+ AML. The study will collect all adverse events, laboratory test results, response rates, and overall survival.

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
- 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 or 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.

PMR/PMC Development Template

PMR Description: Conduct a clinical pharmacokinetic trial to evaluate the effect of multiple doses of enasidenib on the single dose pharmacokinetics of sensitive substrates of CYP3A4, CYP2D6, CYP2C19, CYP2C9, UGTs, P-gp, and BCRP to address the potential for excessive drug toxicity. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

Schedule Milestones: Preliminary Protocol Submission: 09/2017
Final Protocol Submission: 12/2017
Trial Completion: 09/2019
Final Report Submission: 03/2020

6. 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

Drug interaction studies have not been conducted by the applicant. In vitro studies suggest that enasidenib may inhibit metabolism of concomitant medications, which could result in safety adverse events.

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

Only a clinical trial will be sufficient to identify an unexpected serious risk of excessive drug toxicity from drug-drug interactions of enasidenib with substrates of CYP3A4, CYP2D6, CYP2C19, CYP2C9, UGTs, P-gp, and BCRP. This study will address the need for dosing modifications based on concomitant use of drugs that are sensitive substrates for certain drug metabolizing enzymes, which could be reflected in labeling.

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

- 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?

9. 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.

A Drug-Drug Interactions-perpetrator drug as inhibitors of CYP3A4, CYP2D6, CYP2C19, CYP2C9, UGTs, P-gp, and BCRP.

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
- 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:

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

- Does the study or 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.

PMR/PMC Development Template

PMR Description: Conduct a clinical pharmacokinetic trial to determine an appropriate dose of enasidenib in patients with hepatic impairment. This trial should be designed and conducted 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.”

Schedule Milestones: Final Protocol Submission: 09/2017
Trial Completion: 11/2018
Final Report Submission: 05/2019

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

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

Organ impairment studies have not been conducted by the applicant in subjects with moderate or severe hepatic impairment. Based on exposure response for safety data, elevated bilirubin is correlated with enasidenib exposure.

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

Only a clinical trial will be sufficient to identify an unexpected serious risk of excessive drug toxicity from impaired hepatic function on the pharmacokinetics of enasidenib. This study will address the need for dosing modifications based on moderate or severe hepatic impairment which could be reflected in labeling.

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

- 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.

A pharmacokinetic trial to determine an appropriate dose of enasidenib (b) (4) in patients with hepatic impairment.

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
- 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 or 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/

BARRY W MILLER
07/11/2017

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

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

Memorandum

Date: 6/28/17

To: Jennifer Lee, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Katie Davis, Team Leader
OPDP

Subject: Comments on draft labeling (Package Insert) for IDHIFA®
(enasidenib) tablets, for oral use
NDA 209606

In response to your labeling consult request dated January 5, 2017, we have reviewed the draft Package Insert for IDHIFA® (enasidenib) tablets, for oral use (IDHIFA). This review is based upon the version of the draft PI emailed to OPDP on June 14, 2017.

If you have any questions, please contact Rachael Conklin at (240) 402-8189 or Rachael.Conklin@fda.hhs.gov.

PI

<u>Section</u>	<u>Statement from Draft (if applicable)</u>	<u>OPDP Comment</u>
2.2 Recommended Dosage		OPDP notes that section 17 includes a recommendation to advise patients to “swallow whole with a cup of water.” Should information regarding taking the drug with water appear in section 2.2? If so, a specific amount of water (e.g. 8 oz) may be more informative than “a cup.” As TLS is a known adverse reaction related to the drug, specific recommendations for hydration with administration may be beneficial.
5.1 Differentiation	“In the clinical trial, 14%	OPDP notes that the revision to this sentence resulted

<p>Syndrome</p>	<p>of patients treated with IDHIFA experienced (b) (4) Differentiation Syndrome (DS), which may be life-threatening or fatal, (b) (4) ”</p>	<p>in redundancy. We recommend revising to remove this redundancy. Additionally, we note that (b) (4) should this be deleted for consistency?</p> <p>E.g., Differentiation Syndrome (DS), which may be life threatening or fatal, occurred in 14% of patients receiving IDHIFA in the clinical trial.</p>
<p>8.3 Females and Males of Reproductive Potential</p>	<p>“<u>Infertility</u></p> <p>Based on findings in animals, IDHIFA may impair fertility in females and males of reproductive potential [see <i>Nonclinical Toxicology (13.1)</i>].”</p>	<p>Is it known if the infertility is reversible or not?</p> <p>We note that (b) (4) also may impair fertility and that it also includes the statement, “It is not known whether these effects on fertility are reversible.” If applicable, we recommend that this statement be included in section 8.3 in order to characterize this risk.</p>
<p>12.1 Mechanism of Action</p>	<p>“In blood samples from patients with AML with mutated IDH2, enasidenib decreased 2-HG levels, reduced blast counts and increased percentages of mature myeloid cells.” (emphasis added)</p>	<p>We want to confirm that IDHIFA has definitively been shown to reduce blast counts and increase the percentage of mature myeloid cells as these are important clinical benefits of the drug and will likely be used in promotion to represent the product.</p>
<p>(b) (4)</p>	<p>(b) (4)</p>	<p>OPDP acknowledges that this section is labeled as “still under review.”</p> <p>However, we are concerned (b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>OPDP recommends deleting it.</p>
<p>14.1 Acute Myeloid Leukemia</p>	<p>(b) (4)</p>	<p>This statement makes it seem (b) (4) when this is not the case. Additionally, we note (b) (4)</p> <p>OPDP suggests revising this statement (b) (4)</p>

<p>14.1 Acute Myeloid Leukemia</p>	<p>(b) (4)</p>	<p>If available, OPDP recommends (b) (4)</p>
<p>17 PATIENT COUNSELING INFORMATION</p>	<p>Ask patients to immediately report any symptoms suggestive of (b) (4) differentiation syndrome, such as fever, cough or difficulty breathing, rapid weight gain or swelling of their arms or legs to their healthcare provider for further evaluation</p>	<p>For consistency with the medication guide and with the possible symptoms of DS described in 5.1 we recommend that symptoms of lymphadenopathy (e.g., swelling around neck, groin, or underarm area), as well as the the term “bone pain” be added to this section.</p>
<p>17 PATIENT COUNSELING INFORMATION</p>	<p><u>Tumor Lysis Syndrome</u> (b) (4)</p>	<p>OPDP notes that (b) (4) OPDP suggests (b) (4)</p>
<p>17 PATIENT COUNSELING INFORMATION</p>	<p><u>Embryo-Fetal Toxicity and Use of Contraceptives</u></p>	<p>OPDP recommend that the information that, “Coadministration of IDHIFA may increase or decrease the concentrations of combined hormonal contraceptives,” from sections 8.3 and 12.4 be included here as this is pertinent information for patients.</p>
<p>17 PATIENT COUNSELING INFORMATION</p>	<p>“Advise patients not to chew or split the tablets but swallow whole with a cup of water.”</p>	<p>Similar to our comment on section 2.2, including a more specific amount of water may be more informative for patients, otherwise we suggest revising to delete “a cup of” as the term “cup” may mean different things to different people. We also recommend that, consistent with 2.2, that the instruction not to crush the tablets be included here.</p> <p>E.g.,</p> <p>Advise patients not to chew, crush, or split the tablets but to swallow whole with XX oz. of water.</p> <p>Or</p> <p>Advise patients not to chew, crush, or split the tablets, but to swallow whole with water.</p>

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/s/

RACHAEL E CONKLIN
06/28/2017

**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: June 27, 2017

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Rachael Conklin, MS, RN
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): IDHIFA (enasidenib)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 209606

Applicant: Celgene Corporation

1 INTRODUCTION

On December 30, 2016, Celgene Corporation, submitted for the Agency's review a 505 (b) (1) New Drug Application (NDA) for IDHIFA (enasidenib) tablets, for oral use. IDHIFA (enasidenib) tablets is a targeted inhibitor of the mutant isocitrate dehydrogenase-2 (IDH2) enzyme indicated for the treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an IDH2 mutation.

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 Hematology Products (DHP) on January 19, 2017, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for IDHIFA (enasidenib) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft IDHIFA (enasidenib) MG received on December 30, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 14, 2017.
- Draft IDHIFA (enasidenib) Prescribing Information (PI) received on December 30, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 14, 2017.

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 MG 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 MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG 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 MG 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 MG.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
06/27/2017

RACHAEL E CONKLIN
06/27/2017

SHAWNA L HUTCHINS
06/27/2017

CLINICAL INSPECTION SUMMARY

Date	May 17, 2017
From	Anthony Orenca M.D., F.A.C.P., GCPAB Medical Officer Cynthia Kleppinger, M.D., Acting Team Leader, for Janice Pohlman M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D., M.P.H. GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Ashley Ward, M.D., Medical Officer Donna Przepiorka, M.D., Ph.D., Cross-Discipline Team Leader Jennifer Lee, Pharm.D. Regulatory Project Manager Division of Hematology Products
NDA	209606
Applicant	Celgene Corporation
Drug	enasidenib
NME	Yes (Expedited Priority Review)
Therapeutic Classification	Metabolic enzyme inhibitor
Proposed Indication	Treatment of adult patients with relapse or refractory acute myeloid leukemia with an isocitrate dehydrogenase-2 (IDH2) mutation
Consultation Request Date	January 23, 2017
Summary Goal Date	May 30, 2017
Action Goal Date	June 30, 2017
PDUFA Date	July 30, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical sites (Drs. Kantarjian, Stein, and De Botton) and the sponsor Celgene were selected by the Division of Hematology Products (DHP) for inspection of Study AG221-C-001.

Based on the preliminary results, the study data derived from these clinical sites and the sponsor are considered reliable in support of the requested indication.

The final CDER regulatory classification for the inspection of Dr. Stein is No Action Indicated (NAI). The preliminary classification for Dr. de Botton is NAI. The preliminary classification for Dr. Kantarjian is Voluntary Action Indicated (VAI). The preliminary classification of the sponsor inspection is NAI.

2. BACKGROUND

Refractory or relapsed acute myeloid leukemia (AML) is a heterogeneous disease with the success of therapy variable. Enasidenib (also known as AG-221 and CC-90007) is a selective, oral inhibitor of the isocitrate dehydrogenase 2 (IDH2) mutant enzyme, making it a targeted therapeutic candidate for the treatment of patients with IDH2 mutated AML.

The sponsor proposes enasidenib for treatment of adult patients with relapse or refractory acute myeloid leukemia with an isocitrate dehydrogenase-2 (IDH2) mutation. In review of this NDA, CDER/OHOP/DHP requests three clinical study sites and sponsor inspections for Study AG221-C-001. These clinical study sites had high enrollments and differential findings in the primary efficacy results.

Study AG221-C-001

Study AG221-C-001 is an ongoing Phase 1/2, multicenter, open-label, 3-part study which evaluates safety, efficacy, and PK/PD of orally administered enasidenib (AG-221) in subjects who have advanced hematologic malignancies with an IDH2 mutation. This study includes 3 parts: Phase 1 dose escalation, Part 1 (Phase 1) expansion, and Phase 2 expansion (originally referred to as Part 2).

The objectives for the Phase 2 portion of the study (emphasis of the clinical study site inspections) are two-fold: cumulative drug safety experience with enasidenib and Phase 2 efficacy study results. The Phase 2 portion of this study enrolled 91 study patients 18 years and older with IDH-2 mutated acute myeloid leukemia. This study population includes the following study patient subsets: (1) relapse after allogeneic transplantation, (2) second or later relapse, (3) refractory to initial induction or re-induction treatment, or (4) relapse within a year of initial treatment, excluding patients with favorable-risk status according to National Comprehensive Cancer Network (NCCN) Guidelines.

The primary efficacy endpoint of overall response is defined as the rate of responses including complete response (CR), CR with incomplete neutrophil recovery (CRi), CR with incomplete platelet recovery (CRp), partial response (PR), and morphologic leukemia-free state (MLFS) (for acute myeloid leukemia), based on investigator assessment. Only data from the efficacy evaluable patients will be used to evaluate the efficacy of AG-221 for the proposed indication.

This multicenter study was conducted at 18 sites in 2 countries: United States with 15 sites and France with 3 sites. The first subject first visit was on June 10, 2015 and the clinical data had a cutoff date of April 15, 2016.

3. RESULTS (by site):

Name of Clinical Investigator/Sponsor Address	Protocol AG221-C-001 Site #/ # Subjects enrolled in all phases of the study	Inspection Date	Classification
Stephane De Botton, M.D. Institut Gustave Roussy – Service DITEP 114 rue Edouard Vaillant Villejuif, France 94805	Site # 201 45 enrolled 42 evaluable (15 efficacy evaluable)	April 24 to 27, 2017	Preliminary NAI
Hagop M. Kantarjian, M.D. University of Texas MD Anderson Cancer Center Department of Leukemia 1515 Holcome Blvd. Unit #428 Room #FC4.3042 Houston, TX 77030	Site # 111 56 enrolled 52 evaluable (30 efficacy evaluable)	May 1 to 5, 2017	Preliminary VAI
Eytan M. Stein, M.D. Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York, NY 10065	Site # 104 63 enrolled 59 evaluable (15 efficacy evaluable)	March 13 to 16, 2017	NAI
Celgene Corporation 86 Morris Avenue Summit, NJ 07901	Sponsor for: AG221-C-001	March 13 to 17, 2017	Preliminary NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data are 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.

Clinical Investigator

1. Stephane De Botton, M.D./ Site # 201

The inspection was conducted from April 24 to 27, 2017. A total of 49 subjects were screened, 45 subjects were enrolled. Reasons for not completing the study included five subjects who had transplants, 22 subjects who had progressive disease, five subjects developed serious adverse events, eight subjects died, one study subject withdrew from further treatment, and one study subject was withdrawn due to protocol-related issues. The study is ongoing and three subjects are on study drug. An audit of the 18 subjects' records enrolled in the Phase 2 portion of the study at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. No Form FDA 483 (Inspectional Observations) was issued.

2. Hagop M. Kantarjian, M.D./ Site # 111

The inspection was conducted from May 1 to 5, 2017. A total of 56 subjects were screened and enrolled. After enrollment, 19 subjects discontinued due to disease progression, one study subject withdrew out of the study area, five subjects withdrew participation from the study, and three subjects were lost to follow-up. The study is ongoing. An audit of the 17 subjects' records enrolled in the Phase 2 portion of the study was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 was issued at the end of the inspection due to two issues for not following the investigational plan: Subject # 023 was seen and discharged from the emergency room due to a

headache and a fall. This adverse event was not reported. On another occasion, this same patient was admitted to the hospital due to nausea and vomiting, but this SAE was not reported within the 24 hour time period. The Form FDA 483 was shared with CDER DHP (review division). These adverse events in the same study subject were two isolated occurrences and did not lead to study subject harms.

Notwithstanding these isolated regulatory deficiencies, the preliminary inspectional findings indicate that data submitted by this clinical site appears to be acceptable in support of the specific indication.

3. Eytan M. Stein, M.D./ Site # 104

The inspection was conducted from March 13 to 16, 2017. A total of 73 subjects were screened, 63 enrolled. There are 51 study subjects who completed the study and the study is ongoing. Patients did not continue for the following reasons: six patients died, three patients had disease progression, one patient had an unspecified adverse event and withdrew from the study, one patient withdrew out of the study area, and one subject was lost to follow-up. An audit of the 63 subjects' records enrolled at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection. No Form FDA 483 was issued.

Sponsor

4. Celgene Corporation

This inspection was conducted from March 13 to 17, 2017.

The sponsor inspection included review of the following: regulatory site set up, financial disclosures, site management and monitoring, electronic Trial Master File (eTMF) functional services, and the Clinical Trial Management System (CTMS).

Monitoring visits were reviewed; monitoring reports indicated that the sites received adequate periodic monitoring. IRB approvals, site study protocol deviations, serious adverse events and related monitoring reports were assessed, and oversight by the contract research organization appeared to be adequate.

A Form FDA 483 was not issued at the end of the inspection. The sponsor maintained adequate oversight of the clinical trial.

{See appended electronic signature page}

Anthony Orenca, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

CONCURRENCE:

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

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/s/

ANTHONY J ORENCIA
05/17/2017

CYNTHIA F KLEPPINGER
05/17/2017

KASSA AYALEW
05/17/2017

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: April 7, 2017
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 209606
Product Name and Strength: Idhifa (enasidenib) Tablets, 50 mg and 100 mg
Product Type: Single-Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Celgene
Submission Date: December 30, 2016 and March 9, 2017
OSE RCM #: 2017-17
DMEPA Primary Reviewer: Leeza Rahimi, Pharm.D.
DMEPA Team Leader: Hina Mehta, Pharm.D.

1 REASON FOR REVIEW

Celgene Corporation submitted a New Drug Application (NDA) for enasidenib tablets 50 mg (equivalent to 60 mg enasidenib mesylate) and 100 mg (equivalent to 120 mg enasidenib mesylate), under proprietary name, Idhifa on December 30, 2016. The Division of Hematology Products (DHP) consulted DMEPA to review the labels and labeling of the product for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
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 our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Celgene Corporation submitted a 505(b)(1) NDA for Idhifa (enasidenib) tablets. We performed a risk assessment of the container labels and Prescribing Information to identify deficiencies that may lead to medication errors and other areas of improvement. We identified areas of the proposed labeling that could be improved to promote the safe use of the product.

For the Division, we recommended inclusion of important administration information in the Highlights section of the PI. We provide our recommendations for the Division in section 4.1.,

For the Applicant, we recommended changes in the container labels in regard to prominence of proprietary and established names, inclusion of important administration information, bar code, lot number, and expiration number. We provide our recommendations for the Applicant in section 4.2.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information, and promote the safe use of the product and mitigate any confusion. We provide our recommendations for the Division in section 4.1 and for the Applicant in section 4.2 of this review.

4.1 RECOMMENDATIONS FOR DIVISION

- A. Highlights of Prescribing Information, Dosage and Administration Section
 - a. Add a bullet with the information regarding administration of tablets without food to ensure this important information is not overlooked. For example, “Take without food (2 hours before or 1 hour after food)”.
 - b. Add a bullet with the information regarding administration of whole tablets to ensure this important information is not overlooked. For example, “Swallow whole, do not chew or split tablets”.

4.2 RECOMMENDATIONS FOR CELGENE

We recommend the following be implemented prior to approval of this NDA 209606:

A. Container Labels:

1. The proprietary name and established name lack prominence. We recommend you increase the prominence of both names and ensure that the established name is at least half (1/2) the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast and other printing features in accordance with 21 CFR 201.10 (g)(2).
2. We recommend adding the statement “Swallow whole, do not chew or split tablets” to the principal display panel to mitigate wrong administration techniques, and to be consistent with the Prescribing Information.
3. Consider reorienting the barcode to a vertical position to improve the ability to scan the barcode. We note that the bar code is oriented horizontally. Barcodes placed in a horizontal position may not scan due to vial curvature. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore, it is an important safety feature that should be part of the label whenever possible.
4. The location for the lot number and expiration date is not provided on the container label that was submitted. Please include the intended location for the lot number and expiration date on the container label for our review. The lot number statement is required on the immediate container and carton labeling when there is sufficient space per 21 CFR 201.10 (i)(1). In addition

ensure the lot number is clearly differentiated from the expiration date, and that no other numbers are located in close proximity to the expiration date.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Idhifa that Celgene submitted on December 30, 2016 and March 9, 2017.

Table 2. Relevant Product Information for Idhifa	
Initial Approval Date	N/A
Active Ingredient	Enasidenib
Indication	Treatment of patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with an isocitrate dehydrogenase 2 (IDH2) mutation.
Route of Administration	Oral
Dosage Form	Oral tablets
Strength	50 mg, 100 mg
Dose and Frequency	AML: 100 mg once daily until disease progression or unacceptable toxicity.
How Supplied	Bottles of 30 tablets
Storage	Store tablets or below 25°C (77°F). Keep the bottle tightly closed. Store in the original bottle (with a desiccant canister) to protect from moisture

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 2, 2017, we searched the L:drive and AIMS using the terms, Idhifa to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified zero relevant reviews.

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/s/

LEEZA RAHIMI
04/07/2017

HINA S MEHTA
04/10/2017

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

NDA	209606
Brand Name	IDHIFA
Generic Name	Enasidenib (AG-221, CC-90007)
Sponsor	Celgene Corporation
Indication	Treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an IDH2 mutation
Dosage Form	Tablet; EQ 50 mg BASE and EQ 100 mg BASE
Drug Class	Inhibitor of mutant isocitrate dehydrogenase-2 (IDH2) enzyme
Therapeutic Dosing Regimen	100 mg QD
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	<ul style="list-style-type: none"> • Single dose: not reached in patients up to 650 mg and in healthy subjects up to 300 mg • Multiple dose: generally well tolerated at total daily doses up to 650 mg in patients; no study in healthy subjects.
Submission Number and Date	0003 (01/24/2017); 0001 (12/30/2016)
Review Division	DHP

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Based on ECG data from study AG221-C-001, it is reasonable to conclude that no large mean effects (e.g. 20 ms) are anticipated with the steady state therapeutic exposures of enasidenib with 100 mg QD dosing for the oncology indication.

In this Phase 1/2, open-label study in patients with advanced hematologic malignancies and with an IDH2 mutation, 331 patients received at least a single dose of enasidenib. The Phase 1 dose escalation part of study included 30 to 150 mg BID and 50 to 650 mg QD dosing, while Phase 1 expansion and Phase 2 part of the study included 100 mg QD dosing. Based on the QTc data for single dose of 30 to 650 mg (n=119 patients) and multiple doses of 100 mg daily (n=72 patients), no large mean changes in the QTc interval (>20 ms) were observed following the treatment.

The overall summary of mean Δ QTcF findings for the 100 mg QD dose in all phases of the Phase 1/2 study is presented in Table 1 below. Information beyond Cycle 2 is not included because of small sample size. The upper 90% CI was slightly above 10 ms (11 ms) for a time point of 2 h post-dose on Cycle 2 Day 1.

Table 1: Descriptive Summary of Δ QTcF for Enasidenib 100 mg QD in All Phases of Study AG221-C-001 (FDA Analysis)

TREAT	VISIT	N	Mean	Lower Limit of 90% CI	Upper Limit of 90% CI
100 mg QD	Cycle 01 Day 1 (30 minutes post dose)	85	0.1	-3.3	3.4
	Cycle 01 Day 1 (2 hours post dose)	177	2.2	0.3	4.1
	Cycle 01 Day 1 (4 hours post dose)	176	0.0	-2.4	2.3
	Cycle 01 Day 1 (6 hours post dose)	176	-1.4	-3.6	0.7
	Cycle 01 Day 1 (8 hours post dose)	83	-3.4	-7.5	0.8
	Cycle 02 Day 1 (2 hours post dose)	67	6.5	2.1	11.0
	Cycle 02 Day 1 (4 hours post dose)	67	2.0	-2.1	6.0
	Cycle 02 Day 1 (6 hours post dose)	69	1.7	-2.3	5.6

For concentration-QT (C-QT) analysis, 191 patients contributed time matched ECG/PK data from Cycle 1 of treatment after receiving single doses between 30 to 650 mg and from Cycle 1 and Cycle 2 of treatment after receiving multiple dosing of 100 mg QD enasidenib in Study AG221-C-001. Of these, 51 patients contributed time-matched ECG/PK data at steady state on Day 29 after multiple dosing with therapeutic regimen of 100 mg QD. Overall summary of findings is presented in Table 2.

Table 2: The Point Estimates and the 90% CIs for Effect with Administration of Enasidenib 100 mg QD (FDA Analysis)

Treatment	Concentration (μ g/mL)	Δ QTcF (ms)	90% CI (ms)
Geo. Mean C_{max} of Enasidenib at steady state (Day 29) with 100 mg QD	10.51	5.26	[1.13, 9.39]

In this study, subjects with QTc prolongation (presented in Table 3) had other concurrent factors (e.g., prolonged QT interval at baseline, concomitant administration of medications with known QT prolonging potential, or electrolyte imbalances) affecting the QT interval.

Table 3: Maximum Postbaseline QTc by Category for All Subjects and Subjects with R/R AML by Total Daily Dose of 100 mg in the Combined Phase 1/2 of Study AG221-C-001 (Sponsor’s Analysis)

	R/R AML 100 mg dose (n=199)	All R/R AML (n=266)	All Subjects (N=330)
Friderica Correction			
QTcF ≤ 480 msec ^a	180 (90.5)	238 (89.5)	295 (89.4)
QTcF > 480 to ≤ 500 msec ^a	13 (6.5)	21 (7.9)	24 (7.3)
QTcF > 500 msec ^a	6 (3.0)	7 (2.6)	11 (3.3)
QTcF increase from baseline > 30 to ≤ 60 msec ^b	54 (27.1)	73 (27.4)	83 (25.2)
QTcF increase from baseline > 60 msec ^b	10 (5.0)	13 (4.9)	14 (4.2)

Source: 2.7.4 Summary of Clinical Safety, Table 36, page 125

This study evaluated QTc prolongation after the first dose of 30 – 650 mg enasidenib and at steady state after multiple dosing of therapeutic dose of 100 mg QD. Given the 8- to 11-fold accumulation at steady state in the patient population, data after a single dose of 650 mg would not provide adequate exposure coverage for assessing QTc effect when patients take the drug per proposed labeling recommendation (100 mg QD without food). A single dose oral administration of enasidenib under fed conditions (high fat meal) leads to ~50% increase in AUC and a 64% increase in C_{max} compared to fasted conditions. The study did not include any higher doses in multiple dose setting or dosing in fed state to have exposures that can cover highest clinically relevant exposures scenario of dosing in fed state. Considering the several fold accumulation with multiple dosing, the impact of administration of one or a few sporadic doses with food on overall C_{max} may not be significant. But, available exposures are not adequate to evaluate QTc effect in a scenario where patients would frequently take the drug with food.

Dedicated drug-drug interaction (DDI) studies and organ impairment studies have not been conducted to date. Because metabolism of enasidenib is mediated by multiple CYPs and UGTs, the risk of clinically relevant drug interactions with co-administration of inhibitors would be low. Primary route of elimination of this drug is via fecal elimination, which accounts for 73% of total administered drug. Renal elimination accounts for just 8% of total administered drug. As per the sponsor, in a population PK analysis with evaluation of limited data across the spectrum of organ function, neither estimated creatinine clearance, hepatic transaminase levels, nor total bilirubin level were significantly correlated with apparent enasidenib clearance. An organ impairment study is planned to be conducted in 2017 to assess the impact on PK.

2 PROPOSED LABEL

The sponsor included following QT-related language in their current proposed label.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The following is QT-IRT's proposed labeling language which is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The potential for QTc prolongation with enasidenib was evaluated in an open-label (b) (4) study in patients with advanced hematologic malignancies and with an IDH2 mutation. Based on the QTc data for single dose of 30 to 650 mg (b) (4) and multiple doses of 100 mg daily (b) (4) no large mean changes in the QTc interval (>20 ms) were observed following the treatment.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Enasidenib (AG-221, CC-90007) is a first-in-class, selective, potent inhibitor of the IDH2 mutant protein. Direct inhibition of the gain-of-function activity of the IDH2 mutated protein is intended to inhibit the production of the oncogenic metabolite 2- hydroxyglutarate (2-HG).

Enasidenib is available in 50 mg (enasidenib, equivalent to 60 mg enasidenib mesylate) and 100 mg (enasidenib, equivalent to 120 mg enasidenib mesylate) tablets for oral administration.

3.2 MARKET APPROVAL STATUS

Enasidenib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Preclinical Information has been reviewed in QT-IRT report under IND 117631:¹

- In vitro pharmacology studies suggest that AG-221 free base has a weak inhibitory effect on IKr (hERG) with an IC₅₀ of 9.02 μM (4,212 ng/mL) and there was no inhibitory activity of the metabolites, AGI-16903 and AGI-17011, on IKr at >30 μM. The estimated free concentration of AG-221 base in AML patients receiving 100 mg QD is 195 ng/mL which is approximately 22-fold less than hERG IC₅₀ value for AG-221 free base.
- In in vivo cardiovascular (CV) safety study in dogs receiving 75 and 300 mg/kg, QTc prolongations were not dose dependent, did not align with the time course of AG-221 plasma concentration, had no associated changes in ECG waveform morphology, and were observed primarily in a single animal at each dose level. The hERG current inhibition did not appear to contribute in the QTc prolongation in dogs. Dogs at ≥15 mg/kg BID had arterial

¹ Previous QT-IRT Review under IND 117631 dated 01/31/2016 in DARRTS

degeneration/necrosis in heart, and dose-related increased heart rates (≤ 56 beats per minute) were observed in dogs received single/repeated oral dose(s) of 5, 15 or 50 mg/kg BID up to 7 days. These observations are consistent with previous reports on dogs treated with different vasoactive drugs where dogs are considered particularly sensitive to cardiovascular toxicity.²

- In CV safety pharmacology and 28- and 90-day toxicology studies, no changes in ECG parameters were noted in monkeys at exposures comparable to (1980 ng/mL) and higher than (up to 11905 ng/mL) that was estimated in dogs receiving a single dose of 75 mg/kg.

3.4 PREVIOUS CLINICAL EXPERIENCE

Study design features of clinical trials with ECG/QTc data have been reviewed in QT-IRT report under IND 117631.¹ Appendix 6.1 provides a list of Celgene sponsored clinical studies covered in the cardiac safety evaluation (N=467 dosed, including 106 healthy subject and 361 patients). In summary, among patients under the SMQ Torsade de Pointes / QT Prolongation:

- The TEAEs of electrocardiogram QT prolonged were reported in 20 (6.1%) subjects. All 20 subjects had concurrent factors affecting the QT interval (e.g., prolonged QT interval at baseline, concomitant medications with known QT prolonging potential, or electrolytes imbalance).
- The TEAEs of syncope and loss of consciousness were reported in 11 (3.3%) subjects and 3 (0.9%) subjects, respectively. With an exception for 1 subject, these events were single episodes. In the majority of subjects, the events were assessed as not related to the study treatment and caused by the underlying disease.
- The TEAEs of cardiac arrest were reported in 6 (1.8%) subjects. All these TEAEs were reported as unrelated to treatment.
- The TEAE of ventricular tachycardia was reported as non-serious and was unrelated to treatment.
- Detailed investigation of TEAEs did not suggest cardiotoxic or QT interval prolonging potential of AG-221, although, the potential for a AG-221 drug-drug interaction, which would intensify the QT prolonging potential of other medications, cannot be excluded.

In addition, 12-lead ECGs data from 3 clinical studies (AG-221-CP-001, AG-221-CP-002, and AG221-C-002) suggested that there were no clinically significant abnormal ECG findings with single doses (between 50 and 300 mg) of AG-221 in healthy subjects.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of enasidenib's clinical pharmacology. Key clinical pharmacology characteristics are:

- High fat meal increases AUC by approximately 50% and C_{max} by 64%. The proposed label recommends dosing without food (b) (4)
- The accumulation at steady is about 8- to 11-fold in the patient population.
- Terminal half-life is 137 hours in the patient population. Steady state is expected to be reached by Day 29 (Cycle 2 Day 1).

² Histopathology of Preclinical Toxicity Studies - Interpretation and Relevance in Drug Safety Studies (Fourth Edition). Author: Peter Greaves. ISBN: 978-0-444-53856-7

- The drug is metabolized by multiple CYPs and UGTs. There is potential DDI issue when co-administered with inhibitors or inducers of CYPs and UGTs. There is potentially a need for dose adjustment in patients with hepatic impairment. However, DDI studies or dedicated hepatic impairment studies have not been conducted.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the sponsor's QTc evaluation plans under IND 117631.^{1,3} The sponsor had stated that a TQT study in healthy subjects would not be feasible/appropriate due to safety concern at high dose levels in healthy subjects and due to potentially 5~6-fold difference in clearance between healthy subjects and patients (higher clearance in healthy subjects compared to patients). Alternatively, the sponsor stated that they would “perform a rigorous evaluation of QTc interval changes in the Phase 2 expansion of the AG221-C-001 study”, to “continue to monitor and evaluate all available, reported information relevant to the possible effects of AG-221 on QTc prolongation”, and to “conduct a separate exposure-QTc analyses for quantifying the QTc prolongation risk in patients”. The QT-IRT's response stated that the sponsor's QTc evaluation plan was “acceptable” and “adequate to rule out large QTc prolongation (20 ms) for a cancer treatment drug”.

The sponsor submitted the study report “AG221-C-001-QTCPK” for enasidenib, including electronic datasets and waveforms to the ECG warehouse. The submission included enasidenib plasma concentrations and changes in QT/QTc collected from both Phase 1 and Phase 2 portions of Study AG221-C-001.

4.2 QT STUDY

4.2.1 Title

A Phase 1/2, multicenter, open-label, dose escalation and expansion, safety, pharmacokinetic (PK), pharmacodynamic (PD), and clinical activity study of orally administered AG-221 in subjects with advanced hematologic malignancies with an IDH2 mutation.

4.2.2 Protocol Number

AG221-C-001

4.2.3 Study Dates

09/20/2013 – ongoing (data cutoff: 04/15/2016)

4.2.4 Objectives

The primary objects of the study are:

- To assess the safety and tolerability of treatment with AG-221 administered continuously as a single agent dosed orally on Days 1 to 28 of a 28-day cycle in subjects with advanced hematologic malignancies;

³ Previous QT-IRT Review under IND 117631 dated 08/03/2016 in DARRTS

- To determine the MTD or maximum administered dose (MAD) and/or the RP2D of AG-221 in subjects with advanced hematologic malignancies; and
- To assess the efficacy of AG-221 as treatment for subjects with relapsed or refractory AML with an IDH2 mutation.

The primary objective of this report is to assess the effect of AG-221 on QT prolongation by analyzing the relationship between AG-221 plasma concentrations and changes in QT/QTc.

4.2.5 Study Description

4.2.5.1 Design

This is a Phase 1/2, multicenter, open-label, 3-part (Phase 1 Dose Escalation, Part 1 Expansion, and Phase 2) study in subjects with advanced hematologic malignancies with an IDH2 mutation.

4.2.5.2 Controls

There is no placebo or positive (moxifloxacin) control in this study.

4.2.5.3 Blinding

The study was conducted in an open-label manner.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

The planned study drug doses in the Phase 1 Dose Escalation part of study included 30, 50, 75, 100, and 150 mg BID and 50, 75, 100, 150, 200, 300, 450, and 650 mg QD. The Phase 1 Expansion part of the study contained approximately 100 subjects on 100 mg QD doses. The starting dose of AG-221 for the Phase 2 portion of the trial was 100 mg QD. The dose may have been increased to 200 mg QD. Table 4 summarizes the number of subject on each dose schedule at the beginning of study. It should be noted that Study AG221-C-001 contained 331 subjects and 191 of them had matching concentration and ECG data. Study report “AG221-C-001-QT/CPK” covered 191 subjects (N=119 from Phase 1 and N=72 from Phase 2).

Table 4: Number of Subjects on Different Dosing Regimen

	Study Dataset (ECG)	Concentration-QT Dataset (Time-matched ECG/PK)
30 mg BID	7	6
50 mg BID	7	3
75 mg BID	7	5
100 mg BID	8	6
150 mg BID	5	4
50 mg QD	9	7
75 mg QD	7	5
100 mg QD	238	128
150 mg QD	6	6
200 mg QD	16	11
300 mg QD	9	7
450 mg QD	5	2

	Study Dataset (ECG)	Concentration-QT Dataset (Time-matched ECG/PK)
650 mg QD	7	1
Total	331	191

4.2.6.2 Sponsor's Justification for Doses

Phase 1 Escalation Part: The starting dose, 30 mg BID was selected as one tenth of severely toxic dose (STD) in 10% rodents when the dose are normalized to body surface area (360 mg/m²/day). The highest dose to be tested is 650 mg QD.

Phase 1 Expansion and Phase 2: The starting dose, 100 mg QD, was selected based on the safety, PK, PD, and efficacy of AG-221 observed in the dose escalation portion of AG221-C-001. Evaluation of the PD response demonstrated sustained reduction in 2-HG plasma levels by Day 1 of Cycle 2 and up to 98% inhibition in most subjects with R140Q mutation at all doses. Increasing dose was associated with higher exposure and inhibition of 2-HG in subjects with R172K mutation. Although there was less pharmacodynamic inhibition of 2-HG in patients with R172K mutations, the percentage of 2-HG inhibition did not appear to directly correlate with clinical response. The 100 mg total daily dose was well tolerated and the safety profile was generally unchanged with increasing dose.

Reviewer's Comment: Majority of subjects received 100 mg QD, the proposed therapeutic dosing regimen. Furthermore, the evaluation included steady state exposures of the drug after multiple dosing. The sampling was sufficient to evaluate effect at T_{max} and any delayed effects (pre-dose samples after multiple dosing). Overall, the design was adequate to assess QT effect in order to exclude large mean QTc prolongation (20 ms) at the therapeutic exposures of this drug for the oncology indication.

4.2.6.3 Instructions with Regard to Meals

Each daily dose was to be taken at least 2 hours after fasting (water was allowed) and food intake was to be delayed for at least 1 hour after study drug administration.

Reviewer's Comment: Because high fat meal increases C_{max} by 64%, the QT assessment with dosing under fed state would have ensured maximal exposure coverage. But, because the dosing is planned to be in fasted state for labeling, the sponsor conducted the study AG221-C-001 with dosing in fasted state. Considering that the extent of accumulation with multiple dosing is several fold (8- to 11-fold), the impact of administration of one (or a few) doses with food on overall C_{max} would not be significant compared to the overall accumulation. Thus, the followed dosing instruction with regard to meals in this study is reasonably acceptable to assess QTc effects.

4.2.6.4 ECG and PK Assessments

The detailed PK/ECG assessment schedules in both phases of the study are included in Appendix 6.2. A brief summary is included below.

Phase 1:

PK: For the first 3 subjects enrolled in a cohort during the dose escalation phase and the first 15 subjects enrolled in each arm of Part 1 expansion (unless approved by the medical monitor to omit the assessment), a single dose of AG-221 was to be administered on Day -3 (ie, 3 days prior

to their scheduled C1D1 dose). Blood samples were to be drawn prior to the single-dose administration of AG-221 (within 30 minutes) and at the following time points after administration: 30 (\pm 10) minutes and 1, 2, 3, 4, 6, 8, and 10 hours, (\pm 10 minutes), and 24, 48, and 72 hours (\pm 1 hour). After 72 hours of blood sample collection, subjects were to begin oral daily dosing of AG-221 (ie, C1D1). The PK/PD profile from Day -3 through Day 1 was optional for additional subjects enrolled in the dose escalation phase (ie, for any subjects beyond the 3 initial subjects enrolled in a cohort).

All subjects in the dose escalation phase and Part 1 expansion were to undergo 10-hour PK/PD sampling on C1D15, C2D1, and C4D1. For this profile, 1 blood sample was to be drawn immediately prior to (within 30 minutes) that day's first dose of AG-221 (ie, dosing with AG-221 occurred at the clinical site); subsequent blood samples were to be drawn at the following time points after dosing: 30 minutes, and 1, 2, 3, 4, 6, 8, and 10 hours (\pm 10 minutes). Pre-dose blood samples (trough) were to be obtained for subjects in the dose escalation phase and Part 1 expansion on C1D1 (for those subjects who did not undergo the Day -3 sampling), C1D8, C1D22, C2D15, C3D1, C3D15, C5D1 and Day 1 of all cycles thereafter. Additionally, blood samples were to be drawn at the EOT Visit.

ECG: For Phase 1 subjects, a single 12-lead ECG was to be obtained at screening, on Days 8, 15, and 22 of Cycle 1, on Days 1 and 15 of Cycle 2, on Day 1 of each treatment cycle thereafter, at the EOT visit, and at the Follow-up visit. A single 12-lead ECG was also to be obtained, as clinically indicated. Additionally, serial single 12-lead ECGs were to be obtained following the first dose of study treatment (ie, on Day -3 for subjects undergoing the 72-hour PK/PD profile or on C1D1 for subjects who did not have the Day -3 assessment) at the following times: predose, and 30 \pm 10 minutes and 2, 4, 6, and 8 hours (\pm 15 minutes) postdose following the morning administration of study drug.

Phase 2:

PK: Blood samples for PK assessment were to be drawn on C1D1 pre-dose (within 30 minutes) and post-dose at the following time points: 2, 4, 6, and 8 hours (\pm 10 minutes); and on C2D1 pre-dose (within 30 minutes) and post-dose at the following time points: 2, 4, 6, and 8 hours (\pm 10 minutes). Additional blood samples for PK/PD assessments were to be drawn on C1D2, C2D2, and C3D1 pre-dose (within 30 minutes). In addition, blood samples for PK/PD assessments were also to be drawn at the EOT visit.

ECG: Triplicate 12 lead ECGs, were to be obtained approximately 2 minutes apart pre-dose and 2, 4, and 6 hours (\pm 15 minutes) post-dose on Day 1 of Cycles 1 and 2; a triplicate ECG was also to be obtained at the EOT visit. Subjects were to be instructed to take their dose of AG-221 in clinic on these days. Single 12-lead ECGs were to be obtained in these subjects at screening, anytime post-dose on Day 1 of all cycles beginning with Cycle 3, and at the Follow-up visit. A single 12-lead ECG was also to be obtained, as clinically indicated. All single and triplicate 12-lead ECGs were to be obtained following 3 minutes of recumbency.

Reviewer's Comments:

- *Terminal half-life of enasidenib in patients is 137 hrs. Following 100 mg single doses in patients (N=121), T_{max} is about 4 hours (range: 0.7-72 hours). Data collected on Cycle 2 Day 1 (Day 29 from first treatment, up to 6 hours post-dose) in the Phase 2 portion should be*

able to represent steady state exposure around T_{max} . Steady state data is only available for the 100 mg QD treatment.

- Due to high accumulation (8- to 11-fold) at steady state, exposure data collected after single doses (30 mg – 650 mg in the Phase 1 portion and Cycle 1 Day 1 data in the Phase 2 portion) is much lesser than the therapeutic exposures expected with multiple dosing of therapeutic dosing regimen (100 mg QD).
- Any information beyond Cycle 2 is not included in the reviewer's analysis because of small sample size.

4.2.6.5 Baseline

Non-missing value at last visit date after sorting mapped visit in an order of visit 1.01, Day -3, and Day -9.

4.2.7 ECG Collection

Single 12-lead ECGs were obtained from subjects in the Phase 1 portion of the study at daily dose from 50 mg to 650 mg, and triplicate 12-lead ECG results were obtained for subjects in the Phase 2 portion of the study at the starting daily dose of 100 mg.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Phase 1 Dose Escalation + Phase 1 Dose Expansion:

A total of 239 subjects have been treated with AG-221 in combined Phase 1, with 176 subjects having R/R AML, and 63 subjects having other advanced hematologic malignancies including untreated AML (37 subjects), MDS (17 subjects), and other advanced hematologic malignancies (9 subjects).

Phase 2 Dose Expansion:

A total of 91 subjects were treated with AG-221(100 mg QD) as of the 15 Apr 2016 data cutoff. Of the 91 subjects, 54 (59.3%) were ongoing and receiving study treatment and 37 (40.7%) had discontinued treatment at the time of the data cutoff. Reasons for treatment discontinuation included disease progression (11 subjects; 29.7%), death (9 subjects; 24.3%), adverse event (7 subjects; 18.9%), other (5 subjects; 13.5%), withdrawal of consent (3 subjects; 8.1%), and bone marrow transplant (2 subjects; 5.4%).

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary analysis is concentration-QTc analysis. Please refer to section 4.2.8.4.

4.2.8.2.2 Assay Sensitivity

There is no positive control used in this study.

4.2.8.2.3 Categorical Analysis

The sponsor's categorical analysis is presented below.

Table 5: Maximum Postbaseline Absolute QTcF Interval Test Results for All Subjects and Subjects with R/R AML by Total Daily Dose of 100 mg and Overall - Combined Phase 1 (Safety Analysis Set)

QTcF Category	R/R AML 100 mg Daily Dose (N = 109) n (%)	All R/R AML (N = 176) n (%)	All Subjects (N = 239) n (%)
Baseline value ^a			
≤ 480 msec	105 (96.3)	170 (96.6)	230 (96.2)
> 480 to ≤ 500 msec	3 (2.8)	4 (2.3)	6 (2.5)
> 500 msec	1 (0.9)	1 (0.6)	2 (0.8)
QTcF maximum postbaseline value			
≤ 480 msec	97 (89.0)	155 (88.1)	211 (88.3)
> 480 to ≤ 500 msec	6 (5.5)	14 (8.0)	17 (7.1)
> 500 msec	6 (5.5)	7 (4.0)	11 (4.6)
QTcF increased from baseline			
≤ 30 msec	67 (61.5)	111 (63.1)	163 (68.2)
> 30 to ≤ 60 msec	36 (33.0)	55 (31.3)	65 (27.2)
> 60 msec	6 (5.5)	9 (5.1)	10 (4.2)

QTcF = QT corrected based on Fridericia's equation; R/R AML = relapsed or refractory acute myeloid leukemia.

^a Baseline = non-missing value at last visit date after sorting mapped visit in an order of visit 1.01, Day -3 and Day -9.

Data as of the 15 Apr 2016 cutoff.

Source: Sponsor's Clinical Study Report (Phase 1), page 269.

Table 6: Maximum QTcF Interval Values for All Subjects – Phase 2 (Safety Analysis Set)

QTcF Category	100 mg QD (N = 91) n (%)
Baseline value ^a	
≤ 480 ms	89 (97.8)
> 480 to ≤ 500 ms	1 (1.1)
> 500 ms	0 (0.0)
QTcF maximum post-baseline value	
≤ 480 ms	84 (92.3)
> 480 to ≤ 500 ms	7 (7.7)
> 500 ms	0 (0.0)
QTcF increased from baseline	
≤ 30 ms	68 (74.7)
> 30 to ≤ 60 ms	18 (19.8)
> 60 ms	4 (4.4)

Source: Sponsor's Clinical Study Report (Phase 2), page 124.

4.2.8.3 Safety Analysis

Phase 1 Dose Escalation + Phase 1 Dose Expansion:

Treatment-emergent AEs within the MedDRA SOC of Cardiac Disorders were reported for 24.7% of all subjects. The most commonly reported preferred terms ($\geq 2\%$ of all subjects) within this SOC were atrial fibrillation (5.0%), tachycardia (5.0%), and sinus tachycardia (2.1%). A total of 22 subjects had cardiac disorders that were considered SAEs. The most commonly ($\geq 1\%$ of all subjects) reported SAEs within the MedDRA SOC of Cardiac Disorders were atrial fibrillation (3.3%; 8 subjects) and cardiac arrest (1.7%; 4 subjects). Cardiac events considered by the investigator to be related to AG-221 treatment were reported for 5 subjects (2.1%) overall and included atrial fibrillation, cardiac failure, cardiac tamponade, diastolic dysfunction, left ventricular dysfunction, pericardial effusion, and tachycardia (0.4%; 1 subject each). Treatment-related fatal events of cardiac tamponade and pericardial effusion in an 83-year-old subject that were attributed to complications of untreated differentiation syndrome are further discussed. The incidence of TEAEs of atrial fibrillation in subjects ≥ 75 years of age in this study (1 subject; 1.5%) was consistent with what is expected in this age group (5% for > 65 years and 10% for > 80 years of age). Two subjects (0.8%) discontinued study drug due to cardiac events (cardiac tamponade and supraventricular tachycardia).

Treatment-emergent AEs within the SMQ of Torsade de pointes/QT Prolongation were reported in 13.4% of all subjects.

Subjects with TEAEs of QT prolongation or who had prolongation evident through central ECG analysis (postbaseline value > 500 msec or an increase from baseline of > 60 msec) are presented. Overall, these subjects had other concurrent factors affecting the QT interval (eg, prolonged QT interval at baseline, concomitant administration of medications with known QT prolonging potential, or electrolyte imbalance). Among the 33 subjects meeting above listed category,

- 29 subjects had received concomitant medications (often multiple) known for their QT prolonging effect. Such medications often were used for the treatment of concurrent infections, with QTcF interval returning to baseline values after the resolution of infection.
- 14 subjects had concurrent electrolyte abnormalities, such as low potassium, magnesium, or calcium levels that could have triggered QT interval prolongation.
- 9 subjects had prolonged pretreatment QTcF interval and/or experienced small changes from baseline (< 30 msec) in QTcF interval duration postbaseline.
- 5 subjects had heart rate regulated by pacemakers, which might make QT interval uninterruptable.

Treatment-emergent AEs of syncope and loss of consciousness were reported for 13 subjects. The majority of these events were single episodes. In 1 subject, intermittent syncope lasted for 39 days. In the majority of subjects (12 of 13 subjects), the events were assessed as not related to the study drug and were attributed to the underlying disease. One TEAE of syncope was assessed by the investigator as related to AG-221 treatment:

Subject 104-005, with medical history of multiple sclerosis and muscular weakness, experienced a syncopal episode on Day 136 on treatment, concurrent with TEAEs of fall and contusion; all these events were assessed as treatment related by the investigator. The subject experienced

another fall associated with humerus fracture that was attributed to multiple sclerosis and muscular weakness.

All TEAEs of cardiac arrest were reported as unrelated to AG-221 treatment and were assessed as the cause of death in subjects treated for pneumonia, febrile neutropenia with respiratory failure, leukocytosis, and acidosis.

The TEAE of sudden death was assessed as unrelated to AG-221 treatment and was reported as the result of a road traffic accident.

Ventricular tachycardia was reported as a nonserious TEAE that was unrelated to AG-221 treatment, resolved in 1 day, and was concurrent with a TEAE of pyrexia.

Central ECG laboratory assessment showed no clinically meaningful mean changes in heart rate or any of the ECG intervals.

Detailed investigation of TEAEs in the SMQ Torsade de pointes/QT Prolongation and predefined QT interval prolongations based on the central ECG laboratory measurements shows multiple confounding factors that are likely contributing to QT interval prolongation and complicating signal detection

Overall, current clinical data does not indicate a QT prolonging potential of AG-221.

Phase 2 Dose Expansion:

Treatment-emergent adverse events within the MedDRA SOC of Cardiac Disorders were reported for 19.8% of subjects. The most commonly reported preferred terms ($\geq 2\%$ of all subjects) within this SOC were tachycardia (4.4%), palpitations (3.3%), atrial fibrillation, cardiac arrest, and sinus bradycardia (2.2% each). A total of 7 subjects (7.7%) had cardiac disorders that were considered SAEs. The most commonly ($\geq 2\%$ of all subjects) reported SAE within the Cardiac disorder SOC was cardiac arrest (2.2%).

Cardiac events considered by the investigator to be related to AG-221 treatment were reported for 2 subjects (2.2%) and included pericarditis and tachycardia (1.1%; 1 subject each). One subject (1.1%) discontinued study drug due to cardiac events (cardiac failure).

Treatment-emergent adverse events with the SMQ of Torsade de pointes/QT prolongation were reported in 6 (6.6%) of all subjects. Overall, subjects with TEAEs of QT prolongation or who had prolongation evident though central ECG analysis (post-baseline value > 500 msec or an increase > 60 msec) had concurrent factors affecting the QT interval (eg, concomitant administration of medications with known QT prolonging potential, or electrolytes imbalance).

An adverse event of loss of consciousness was reported in 1 subject and was assessed as not related to the study treatment. All TEAEs of cardiac arrest were reported as unrelated to AG-221 treatment and were assessed as the cause of death in subjects who did not experience QT interval prolongation.

Central ECG laboratory assessment showed no clinically meaningful mean changes in heart rate or any of the ECG intervals.

Detailed investigation of TEAEs in the SMQ Torsade de pointes/QT Prolongation and predefined QT interval prolongations based on the central ECG laboratory measurements shows multiple confounding factors that are likely contributing to QT interval prolongation and complicating signal detection.

The current clinical data does not indicate a QT prolonging potential of AG-221.

4.2.8.4 Clinical Pharmacology

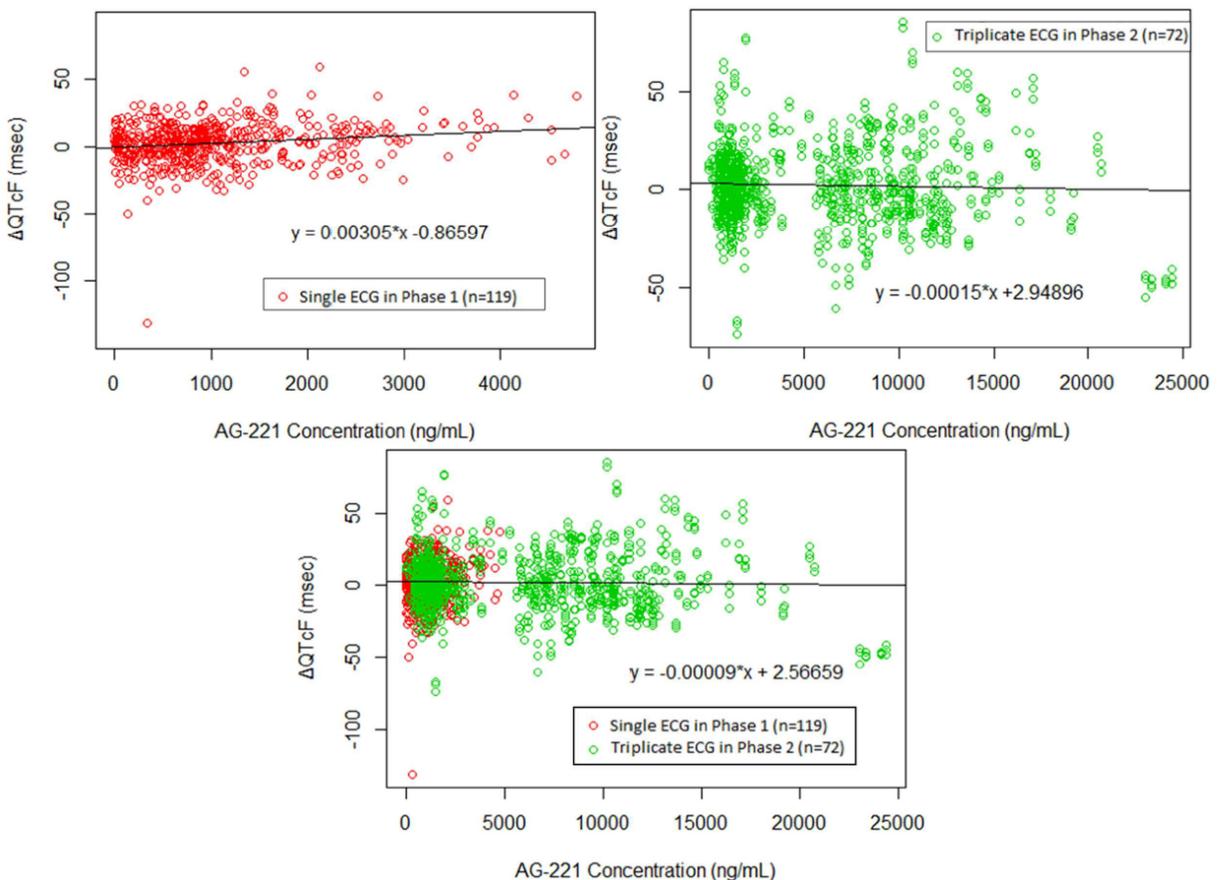
4.2.8.4.1 Pharmacokinetic Analysis

The sponsor did not present enasidenib PK results for the analysis dataset.

4.2.8.4.2 Exposure-Response Analysis

The sponsor's analysis (Figure 1) suggested there was no obvious correlation between Δ QTcF and AG-221 plasma concentrations after a single dose up to 650 mg with a concentration up to 4790 ng/mL (Phase 1 portion) or after single and multiple doses of 100 mg QD with a concentration up to 24400 ng/mL (Phase 2 portion, Cycle 1 Day 1 and Cycle 2 Day 1). A linear regression model was used to fit the data and the slope and intercept of regression equations were summarized in Table 7.

Figure 1: Change-from-Baseline in Corrected QTcF Interval versus AG-221 Concentration for Subjects in Study AG221-C-001 Phase 1 (Upper Left), Phase 2 (Upper Right), and Phase 1 and 2 combined (Lower).



Source: Study AG221-C-001 QTCPK report, Figures 1-3

Table 7: Slope and Intercept of Regression Equations in Change-from-Baseline in Corrected QTcF (Δ QTcF) versus Concentration Analyses

Study Phase	Number of subjects with both PK and QTcF data	Dose	Concentration ^a (ng/mL)	Δ QTcF ^b (ms)	Estimates of slope	Estimates of intercept
Phase 1	119	Single dose of 50-650 mg	849 (1.2, 4790)	2.4 ± 14.9	0.00305	-0.86597
Phase 2	72	Single and Multiple doses of 100 mg QD	2600 (21, 24400)	2.2 ± 10.4	-0.00015	2.84896
Combined Phase 1 and 2	191	Single dose of 50-650 mg in Phase 1 and Multiple doses of 100 mg QD in Phase 2	1470 (1.2, 24400)	2.2 ± 18.0	-0.00009	2.56659

Δ QTcF=Change-from-baseline of corrected QT interval using Fridericia formula; PK=pharmacokinetics; QD=once daily.

^a median (minimum, maximum)

^b mean ± SD.

Source: Study AG221-C-001 QTCPK report, Table 2

Reviewer's Analysis: A plot of Δ QTcF vs. drug concentrations is presented in Section 5.3.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

QTcF will be used in central tendency analysis and outlier analyses. There was no significant heart rate effect with treatment.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 Central Tendency Analysis

The descriptive statistics for AG-221 100 mg QD is listed in the following table:

Table 8: Descriptive Summary of Δ QTcF for AG-221 100 mg QD (Dose Escalation + Phase 1 Dose Expansion + Phase 2 Dose Expansion)

TREAT	VISIT	N	Mean	Lower Limit of 90% CI	Upper Limit of 90% CI
100 mg QD	Cycle 01 Day 1 (30 minutes post dose)	85	0.1	-3.3	3.4
	Cycle 01 Day 1 (2 hours post dose)	177	2.2	0.3	4.1
	Cycle 01 Day 1 (4 hours post dose)	176	0.0	-2.4	2.3
	Cycle 01 Day 1 (6 hours post dose)	176	-1.4	-3.6	0.7
	Cycle 01 Day 1 (8 hours post dose)	83	-3.4	-7.5	0.8
	Cycle 02 Day 1 (2 hours post dose)	67	6.5	2.1	11.0
	Cycle 02 Day 1 (4 hours post dose)	67	2.0	-2.1	6.0
	Cycle 02 Day 1 (6 hours post dose)	69	1.7	-2.3	5.6

5.2.1.2 Assay Sensitivity Analysis

Assay sensitivity analysis cannot be performed as there is no positive control in this study.

5.2.1.3 Categorical Analysis

Categorical analysis of QTcF is presented in Table 9 and Table 10 . There are 2 subjects with QTcF above 500 ms during the Phase 1 dose escalation period. Nine subjects treated with 100 mg QD had QTcF above 500 ms during the Phase 1 dose expansion and Phase 2 dose expansion period.

Table 9: Categorical Analysis for QTcF (Phase 1 Dose Escalation)

Treatment Group	Total N		Value<=450 ms		450 ms<Value<=480 ms		480 ms<Value<=500 ms		Value>500	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
All Doses	114	1726	62 (54.4%)	1525 (88.4%)	38 (33.3%)	173 (10.0%)	12 (10.5%)	26 (1.5%)	2 (1.8%)	2 (0.1%)

Table 10: Categorical Analysis for QTcF (Phase 1 Dose Expansion + Phase 2 Dose Expansion)

Treatment Group	Total N		Value<=450 ms		450 ms<Value<=480 ms		480 ms<Value<=500 ms		Value>500	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
100 mg QD	215	2370	120 (55.8%)	1960 (82.7%)	78 (36.3%)	332 (14.0%)	8 (3.7%)	57 (2.4%)	9 (4.2%)	21 (0.9%)

Categorical analysis of Δ QTcF is presented in Table 11 and Table 12. There are 6 subjects with Δ QTcF above 60 ms during the Phase 1 dose escalation period. Eight subjects treated with 100 mg QD had Δ QTcF above 60 ms during the Phase 1 dose expansion and Phase 2 dose expansion period.

Table 11: Categorical Analysis of Δ QTcF (Phase 1 Dose Escalation)

Treatment Group	Total N		Value<=30 ms		30 ms<Value<=60 ms		Value>60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
All Doses	113	1725	78 (69.0%)	1641 (95.1%)	29 (25.7%)	75 (4.3%)	6 (5.3%)	9 (0.5%)

Table 12: Categorical Analysis of Δ QTcF (Phase 1 Dose Expansion + Phase 2 Dose Expansion)

Treatment Group	Total N		Value \leq 30 ms		30 ms<Value \leq 60 ms		Value>60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
100 mg QD	214	2368	158 (73.8%)	2223 (93.9%)	48 (22.4%)	136 (5.7%)	8 (3.7%)	9 (0.4%)

5.2.2 HR Analysis

The categorical analysis results for HR are presented in Table 13 and Table 14 . There are 40 subjects with HR above 100 bpm during the Phase 1 dose escalation period. Fifty-one subjects treated with 100 mg QD had HR above 100 bpm during the Phase 1 dose expansion and Phase 2 dose expansion period.

Table 13: Categorical Analysis of HR (Phase 1 Dose Escalation)

Treatment Group	Total N		Value \leq 100 bpm		Value>100 bpm	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
All Doses	114	1734	74 (64.9%)	1622 (93.5%)	40 (35.1%)	112 (6.5%)

Table 14: Categorical Analysis of HR (Phase 1 Dose Expansion + Phase 2 Dose Expansion)

Treatment Group	Total N		Value \leq 100 bpm		Value>100 bpm	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
100 mg QD	215	2375	164 (76.3%)	2264 (95.3%)	51 (23.7%)	111 (4.7%)

5.2.3 PR Analysis

The outlier analysis results for PR are presented in Table 15 and Table 16. There are 25 subjects with PR above 200 ms during the Phase 1 dose escalation period. Thirty-seven subjects treated with 100 mg QD had PR above 200 ms during the Phase 1 dose expansion and Phase 2 dose expansion period.

Table 15: Categorical Analysis for PR (Phase 1 Dose Escalation)

Treatment Group	Total N		Value \leq 200 ms		Value>200 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
100 mg QD	215	2375	164 (76.3%)	2264 (95.3%)	51 (23.7%)	111 (4.7%)

Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
All Doses	114	1701	89 (78.1%)	1515 (89.1%)	25 (21.9%)	186 (10.9%)

Table 16: Categorical Analysis for PR (Phase 1 Dose Expansion + Phase 2 Dose Expansion)

Treatment Group	Total N		Value<=200 ms		Value>200 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
100 mg QD	209	2282	172 (82.3%)	2097 (91.9%)	37 (17.7%)	185 (8.1%)

5.2.4 QRS Analysis

The outlier analysis results for PR are presented in Table 17 and Table 18. There are 16 subjects with QRS interval above 110 ms during the Phase 1 dose escalation period. Twenty-five subjects treated with 100 mg QD had QRS interval above 110 ms during the Phase 1 dose expansion and Phase 2 dose expansion period.

Table 17: Categorical Analysis for QRS (Phase 1 Dose Escalation)

Treatment Group	Total N		Value<=100 ms		100 ms<Value<=110 ms		Value>110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
All Doses	114	1734	87 (76.3%)	1470 (84.8%)	11 (9.6%)	86 (5.0%)	16 (14.0%)	178 (10.3%)

Table 18: Categorical Analysis for QRS (Phase 1 Dose Expansion + Phase 2 Dose Expansion)

Treatment Group	Total N		Value<=100 ms		100 ms<Value<=110 ms		Value>110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
100 mg QD	215	2375	160 (74.4%)	2004 (84.4%)	30 (14.0%)	153 (6.4%)	25 (11.6%)	218 (9.2%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The analysis dataset contained 331 subjects in Study AG221-C-001; 191 of these have time-matched ECG/PK data.

- 73 out of 191 subjects participated in Phase 2 part of the study with triplicate ECG data, where only 100 mg QD dosing was used. 65 out of the 73 subjects provided data on Cycle 1 Day 1 (Phase 2 Cycle 1) and 51 out of the 73 provided data on Cycle 2 Day 1 (Phase 2 Cycle 2).

- 118 out of 191 subjects participated in Phase 1 part of the study with single ECG data. One subject (SUBJID=104-002) had 1 QTcF.CFB value of -131 ms (potential outlier observation), and this observation was removed from further analysis.

Drug exposures on Cycle 2 Day 1 with multiple 100 mg QD dosing are substantially higher than the single dose data with doses as high as 650 mg in Phase 1 (Table 19). This review deals with pooled data from both Phase 1 and Phase 2 for concentration-QT analysis, with Phase 2 Cycle 2 data representing the clinically relevant exposures and Phase 1 and Phase 2 Cycle 1 data providing information at lower exposure ranges.

Table 19: C_{max} (Mean / SD) by Phase of the Study and Treatment Regimens

		Number of Subjects	Mean C _{max} (ng/mL)	SD for C _{max}
Phase 1	30 mg BID	6	528	276
	50 mg BID	3	599	379
	75 mg BID	5	1116	415
	100 mg BID	7	1513	521
	150 mg BID	4	1905	350
	50 mg QD	7	620	236
	75 mg QD	5	840	416
	100 mg QD	54	1336	843
	150 mg QD	6	1627	477
	200 mg QD	11	2072	870
	300 mg QD	7	2814	1306
	450 mg QD	2	2465	290
	650 mg QD	1	4670	NA
Phase 2 Cycle 1	100 mg QD	65	1470	650
Phase 2 Cycle 2	100 mg QD	51	11393	4341
Full		191	NA	NA

The drug concentration-time profiles, Δ QTcF-time profiles, and Δ HR-time profiles in Phase 2 (Cycle 1 and Cycle 2) are illustrated in Figure 2 and exploration of hysteresis for Δ QTcF is shown in Figure 3. Substantial accumulation in drug exposure was observed between the 2 cycles. Large variations were observed with drug concentration at each time point.

Figure 2: Mean Time Profiles for Drug Concentration, Δ QTcF, and Δ HR in Phase 2 Cycle 1 (Left, N=65) and Phase 2 Cycle 2 (Right, N=51).

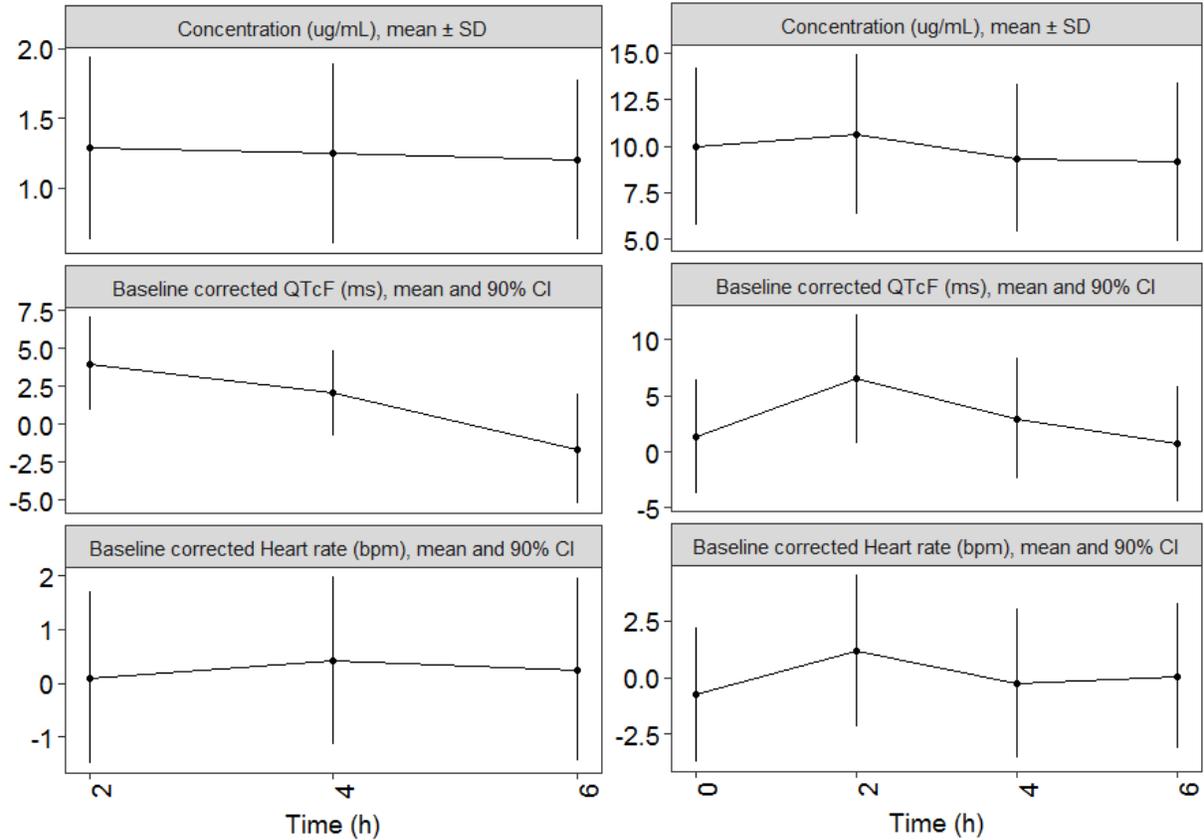
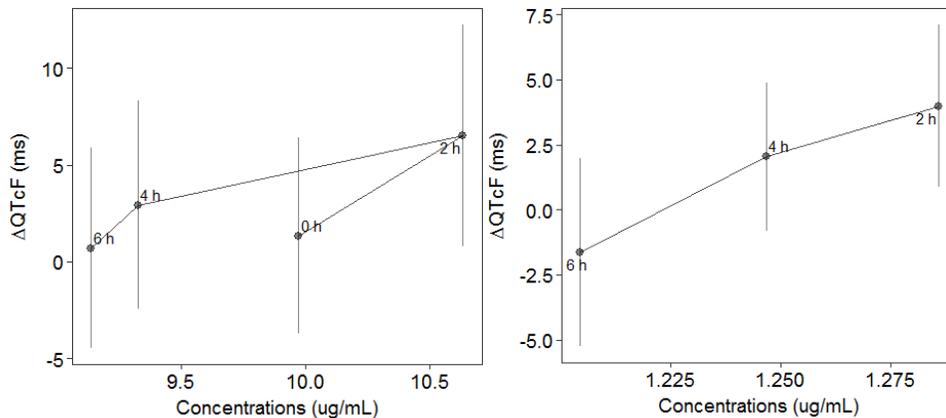


Figure 3: Hysteresis Examination in Phase 2 Cycle 1 (Left, N=65) and Phase 2 Cycle 2 (Right, N=51).



The relationship between Δ QTcF and enasidenib concentrations at steady state is visualized in Figure 4 with no evident exposure-response relationship. For this analysis, the full dataset for time-matched ECG/PK was fitted with linear mixed-effects model, with Δ QTcF as the response variable, fixed effect for concentration and random effect (subject) on both slope and intercept. The parameter estimates for the model are presented in Table 20. The relationship between Δ QTcF and enasidenib concentration was not statistically significant ($p=0.16$), with slope

estimate being 0.35 and 90% CI being [-0.14, 0.84] ms/($\mu\text{g}/\text{mL}$). The geometric mean C_{max} at steady state with 100 mg QD dose was 10.51 $\mu\text{g}/\text{mL}$. The predicted ΔQTcF at this concentration was 5.26 ms (90% CI: [1.13, 9.39]) as shown in Table 21. Thus, the predicted upper bound of 90% CI for the ΔQTcF response at this therapeutic C_{max} was below the threshold of 10 ms.

Figure 4: ΔQTcF - Enasidenib Concentration Relationship Based on Data from Study AG221-C-001. The points and bars represent ΔQTcF mean and 90% CI at the median concentration in a bin. Black line represents predictions from the prespecified linear mixed effects model for concentration- ΔQTcF relationship. The shaded area represents the 90% CI of the prediction.

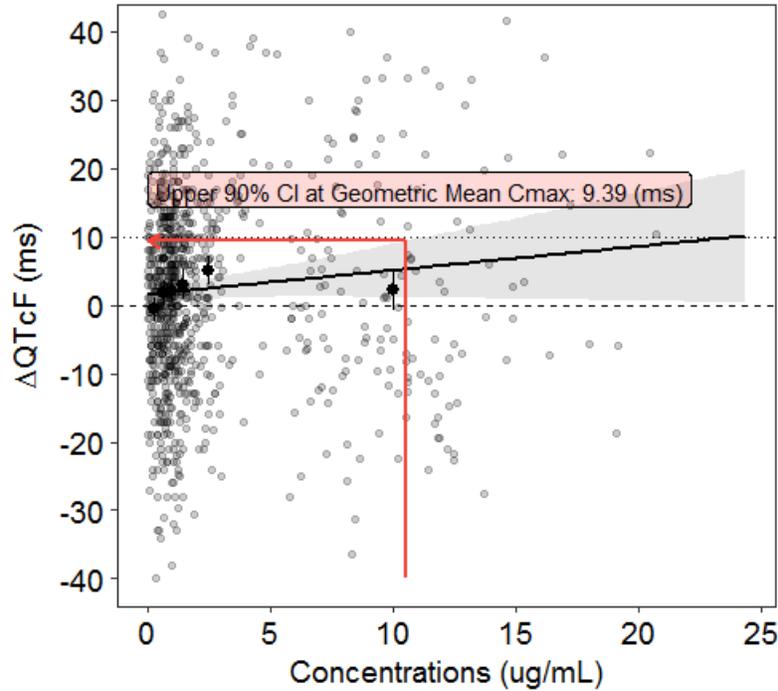


Table 20: Enasidenib Concentration- ΔQTcF Relationship Fixed Effects Parameter Estimates and Associated Precision, Based on Kenward-Roger Approximation

Fixed effect parameter	Estimate	Lower 95% CI	Upper 95% CI	Relative Standard Error (%)	p-value
Intercept, ms	1.58	-0.24	3.41	58.60	0.09
Concentration, ms/($\mu\text{g}/\text{mL}$)	0.35	-0.14	0.84	71.09	0.16

Table 21: ΔQTcF Estimates at the Geometric Mean C_{max} at Steady State (Phase 2 Cycle 2 Day 1) for 100 mg QD Dosing

Concentration ($\mu\text{g}/\text{ml}$)	Estimate (ms)	Lower 90% CI (ms)	Upper 90% CI (ms)
10.51	5.26	1.13	9.39

5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

Adverse events identified to be of clinical importance per the ICH E14 guidelines such as prolonged QTc interval, ventricular arrhythmia and syncope occurred in this study. A summary of cardiac AEs are presented in section 4.2.8.3 of this review. Subjects with QTc prolongation had other concurrent factors (eg, prolonged QT interval at baseline, concomitant administration of medications with known QT prolonging potential, or electrolyte imbalances) affecting the QT interval.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There were no clinically meaningful mean changes in heart rate and other ECG intervals (e.g. PR and QRS) as reported in Sponsor's Table 14.3.5.16.6.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

<p>Therapeutic dose and exposure <i>Include maximum proposed clinical dosing regimen</i> <i>Mean (%CV)</i> <i>C_{max} and AUC at the single maximum proposed clinical dose</i> <i>Mean (%CV)</i> <i>C_{max} and AUC at the steady state with the maximum proposed clinical dosing regimen</i></p>	<p>The proposed starting and maximum dose for all patients is 100 mg once daily.</p> <ul style="list-style-type: none"> • <u>Single 100mg oral doses</u> in fasted healthy volunteers (Study AG-221-CP-001; N=10) yielded geometric mean (%CV) AG-221 C_{max} and AUC_{0h-72h} of 822 ng/mL (38.5) and 33,510 ng·h/mL (22.1), respectively.¹ • <u>Single 100mg oral doses</u> in fasted advanced hematologic malignancy patients (Study AG221-C-001 Phase 1; N=57) demonstrated geometric mean (%CV) AG-221 C_{max} and AUC_{0h-72h} of 1272 ng/mL (56.4) and 58,381 ng·hr/mL (60.7), respectively.¹ • No multiple dose studies were performed in healthy volunteers. • <u>Steady state oral dosing of 100mg QD</u> in hematologic malignancy patients (Study AG221-C-001 Phase 1; N=102) yielded geometric mean (%CV) AG-221 C_{max} and AUC_{0h-10h} of 13,255 ng/mL (46.3) and 106,661 ng·h/mL (47.7), respectively.² <p>¹ With single doses in healthy volunteers, AUC₀₋₇₂ represents ~68% of AUC_{0-∞}. ² Steady state AUC over the 24h dosing interval was observed to be 258,506 ng·h/mL (36.8) in Study AG221-C-001 Phase 2 (N=17).</p>
<p>Maximum tolerated dose <i>Include if studied or NOAEL dose</i></p>	<p>Phase 1/2 clinical safety data (Study AG221-C-001; n = 330) have shown that AG-221 is generally well tolerated at total daily doses up to 650 mg.</p> <p>In the dose escalation portion of this study (n=113), the maximum tolerated dose was not reached.</p>
<p>Principal adverse events <i>Include most common adverse events; dose limiting adverse events</i></p>	<p>Among 330 subjects treated in the Phase 1/2 AG221-C-001 (advanced hematologic malignancy) study.</p> <p>The most commonly reported TEAEs (≥ 20% of all subjects) were nausea (45.8%), fatigue (40.0%), diarrhea (35.8%), blood bilirubin increased (33.0%), decreased appetite (31.5%), anemia and vomiting (30.3% each), dyspnea (29.4%), febrile neutropenia (27.9%), cough (27.3%), edema peripheral (26.1%), pyrexia (25.5%), constipation (24.8%), and hypokalemia (23.3%).</p> <p>In the overall population of 330 subjects, among the most commonly reported TEAEs, many were disorders characteristic for hematologic malignancies: blood disorders, such as anemia (30.3%), febrile neutropenia (27.9%), leukocytosis (17.9%), and thrombocytopenia (19.1%); associated infections and respiratory disorders, including dyspnea (29.4%) and cough (27.3%), as well as pneumonia (19.4%) and sepsis (13.6%), and hypotension (13.3%) commonly co-occurring with severe infection; neurologic and psychiatric symptoms, such as dizziness (11.5%), headache (16.7%), anxiety (10.6%), and insomnia (13.9%); bleeding events, such as epistaxis (13.9%); rash (11.5%); weight decreased (10.6%), and general disorders that included fatigue (40.0%) and asthenia (14.2%), pyrexia (25.5%), and peripheral edema (26.1%).</p> <p>Laboratory electrolytes abnormalities commonly observed in patients with AML (Milionis, 1999) are represented by TEAEs, hypocalcemia, hypokalemia, hypomagnesemia, and hyponatremia.</p> <p>Acute renal failure (10.0%) and blood creatinine increased (11.5%) are quite</p>

	<p>prevalent among the population of patients with hematologic malignancies, including AML (Luciano, 2014), often complicating the course of severe infection (Harris, 1991).</p> <p>Liver abnormalities are not uncommon with acute leukemia (Murakami, 2013) due to poly-pharmacy, bacterial or fungal infections, or infiltration by leukemic cells. Aspartate transaminase increased was reported in 10.0% of subjects.</p> <p>Other common TEAE, such as constipation (24.8%), back pain (13.9%), and arthralgia (12.4%), did not exceed the incidence expected in this population.</p> <p>Commonly reported TEAEs that could be associated with AG-221 treatment were represented by gastrointestinal and associated disorders including nausea (45.8%), diarrhea (35.8%), vomiting (30.3%), as well as associated decreased appetite (31.5%) and dysgeusia (10.3%). Abdominal pain reported in 13.6% of the study population is both commonly observed in AML patients (Kirkpatrick, 2003) and is a sign of above described iatrogenic effects of AG-221 treatment.</p> <p>Blood bilirubin increased, a known pharmacologic effect of AG-221, is caused by the inhibition of the UGT1A1 enzyme responsible for metabolism of bilirubin. The effect is similar to congenital UGT1A1 deficiency (eg, Gilbert's syndrome). A total of 109 (33.0%) subjects had a TEAE of blood bilirubin increased.</p> <p>Total daily doses from 50 to 650 mg were evaluated in the dose escalation portion of the study. No MTD was reached, although the 28.6%, 60.0%, and 85.7% of subjects in the 300 mg, 450 mg, and 650 mg dose groups, respectively, required dose reductions for TEAEs that did not qualify as DLT. One subject in the 650 mg dose group experienced a DLT of a non-serious TEAE of Grade 3 diarrhea requiring dose reduction.</p> <p>AG221-C-003 (solid tumor): As of the study termination, 21 subjects were enrolled into Study AG221-C-003. The TEAEs reported in $\geq 20\%$ of subjects overall were nausea (57.1%), fatigue (42.9%), anemia, diarrhea, and decreased appetite (33.3% each), and blood bilirubin increased (28.6%). One DLT of Grade 3 blood bilirubin increased was reported in the 400 mg dose group.</p> <p>Overall, no new safety signals related to AG-221 were identified based on data from Study AG221-C-003, as compared with Study AG221-C-001.</p> <p>Study AG120-221-C-001 (combination therapy for newly diagnosed AML): As of the 01 Jul 2016 data cutoff date, of the 8 subjects enrolled, 6 subjects were treated with AG-221 treatment (100 mg) in combination with induction/consolidation therapy. Five (83.3%) subjects reported at least 1 TEAE; the TEAEs reported in ≥ 2 of subjects overall were edema peripheral (4 subjects), febrile neutropenia (3 subjects), anemia, thrombocytopenia, diarrhea, bacteremia, platelet count decreased, decreased appetite, hyperuricemia, hypomagnesaemia, headache, dyspnea, and hypotension (2 subjects each).</p> <p>Study AG-221-AML-004 (R/R AML): As of the 12 Jul 2016 data cutoff date (with study treatment blinded), all 6 enrolled subjects (including the 4 subjects treated with AG-221) reported at least 1 TEAE; the TEAEs reported in ≥ 2 of</p>
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	<p>subjects were nausea (3 subjects), febrile neutropenia, fatigue, pyrexia, fall, and decreased appetite (2 subjects each).</p> <p>Studies in Healthy Subjects</p> <p>Study AG221-C-002 (food effect): Nine (30.0%) subjects reported at least 1 TEAE. Mild to moderate headache was the most common TEAE, reported in 5 (16.7%) subjects and occurring more often under fasted conditions (4 subjects, 13.8%) than under fed conditions (1 subject, 3.4%), and was the only TEAE assessed as related to AG-221.</p> <p>Study AG-221-CP-001 (Japanese PK): Twenty-one (33.9%) subjects reported at least 1 TEAE. Mild to moderate headache was the most common TEAE with an incidence of 1 (5.0%) subject in 50 mg dose level, 2 (9.1%) subjects in 100 mg dose group, and 14 (70.0%) subjects in the 300 mg AG-221 dose level, with all events reported as related to AG-221.</p> <p>Study AG-221-CP-002 (ADME): Ten (71.4%) subjects reported at least 1 TEAE. The most common TEAEs overall were gastrointestinal disorders, with a total of 10 TEAEs reported by 5 subjects.</p> <p>Overall, AG-221 was generally well tolerated at all dose levels and by all study subgroups and subpopulations. Key safety concerns identified in Study AG221-C-001 and supported by other studies in subjects and healthy volunteers were differentiation syndrome in patients with hematologic malignancies (affects > 10% population), treatment-related leukocytosis (< 10%), tumor lysis syndrome (< 10%), gastrointestinal disturbances (> 10%), and elevation of blood bilirubin (> 10%).</p>	
<p>Maximum dose tested</p>	<p>Single Dose <i>Specify dose</i></p>	<p>In healthy subjects: 300 mg In patients: 650 mg</p>
	<p>Multiple Dose <i>Specify dosing interval and duration</i></p>	<p>No multiple doses tested in healthy subjects. 650 mg QD in patients</p>
<p>Exposures Achieved at Maximum Tested Dose</p>	<p>Single Dose <i>Mean (%CV) C_{max} and AUC</i></p>	<p><u>In healthy subjects:</u> Exposure following 300 mg single doses: (in Japanese), AUC_{0-∞} = 170,000 ng•h/mL (44.6), C_{max} = 2030 ng/mL (34.3); (in Caucasians), AUC_{0-∞} = 163,000 ng•h/mL (44.9), C_{max} = 1780 ng/mL (27.8).</p> <p><u>In patients:</u> Exposure following 650 mg single dose (N=1) was AUC_{0h-10h} = 38,711 ng•h/mL and C_{max} = 4670 ng/mL</p> <p>Given the limited sample size, the data of exposure at 450 mg single dose is also provided below: Exposure following 450 mg single doses (N=2)</p>

		AUC _{0h-10h} = 19,961 ng·h/mL, AUC _{0h-72h} = 244,130 ng·h/mL, C _{max} = 3031 ng/mL (N=2).
	Multiple Dose <i>Mean (%CV) Cmax and AUC</i>	<u>In patients (AG221-C-001 Phase 1):</u> Steady state exposure following 650 mg QD oral dosing (N=3) was AUC _{0h-10h} = 269,750 ng·h/mL (CV% not calculated), C _{max} = 35,269 ng/mL (10.7).
Range of linear PK <i>Specify dosing regimen</i>	In patients with advanced hematologic malignancies, systemic exposure of AG-221 following single oral dose and multiple doses at steady state generally increased with dose in an approximately dose proportional manner over 50 mg to 450 mg daily dose range.	
Accumulation at steady state <i>Mean (%CV); specify dosing regimen</i>	Accumulation was 8- to 11-fold in patients with advanced hematologic malignancies when administered once daily.	
Metabolites <i>Include listing of all metabolites and activity</i>	Biotransformation of AG-221 in humans included N-dealkylation (AGI-16903, M1), oxidation (M2 [AGI-17011] and M6), glucuronidation and a combination of these pathways. Based on the results from AG-221-CP-002 study: TRA: AUC _{24hr} = 24200 h*ngEq/mL, AG-221: AUC _{24hr} = 21600 h*ngEq/mL, %AUC Ratio to TRA=89% M1: AUC _{24hr} = 2520 h*ngEq/mL, %AUC Ratio to TRA=10% M2: AUC _{24hr} = 61.4 h*ngEq/mL, %AUC Ratio to TRA=0.3% M6: AUC _{24hr} = 15.1 h*ngEq/mL, %AUC Ratio to TRA=0.06%	
Absorption	Absolute/Relative Bioavailability <i>Mean (%CV)</i>	57.2% (10.8)
	T_{max} • <i>Median (range) for parent</i> • <i>Median (range) for metabolites</i>	<ul style="list-style-type: none"> • Median (range) for parent <u>Following 100 mg single doses in healthy male subjects: T_{max} is ~3-4 (1, 48) h based on combined results from Studies AG221-C-002, AG-221-CP-001 (Caucasian), and AG-221-CP-002 (N=45 total)</u> <u>Following 100 mg single doses in patients, T_{max} is ~4 (0.7, 72) h based on combined Phase 1 & 2 results from Study AG221-C-001 (N=121).</u> • Median (range) on metabolite M1 (AGI-16903) <u>Following 100 mg single doses in healthy male subjects: T_{max} is ~4 (1, 48) h based on results from Study AG-221-CP-001 (N=10)</u> <u>Following 100 mg single doses in patients, T_{max} is ~ 23 (2 - 74) h based on combined Phase 1 & 2 results from Study AG221-C-001 (N=118).</u>
Distribution	V_d/F or V_d <i>Mean (%CV)</i>	V _d is ~56 L following IV administration in healthy subjects.
	% bound <i>Mean (%CV)</i>	98.5% and 96.6% for AG-221 and metabolite M1 (AGI-16903), respectively.
Elimination	Route • <i>Primary route; percent</i>	<u>Primary route; percent dose eliminated</u> Fecal elimination was the primary route.

	<p><i>dose eliminated</i></p> <ul style="list-style-type: none"> • <i>Other routes</i> 	<p>accounting for 73% of total administered drug.</p> <p><u>Other routes</u></p> <p>Renal elimination accounts for 8% of total administered drug.</p>
	<p>Terminal t_{1/2}</p> <ul style="list-style-type: none"> • <i>Mean (%CV) for parent</i> • <i>Mean (%CV) for metabolites</i> 	<ul style="list-style-type: none"> • Mean (%CV) for parent In healthy subjects, t_{1/2} is ~20-32 h (37-51). In patients, t_{1/2} is ~137 h (41) by population PK analysis. • Mean (%CV) for metabolite M1 (AGI-16903) In healthy subjects, t_{1/2} is ~27-37 h (30-52).
	<p>CL/F or CL</p> <p><i>Mean (%CV)</i></p>	<p>AG-221 had a mean clearance (CL) of 1.37 L/hr in healthy subjects, and an apparent clearance (CL/F) of 0.74 L/hr in patients.</p>
Intrinsic Factors	<p>Age</p> <p><i>Specify mean changes in C_{max} and AUC</i></p>	<p>Age is not a significant covariate on AG-221 exposure.</p>
	<p>Sex</p> <p><i>Specify mean changes in C_{max} and AUC</i></p>	<p>Sex is not a significant covariate on AG-221 exposure.</p>
	<p>Race</p> <p><i>Specify mean changes in C_{max} and AUC</i></p>	<p>Race is not a significant covariate on AG-221 exposure.</p>
	<p>Hepatic & Renal Impairment</p> <p><i>Specify mean changes in C_{max} and AUC</i></p>	<p>Not formally studied.</p> <p>In population PK analyses with evaluation of limited data across the spectrum of organ function, neither estimated creatinine clearance, hepatic transaminase levels, nor total bilirubin level were significantly correlated with apparent AG-221 clearance.</p> <p>An organ impairment study is planned to be conducted in 2017.</p>
Extrinsic Factors	<p>Drug interactions</p> <p><i>Include listing of studied DDI studies with mean changes in C_{max} and AUC</i></p>	<p>Clinical drug-drug interaction (DDI) studies have not been conducted. A DDI study is planned in 2017.</p> <p><u>Potential for AG-221 to Affect Other Drugs</u></p> <p>AG-221 and the predominant human metabolite, AGI-16903 have been shown <i>in vitro</i> to inhibit the activity of cytochrome (CYP) 450 enzymes CYP2C8, CYP2C9, CYP2C19, and CYP2D6. The metabolite AGI-16903 also inhibited CYP1A2. AG-221 and its metabolite did not inhibit CYP3A4/5, but induced CYP3A4 <i>in vitro</i>. <i>In vitro</i>, AG-221 inhibited human P-glycoprotein (P-gp), BCRP, OAT1, OATP1B1, OATP1B3, and OCT2, but not MPR2 or OAT3. <i>In vitro</i>, AGI-16903 inhibited BCRP, OAT1, OAT3, OATP1B1, and OCT2, but not MDR1, MRP2, or</p>

		<p>OATP1B3. AG-221 inhibits UGT1A1 and its allelic variants UGT1A1*1/*28 and *28/*28 (Gilbert's syndrome genotypes) in vitro and is the likely cause of increased serum bilirubin.</p> <p><u>Potential for Other Drugs to Affect AG-221</u></p> <p>Metabolism of AG-221 and metabolite AGI-16903 is mediated by multiple CYPs and UGTs. Given the multiple metabolic pathways involved in the metabolism of AG-221, the risk is low for clinically relevant drug interactions when AG-221 is co-administered with inhibitors or inducers of CYPs and UGTs.</p> <p>AG-221 is not a substrate for human P-gp or BCRP in vitro, while AGI-16903 is a substrate of both P-gp and BCRP. AG-221 and AGI-16903 are not substrates of MRP2, OAT1, OAT3, OATP1B1, OATP1B3, and OCT2. Thus, the risk is low for clinically relevant interactions when AG-221 is co-administered with inhibitors or inducers of these transporters.</p>
	<p>Food Effects <i>Specify mean changes in C_{max} and AUC and meal type (i.e., high-fat, standard, low-fat)</i></p>	<p>There was an approximate 50% increase in AUC, and a 64% increase in C_{max} when AG-221 was administered under fed (with high fat) conditions compared with fasted conditions.</p>
<p>Expected High Clinical Exposure Scenario <i>Describe worst case scenario and expected fold-change in C_{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose.</i></p>	<p>AG-221 has low risk of significantly increased exposure with inhibitors of CYPs, UGTs, and transporters. Furthermore, intrinsic factors of renal impairment, age, weight, sex, and race did not correlate with apparent clearance in the population PK analysis. In the context of normal or near-normal liver function, food and repeat dosing are the only known important modifiers of AG-221 exposure (see above). A liver impairment study is planned for 2017.</p> <p>Hence the high exposure clinical scenario in the setting of normal or near-normal hepatic function entails patients taking 100 mg PO AG-221 QD with food at steady state. In this case, geometric mean C_{max} of approximately 1.64 x 13,255 ng/mL = 21,320 ng/mL with an approximate geometric mean AUC_{0-24h} of 1.5 x 258,506 ng·h/mL = 387,759 ng·h/mL, would be expected. Percent CV would be expected to remain in the range of 10-50 (Table 13 in NDA Module 2.7.2).</p> <p>In Study AG221 C 001, 9 patients were treated with multiple doses of 300 mg QD. The geometric mean exposure after multiple dose of 300 mg was AUC₀₋₁₀ = 172,200 (49.7) ng·h/mL, and C_{max} = 24,800 (35.4) ng/mL.</p>	
<p>Preclinical Cardiac Safety <i>Summarize in vitro and in vivo results per S7B guidance.</i></p>	<p>The in vitro safety pharmacology studies assessed the potential of AG-221 mesylate salt), its N-dealkylated metabolite, AGI-16903 and/or hydroxylated metabolite, AGI-17011 to inhibit potassium, calcium and sodium ion channel currents. In in vivo safety pharmacology studies, conscious Beagle dogs and Cynomolgus monkeys were used to assess cardiovascular (CV) parameters following single oral dose of AG-221 (also known as AGI-12910 mesylate).</p>	

	<p>Electrocardiogram (ECG) assessments were also conducted in three repeat dose oral toxicity studies (7-day study in dogs received AGI-14405, AG-221 phosphate pro-drug; and 28- and 90-day studies in monkeys received AG-221).</p> <p>In the CV safety pharmacology study, dogs had non-dose-related decreased blood pressure (≤ 21 mm Hg) accompanied with dose-related increased heart rates (≤ 67 beats per minute) after single oral dose of 75 and 300 mg/kg. In addition, dose-related increased heart rates (≤ 56 beats per minute) were observed in dogs received single/repeated oral dose(s) of 5, 15 or 50 mg/kg BID up to 7 days of dosing. In addition, dogs at ≥ 15 mg/kg BID had arterial degeneration/necrosis in heart. No AG-221-related changes in blood pressure and heart rate were noted in a CV safety pharmacology study in monkeys that received a single dose of 10 mg/kg (C_{max} of 1980 ng/mL) or repeated highest dose of 24 mg/kg/day (C_{max} of 11905 ng/mL). The C_{max} values in monkeys were comparable to or higher than an estimated C_{max} (1750 ng/mL) at a single dose of 75 mg/kg in dogs showing decreased blood pressure and increased heart rate.</p> <p>The risk for QT/QTc interval prolongation was investigated with in vitro and in vivo nonclinical studies. AG-221 has a weak inhibitory effect on I_{Kr} (hERG) with an IC_{50} of 9.02 μM (4,212 ng/mL) and there was no I_{Kr} inhibitory activity of the metabolites, AGI-16903 and AGI-17011, on I_{Kr} at 30 μM, the highest concentration tested. In a CV safety pharmacology study in dogs received 75 and 300 mg/kg, QTc interval prolongations (≤ 26 msec) were not dose dependent, did not align with the time course of AG-221 plasma concentration, had no associated changes in ECG waveform morphology, and were observed primarily in a single animal at each dose level. Also in a 7-day repeat-dose toxicity study in dogs, QTc interval prolongations (maximum increase of 57 msec) were observed only at 50 mg/kg BID. Based upon AG-221 plasma protein binding in dogs (92.6%), the free C_{max} values of 131 ng/mL at 75 mg/kg and 1458 ng/mL at 100 mg/kg is approximately 32- and 4-fold less than hERG IC_{50} value for AG-221, respectively. Thus, hERG current inhibition did not appear to contribute in the QTc prolongation in dogs. In CV safety pharmacology and 28- and 90-day toxicology studies, no changes in ECG parameters were noted in monkeys at exposures comparable to (1980 ng/mL) and higher than (up to 11905 ng/mL) that was estimated in dogs receiving a single dose of 75 mg/kg with a prolongation of QTc interval.</p> <p>Arterial lesions noted in AG-221-treated dogs were consistent with similar lesions reported in dogs treated with different vasoactive drugs (Clemons, 2003; Greaves, 2012; Sahota, 2013). Dogs are considered particularly sensitive to cardiovascular toxicity associated with vasoactive modulation (Greaves, 2012).</p> <p>Above information has been described in details in the Section 2.6.6, Toxicology Written Summary and the Section 2.6.2, Pharmacology Written Summary, submitted in the NDA.</p>								
<p>Clinical Cardiac Safety Describe total number of clinical trials and number of</p>	<p>ECG/QTc data are available and reviewed from the following list of studies.</p> <p>LIST OF CELGENE SPONSORED AG-221 STUDIES INCLUDED IN THE ECG/QTc EVALUATION</p> <table border="1" data-bbox="430 1705 1312 1768"> <thead> <tr> <th data-bbox="430 1705 662 1768">Study Number</th> <th data-bbox="662 1705 938 1768">Study Title</th> <th data-bbox="938 1705 1170 1768">Number of Subjects/Dose</th> <th data-bbox="1170 1705 1312 1768">Status</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Study Number	Study Title	Number of Subjects/Dose	Status				
Study Number	Study Title	Number of Subjects/Dose	Status						

<p><i>subjects at different drug exposure levels.</i></p> <p><i>Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).</i></p>	AG221-C-001	<p>Phase 1/2, multicenter, open-label, dose-escalation and expansion, safety, PK/PD, and clinical activity evaluation of orally administered AG-221 in subjects with advanced hematologic malignancies that harbor an IDH2 mutation.</p> <p>Consists of 3 parts:</p> <ul style="list-style-type: none"> • Phase 1 Dose Escalation • Phase 1 Expansion • Phase 2 Expansion 	<p>Total dosed with AG-221 N=330</p> <p>N= 23 dosed < 100 mg N= 246 dosed with 100 mg N= 61 dosed with > 100 mg</p> <p>Data cut-off: 15Apr2016</p>	Ongoing
	AG-221-AML-004	<p>A Phase 3, multicenter, open-label, randomized study comparing the efficacy and safety of AG-221 versus conventional care regimens in older subjects with late stage AML harboring an IDH2 mutation</p>	<p>Total dosed with AG-221: N=4</p> <p>N=4 at 100 mg</p> <p>Data Cut-off: 12Jul2016</p>	Ongoing
	AG120-221-C-001	<p>A Phase 1, multicenter, open-label, safety study of AG-120 or AG-221 in combination with induction therapy and consolidation therapy in subjects with newly diagnosed AML with an IDH1 and/or IDH2 mutation</p>	<p>Total dosed with AG-221: N=6</p> <p>N=6 at 100 mg</p> <p>Data Cut-off: 01Jul2016</p>	Ongoing
	AG221-C-003	<p>Phase 1/2, multicenter, open-label, dose-escalation study of AG-221 in subjects with advanced solid tumors, including glioma, and with</p>	<p>Total dosed with AG-221: N=21</p> <p>N=3 dosed at 100 mg N=4 dosed at 200 mg N=7 dosed at 400 mg</p>	Clinically complete

		<p>angioimmunoblastic T-cell lymphoma, that harbor an IDH2 mutation.</p> <p>Consists of 2 parts:</p> <ul style="list-style-type: none"> Phase 1 Dose Escalation (halted after enrollment of 21 subjects) Phase 2 Dose Expansion (cancelled) 	N=7 dosed at 650mg	
	AG221-C-002	Phase 1, 2-way crossover study to assess PK and safety of a single dose of AG-221 in healthy male subjects when administered under fed and fasted conditions	30 subjects at single-dose of 100 mg AG-221 in fasted versus fed conditions	Completed
	AG221-CP-001	Phase 1, single dose, open-label study to evaluate the PK and safety of AG-221 in healthy adult male Japanese subjects relative to healthy adult male Caucasian subjects	<p>Total dosed with AG-221 N=62</p> <p>11 Japanese and 11 Caucasian at single dose of 100 mg, 10 Japanese and 10 Caucasian at single dose of 50 mg, 10 Japanese and 10 Caucasian at single dose of 300 mg.</p>	Completed
	AG221-CP-002	Phase 1, open-label, 2-part study to evaluate the metabolism and excretion and determine absolute bioavailability of AG-221 in healthy male adult subjects	<p>Total dosed with AG-221 N=14</p> <p>8 subjects at a single dose of 100 mg solution containing a microtracer of [14C]-AG- 221 solution (~300 nCi) under fasting conditions</p>	Completed

			<p>6 subjects at a single oral dose of 100 mg followed 4 hours later by a 2-minute IV bolus of 100 µg AG-221 containing ~300 nCi of [14C]-AG-221</p>	
<p>Among PTs under the SMQ Torsade de Pointes / QT Prolongation, the TEAEs of electrocardiogram QT prolonged were reported in 20 (6.1%) subjects. Assessments of individual cases revealed that all subjects experiencing adverse events electrocardiogram QT prolonged had concurrent factors affecting the QT interval (eg, prolonged QT interval at baseline, concomitant administration of medications with known QT prolonging potential, or electrolytes imbalance):</p> <ul style="list-style-type: none"> • Concomitant medications (often multiple) known for their QT prolonging effect. Such medications often were used for the treatment of concurrent infections, with QT interval returning to baseline values after the resolution of infection • Concurrent electrolytes abnormalities, such as low potassium, magnesium, or calcium levels that could have triggered QT interval prolongation • Prolonged pre-treatment QT interval, or only small changes in QT interval duration in post-baseline • Heart rate regulated by pacemakers makes QT interval uninterpretable <p>The TEAEs of syncope and loss of consciousness were reported in 11 (3.3%) subjects and 3 (0.9%) subjects, respectively. With an exception for 1 subject, these events were single episodes. In 1 subject, intermittent syncope lasted for 39 days. In the majority of subjects, the events were assessed as not related to the study treatment and caused by the underlying disease.</p> <p>The TEAEs of cardiac arrest were reported in 6 (1.8%) subjects. All these TEAEs were reported as unrelated to treatment and were assessed as the cause of death in subjects treated for pneumonia, febrile neutropenia with respiratory failure, leukocytosis, acidosis, gastrointestinal hemorrhage, leukocytosis, and disseminated intravascular coagulation.</p> <p>The TEAE of sudden death was assessed as unrelated to treatment and was reported as the result of road traffic accident.</p> <p>The TEAE of ventricular tachycardia was reported as a non-serious TEAE that was unrelated to treatment, resolved in 1 day, and was concurrent with a TEAE of pyrexia.</p> <p>In Study AG221-C-003, the TEAEs of electrocardiogram QT prolonged and syncope (1 subject each) were the only TEAEs reported from the SMQ of</p>				

Torsade de pointes / QT Prolongation. Subjects continued in the study without reoccurrence of these TEAE.

In Study AG120-221-C-001, no TEAEs were reported from the SMQ of Torsade de pointes / QT Prolongation.

In Study AG-221-AML-004, electrocardiogram QT prolonged (1 subject) was the only TEAE reported from the SMQ of Torsade de pointes / QT Prolongation.

In Study AG221-C-002, the TEAE of syncope was reported in 1 subject, and in Studies AG-221-CP-001 and AG-221-CP-002, no subjects reported a TEAE from the SMQ of Torsade de pointes / QT Prolongation.

Above information, as well as central ECG laboratory assessment has been described in details in the Section 2.1.5.7, Cardiac Safety of the Module 2.7.4 Summary of Clinical Safety, submitted in the NDA.

In summary, detailed investigation of TEAEs in the SMQ Torsade de pointes / QT Prolongation, LVEF, and predefined QT interval prolongations based on the central ECG laboratory measurements did not suggest cardiotoxic or QT interval prolonging potential of AG-221.

Subjects experiencing QT interval prolongation had multiple confounding factors that likely contributed to QT interval prolongation, although, the potential for a AG-221 drug-drug interaction, which would intensify the QT prolonging potential of other medications, cannot be excluded.

6.2 PK/ECG ASSESSMENT SCHEDULE

Phase 1 Dose Escalation and Part 1 Expansion

Visit/Cycle	Screening	Cycle 1												Cycle 2				Cycle 3			Cycle 4+			F/U D +28	
		D -28			D -3 ^{a,b}			D1 ^c		D8	D15		D22		D1		D15		D1		EOT				
Assessment	Blood/ Urine/ ECG	Blood	Urine	ECG	Blood/ Urine	ECG	Blood	ECG	Blood	Urine	ECG	Blood	ECG	Blood	Urine	ECG	Blood	Urine	ECG	Blood	Urine	ECG	Blood	Urine	ECG
Pre-dose ^d	X ^e	X	X	X	X	X	X		X	X		X		X	X		X	X		X	X				
Post-dose																									
Anytime							X			X		X			X						X	X	X	X	X
0.5 hr		X ^f	X ^f		X ^f				X ^f			X ^f									X ^g				
1 hr		X ^f							X ^f			X ^f									X ^g				
2 hr		X ^f	X ^h		X ^h				X ^f			X ^f									X ^g				
3 hr		X ^f							X ^f			X ^f									X ^g				
4 hr		X ^f	X ^h		X ^h				X ^f			X ^f									X ^g				
6 hr		X ^f	X ^h		X ^h				X ^f			X ^f									X ^g				
8 hr		X ^f	X ^h		X ^h				X ^f			X ^f									X ^g				
10 hr		X ^f	X						X ^f			X ^f									X ^g				
24 hr		X ⁱ	X																						
48 hr		X ⁱ	X																						
72 hr		X ⁱ	X																						

C = cycle, D = day; ECG = electrocardiogram. EOT = end of treatment, F/U = follow-up and follow-up post HSCT, hr = hour, PD = pharmacodynamic. Notes: For all days with pre-dose samples, subjects were instructed to take their dose of AG-221 in clinic. All 12-lead ECGs were conducted after 3 minutes of recumbency. A 12-lead single ECG was also obtained as clinically indicated. Serial ECGs (Day -3 or C1D1) were obtained following vital signs assessments. A subset of samples collected for pharmacokinetic (PK) also was used to assess cholesterol and 4beta-hydroxy (4β-OH)-cholesterol levels (Section 10.11 of the protocol).

- ^{a)} Day -3 assessments, including 72-hour PK/PD and serial 12-lead ECGs were conducted for the first 3 subjects enrolled in each cohort during the dose escalation phase and the first 15 subjects in each arm of Part 1 expansion following a single dose of AG-221 administered on Day -3; these procedures were optional (based on medical monitor evaluation) for any additional subjects enrolled in these cohorts. All screening assessments were completed prior to single dose administration on Day -3.
- ^{b)} Five urine collections were obtained during the 72-hour PK/PD sampling time: pre-dose (at least 20 mL) and at the 10-, 24-, 48- and 72-hour blood draws (± 1 hour).
- ^{c)} Only for subjects who did not undergo the Day -3 assessments. Additional urine samples were required during the treatment period for PD assessment (2-hydroxyglutarate [2-HG] and α-ketoglutarate [α-KG]).
- ^{d)} Obtained within 30 minutes before dose; done at any time during screening.
- ^{e)} Screening blood sample for analysis of 2-HG and α-KG only.
- ^{f)} Obtained within ± 10 minutes of specified time.
- ^{g)} Assessments conducted on C4D1 only
- ^{h)} Obtained within ± 15 minutes of specified time.
- ⁱ⁾ Obtained within ± 1 hour of specified time.

Phase 2

Visit/Cycle:	Screening	Cycle 1			Cycle 2			Cycle 3+			EOT		F/U
Study Day:	D -28	D1		D2	D1		D2	D1					D +28
Assessment	Blood ^{a)} / Single ECG	Blood	Triplicate ECG ^{b)}	Blood	Blood	Triplicate ECG ^{b)}	Blood	Blood	Single ECG	Blood	Triplicate ECG ^{b)}	Single ECG	
Pre-dose ^{c)}	X	X	X	X	X	X	X	X ^{d)}		X			
Post-dose													
2 hr		X ^{e)}	X ^{f)}		X ^{e)}	X ^{f)}							
4 hr		X ^{e)}	X ^{f)}		X ^{e)}	X ^{f)}							
6 hr		X ^{e)}	X ^{f)}		X ^{e)}	X ^{f)}							
8 hr		X ^{e)}			X ^{e)}								
Anytime									X		X	X	

D = day; ECG = electrocardiogram; EOT = end of treatment; F/U = follow-up and follow-up hematopoietic stem cell transplant (HSCT); hr = hour. Notes: PK refers to blood sample only. For all days with pre-dose samples, subjects were instructed to take their dose of AG-221 in clinic. All 12-lead ECGs were conducted after 3 minutes of recumbency. A 12-lead single ECG was also obtained as clinically indicated.

- ^{a)} Screening blood sample for analysis of 2-HG and α-KG only.
- ^{b)} 12-lead triplicate ECGs, done approximately 2 minutes apart, were obtained on Day 1 of Cycles 1 and 2 and at EOT. ECGs were done before pharmacokinetic (PK) sampling on these days.
- ^{c)} Obtained within 30 minutes before dose. Could have been done at any time during screening.
- ^{d)} Assessments were required on C3D1 only; not subsequent cycles.
- ^{e)} Obtained within ± 10 minutes of specified time. When the timing of a blood sample coincided with the timing of an ECG measurement, the ECG was completed before the collection of the blood sample (within 10 minutes).
- ^{f)} ECG was obtained within ± 15 minutes of specified time.

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/s/

NAN ZHENG
03/28/2017

DHANANJAY D MARATHE
03/28/2017

DALONG HUANG
03/28/2017

QIANYU DANG
03/28/2017

MICHAEL Y LI
03/29/2017

CHRISTINE E GARNETT
03/30/2017

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 # 209606 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Idhifa™ Established/Proper Name: enasidenib Dosage Form: tablet Strengths: 50 mg, 100 mg Route(s) of Administration: oral		
Applicant: Celgene Corporation Agent for Applicant (if applicable):		
Date of Application: December 30, 2016 Date of Receipt: December 30, 2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: August 30, 2017	Action Goal Date (if different):	
Filing Date: February 28, 2017	Date of Filing Meeting: February 8, 2017	
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	

Review Classification: <i>The application will be a priority review if:</i> <ul style="list-style-type: none"> • <i>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)</i> • <i>The product is a Qualified Infectious Disease Product (QIDP)</i> • <i>A Tropical Disease Priority Review Voucher was submitted</i> • <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher			
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>			
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)			
<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 117631				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in electronic archive? <i>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 archive.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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)? <i>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</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>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.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>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.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>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</i>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes , answer the bulleted questions below:	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>		

<ul style="list-style-type: none"> 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)]. 	<input type="checkbox"/>	<input type="checkbox"/>																		
<ul style="list-style-type: none"> 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)]? <p><i>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.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>																		
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p>	<input type="checkbox"/>	<input type="checkbox"/>																		
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 25%;">Application No.</th> <th style="width: 30%;">Drug Name</th> <th style="width: 25%;">Exclusivity Code</th> <th style="width: 20%;">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>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 and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 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.</i></p>																				
<ul style="list-style-type: none"> If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If no, include template language in the 74-day letter.</p> <p>Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]</p> <p><i>Note: Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>																		

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
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)(14)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
NDA/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
NDA only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>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.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>Index: Does the submission contain an accurate comprehensive index?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i>s/<i>NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLA</i>s/<i>BLA efficacy supplements</i>) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<p><i>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.</i> 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.</p>				
Application Form	YES	NO	NA	Comment
<p>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</p> <p><i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Are all establishments and their registration numbers listed on the form/attached to the form?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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

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)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>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..."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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? <i>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)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p>For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p>For non-NMEs: <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p> <p><i>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.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Orphan-drug designation granted 6/12/2014
<p>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Due to orphan designation, enasidenib is exempt from PREA
<p>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p><u>BPCA:</u></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

Version: 12/05/2016

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Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labeling <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent labeling <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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?	<input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	
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? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent: IRT/QT (1/19/17); OSI (1/23/17)</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): July 26, 2016	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 8, 2017

BACKGROUND: IDHIFA™ (enasidenib, AG-221) is a first in class, proposed inhibitor of the mutant isocitrate dehydrogenase-2 (IDH2) enzyme with a proposed indication for the treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an IDH2 mutation.

On June 12, 2014, AG-221 received orphan-drug designation for the treatment of AML that harbor IDH2 mutation and subsequently, Fast Track Designation was granted on July 31, 2014, for the treatment of patients with AML that harbor IDH2 mutation. On December 9, 2016, Celgene Corporation submitted a New Drug Application (NDA) for IDHIFA™ and is requesting priority review and accelerated approval under 21 CFR 314 subpart H.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jennifer Lee	Y
	TL:	Patricia Garvey	Y
	CPMS:	Theresa Carioti	Y
Cross-Discipline Team Leader (CDTL)	Donna Przepiorka		Y
Division Director/Deputy	Ann Farrell		N
Supervisory Associate Division Director	Al Deisseroth		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Ashley Ward	Y
	TL:	Donna Przepiorka	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Liang Li	Y

	TL:	Stacy Shord	Y
• Pharmacogenomics	Reviewer:	Sarah Dorff	Y
	TL:	Rosane Charla Orbach	
• Pharmacometrics	Reviewer:	Walt Cao	Y
	TL:	Nitin Mehrotra	
Biostatistics	Reviewer:	Qing Xu	Y
	TL:	Yuan Li Shen	Y

Nonclinical Pharmacology/Toxicology)	Reviewer:	Rama Gudi	Y
	TL:	Chris Sheth	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Sherita McLamore-Hines	Y
	RBPM:	Rabiya Laiq	Y
• Drug Substance	Reviewer:	Rohit Tiwari	
• Drug Product	Reviewer:	Nina Ni	
		Lindsey Saunders	Y
• Process	Reviewer:	David Dean Anderson, Ying Zhang	
• Microbiology	Reviewer:		
• Facility	Reviewer:	Zhihao Peter Qiu, Zhong Li	
• Biopharmaceutics	Reviewer:	Banu Zolnik	Y
		Okponanabofa Eradiri	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Rowe Medina	
	TL:	Barbara Fuller	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Rachael Conklin	
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Leeza Rahimi	
	TL:	Hina Mehta	Y

	OSE RPM:	Neil Vora	Y
OSE/DRISK (REMS)	Reviewer:	Till Olickal	Y
	TL:	Naomi Redd	N
OSE/DEPI	Reviewer:	Carolyn McCloskey	Y
	TL:	Steve Bird	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline	Reviewer:		
	TL:		
Other attendees	Anthony Orenca, OSI		Y
	Rosa Lee-Alonzo, RPM, DHP		Y
	Donna Roscoe, CDRH Branch Chief		Y
	Aaron Schetter, CDRH Reviewer		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>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</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
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described in published literature):	
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments

<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>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</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: <i>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.</i>
<ul style="list-style-type: none"> 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>• Clinical pharmacology study site(s) inspections(s) needed?</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>New Molecular Entity (NDAs only)</u></p> <p>• Is the product an NME?</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <p>• Categorical exclusion for environmental assessment (EA) requested?</p> <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> 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? 	<input type="checkbox"/> N/A <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Richard Pazdur, MD

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): April 28, 2017

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

Comments: NDA will be reviewed under accelerated approval regulations, 314 Subpart H.

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review</p>

ACTION ITEMS

<input type="checkbox"/>	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).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	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.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs 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/

JENNIFER J LEE
02/28/2017

THERESA A CARIOTI
02/28/2017

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 209606

Application Type: New NDA

Drug Name(s)/Dosage Form(s): IDHIFA™ (enasidenib)/Tablets

Applicant: Celgene Corporation

Receipt Date: December 30, 2016

Goal Date: August 30, 2017

1. Regulatory History and Applicant's Main Proposals

IDHIFA™ (enasidenib, AG-221) is a first in class, proposed inhibitor of the mutant isocitrate dehydrogenase-2 (IDH2) enzyme with a proposed indication for the treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an IDH2 mutation.

On June 12, 2014, orphan-drug designation was granted for the “treatment of AML that harbor IDH2 mutation” and subsequently Fast Track Designation was granted on July 31, 2014 for AG-221 for the treatment of patients with AML that harbor IDH2 mutation.

A type B Pre-NDA meeting was held with the sponsor on July 26, 2016 to discuss the AG-221 drug development program, specifically to obtain the Agency's feedback on the clinical efficacy and safety data from Study AG221-C-001 to support the initial NDA submission of AG-221 for the treatment of R/R AML patients with an IDH2 mutation for accelerated approval under 21 CFR 314.510 Subpart H.

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.

Selected Requirements of Prescribing Information

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

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

Comment:

- YES** 2. The length of HL must be one-half page or less 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:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 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:

- 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:

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

Comment:

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

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

Selected Requirements of Prescribing Information

• 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:

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:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

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:

Boxed Warning (BW) in Highlights

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

Comment:

- N/A** 13. The BW must have a 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**”

Selected Requirements of Prescribing Information

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:

- 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:

- 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:

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:

- 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:

- 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:

Dosage Forms and Strengths in Highlights

- NO** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment: *The different strengths of tablets should be combined into one bullet point.*

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:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

- YES** 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:

Patient Counseling Information Statement in Highlights

- NO** 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: *Change statement to "See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."*

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:

Selected Requirements of Prescribing Information

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:
- YES** 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:
- 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:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- 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:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- 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:

Selected Requirements of Prescribing Information

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:

- 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:

Selected Requirements of Prescribing Information

- 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:

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:

BOXED WARNING Section in the FPI

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

Comment:

- 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:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

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:

- 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:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- NO** 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: Change statement to "Advise the patient to read the FDA-approved patient labeling (Patient Information)."

- 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:

Selected Requirements of Prescribing Information

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*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in 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

8.6 Subpopulation X

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

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* 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/

JENNIFER J LEE
02/28/2017

THERESA A CARIOTI
02/28/2017