# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209606Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

# EXCLUSIVITY SUMMARY

NDA # **209606** SUPPL # HFD # **161**

Trade Name **IDHIFA®**

Generic Name **enasidenib**

Applicant Name **Celgene Corporation**

Approval Date, If Known **August 1, 2017**

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505 (b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

(b) (4) years (orphan drug exclusivity)
years (new chemical entity)

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation

duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

| | |
|---|---|
| Investigation #1 | ! |
| | ! |
| YES ☐ | ! NO ☐ |
| Explain: | ! Explain: |

| | |
|---|---|
| Investigation #2 | ! |
| | ! |
| YES ☐ | ! NO ☐ |
| Explain: | ! Explain: |

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Jennifer J. Lee, PharmD
Title: Regulatory Project Manager
Date: July 19, 2017

Name of Division Director signing form: Albert Deisseroth, MD
Title: Supervisory Associate Division Director

APPEARS THIS WAY ON ORIGINAL

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

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/s/

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JENNIFER J LEE
08/01/2017

ALBERT B DEISSEROTH
08/01/2017

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION[1]

| | | |
|---|---|---|
| NDA # 209606<br>BLA # | NDA Supplement #<br>BLA Supplement # | If NDA, Efficacy Supplement Type:<br>*(an action package is not required for SE8 or SE9 supplements)* |
| Proprietary Name: IDHIFA®<br>Established/Proper Name: enasidenib<br>Dosage Form: Tablet | | Applicant: Celgene Corporation<br>Agent for Applicant (if applicable): |
| RPM: Jennifer J. Lee, PharmD | | Division: Division of Hematology Products |

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

**For ALL 505(b)(2) applications, two months prior to EVERY action:**

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

***Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.***

| | |
|---|---|
| ❖ Actions | |
| • Proposed action<br>• User Fee Goal Date is August 30, 2017 | ☒ AP ☐ TA ☐ CR |
| • Previous actions *(specify type and date for each action taken)* | ☒ None |
| ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?<br>Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ | ☐ Received |
| ❖ Application Characteristics[3] | |

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): Isocitrate dehydrogenase 2 inhibitor
***(confirm chemical classification at time of approval)***

☒ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

***(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)***

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

| | |
|---|---|
| ❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)* | ☐ Yes ☐ No |
| ❖ Public communications *(approvals only)* | |
| • Office of Executive Programs (OEP) liaison has been notified of action | ☒ Yes ☐ No |
| • Indicate what types (if any) of information were issued | ☐ None<br>☒ FDA Press Release<br>☐ FDA Talk Paper<br>☐ CDER Q&As<br>☒ Other – ASCO Burst |
| ❖ Exclusivity | |
| • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?<br>• If so, specify the type | ☒ No ☐ Yes |
| ❖ Patent Information (NDAs only) | |
| • Patent Information:<br>Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. | ☒ Verified<br>☐ Not applicable because drug is an old antibiotic. |

## CONTENTS OF ACTION PACKAGE

### Officer/Employee List

| | |
|---|---|
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)* | ☒ Included |
| Documentation of consent/non-consent by officers/employees | ☒ Included |

| Action Letters | |
|---|---|
| ❖ Copies of all action letters *(including approval letter with final labeling)* | Approval; 8/1/2017 |
| **Labeling** | |
| ❖ Package Insert *(write submission/communication date at upper right of first page of PI)* | |
| • Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)* | See Action Letter 8/1/2017 |
| • Original applicant-proposed labeling | ☒ Included - 12/30/2016 |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)* | ☒ Medication Guide<br>☒ Patient Package Insert<br>☐ Instructions for Use<br>☐ Device Labeling<br>☐ None |
| • Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)* | See Action Letter 8/1/2017 |
| • Original applicant-proposed labeling | ☒ Included<br>Med Guide (6/8/2017)<br>Patient Package Insert (12/30/2016) |
| ❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)* | |
| • Most-recent draft labeling | ☒ Included – container labels 7/21/2017 |
| ❖ Proprietary Name<br>• Acceptability/non-acceptability letter(s) *(indicate date(s))*<br>• Review(s) *(indicate date(s)* | Letter 3/30/2017 (acceptability)<br>Review 3/21/2017 |
| ❖ Labeling reviews *(indicate dates of reviews)* | RPM: 2/28/2017<br>DMEPA: 4/7/2017, 7/13/2017<br>DMPP/PLT (DRISK): 6/27/2017<br>OPDP: 6/28/2017<br>SEALD: ☒ None<br>CSS: ☒ None<br>Product Quality: See Integrated Quality Assessment 5/31/2017<br>Other: ☒ None |
| **Administrative / Regulatory Documents** | |
| ❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)*<br>❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee | 2/28/2017<br>☒ Not a (b)(2) |
| ❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)* | ☒ Completed (Do not include) |
| ❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

| | |
|---|---|
| • Applicant is on the AIP | ☐ Yes ☒ No |
| • This application is on the AIP<br>○ If yes, Center Director's Exception for Review memo *(indicate date)*<br>○ If yes, OC clearance for approval *(indicate date of clearance communication)* | ☐ Yes ☒ No<br>☐ Not an AP action |
| ❖ Pediatrics *(approvals only)*<br>• Date reviewed by PeRC _____<br>If PeRC review not necessary, explain: Orphan designation granted 6/12/2014 | |
| ❖ Breakthrough Therapy Designation | ☒ N/A |
| • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) | |
| • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)* | |
| • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)*<br><br>*(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)* | |
| ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)* | 8/1/2017, 7/26/2017, 7/21/2017, 7/20/2017, 7/19/2017, 7/14/2017, 7/7/2017 (2), 7/6/2017, 7/5/2017, 7/3/2017, 6/30/2017 (2), 6/20/2017, 6/14/2017 (2), 6/12/2017, 6/8/2017, 6/7/2017, 6/6/2017 (2), 6/5/2017 (2), 6/2/2017 (2), 5/30/2017, 5/12/2017, 5/5/2017, 5/3/2017, 5/2/2017, 4/28/2017, 4/27/2017, 4/26/2017 (2), 4/25/2017 (3), 4/24/2017 (2), 4/6/2017, 4/4/2017, 3/30/2017, 3/27/2017, 3/24/2017, 3/15/2017, 3/9/2017, 3/2/2017, 2/28/2017, 2/17/2017, 2/14/2017, 2/7/2017, 2/1/2017, 1/27/2017, 1/24/2017, 1/19/2017 (2), 1/17/2017, 1/11/17, 1/6/2017, 12/30/2016 |
| ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) | |
| ❖ Minutes of Meetings | |
| • If not the first review cycle, any end-of-review meeting *(indicate date of mtg)* | ☒ N/A or no mtg |
| • Pre-NDA/BLA meeting *(indicate date of mtg)* | 7/26/2016 |
| • EOP2 meeting *(indicate date of mtg)* | ☒ No mtg |
| • Mid-cycle Communication *(indicate date of mtg)* | 4/28/2017 |
| • Late-cycle Meeting *(indicate date of mtg)* | 6/16/2017 |
| • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)* | |

| | |
|---|---|
| ❖ Advisory Committee Meeting(s) | ☒ No AC meeting |
| • Date(s) of Meeting(s) | |
| **Decisional and Summary Memos** | |
| ❖ Office Director Decisional Memo *(indicate date for each review)* | 7/28/2017, Multidisciplinary Review (Section 18) |
| Division Director Summary Review *(indicate date for each review)* | See 7/28/2017 Multidisciplinary Review (Section 17) |
| Cross-Discipline Team Leader Review *(indicate date for each review)* | 6/30/2017, See 7/28/2017 Multidisciplinary Review (Section 1) |
| PMR/PMC Development Templates *(indicate total number)* | 7/11/2017, See 7/28/2017 Multidisciplinary Review (Section 12)<br>Total: 5 PMRs and 1 PMC |
| **Clinical** | |
| ❖ Clinical Reviews | |
| • Clinical Team Leader Review(s) *(indicate date for each review)* | ☒ No separate review<br>See 7/28/2017 Multidisciplinary Review (Sections 2, 3, 4 and 7) |
| • Clinical review(s) *(indicate date for each review)* | 5/30/2017, See 7/28/2017 Multidisciplinary Review (Sections 2, 3, 4 and 7) |
| • Social scientist review(s) (if OTC drug) *(indicate date for each review)* | ☒ None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)* | See 7/28/2017 Multidisciplinary Review (Sections 7.2.2, and 13.2) |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5] | ☒ None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)* | ☒ N/A |
| ❖ Risk Management<br>• REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))*<br>• REMS Memo(s) and letter(s) *(indicate date(s))*<br>• Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* | Review 6/27/2017 |
| ❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)* | 5/17/2017 |

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

| | |
|---|---|
| **Clinical Microbiology** ☒ None | |
| ❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)* | ☐ No separate review |
| Clinical Microbiology Review(s) *(indicate date for each review)* | ☐ None |
| **Biostatistics** ☐ None | |
| ❖ Statistical Division Director Review(s) *(indicate date for each review)* | ☒ No separate review<br>See 7/28/2017 Multidisciplinary Review (Section 16) |
| Statistical Team Leader Review(s) *(indicate date for each review)* | ☒ No separate review<br>See 7/28/2017 Multidisciplinary Review (Section 7) |
| Statistical Review(s) *(indicate date for each review)* | 5/30/2017, See 7/28/2017 Multidisciplinary Review (Section 7) |
| **Clinical Pharmacology** ☐ None | |
| ❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)* | ☒ No separate review<br>See 7/28/2017 Multidisciplinary Review (Section 6) |
| Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)* | ☒ No separate review<br>See 7/28/2017 Multidisciplinary Review (Section 6) |
| Clinical Pharmacology review(s) *(indicate date for each review)* | 5/30/2017, See 7/28/2017 Multidisciplinary Review (Section 6)<br><br>IRT-QT Review 3/30/2017 |
| ❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)* | ☒ None requested |
| **Nonclinical** ☐ None | |
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) *(indicate date for each review)* | ☒ No separate review<br>See 7/28/2017 Multidisciplinary Review (Section 14) |
| • Supervisory Review(s) *(indicate date for each review)* | ☒ No separate review<br>See 7/28/2017 Multidisciplinary Review (Section 5) |
| • Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* | 5/30/2017, See 7/28/2017 Multidisciplinary Review (Section 5) |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)* | ☒ None |
| ❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | ☒ No carc |
| ❖ ECAC/CAC report/memo of meeting | ☒ None |
| ❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)* | ☒ None requested |

| **Product Quality** ☐ None | |
|---|---|
| ❖ Product Quality Discipline Reviews[6] | |
| • Tertiary review (*indicate date for each review*) | ☒ None |
| • Secondary review (e.g., Branch Chief) *(indicate date for each review)* | ☒ None |
| • Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)* | Executive Summary: 6/19/2017<br>Drug Substance: 5/22/2017<br>Drug Product: 5/31/2017<br>Process: 5/12/2017<br>Facilities: 5/31/2017<br>Biopharmaceutics: 6/1/2017 |
| ❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)* | ☒ None |
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)* | See Drug Product Review (page 79) in Integrated Quality Assessment 5/31/2017 |
| ☐ Review & FONSI *(indicate date of review)* | |
| ☐ Review & Environmental Impact Statement *(indicate date of each review)* | |
| ❖ Facilities Review/Inspection | |
| ☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)* | ☒ Acceptable: See Facilities Review in Integrated Quality Assessment 5/31/2017<br>☐ Withhold recommendation<br>☐ Not applicable |

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

| Day of Approval Activities | |
|---|---|
| ❖ For all 505(b)(2) applications:<br>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) | ☐ No changes<br>☐ New patent/exclusivity *(Notify CDER OND IO)* |
| • Finalize 505(b)(2) assessment | ☐ Done |
| ❖ For Breakthrough Therapy (BT) Designated drugs:<br>• Notify the CDER BT Program Manager | ☐ Done<br>*(Send email to CDER OND IO)* |
| ❖ For products that need to be added to the flush list (generally opioids): Flush List<br>• Notify the Division of Online Communications, Office of Communications | ☐ Done |
| ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email | ☒ Done |
| ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter | ☒ Done |
| ❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name | ☒ Done |
| ❖ Ensure Pediatric Record is accurate | ☐ Done |
| ❖ Send approval email within one business day to CDER-APPROVALS | ☒ Done |

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/s/

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JENNIFER J LEE
08/01/2017

**From:** Lee, Jennifer (CDER)
**To:** "Penny Ng"
**Subject:** RE: Enasidenib NDA 209606 Safety Reporting Post-approval
**Date:** Tuesday, August 01, 2017 10:49:00 AM

---

Hi Penny,

Yes, I can confirm that enasidenib is not considered part of a Part 3 combination product.

In addition, in regards to your other question, the FDA Office of Media Affairs does not share any information regarding press releases and timing of releases with Applicants. Thanks for your understanding.

Kind regards,
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Tuesday, August 01, 2017 10:08 AM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: Enasidenib NDA 209606 Safety Reporting Post-approval

Good morning Jennie,

Thank you again for following up on my question on the public communication, I appreciate your guidance as always.

Regarding my question below, I understand from the FDA approval letter (received today) that the reporting requirement of the NDA is a follows:

> **REPORTING REQUIREMENTS**
> We remind you that you must comply with reporting requirements for an approved NDA
> (21 CFR 314.80 and 314.81).

Based on this note, my understanding is that safety reporting of enasidenib is under 21 CFR 314 requirement only, and not considered to be Part 3 combination product (21 CFR 3.2.e.3) that is subject to 21 CFR 4.100-105 and combination product post marketing reporting requirement.

If this is not correct, please kindly advise. Thank you.

Kind regards,
Penny

---

**From:** Penny Ng
**Sent:** Thursday, July 27, 2017 3:08 PM
**To:** Lee, Jennifer (CDER) <Jennifer.Lee1@fda.hhs.gov>

**Subject:** Enasidenib NDA 209606 Safety Reporting Post-approval

Good afternoon Jennie,

Celgene will be reporting AG-221 (enasidenib) Safety Report per the requirement under 21 CFR 314 post approval.

As enasidenib (IDHIFA®) is labeled with specific an in vitro diagnostic device from Abbott Molecular (Abbott RealTi*me*™ IDH2 assay), we would like to confirm with the Agency if the above understanding is correct, i.e. safety reporting of enasidenib is under 21 CFR 314 requirement only, or if this drug application is considered to be Part 3 combination product (21 CFR 3.2.e.3) that is subject to 21 CFR 4.100-105 and combination product post marketing reporting requirement?

As always, I appreciate your guidance.

Kind regards,
***Penny***

---

**Penny Ng**, M.Sc., MBA, RAC **Regulatory Affairs**
Celgene Corporation | Corporate Woods Bldg 32, Suite 900
9225 Indian Creek Parkway | Overland Park, KS 66210 USA
Work 913-266-0505 | Mobile (b) (6) | Fax 913-266-0394
png@celgene.com | www.celgene.com

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/s/

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JENNIFER J LEE
08/01/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Wednesday, July 26, 2017 2:07 PM
**To:** 'Penny Ng'
**Subject:** NDA 209606 enasidenib -- Labeling Update
**Attachments:** NDA 209606 Idhifa -- Draft US PI FDA 7-26-2017.docx

Good afternoon Penny,

Please find attached the final and agreed upon version of the USPI for NDA 209606 enasidenib. All revisions have been accepted by the Agency. Please submit both the final versions of the USPI and the Med Guide to your NDA file.

In regards to the container labels, the version of the container labels received by email July 19 are provisionally acceptable, and we have no additional comments at this time. The final determination will be conveyed in correspondence when a final action is taken.

Please do not hesitate to contact me should you have any additional questions.

Kind regards,
Jennie

_____

**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
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jennifer.lee1@fda.hhs.gov


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JENNIFER J LEE
07/26/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Friday, July 21, 2017 6:24 AM
**To:** 'Penny Ng'
**Subject:** NDA 209606 enasidenib -- FDA Labeling Revisions Response Due COB 7/24
**Attachments:** NDA 209606 Idhifa -- Draft US PI FDA Revisions 7-21-2017.docx; NDA 209606 enasidenib -- Draft Med Guide FDA Revisions 7-21-2017.docx

Dear Penny,

Please find attached the FDA labeling revisions of the USPI and the final and agreed upon version of the Med Guide for NDA 209606 enasidenib. Please review the FDA revised labeling with your team and accept changes that you agree with, and make any edits that you do not agree with using track-changes only (*do not reject any changes that the FDA proposed and do not delete any of the FDA's comments*). Please provide a response to me via email by **COB Monday, July 24, 2017** and then follow up with a formal submission of your response to the NDA file.

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

_____

**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
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JENNIFER J LEE
07/21/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Thursday, July 20, 2017 10:33 AM
**To:** 'Penny Ng'
**Subject:** NDA 209606 enasidenib -- PMR/PMC
**Attachments:** NDA 209606 Idhifa -- Draft PMR_PMC FDA Revisions 7-20-2017.docx

Dear Penny,

Please find attached the draft PMR/PMCs for NDA 209606 enasidenib. Celgene's revisions have been accepted by the Agency. Please review this version with your team and, if in agreement, submit them formally to your NDA as the final and agreed upon PMR/PMCs.

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

---

**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov


**PMR-1-Agreed**

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.

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

**PMR-2-Agreed**

Characterize the long-term safety of enasidenib in patients with relapsed or refractory acute myeloid leukemia (AML). Submit the final study report and data set with 3 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.

| | | |
|---|---|---|
| PMR/PMC Schedule Milestones: | Preliminary Protocol Submission | 06/2013 |
| | Final Protocol Submission: | 10/2015 |
| | Study/Trial Completion: | 05/2019 |
| | Final Report Submission: | 03/2020 |

**PMR-3-Agreed**

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 data set with 3 years of follow-up from ongoing 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. Include in the final study report the exploratory subgroup analyses and corresponding subject-level data related to pre- and post-treatment cytogenetics, specific IDH2 mutations, and mutation analyses for other genes (e.g., IDH2, FLT3, NPM1, CEBPA, DNMT3A, NRAS) as obtained under the trial protocol or from medical history prior to trial enrollment.

| | | |
|---|---|---|
| PMR/PMC Schedule Milestones: | Preliminary Protocol Submission | Not applicable |
| | Final Protocol Submission: | 08/2015 |
| | Study/Trial Completion: | 09/2022 |
| | Final Report Submission: | 07/2023 |

**PMR-4 - Agreed**

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."

| | | |
|---|---|---|
| PMR/PMC Schedule Milestones: | Preliminary Protocol Submission | 09/2017 |
| | Final Protocol Submission: | 12/2017 |
| | Study/Trial Completion (PK portion): | 09/2019 |
| | Final Report Submission: | 03/2020 |

**PMR-5 - Agreed**

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."

| | | |
|---|---|---|
| PMR/PMC Schedule Milestones: | Final Protocol Submission: | 09/2017 |
| | Study/Trial Completion: | 11/2018 |
| | Final Report Submission: | 05/2019 |

**PMC-1 - Agreed**

Develop and report a control strategy for the drug product to minimize the risk of (b) (4)

| | | |
|---|---|---|
| PMC Schedule Milestones: | CBE-30 submission of Control Strategy | 09/2017 |
| | Implementation of Control Strategy | 11/2017 |

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JENNIFER J LEE
07/20/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Wednesday, July 19, 2017 10:08 AM
**To:** 'Penny Ng'
**Subject:** RE: Enasidenib NDA: Formatting of the Medication Guide (Manufacturing and patent infoinformation)

Hello Penny,

In response to your question regarding the font size for the manufacturing and patent information in the Med Guide, it is preferred that this information appear in the Med Guide in Arial 7 point font. All other font in the Med Guide should appear in Arial 10 point font.

Kind regards,
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Tuesday, July 18, 2017 5:16 PM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: Enasidenib NDA: Formatting of the Medication Guide (Manufacturing and patent infoinformation)

Dear Jennie,

I have checked some examples of the recent approved MG and noticed the fonts of manufacturing and patent information are shown in smaller font size than the MG content so I will move forward as-is for now (per screen shot below, smaller font size for this info). Please advise if otherwise though. Thanks again.

Kind regards,
*Penny*

---

**From:** Penny Ng
**Sent:** Tuesday, July 18, 2017 2:46 PM
**To:** Lee, Jennifer (CDER) <Jennifer.Lee1@fda.hhs.gov>
**Subject:** Enasidenib NDA: Formatting of the Medication Guide (Manufacturing and patent infoinformation)

Good afternoon Jennie,

I am about to finalize the Medication Guide for submission tomorrow, but have a minor formatting question.

The manufacturing info and patent information are revised to the small fonts upon receipt from the Agency since late 31 August. For consistency, some of my team members suggested to use the same font size as the rest of the document. Before making such change, I would like to check with you if it is the Agency's intent or preference with the smaller size before making such change.

Please kindly advise if there is a concern in revising the size to the same font size as the remaining of the MG. Or if it is the Agency's preference to keep the font size as is (smaller than other part of the MG). I will follow so accordingly. Thanks again.

Draft Labeling have been Withheld in Full as b4 (CCI/TS)

Kind regards,
*Penny*

---

**Penny Ng**, M.Sc., MBA, RAC **Regulatory Affairs**
Celgene Corporation | Corporate Woods Bldg 32, Suite 900
9225 Indian Creek Parkway | Overland Park, KS 66210 USA
Work 913-266-0505 | Mobile (b) (6) | Fax 913-266-0394
png@celgene.com | www.celgene.com

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JENNIFER J LEE
07/19/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Friday, July 14, 2017 6:12 PM
**To:** 'Penny Ng'
**Subject:** NDA 209606 enasidenib -- FDA Labeling and PMR/PMC Revisions -- Response Due COB 7/19
**Attachments:** NDA 209606 enasidenib -- Draft Med Guide FDA revisions 7-14-2017.docx; NDA 209606 enasidenib -- Draft USPI FDA revisions 7-14-2017.docx; NDA 209606 Idhifa -- Draft PMR_PMC FDA Revisions 7-14-2017.docx

**Importance:** High

Dear Penny,

Please find attached the FDA revisions to the USPI and Med Guide for NDA 209606 enasidenib. Please accept changes that you agree with, make any edits that you do not agree with using tracked changes (do not reject any changes that the FDA proposed and do not delete any of the FDA's comments).

There were also additional FDA revisions to the PMR/PMC document. As a reminder, please accept changes that you agree with, and make any edits that you do not agree with using tracked changes (do not reject any changes that the FDA proposed).

In addition, I have the following comments regarding the Idhifa® container labels. Please provide a response and your revised labels with your response to the above.

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.*

2. *We have provisionally determined that the data in your NDA supports an 18-month expiry for the drug product.*

Send your revised track changed documents to me via email by **COB Wednesday, July 19, 2017** and also formally submit a copy of your responses to your NDA file. Kindly confirm receipt of this correspondence and do not hesitate to contact me should you have any questions.

Kind regards,
Jennie

_____

**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
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JENNIFER J LEE
07/14/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Friday, July 07, 2017 1:28 PM
**To:** 'Penny Ng'
**Subject:** NDA 209606 enasidenib -- FDA Information Request Response Due COB 7/10

Dear Penny,

I have the following information request for NDA 209606 enasidenib. Please provide a response to me via email by **COB Monday, July 10, 2017** and also follow up with a formal submission of your response to your NDA file.

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

---

***FDA Information Request***

***In the updated table 4 of the draft labeling with N=199 (Baseline Demographic and Disease Characteristics in Patients with Relapsed or Refractory AML), Celgene listed 155 patients with R140 and 44 patients with R172 IDH2 mutation. Celgene stated (Celgene 42) that "In the 199 R/R AML, 2 patients, instead of 3, had different mutations detected across sample types."***

***FDA is finding 156 patients with R140 and 43 patients with R172. The 3 subject IDs listed below had different mutations across sample types based on the cdxmay17.xpt file sent by Celgene on 6/19/2017.***

| SAMPTYPE | RESULT | **SUBJID** |
|---|---|---|
| BMA | R172K | **101-007** |
| PB | 140Q | **101-007** |
| BMA | R140Q | **112-004** |
| PB | R172K | **112-004** |
| BM | R140Q | **111-029** |
| PB | R172K | **111-029** |

***Please confirm the numbers of patients with R140 or R172 (N=199) and how many patients had different mutations (R140 vs R172) detected across sample types.***

---

**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
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JENNIFER J LEE
07/07/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Friday, July 07, 2017 12:04 PM
**To:** 'Penny Ng'
**Subject:** RE: NDA 209606 enasidenib -- FDA Labeling Revisions, PMR/PMC and Review Update -- Response Due 7/6 COB
**Attachments:** NDA 209606 Idhifa -- PMR_PMC Final 7-7-2017.docx

Hello Penny,

As an update, your revisions to the PMR/PMC document are acceptable. Please submit the attached version of the wording and timelines formally to your NDA file as the final agreed upon PMR/PMCs for Idhifa®.

Kind regards,
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Thursday, July 06, 2017 3:36 PM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- FDA Labeling Revisions, PMR/PMC and Review Update -- Response Due 7/6 COB

Good afternoon Jennie,

Thank you again for the clarification and guidance provided during the preparation of this submission.

Please find attached the following:

- Celgene's revisions to the draft US PI
- Celgene's revisions to the Medication Guide
- Celgene's revisions to the PMC/PMR document

As requested by the Agency, in all 3 documents, Celgene has accepted the agreed changes and included any edits using track-changes only (we also did not reject any changes that the FDA proposed).

I will also submit these documents formally to the NDA early next week.

Kind regards,
*Penny*

---

**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Friday, June 30, 2017 10:10 AM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** NDA 209606 enasidenib -- FDA Labeling Revisions, PMR/PMC and Review Update -- Response Due 7/6 COB

Good morning Penny,

Please find attached the following documents and responses related to NDA 209606 enasidenib:

1. **Draft USPI and Med Guide (MG) with FDA revisions:** Please accept changes that you agree with, make any edits that you do not agree with using track-changes only (do not reject any changes that the FDA proposed and do

not delete any of the FDA's comments). Send your revised tracked changed USPI and MG to me via email by **COB Thursday, July 6, 2017** and then formally submit a copy to your NDA file.

2. **Draft PMR/PMC document:** All changes were accepted by the Agency. Please submit the final and agreed upon PMR/PMC wording and proposed timelines formally to the NDA file by **COB Thursday, July 6, 2017**.

3. **Response to your June 22, 2017 correspondence (Seq. No. 0040):**

    a. Celgene respectfully asks for an update on the Agency's review timeline, specifically if an earlier action date would be possible.

    ***FDA Response*: If there is no change in review staff workload overall and no delay in achieving agreement on the final labeling for Idhifa, we may choose to take an action as early as August 1, 2017.**

    b. Celgene respectfully asks for written confirmation on agreed-upon labeling (US Prescription Information and Container Label) when the Agency has completed the review, pending the approval decision.

    ***FDA Response*: FDA will confirm when we have received the provisionally agreed-upon US Prescribing Information and Container Label with the understanding that there may be additional revisions if new information comes to light before any approval decision is issued.**

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

_____

**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov


sender to notify us of the error and delete the original message. Thank You.

APPEARS THIS WAY ON ORIGINAL

**PMR-1-Agreed**

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.

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

**PMR-2-Agreed**

Characterize the long-term safety of enasidenib in patients with relapsed or refractory acute myeloid leukemia (AML). Submit the final study report and data set with 3 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.

| | | |
|---|---|---|
| PMR/PMC Schedule Milestones: | Preliminary Protocol Submission | 06/2013 |
| | Final Protocol Submission: | 10/2015 |
| | Study/Trial Completion: | 05/2019 |
| | Final Report Submission: | 03/2020 |

**PMR-3-Agreed**

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 data set with 3 years of follow-up from ongoing 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.

| | | |
|---|---|---|
| PMR/PMC Schedule Milestones: | Preliminary Protocol Submission | Not applicable |
| | Final Protocol Submission: | 08/2015 |
| | Study/Trial Completion: | 09/2022 |
| | Final Report Submission: | 07/2023 |

**PMR-4 - Agreed**

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."

| | | |
|---|---|---|
| PMR/PMC Schedule Milestones: | Preliminary Protocol Submission | 09/2017 |
| | Final Protocol Submission: | 12/2017 |
| | Study/Trial Completion (PK portion): | 09/2019 |
| | Final Report Submission: | 03/2020 |

**PMR-5 - Agreed**

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."

| | | |
|---|---|---|
| PMR/PMC Schedule Milestones: | Final Protocol Submission: | 09/2017 |
| | Study/Trial Completion: | 11/2018 |
| | Final Report Submission: | 05/2019 |

**PMC-1 - Agreed**

Develop and report a control strategy for the drug product to minimize the risk of (b) (4)

| | | |
|---|---|---|
| PMC Schedule Milestones: | CBE-30 submission of Control Strategy | 09/2017 |
| | Implementation of Control Strategy | 11/2017 |

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JENNIFER J LEE
07/07/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Thursday, July 06, 2017 8:44 AM
**To:** 'Penny Ng'
**Subject:** RE: NDA 209606 enasidenib -- FDA Labeling Revisions, PMR/PMC and Review Update -- Response Due 7/6 COB
**Attachments:** ENASIDEN.xpt

Dear Penny,

In regards to your request for clarification sent by email on July 5th, please see the attached .xpt file. The FDA-created variable names are as follows:

| | |
|---|---|
| BESTRSP2 and BRSPDT2 | BESTRSPC and BRSPDT from ADEFF2.xpt |
| BESTRSP1 and BRSPDT1 | BESTRSPC from ADEFF.xpt |
| BESTRSP3 and BRSPDT3 | FDA-adjudicated BESTRSPC and BRSPDT3 |
| RELPDDT1 | RELPDDT1 from ADEFF2.xpt (with one value changed as noted below) |
| RSPENDDT | Response end date as determined by FDA (earliest of RELPDDT1, DTHDT or 10/14/16) |
| DORCS | DOR censor code (1= censored at 10/14/16) |
| DOR | FDA-calculated DOR (difference between BRSPDT3 and RSPENDDT in months) |

BRSPDT3 is the same as BRSPDT in the submitted ADEFF2.xpt file (BRSPDT2 in the attached file) in all subjects except for:

- 104-058 (5/5/2016 – date of investigator-determined best response)
- 105-016 (6/18/2015 – date of investigator-determined best response)
- 106-005 (6/11/2015 – as previously explained)
- 108-009 (8/2/2016 – date of investigator-determined best response)
- 108-010 (7/6/2016 – date of investigator-determined best response)
- 900-020 (3/7/2016 – date of investigator-determined best response)

RELPDDT1 is the same as RELPDDT1 in the submitted ADEFF2.xpt file in all subjects except for:

- 106-005 (3/30/2016 – as previously explained)

DOR was calculated as the number of months from the date of best response to the date of relapse, death, or data cut (10/14/16), whichever came first. Please note that the FDA identified an error in Table 5 of the latest FDA draft revisions to the USPI: the 95% CI for duration of response for CR/CRh (last line of the table) should be (4.3, 19.4).

If you identify any additional errors or are requesting any changes, please submit a summary of your proposed changes with a justification for each, a revised Table 5 of the USPI, and a .xpt file containing all of the data required to recreate the analysis, with your response to the FDA Labeling Revisions.

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Wednesday, July 05, 2017 6:53 AM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- FDA Labeling Revisions, PMR/PMC and Review Update -- Response Due 7/6 COB

Good morning Jennie,

Hope you had a good 4th July.

Thanks again for the information provided in the e-mail below. I have shared with my stat. team as we are using this information to repeat DOR in CRs. However, we believe that there are probably other discrepancies in the DORs analysis in CR and CRh subjects using our current investigator assessments, sponsor derived assessments, and verified response vs. the Agency's adjudicated response. Would the Agency be able to provide the response date, relapse date, and DOR based on the Agency's adjudication for the 46 CR/CRh subjects in order for us to understand the Agency's analyses included in Table 5 of the US PI?

Thank you again for your guidance.

Kind regards,
*Penny*

**From:** Penny Ng
**Sent:** Monday, July 03, 2017 10:29 AM
**To:** Lee, Jennifer (CDER) <Jennifer.Lee1@fda.hhs.gov>
**Subject:** Re: NDA 209606 enasidenib -- FDA Labeling Revisions, PMR/PMC and Review Update -- Response Due 7/6 COB

Thank you Jennie. I will share with my team.

Kind regards,
Penny

-sent from my iPhone

On Jul 3, 2017, at 9:36 AM, Lee, Jennifer (CDER) <Jennifer.Lee1@fda.hhs.gov> wrote:

> Good morning Penny,
>
> In response to your question below, as stated in Comment A17 in the FDA labeling revisions, the FDA adjusted the date of relapse for subject 106-005 to reflect time of relapse after CR (rather than date of initial investigator-determined PD). The FDA used a date of best response as 06/11/2015 and a relapse date of 03/30/2016 for subject 106-005, as per FDA review of data tabulated in ADEDRT2.xpt. The FDA recognizes that the response evaluation dated 05/12/15 (visit code = End of Treatment, response = CR), was the earliest documented CR for the subject. However, as the subject did not stop treatment at that time, that response assessment was interpreted by the FDA as an unscheduled response assessment per protocol, and was therefore excluded from FDA analysis of best response.
>
> Feel free to let me know if you have further questions.
>
> Kind regards,
> Jennie

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Monday, July 03, 2017 7:25 AM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- FDA Labeling Revisions, PMR/PMC and Review Update -- Response Due 7/6 COB

Hello Jennie,

My team is working on Section 14 of the US PI. We are trying to repeat the analysis. For Subject 106-005, would you kindly advise if the Agency has updated the relapse date of this subject as we are trying to understand the Agency's analysis of DOR in CRs? Thank you in advance for the clarification.

Kind regards,
*Penny*

**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Friday, June 30, 2017 2:15 PM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** RE: NDA 209606 enasidenib -- FDA Labeling Revisions, PMR/PMC and Review Update -- Response Due 7/6 COB

Hello Penny,

My apologies, the subject that should be excluded is **201-036**, not 210-036. Thank you for double checking!

Have a nice weekend,
Jennie

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Friday, June 30, 2017 12:20 PM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- FDA Labeling Revisions, PMR/PMC and Review Update -- Response Due 7/6 COB

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> **To Applicant:** The FDA has insufficient information to confirm relapse (as identified by IWG criteria) in the following subjects, which were removed from the denominator:
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>
> 102-008
>
> 102-012
>
> 108-013
>
> 111-053

111-057

113-004

210-036

900-006

Note: The FDA considers that lack of intervening treatment between pre-screening BM showing blasts ≥ 5% and screening BM showing blasts < 5% for subjects 108-013 and 111-053 is insufficient to conclude that the patient is in relapse at the time of screening.

The FDA also believes that subject 108-003 is CDx positive, although this subject was listed in Celgene's response to IR submitted to the NDA as part of eCTD 0029 on 05/24/17 (Module 1.11.3, page 2) as CDx negative. This subject was added back to the denominator.

For the patient ID highlighted above, 210-036, would the Agency clarify if this should read 201-036 based on the dataset/database? If yes, we will exclude Subject 201-036 when addressing the updates in Section 14.

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**Subject:** RE: NDA 209606 enasidenib -- FDA Labeling Revisions, PMR/PMC and Review Update -- Response Due 7/6 COB

Good morning Jennie,

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Have a good weekend.

Kind regards,
*Penny*

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**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Friday, June 30, 2017 9:10 AM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** NDA 209606 enasidenib -- FDA Labeling Revisions, PMR/PMC and Review Update -- Response Due 7/6 COB

Good morning Penny,

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changes that the FDA proposed and do not delete any of the FDA's comments). Send your revised tracked changed USPI and MG to me via email by **COB Thursday, July 6, 2017** and then formally submit a copy to your NDA file.

2. **Draft PMR/PMC document:** All changes were accepted by the Agency. Please submit the final and agreed upon PMR/PMC wording and proposed timelines formally to the NDA file by **COB Thursday, July 6, 2017**.

3. **Response to your June 22, 2017 correspondence (Seq. No. 0040):**

    a. Celgene respectfully asks for an update on the Agency's review timeline, specifically if an earlier action date would be possible.

    ***FDA Response*: If there is no change in review staff workload overall and no delay in achieving agreement on the final labeling for Idhifa, we may choose to take an action as early as August 1, 2017.**

    b. Celgene respectfully asks for written confirmation on agreed-upon labeling (US Prescription Information and Container Label) when the Agency has completed the review, pending the approval decision.

    ***FDA Response*: FDA will confirm when we have received the provisionally agreed-upon US Prescribing Information and Container Label with the understanding that there may be additional revisions if new information comes to light before any approval decision is issued.**

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

_____

**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov

<image001.png>

<image002.jpg> <image003.jpg> <image004.jpg> <image005.jpg> <image006.jpg>

intended recipient, you are hereby notified that any dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please reply to the sender to notify us of the error and delete the original message. Thank You.

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/s/

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JENNIFER J LEE
07/06/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Wednesday, July 05, 2017 1:00 PM
**To:** 'Penny Ng'
**Subject:** RE: NDA 209606 enasidenib -- A question regarding Agency's comment on the Medication Guide

Dear Penny,

In response to your question below regarding the med guide, the copyright information was moved inside the box, right below Celgene's website URL. Information should not be listed outside the box after the statement *"This Medication Guide has been approved by the U.S. Food and Drug Administration"*. You may replace the current copyright information with the previous wording as long as it is located within the box.

The team is still working on our response to your question regarding our analyses included in Table 5 of the USPI. I will let you know when I have more information to share.

Kind regards,
Jennie

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**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Wednesday, July 05, 2017 11:56 AM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- A question regarding Agency's comment on the Medication Guide

Good afternoon Jennie,

I have a follow-up question regarding the Agency's comment on the Medication Guide. The Agency has removed the copyright information (yellow highlighted in the screen shot below) in the Medication Guide. Based on other approved Medication Guides, including the Celgene's ones, the copying right information is on both the USPI and the Medication Guide; therefore, we would like to understand the Agency's request for deleting this information in the IDHIFA Medication Guide.

Thank you again for your guidance.

Draft Labeling have been Withheld in Full as b4 (CCI/TS)

Kind regards,
*Penny*

---

**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Friday, June 30, 2017 10:10 AM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** NDA 209606 enasidenib -- FDA Labeling Revisions, PMR/PMC and Review Update -- Response Due 7/6 COB

Good morning Penny,

Please find attached the following documents and responses related to NDA 209606 enasidenib:

1. **Draft USPI and Med Guide (MG) with FDA revisions:** Please accept changes that you agree with, make any edits that you do not agree with using track-changes only (do not reject any changes that the FDA proposed and do not delete any of the FDA's comments). Send your revised tracked changed USPI and MG to me via email by **COB Thursday, July 6, 2017** and then formally submit a copy to your NDA file.

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3. **Response to your June 22, 2017 correspondence (Seq. No. 0040):**

a. Celgene respectfully asks for an update on the Agency's review timeline, specifically if an earlier action date would be possible.

***FDA Response*: If there is no change in review staff workload overall and no delay in achieving agreement on the final labeling for Idhifa, we may choose to take an action as early as August 1, 2017.**

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***FDA Response*: FDA will confirm when we have received the provisionally agreed-upon US Prescribing Information and Container Label with the understanding that there may be additional revisions if new information comes to light before any approval decision is issued.**

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

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**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
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jennifer.lee1@fda.hhs.gov

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/s/

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JENNIFER J LEE
07/05/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Monday, July 03, 2017 9:36 AM
**To:** 'Penny Ng'
**Subject:** RE: NDA 209606 enasidenib -- FDA Labeling Revisions, PMR/PMC and Review Update -- Response Due 7/6 COB

Good morning Penny,

In response to your question below, as stated in Comment A17 in the FDA labeling revisions, the FDA adjusted the date of relapse for subject 106-005 to reflect time of relapse after CR (rather than date of initial investigator-determined PD). The FDA used a date of best response as 06/11/2015 and a relapse date of 03/30/2016 for subject 106-005, as per FDA review of data tabulated in ADEDRT2.xpt. The FDA recognizes that the response evaluation dated 05/12/15 (visit code = End of Treatment, response = CR), was the earliest documented CR for the subject. However, as the subject did not stop treatment at that time, that response assessment was interpreted by the FDA as an unscheduled response assessment per protocol, and was therefore excluded from FDA analysis of best response.

Feel free to let me know if you have further questions.

Kind regards,
Jennie

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Have a nice weekend,
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> Note: The FDA considers that lack of intervening treatment between pre-screening BM showing blasts ≥ 5% and screening BM showing blasts < 5% for subjects 108-013 and 111-053 is insufficient to conclude that the patient is in relapse at the time of screening.
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Thank you,
Jennie

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**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
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**Division of Hematology Products**
**U.S. Food and Drug Administration**

Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov



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/s/

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JENNIFER J LEE
07/03/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Friday, June 30, 2017 3:15 PM
**To:** 'Penny Ng'
**Subject:** RE: NDA 209606 enasidenib -- FDA Labeling Revisions, PMR/PMC and Review Update -- Response Due 7/6 COB

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**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov


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JENNIFER J LEE
06/30/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Friday, June 30, 2017 10:10 AM
**To:** 'Penny Ng'
**Subject:** NDA 209606 enasidenib -- FDA Labeling Revisions, PMR/PMC and Review Update -- Response Due 7/6 COB
**Attachments:** NDA 209606 enasidenib -- Draft USPI FDA Revisions 6-30-2017.docx; NDA 209606 enasidenib -- Draft Med Guide FDA Revisions 6-30-2017.docx; NDA 209606 Idhifa -- Draft PMR_PMC 06-30-2017.docx

Good morning Penny,

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**U.S. Food and Drug Administration**

Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

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

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/s/

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JENNIFER J LEE
06/30/2017

| | |
|---|---|
| **From:** | Lee, Jennifer (CDER) |
| **To:** | "Penny Ng" |
| **Subject:** | RE: NDA 209606 enasidenib -- PMR/PMC Comments Response Received on 14 Jun 2017: clarification/confirmation required on definition of "3 years of follow-up" |
| **Date:** | Tuesday, June 20, 2017 10:40:00 AM |
| **Attachments:** | image001.png |

Hello Penny,

I would like to confirm that what you propose below in regards to the follow-up timeline is acceptable.

Kind regards,
Jennie

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**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Monday, June 19, 2017 8:24 PM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- PMR/PMC Comments Response Received on 14 Jun 2017: clarification/confirmation required on definition of "3 years of follow-up"

Good afternoon Jennie,

My team is working on the PMC/PMR comments. For PMR-2 and PMR-3, as discussed at the LCM on Friday, we agreed with the Agency's wording:

PMR-2:

Characterize the long-term safety of enasidenib in patients with relapsed or refractory acute myeloid leukemia (AML). Submit the final study report and data set with 3 years of follow-up from ongoing Study AG-221-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.

And

PMR-3:

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 data set with 3 years of follow-up from ongoing 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.

We are currently updating PMR-2 and PMR-3 final CSR timeline per comments from the Agency "**To Applicant:** Modify the date to account for protocol amendment described above to capture long-term safety data."

Our team is using the understanding of "3 years of follow-up" is defined in the studies as **3 years after first dose of the last enrolled patient** given the life expectancy of the R/R AML subjects.

Please kindly confirm if this definition of 3 years of follow-up meets the Agency's expectation.

Thank you in advance for the guidance. This confirmation will be very helpful for us to finalize the timing of the final CSR timeline and include in the PMC/PMR comments due this Wednesday.

Kind regards,
Penny

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**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Wednesday, June 14, 2017 4:01 PM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** NDA 209606 enasidenib -- FDA Revisions to the USPI and PMR/PMC Comments Response Due 6/21 Noon ET

Dear Penny,

Please find attached the FDA revisions to the USPI and the PMR/PMC comments for NDA 209606 enasidenib. The Med Guide is still currently under review. For both documents, please accept any changes you agree with, make any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***) and send the revised tracked changed documents to me via email by **Wednesday, June 21, 2017 Noon ET** before you make your official submission electronically to the NDA file.

Also, you will find attached a document of preferred term groupings for your team's reference.

Kindly confirm receipt of this correspondence.

Thank you,
Jennie


**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov


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/s/

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JENNIFER J LEE
06/20/2017

| | |
|---|---|
| **From:** | Lee, Jennifer (CDER) |
| **To:** | "Penny Ng" |
| **Subject:** | NDA 209606 enasidenib -- FDA Revisions to the USPI and PMR/PMC Comments Response Due 6/21 Noon ET |
| **Date:** | Wednesday, June 14, 2017 5:01:00 PM |
| **Attachments:** | NDA 209606 enasidenib -- USPI FDA Revisions 6-14-2017.docx<br>NDA 209606 Idhifa -- PMRs FDA revisions 6-14-2017.docx<br>Grouped Terms for IDHIFA.docx<br>image013.png |

Dear Penny,

Please find attached the FDA revisions to the USPI and the PMR/PMC comments for NDA 209606 enasidenib. The Med Guide is still currently under review. For both documents, please accept any changes you agree with, make any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***) and send the revised tracked changed documents to me via email by **Wednesday, June 21, 2017 Noon ET** before you make your official submission electronically to the NDA file.

Also, you will find attached a document of preferred term groupings for your team's reference.

Kindly confirm receipt of this correspondence.

Thank you,
Jennie


**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
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/s/

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JENNIFER J LEE
06/14/2017

| | |
|---|---|
| **From:** | Lee, Jennifer (CDER) |
| **To:** | "Penny Ng" |
| **Subject:** | NDA 209606 enasidenib -- FDA Information Request Response Due 6/14 3PM ET |
| **Date:** | Monday, June 12, 2017 2:47:00 PM |
| **Attachments:** | image002.png |

Dear Penny,

I have the following FDA information request for NDA 209606 enasidenib. Please provide a response to me via email by **Wednesday, June 14, 2017 3PM ET** and also follow up with a formal submission to your NDA file.

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

_____

***FDA Information Request***

> ***Based on the dataset CDXMAY17.xpt, the IDH2 genotyping results of 3 patients (subject IDs 101-007, 111-029, 112-004) varied across the biospecimens tested with the proposed companion diagnostic assay. Please clarify the rules for how these 3 patients were assigned to one of the two IDH2 mutation groups (i.e., R140 or R172) in the efficacy dataset.***


_____

**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov



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/s/

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JENNIFER J LEE
06/12/2017

**From:** Lee, Jennifer (CDER)
**To:** "Penny Ng"
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response submitted on 05 June. Thanks.
**Date:** Thursday, June 08, 2017 3:00:00 PM
**Attachments:** image002.png

Hello Penny,

In reference to your email below, please submit a PDF version of the USPI with the hyperlinks included in the comment bubbles. This version should be otherwise exactly the same as the Word version you submitted to eCTD on June 8th, 2017.

In terms of the next round of FDA labeling comments, my goal is to get it to you before the LCM background package. However, I'm sure you can understand that this may change as the team is reviewing all of your responses. I will be in touch if I have any other updates on the timeline.

Kind regards,
Jennie

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**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Thursday, June 08, 2017 9:57 AM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response submitted on 05 June. Thanks.

Good morning Jennie,

I would like to let you know that the submission noted below has been submitted via the gateway this morning.

During the publishing process of the eCTD submission, we were trying to address the Agency's request to add an external link to the supporting document from the US PI Word Document comment bubbles when addressing the Agency's comment (for this US PI, that would be the Celgene's Response Document). Celgene's publishing team can only create an external link from a PDF document (not from a Word document); therefore, we apologize for not able to create a hyperlink from the US PI Word document to the Response Document (PDF). The response document is located in the XML under 1.11.4 Multiple Module Information Amendment, file name: Response to FDA US PI Comments Dated 30 May 2017.

Please do not hesitate to let me know if you or the Review Team have any questions. If the Agency would like to have a version with hyperlinks included, we can prepare one based on the PDF version of the US PI (I understand that the Agency may want to use the Word version to make direct changes so have not included a PDF version in the submission but can do so if this can facilitate review due to the technical difficulty in not adding the links).

Would you kindly advise if we should expect the next round of US PI comments before the arrival of the Late-Cycle Review Meeting Agency's Briefing Document (by 14 Jun) or before the Late-Cycle

Review Meeting (16 Jun)? This information will be very helpful for me in planning out the meeting preparation activities with my team. Thank you in advance for the guidance.

I look forward meeting you again in person next week.

Kind regards,
Penny

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**From:** Penny Ng
**Sent:** Wednesday, June 07, 2017 11:35 AM
**To:** Lee, Jennifer (CDER) <Jennifer.Lee1@fda.hhs.gov>
**Cc:** Patricia Callahan <pcallahan@celgene.com>
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response submitted on 05 June. Thanks.

Hello Jennie,

Thanks for the very clear guidance as always.

Based on this clarification, we will not be including the APVPD dataset and defined file in the eCTD submission today. I will work with my team to prepare this per the clarification below and target to submit to the NDA next week.

The eCTD follow-up submission to the NDA today will include the following:

- Response to FDA IR received on 02 Jun 2017 (response submitted by e-mail on 05 Jun 2017)
- Response to FDA PMC/PMR comments received on 30 May 2017 ( response in pdf submitted by e-mail on 06 Jun 2017)
- Response to FDA Labeling comments received on 30 May 2017 (response in pdf submitted by e-mail on 06 Jun 2017)
- Revised US PI based on FDA Labeling comments received on 30 May 2017 (word document with track-changes submitted by e-mail on 06 June 2017), the Word file will be included in the e-CTD submission
- Draft Medication Guide based on FDA Labeling comments received on 30 May 2017 (word document submitted by e-mail on 06 June 2017), the Word file will be included in the eCTD submission

Thank you again. I will submit the response to IR (received on 05 Jun regarding ADEFF2.BESTRSPC, response submitted on 06 Jun) and the ongoing IR related to the translational development report (received yesterday, response due on 08 Jun) formally to the NDA next week in a separate submission.

Kind regards,
Penny

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**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Wednesday, June 07, 2017 10:39 AM

**To:** Penny Ng <PNg@celgene.com>
**Cc:** Patricia Callahan <pcallahan@celgene.com>
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response submitted on 05 June - a question regarding dataset submission (replace or new for ADPVPD). Thanks.

Hello Penny,

In regards to your submission, it should include a complete, cumulative data file that includes all protocol violations from the start of the study through the 14-OCT-2016 data cut date (NOT just the violations from April through October 2016). It should be submitted as a replacement to the original ADPVPD data file (the one that used a 15-APR-2016 data cut date).

Please let me know if this helps clear up all questions surrounding your formal submission. I would also like to confirm receipt of your tracked change version of the PMR/PMC comments.

Thank you,
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Wednesday, June 07, 2017 10:59 AM
**To:** Lee, Jennifer (CDER)
**Cc:** Patricia Callahan
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response submitted on 05 June - a question regarding dataset submission (replace or new for ADPVPD). Thanks.
**Importance:** High

Dear Jennie,

I had a follow-up discussion with my team (programming and stat. team) and they shared the following proposal with me. I understand that the Agency has provided comments previously advising not submitting Phase 1/2 dataset to the 4MSU folder but submit to the study folder as "replacement" so I would appreciate your feedback before we submit to ensure we meet the requirement/expectation:

ADPVPD submitting to the NDA today will only include the PVPDs between 16 Apr 2016 to 14 Oct 2016, not including the data in the original ADPVPD (data-cut of 15 Apr2016) in the original NDA; therefore, my team suggested that this should be submitted as "new" in the eCTD today as this will not replace the information submitted in the original ADPVPD.

For the defined file that is being submitted today, it will only include the updated source info supporting the PVPD dataset between 16 Apr 2016 to 14 Oct 2016, so my team has suggested to submit as "new" as well since the defined file submitting today does not include other descriptions currently in the defined file in the NDA.

In summary, this is Celgene's proposal based on above rationale:

- ADPVPD (PVPDs between 16 Apr 2016 to 14 Oct 2016) dataset (in xpt): "new" under the ISS

"4Month Safety Update folder" due to the datacut of 14 Oct 2016, and not a replacement to the ADPVPD file (with 15 April 2016 datacut) in the NDA

- Defined file describing above: "new" under ISS "4Month Safety Update folder", together with the ADPVPD file above.

There will be a total of 4 files (ADPVPD in .xpt, 2 supporting files in pdfs, and one defined file).

Please kindly advise if the Agency agrees with the above for the submission of the ADPVPD dataset/defined files to the NDA today.

As always, we appreciated your guidance.

Kind regards,
Penny

---

**From:** Penny Ng
**Sent:** Wednesday, June 07, 2017 8:17 AM
**To:** Lee, Jennifer (CDER) <Jennifer.Lee1@fda.hhs.gov>
**Cc:** Patricia Callahan <pcallahan@celgene.com>
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response submitted on 05 June - a question regarding dataset submission (replace or new for ADPVPD). Thanks.

Good morning Jennie,

We are targeting to submit today to the eCTD the ADPVPD dataset and programming of PVPDs between 16 Apr 2016 to 14 Oct 2016 as noted in our response to the IR submitted on Monday.

Would you please advise if the ADPVPD dataset/programming/defined file (16 Apr 2016 to 14 Oct 2016) should be a replacement of the original ADPVPD dataset (15 Apr 2016 data-cut) included in the original NDA? Or should we submit as "new" since this is a different data cut date and mainly covers the 16 Apr 2016 to 14 Oct 2016 PVPDs?

Please kindly advice. I am also copying my Regulatory Operations colleague, Pat Callahan, in this e-mail. She is working with FDA ESUB/dataset team per the IR dated 02 Jun 2017.

Kind regards,
Penny

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**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Monday, June 05, 2017 8:18 PM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Thank you, Penny. I confirm receipt of your response.

Have a good evening,
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Monday, June 05, 2017 5:49 PM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Dear Jennie,

My apologies again for the delay. Please see attached the response to IR received on 02 Jun.

We plan to submit this formally, including the SAS programming of PVPD (noted in the response document), to the NDA on 07 Jun 2017.

Thanks again for the feedback and confirmation received today.

Kind regards,
Penny

---

**From:** Penny Ng
**Sent:** Monday, June 05, 2017 3:26 PM
**To:** 'Lee, Jennifer (CDER)' <Jennifer.Lee1@fda.hhs.gov>
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Dear Jennie,

My apologies, as I may need until 6 pm ET to submit this response to you by e-mail.

Kind regards,
Penny

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**From:** Penny Ng
**Sent:** Monday, June 05, 2017 12:25 PM
**To:** Lee, Jennifer (CDER) <Jennifer.Lee1@fda.hhs.gov>
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Thanks again! I will be submitting the response to the 3 comments to you by e-mail by COB today.

Kind regards,
Penny

---

**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Monday, June 05, 2017 11:54 AM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Yes, that is correct. Thank you for clarifying.

Kindly,
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Monday, June 05, 2017 12:22 PM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Hello Jennie,

Thanks for reaching out to your team, very much appreciated.

Just want to clarify that if this implies that we do not need to submit the dataset and programming of the ADEFF2 dataset (of the 207 R/R AML 100 mg daily dose, confirmed with CDx), and for our response document due today, we only need to address the following 3 questions:

***FDA Information Request***

1. *The dataset for Study AG221-C-001 (combined parts I and II) submitted electronically to the NDA on 5/10/17 is missing the ADPDPV (protocol violations) dataset. Please clarify if there have been any new protocol violations, and if so, provide the APPDPV dataset updated with a data cut date of October 15, 2016.*

2. *For the file ADSL, please explain why subjects 101-007 and 111-037 have STDIS = blank but death dates are prior to the October 15, 2016 data cut-off date.*

***Please provide a response for #1 and #2 by COB Monday, June 5, 2017.***

3. *The update of the dataset for Study AG221-C-001 (combined parts I and II) on 5/10/2017 was successful in resolving the duplicate file issue. Unfortunately, the submission of files on 5/24/2017 again included duplicate files. Please correct the submission so that there are no duplicate files. We strongly recommend that you work with the ESUB team (esub@fda.hhs.gov) to determine the most efficient way to correct the error and how to avoid file duplications in future submissions.*

Thanks again!

Kind regards,
Penny

---

**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Monday, June 05, 2017 11:10 AM

**To:** Penny Ng <PNg@celgene.com>
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Hello Penny,

I just wanted to let you know that I've touched base with my team and we will be rescinding the second set of IRs (sent on Friday, June 02, 2017 7:02 AM).

Kindly confirm receipt of this update.

Thank you,
Jennie

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**From:** Lee, Jennifer (CDER)
**Sent:** Monday, June 05, 2017 9:55 AM
**To:** 'Penny Ng'
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Good morning Penny,

I confirm receipt of your question below. I will circle back with my team and will let you know.

Kind regards,
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Monday, June 05, 2017 7:59 AM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Good morning Jennie,

For the eCTD submission of the dataset and programming below to the NDA:

***FDA Information Request***

*No updated adeff2 data or analysis results by using adeff2 data have been submitted as a response to our information request sent on May 12 , 2017.*

*By using updated adeff2 data, please submit the following analysis results in patients with R/R AML who were assigned enasidenib at 100 mg total daily dose (Phase I, Phase II and combined Phase I & Phase II) for the efficacy endpoints of CR, CRh, CR/CRh, ORR, DOR, RBC/Platelet transfusion…etc., as well as important subgroup analyses of these endpoints (i.e., forest plots of subgroup analysis) based on the following requirements:*

- *Exclude patients from the numerator and denominator who did not have IDH2 mutation identified in either their blood or marrow based on the companion diagnostic.*

- *Exclude responses that occurred only after other therapy given after IDHIFA (e.g., HSCT). Specifically, exclude the CRs that occurred in subjects 110-006 and 111-046.*

*Provide the datasets and SAS programs used to generate the above analyses.*

Would you kindly advise if the ADEFF2 dataset (of the 207 R/R AML 100 mg daily dose, confirmed with CDx) should replace the ADEFF2 dataset of previously submitted population (of the 214 R/R AML 100 mg daily dose)? Or should this dataset be submitted as new?

Thanks in advance for your guidance and we will submit to the NDA accordingly.

Kind regards,
Penny

---

**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Friday, June 02, 2017 7:02 AM
**To:** Penny Ng <PNg@celgene.com>
**Cc:** Paul McInulty <pmcinulty@celgene.com>
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Dear Penny,

I have an additional information request that is also due on **Monday, June 5th, 2017 COB**. Kindly confirm receipt of both sets of information requests.

Thank you,
Jennie

***FDA Information Request***

*No updated adeff2 data or analysis results by using adeff2 data have been submitted as a response to our information request sent on May 12 , 2017.*

*By using updated adeff2 data, please submit the following analysis results in patients with R/R AML who were assigned enasidenib at 100 mg total daily dose (Phase I, Phase II and combined Phase I & Phase II) for the efficacy endpoints of CR, CRh, CR/CRh, ORR, DOR, RBC/Platelet transfusion…etc., as well as important subgroup analyses of these endpoints (i.e., forest plots of subgroup analysis) based on the following requirements:*

- *Exclude patients from the numerator and denominator who did not have IDH2 mutation identified in either their blood or marrow based on the companion diagnostic.*
- *Exclude responses that occurred only after other therapy given after IDHIFA (e.g., HSCT). Specifically, exclude the CRs that occurred in subjects 110-006 and 111-046.*

*Provide the datasets and SAS programs used to generate the above analyses.*

**From:** Lee, Jennifer (CDER)
**Sent:** Friday, June 02, 2017 6:39 AM
**To:** 'Penny Ng'
**Cc:** 'Paul McInulty'
**Subject:** NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Good morning Penny,

I have the following information request from the FDA review team for NDA 209606 enasidenib. Please send a response to #1 and #2 to me via email by **COB Monday, June 5th, 2017,** and then follow up with a formal submission to your NDA file**.**

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

***FDA Information Request***

1. *The dataset for Study AG221-C-001 (combined parts I and II) submitted electronically to the NDA on 5/10/17 is missing the ADPDPV (protocol violations) dataset. Please clarify if there have been any new protocol violations, and if so, provide the APPDPV dataset updated with a data cut date of October 15, 2016.*

2. *For the file ADSL, please explain why subjects 101-007 and 111-037 have STDIS = blank but death dates are prior to the October 15, 2016 data cut-off date.*

***Please provide a response for #1 and #2 by COB Monday, June 5, 2017.***

3. *The update of the dataset for Study AG221-C-001 (combined parts I and II) on 5/10/2017 was successful in resolving the duplicate file issue. Unfortunately, the submission of files on 5/24/2017 again included duplicate files. Please correct the submission so that there are no duplicate files. We strongly recommend that you work with the ESUB team (esub@fda.hhs.gov) to determine the most efficient way to correct the error and how to avoid file duplications in future submissions.*

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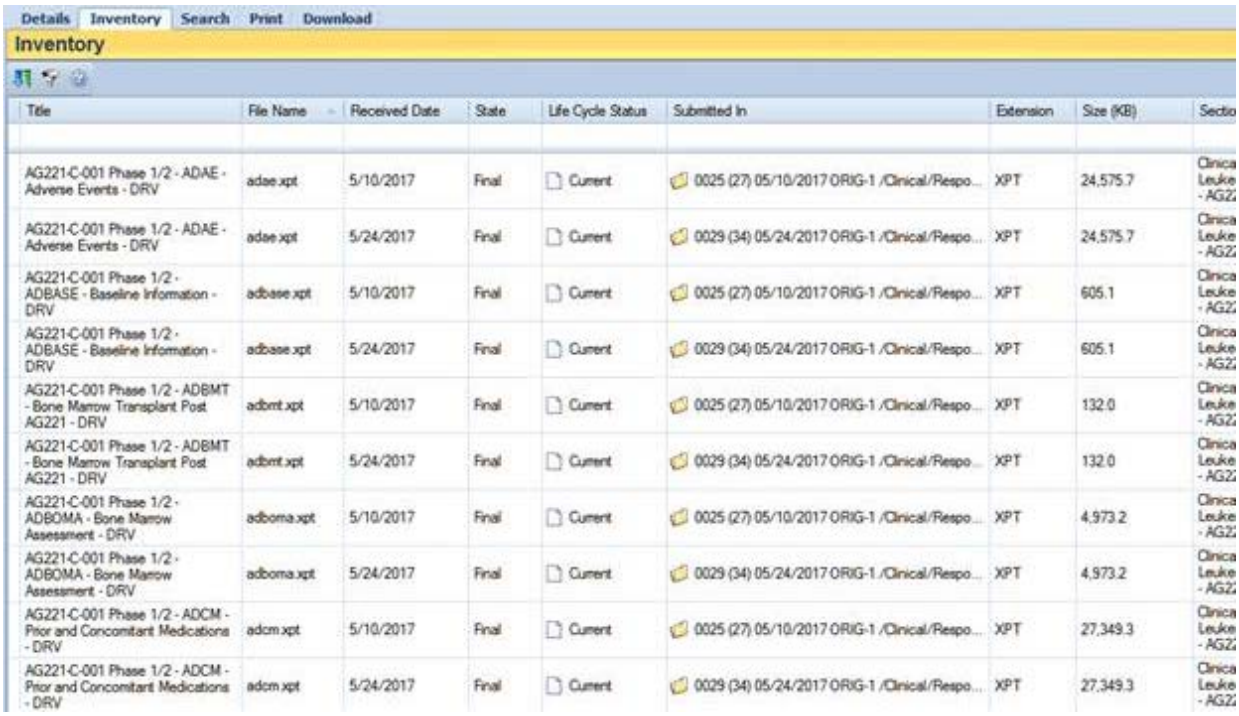

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Inventory

| Title | File Name | Received Date | State | Life Cycle Status | Submitted In | Extension | Size (KB) | Sectio |
|---|---|---|---|---|---|---|---|---|
| AG221-C-001 Phase 1/2 - ADAE - Adverse Events - DRV | adae.xpt | 5/10/2017 | Final | Current | 0025 (27) 05/10/2017 ORIG-1 /Clinical/Respo... | XPT | 24,575.7 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADAE - Adverse Events - DRV | adae.xpt | 5/24/2017 | Final | Current | 0029 (34) 05/24/2017 ORIG-1 /Clinical/Respo... | XPT | 24,575.7 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADBASE - Baseline Information - DRV | adbase.xpt | 5/10/2017 | Final | Current | 0025 (27) 05/10/2017 ORIG-1 /Clinical/Respo... | XPT | 605.1 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADBASE - Baseline Information - DRV | adbase.xpt | 5/24/2017 | Final | Current | 0029 (34) 05/24/2017 ORIG-1 /Clinical/Respo... | XPT | 605.1 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADBMT - Bone Marrow Transplant Post AG221 - DRV | adbmt.xpt | 5/10/2017 | Final | Current | 0025 (27) 05/10/2017 ORIG-1 /Clinical/Respo... | XPT | 132.0 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADBMT - Bone Marrow Transplant Post AG221 - DRV | adbmt.xpt | 5/24/2017 | Final | Current | 0029 (34) 05/24/2017 ORIG-1 /Clinical/Respo... | XPT | 132.0 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADBOMA - Bone Marrow Assessment - DRV | adboma.xpt | 5/10/2017 | Final | Current | 0025 (27) 05/10/2017 ORIG-1 /Clinical/Respo... | XPT | 4,973.2 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADBOMA - Bone Marrow Assessment - DRV | adboma.xpt | 5/24/2017 | Final | Current | 0029 (34) 05/24/2017 ORIG-1 /Clinical/Respo... | XPT | 4,973.2 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADCM - Prior and Concomitant Medications - DRV | adcm.xpt | 5/10/2017 | Final | Current | 0025 (27) 05/10/2017 ORIG-1 /Clinical/Respo... | XPT | 27,349.3 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADCM - Prior and Concomitant Medications - DRV | adcm.xpt | 5/24/2017 | Final | Current | 0029 (34) 05/24/2017 ORIG-1 /Clinical/Respo... | XPT | 27,349.3 | Clinica Leuke - AG2 |


**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

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/s/

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JENNIFER J LEE
06/08/2017

| | |
|---|---|
| **From:** | Lee, Jennifer (CDER) |
| **To:** | "Penny Ng" |
| **Cc:** | Patricia Callahan |
| **Subject:** | RE: NDA 209606 enasidenib -- FDA Information Request Response submitted on 05 June - a question regarding dataset submission (replace or new for ADPVPD). Thanks. |
| **Date:** | Wednesday, June 07, 2017 11:39:00 AM |
| **Attachments:** | image002.png |

Hello Penny,

In regards to your submission, it should include a complete, cumulative data file that includes all protocol violations from the start of the study through the 14-OCT-2016 data cut date (NOT just the violations from April through October 2016). It should be submitted as a replacement to the original ADPVPD data file (the one that used a 15-APR-2016 data cut date).

Please let me know if this helps clear up all questions surrounding your formal submission. I would also like to confirm receipt of your tracked change version of the PMR/PMC comments.

Thank you,
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Wednesday, June 07, 2017 10:59 AM
**To:** Lee, Jennifer (CDER)
**Cc:** Patricia Callahan
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response submitted on 05 June - a question regarding dataset submission (replace or new for ADPVPD). Thanks.
**Importance:** High

Dear Jennie,

I had a follow-up discussion with my team (programming and stat. team) and they shared the following proposal with me. I understand that the Agency has provided comments previously advising not submitting Phase 1/2 dataset to the 4MSU folder but submit to the study folder as "replacement" so I would appreciate your feedback before we submit to ensure we meet the requirement/expectation:

ADPVPD submitting to the NDA today will only include the PVPDs between 16 Apr 2016 to 14 Oct 2016, not including the data in the original ADPVPD (data-cut of 15 Apr2016) in the original NDA; therefore, my team suggested that this should be submitted as "new" in the eCTD today as this will not replace the information submitted in the original ADPVPD.

For the defined file that is being submitted today, it will only include the updated source info supporting the PVPD dataset between 16 Apr 2016 to 14 Oct 2016, so my team has suggested to submit as "new" as well since the defined file submitting today does not include other descriptions currently in the defined file in the NDA.

In summary, this is Celgene's proposal based on above rationale:

- ADPVPD (PVPDs between 16 Apr 2016 to 14 Oct 2016) dataset (in xpt): "new" under the ISS "4Month Safety Update folder" due to the datacut of 14 Oct 2016, and not a replacement to the ADPVPD file (with 15 April 2016 datacut) in the NDA

- Defined file describing above: "new" under ISS "4Month Safety Update folder", together with the ADPVPD file above.

There will be a total of 4 files (ADPVPD in .xpt, 2 supporting files in pdfs, and one defined file).

Please kindly advise if the Agency agrees with the above for the submission of the ADPVPD dataset/defined files to the NDA today.

As always, we appreciated your guidance.

Kind regards,
Penny

---

**From:** Penny Ng
**Sent:** Wednesday, June 07, 2017 8:17 AM
**To:** Lee, Jennifer (CDER) <Jennifer.Lee1@fda.hhs.gov>
**Cc:** Patricia Callahan <pcallahan@celgene.com>
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response submitted on 05 June - a question regarding dataset submission (replace or new for ADPVPD). Thanks.

Good morning Jennie,

We are targeting to submit today to the eCTD the ADPVPD dataset and programming of PVPDs between 16 Apr 2016 to 14 Oct 2016 as noted in our response to the IR submitted on Monday.

Would you please advise if the ADPVPD dataset/programming/defined file (16 Apr 2016 to 14 Oct 2016) should be a replacement of the original ADPVPD dataset (15 Apr 2016 data-cut) included in the original NDA? Or should we submit as "new" since this is a different data cut date and mainly covers the 16 Apr 2016 to 14 Oct 2016 PVPDs?

Please kindly advice. I am also copying my Regulatory Operations colleague, Pat Callahan, in this e-mail. She is working with FDA ESUB/dataset team per the IR dated 02 Jun 2017.

Kind regards,
Penny

---

**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Monday, June 05, 2017 8:18 PM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Thank you, Penny. I confirm receipt of your response.

Have a good evening,
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Monday, June 05, 2017 5:49 PM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Dear Jennie,

My apologies again for the delay. Please see attached the response to IR received on 02 Jun.

We plan to submit this formally, including the SAS programming of PVPD (noted in the response document), to the NDA on 07 Jun 2017.

Thanks again for the feedback and confirmation received today.

Kind regards,
Penny

---

**From:** Penny Ng
**Sent:** Monday, June 05, 2017 3:26 PM
**To:** 'Lee, Jennifer (CDER)' <Jennifer.Lee1@fda.hhs.gov>
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Dear Jennie,

My apologies, as I may need until 6 pm ET to submit this response to you by e-mail.

Kind regards,
Penny

---

**From:** Penny Ng
**Sent:** Monday, June 05, 2017 12:25 PM
**To:** Lee, Jennifer (CDER) <Jennifer.Lee1@fda.hhs.gov>
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Thanks again! I will be submitting the response to the 3 comments to you by e-mail by COB today.

Kind regards,
Penny

---

**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Monday, June 05, 2017 11:54 AM
**To:** Penny Ng <PNg@celgene.com>

**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Yes, that is correct. Thank you for clarifying.

Kindly,
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Monday, June 05, 2017 12:22 PM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Hello Jennie,

Thanks for reaching out to your team, very much appreciated.

Just want to clarify that if this implies that we do not need to submit the dataset and programming of the ADEFF2 dataset (of the 207 R/R AML 100 mg daily dose, confirmed with CDx), and for our response document due today, we only need to address the following 3 questions:

***FDA Information Request***

1. *The dataset for Study AG221-C-001 (combined parts I and II) submitted electronically to the NDA on 5/10/17 is missing the ADPDPV (protocol violations) dataset. Please clarify if there have been any new protocol violations, and if so, provide the APPDPV dataset updated with a data cut date of October 15, 2016.*

2. *For the file ADSL, please explain why subjects 101-007 and 111-037 have STDIS = blank but death dates are prior to the October 15, 2016 data cut-off date.*

***Please provide a response for #1 and #2 by COB Monday, June 5, 2017.***

3. *The update of the dataset for Study AG221-C-001 (combined parts I and II) on 5/10/2017 was successful in resolving the duplicate file issue. Unfortunately, the submission of files on 5/24/2017 again included duplicate files. Please correct the submission so that there are no duplicate files. We strongly recommend that you work with the ESUB team (esub@fda.hhs.gov) to determine the most efficient way to correct the error and how to avoid file duplications in future submissions.*

Thanks again!

Kind regards,
Penny

---

**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]

**Sent:** Monday, June 05, 2017 11:10 AM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Hello Penny,

I just wanted to let you know that I've touched base with my team and we will be rescinding the second set of IRs (sent on Friday, June 02, 2017 7:02 AM).

Kindly confirm receipt of this update.

Thank you,
Jennie

---

**From:** Lee, Jennifer (CDER)
**Sent:** Monday, June 05, 2017 9:55 AM
**To:** 'Penny Ng'
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Good morning Penny,

I confirm receipt of your question below. I will circle back with my team and will let you know.

Kind regards,
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Monday, June 05, 2017 7:59 AM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Good morning Jennie,

For the eCTD submission of the dataset and programming below to the NDA:

***FDA Information Request***

*No updated adeff2 data or analysis results by using adeff2 data have been submitted as a response to our information request sent on May 12 , 2017.*

*By using updated adeff2 data, please submit the following analysis results in patients with R/R AML who were assigned enasidenib at 100 mg total daily dose (Phase I, Phase II and combined Phase I & Phase II) for the efficacy endpoints of CR, CRh, CR/CRh, ORR, DOR, RBC/Platelet transfusion…etc., as well as important subgroup analyses of these endpoints (i.e., forest plots of subgroup analysis) based on the following requirements:*

- *Exclude patients from the numerator and denominator who did not have IDH2 mutation identified in either their blood or marrow based on the companion*

*diagnostic.*

- *Exclude responses that occurred only after other therapy given after IDHIFA (e.g., HSCT). Specifically, exclude the CRs that occurred in subjects 110-006 and 111-046.*

*Provide the datasets and SAS programs used to generate the above analyses.*

Would you kindly advise if the ADEFF2 dataset (of the 207 R/R AML 100 mg daily dose, confirmed with CDx) should replace the ADEFF2 dataset of previously submitted population (of the 214 R/R AML 100 mg daily dose)? Or should this dataset be submitted as new?

Thanks in advance for your guidance and we will submit to the NDA accordingly.

Kind regards,
Penny

---

**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Friday, June 02, 2017 7:02 AM
**To:** Penny Ng <PNg@celgene.com>
**Cc:** Paul McInulty <pmcinulty@celgene.com>
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Dear Penny,

I have an additional information request that is also due on **Monday, June 5th, 2017 COB**. Kindly confirm receipt of both sets of information requests.

Thank you,
Jennie

***FDA Information Request***

*No updated adeff2 data or analysis results by using adeff2 data have been submitted as a response to our information request sent on May 12 , 2017.*

*By using updated adeff2 data, please submit the following analysis results in patients with R/R AML who were assigned enasidenib at 100 mg total daily dose (Phase I, Phase II and combined Phase I & Phase II) for the efficacy endpoints of CR, CRh, CR/CRh, ORR, DOR, RBC/Platelet transfusion…etc., as well as important subgroup analyses of these endpoints (i.e., forest plots of subgroup analysis) based on the following requirements:*

- *Exclude patients from the numerator and denominator who did not have IDH2 mutation identified in either their blood or marrow based on the companion diagnostic.*
- *Exclude responses that occurred only after other therapy given after IDHIFA (e.g., HSCT). Specifically, exclude the CRs that occurred in subjects 110-006 and 111-046.*

*Provide the datasets and SAS programs used to generate the above analyses.*

---

**From:** Lee, Jennifer (CDER)
**Sent:** Friday, June 02, 2017 6:39 AM
**To:** 'Penny Ng'
**Cc:** 'Paul McInulty'
**Subject:** NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Good morning Penny,

I have the following information request from the FDA review team for NDA 209606 enasidenib. Please send a response to #1 and #2 to me via email by **COB Monday, June 5th, 2017,** and then follow up with a formal submission to your NDA file**.**

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

***FDA Information Request***

1. *The dataset for Study AG221-C-001 (combined parts I and II) submitted electronically to the NDA on 5/10/17 is missing the ADPDPV (protocol violations) dataset. Please clarify if there have been any new protocol violations, and if so, provide the APPDPV dataset updated with a data cut date of October 15, 2016.*

2. *For the file ADSL, please explain why subjects 101-007 and 111-037 have STDIS = blank but death dates are prior to the October 15, 2016 data cut-off date.*

***Please provide a response for #1 and #2 by COB Monday, June 5, 2017.***

3. *The update of the dataset for Study AG221-C-001 (combined parts I and II) on 5/10/2017 was successful in resolving the duplicate file issue. Unfortunately, the submission of files on 5/24/2017 again included duplicate files. Please correct the submission so that there are no duplicate files. We strongly recommend that you work with the ESUB team (esub@fda.hhs.gov) to determine the most efficient way to correct the error and how to avoid file duplications in future submissions.*

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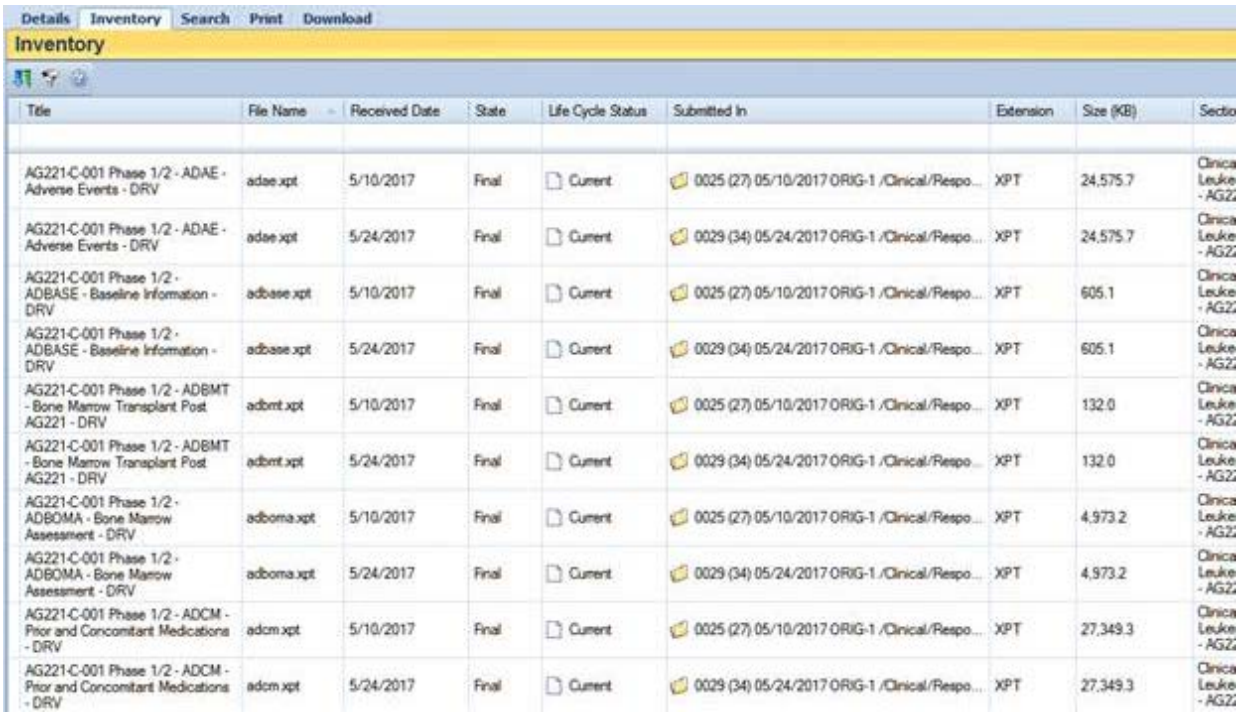

Details | Inventory | Search | Print | Download

Inventory

| Title | File Name | Received Date | State | Life Cycle Status | Submitted In | Extension | Size (KB) | Sectio |
|---|---|---|---|---|---|---|---|---|
| AG221-C-001 Phase 1/2 - ADAE - Adverse Events - DRV | adae.xpt | 5/10/2017 | Final | Current | 0025 (27) 05/10/2017 ORIG-1 /Clinical/Respo... | XPT | 24,575.7 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADAE - Adverse Events - DRV | adae.xpt | 5/24/2017 | Final | Current | 0029 (34) 05/24/2017 ORIG-1 /Clinical/Respo... | XPT | 24,575.7 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADBASE - Baseline Information - DRV | adbase.xpt | 5/10/2017 | Final | Current | 0025 (27) 05/10/2017 ORIG-1 /Clinical/Respo... | XPT | 605.1 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADBASE - Baseline Information - DRV | adbase.xpt | 5/24/2017 | Final | Current | 0029 (34) 05/24/2017 ORIG-1 /Clinical/Respo... | XPT | 605.1 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADBMT - Bone Marrow Transplant Post AG221 - DRV | adbmt.xpt | 5/10/2017 | Final | Current | 0025 (27) 05/10/2017 ORIG-1 /Clinical/Respo... | XPT | 132.0 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADBMT - Bone Marrow Transplant Post AG221 - DRV | adbmt.xpt | 5/24/2017 | Final | Current | 0029 (34) 05/24/2017 ORIG-1 /Clinical/Respo... | XPT | 132.0 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADBOMA - Bone Marrow Assessment - DRV | adboma.xpt | 5/10/2017 | Final | Current | 0025 (27) 05/10/2017 ORIG-1 /Clinical/Respo... | XPT | 4,973.2 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADBOMA - Bone Marrow Assessment - DRV | adboma.xpt | 5/24/2017 | Final | Current | 0029 (34) 05/24/2017 ORIG-1 /Clinical/Respo... | XPT | 4,973.2 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADCM - Prior and Concomitant Medications - DRV | adcm.xpt | 5/10/2017 | Final | Current | 0025 (27) 05/10/2017 ORIG-1 /Clinical/Respo... | XPT | 27,349.3 | Clinica Leuke - AG2 |
| AG221-C-001 Phase 1/2 - ADCM - Prior and Concomitant Medications - DRV | adcm.xpt | 5/24/2017 | Final | Current | 0029 (34) 05/24/2017 ORIG-1 /Clinical/Respo... | XPT | 27,349.3 | Clinica Leuke - AG2 |


**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov


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JENNIFER J LEE
06/07/2017

**From:** Lee, Jennifer (CDER)
**To:** "Penny Ng"
**Subject:** RE: NDA 209606 enasidenib -- FDA Labeling and PMR/PMC Comments Response Due 6/7 Noon EST
**Date:** Tuesday, June 06, 2017 11:47:00 AM
**Attachments:** image001.png

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Hi Penny,

I have the following comment from the review team in regards to Celgene's PMR/PMC response.

***The PDF version of the PMRs that you sent is not reviewable. Please provide your proposed revisions in tracked changes in the Word document. If you have no tracked changes, we will assume that the PMR as written is acceptable to you. Please provide a response by noon Wednesday, June 7, 2017.***

Thank you,
Jennie

---

**From:** Lee, Jennifer (CDER)
**Sent:** Tuesday, June 06, 2017 11:07 AM
**To:** 'Penny Ng'
**Subject:** RE: NDA 209606 enasidenib -- FDA Labeling and PMR/PMC Comments Response Due 6/6 Noon EST

Thank you, Penny. I confirm receipt of your PMR/PMC response.

Thank you,
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Tuesday, June 06, 2017 10:56 AM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- FDA Labeling and PMR/PMC Comments Response Due 6/6 Noon EST

Good morning Jennie,

Please see attached Celgene's response to the Agency's PMR/PMC Comments.

The labeling comments will be sent in a separate e-mail later.

Thanks again.

Kind regards,
Penny

---

**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Tuesday, May 30, 2017 11:33 AM

**To:** Penny Ng <PNg@celgene.com>
**Cc:** Paul McInulty <pmcinulty@celgene.com>
**Subject:** NDA 209606 enasidenib -- FDA Labeling and PMR/PMC Comments Response Due 6/6 Noon EST

Dear Penny,

Please refer to the attached FDA labeling revisions to the prescribing information (PI) for NDA 209606 enasidenib.

Please review the FDA revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

After you have made any necessary changes, please send the revised tracked changes labeling documents to me via email before you make your official submission electronically to the NDA file. **Any edits you make should be in tracked changes.**

In addition, we are also providing you with proposed post marketing studies. Please review the attached FDA proposed PMR/PMCs and provide your response. Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR/PMC studies/trials description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial.

Please submit your responses to the labeling and PMR/PMC comments by **Tuesday, June 6th, 2017, Noon EST.**

Kindly confirm receipt of this correspondence and do not hesitate to contact me should you have any questions.

Kind regards,
Jennie

_____

**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov


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/s/

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JENNIFER J LEE
06/06/2017

| | |
|---|---|
| **From:** | Lee, Jennifer (CDER) |
| **To:** | "Penny Ng" |
| **Subject:** | NDA 209606 enasidenib -- FDA Information Request Due 6/8 3PM EST |
| **Date:** | Tuesday, June 06, 2017 10:09:00 AM |
| **Attachments:** | image002.png |

Good morning Penny,

I have another information request for NDA 209606 enasidenib. Please provide your response via email to me by **Thursday, June 8, 2017 3PM EST** and also follow up with a formal submission to your NDA file.

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

***FDA Information Request***

***Regarding Table 5 – Drug Discovery Report AG221-C-001-TD-CoMut, please clarify the following:***

1. ***Why several subjects are listed in more than one row, with a different number and/or type of "known somatic mutations" or "likely somatic mutations" indicated in each of the rows for the same subject ID. Examples include but are not limited to subjects 109-009, 109-011, 111-007, and 900-006.***
2. ***How these differences where reconciled to calculate the number of co-occurring mutations per subject.***
3. ***Whether mutations in the same gene were aggregated as one mutation or added when the number of co-occurring mutations per subject was calculated.***
4. ***Why the number/type of "known somatic mutations" or "likely somatic mutations" appear to be different for the subjects 104-009, 110-001, 201-003, and 201-004 between Table 5 of the report Drug Discovery Report AG221-C-001-TD-CoMut and the file found.xpt submitted with the IR response received May 10, 2017.***


**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov

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/s/

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JENNIFER J LEE
06/06/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Monday, June 05, 2017 9:15 PM
**To:** 'Penny Ng'
**Subject:** NDA 209606 enasidenib -- FDA Information Request Response Due 6/6 COB

Good evening Penny,

I have the following information request for NDA 209606 enasidenib from the review team. Please submit your response via email by **COB Tuesday, June 6th, 2017** and also follow up with a formal submission to your NDA file.

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

***FDA Information Request***

***We are writing to clarify Comment A38 on the Prescribing Information in the labeling IR sent 5/30/2017. As indicated in the comment, we requested that you display in Section 14 the sponsor-derived CR and CRh for all Phase 1 and Phase 2 subjects as delineated in Comment A36.***

***We understand from Table 3 of the Analysis Datasets Reviewer's Guide that the variable ADEFF2.BESTRSPC has the sponsor-derived CR and CRh. Please confirm that this is correct.***

Table 3 Key Response Related Efficacy Endpoints in ADEFF and ADEFF2

| | Investigator Assessed Response (Derived from ADEDRT) | Sponsor Derived Response Based on mIWG (Derived from ADEDRT3) | Sponsor Derived Response Based on FDA CRh Definition (Derived from ADEDRT2) |
|---|---|---|---|
| Best Response | ADEFF.BESTRSP<br>ADEFF.BESTRSPC | ADEFF.DBRSP<br>ADEFF.DBRSPC | ADEFF2.BESTRSP<br>ADEFF2.BESTRSPC |

***When you submit the revisions to the Prescribing Information on June 6, 2017, please also include the sas code used to derive the results for the subset of patients as delineated in Comment A36. Please note for that the data files listed as "current" in your NDA, the version of ADEFF2 is as submitted on 5/10/2017 (see table below). Please confirm that this is the most updated version of ADEFF2 and is used for determining the CR/CRh results in the revised Prescribing Information.***

| NDA 209606 - List of "Current" Data Files by Date Submitted |
|---|

| | File | 12/30/2016 | 5/10/2017 | 5/24/2017 |
|---|---|---|---|---|
| 1 | "adae.xpt" | | "adae.xpt" | "adae.xpt" |
| 2 | "adbase.xpt" | | "adbase.xpt" | "adbase.xpt" |
| 3 | "adbmt.xpt" | | "adbmt.xpt" | "adbmt.xpt" |
| 4 | "adboma.xpt" | | "adboma.xpt" | "adboma.xpt" |
| 5 | "adcm.xpt" | | "adcm.xpt" | "adcm.xpt" |
| 6 | "adcp.xpt" | | "adcp.xpt" | "adcp.xpt" |
| 7 | "adcyc.xpt" | | "adcyc.xpt" | "adcyc.xpt" |
| 8 | "addose.xpt" | | "addose.xpt" | "addose.xpt" |
| 9 | "addt.xpt" | | "addt.xpt" | "addt.xpt" |
| 10 | "adecho.xpt" | | "adecho.xpt" | "adecho.xpt" |
| 11 | "adecog.xpt" | | "adecog.xpt" | "adecog.xpt" |
| 12 | "adedrt.xpt" | | "adedrt.xpt" | "adedrt.xpt" |
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| 14 | "adedrt3.xpt" | | "adedrt3.xpt" | |
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| 38 | "advs.xpt" | | "advs.xpt" | "advs.xpt" |
| 39 | "cdxmay17.xpt" | | | "cdxmay17.xpt" |

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**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov


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

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/s/

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JENNIFER J LEE
06/05/2017

**From:** Lee, Jennifer (CDER)
**To:** "Penny Ng"
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB
**Date:** Monday, June 05, 2017 12:54:00 PM
**Attachments:** image002.png

---

Yes, that is correct. Thank you for clarifying.

Kindly,
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Monday, June 05, 2017 12:22 PM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Hello Jennie,

Thanks for reaching out to your team, very much appreciated.

Just want to clarify that if this implies that we do not need to submit the dataset and programming of the ADEFF2 dataset (of the 207 R/R AML 100 mg daily dose, confirmed with CDx), and for our response document due today, we only need to address the following 3 questions:

***FDA Information Request***

1. *The dataset for Study AG221-C-001 (combined parts I and II) submitted electronically to the NDA on 5/10/17 is missing the ADPDPV (protocol violations) dataset. Please clarify if there have been any new protocol violations, and if so, provide the APPDPV dataset updated with a data cut date of October 15, 2016.*

2. *For the file ADSL, please explain why subjects 101-007 and 111-037 have STDIS = blank but death dates are prior to the October 15, 2016 data cut-off date.*

***Please provide a response for #1 and #2 by COB Monday, June 5, 2017.***

3. *The update of the dataset for Study AG221-C-001 (combined parts I and II) on 5/10/2017 was successful in resolving the duplicate file issue. Unfortunately, the submission of files on 5/24/2017 again included duplicate files. Please correct the submission so that there are no duplicate files. We strongly recommend that you work with the ESUB team (esub@fda.hhs.gov) to determine the most efficient way to correct the error and how to avoid file duplications in future submissions.*

Thanks again!

Kind regards,
Penny

**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Monday, June 05, 2017 11:10 AM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Hello Penny,

I just wanted to let you know that I've touched base with my team and we will be rescinding the second set of IRs (sent on Friday, June 02, 2017 7:02 AM).

Kindly confirm receipt of this update.

Thank you,
Jennie

---

**From:** Lee, Jennifer (CDER)
**Sent:** Monday, June 05, 2017 9:55 AM
**To:** 'Penny Ng'
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Good morning Penny,

I confirm receipt of your question below. I will circle back with my team and will let you know.

Kind regards,
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Monday, June 05, 2017 7:59 AM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Good morning Jennie,

For the eCTD submission of the dataset and programming below to the NDA:

***FDA Information Request***

*No updated adeff2 data or analysis results by using adeff2 data have been submitted as a response to our information request sent on May 12 , 2017.*

*By using updated adeff2 data, please submit the following analysis results in patients with R/R AML who were assigned enasidenib at 100 mg total daily dose (Phase I, Phase II and combined Phase I & Phase II) for the efficacy endpoints of CR, CRh, CR/CRh, ORR, DOR, RBC/Platelet transfusion…etc., as well as important subgroup analyses of these endpoints (i.e., forest plots of subgroup analysis) based on the following requirements:*

- *Exclude patients from the numerator and denominator who did not have IDH2 mutation identified in either their blood or marrow based on the companion diagnostic.*

- *Exclude responses that occurred only after other therapy given after IDHIFA (e.g., HSCT). Specifically, exclude the CRs that occurred in subjects 110-006 and 111-046.*

*Provide the datasets and SAS programs used to generate the above analyses.*

Would you kindly advise if the ADEFF2 dataset (of the 207 R/R AML 100 mg daily dose, confirmed with CDx) should replace the ADEFF2 dataset of previously submitted population (of the 214 R/R AML 100 mg daily dose)? Or should this dataset be submitted as new?

Thanks in advance for your guidance and we will submit to the NDA accordingly.

Kind regards,
Penny

---

**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Friday, June 02, 2017 7:02 AM
**To:** Penny Ng <PNg@celgene.com>
**Cc:** Paul McInulty <pmcinulty@celgene.com>
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Dear Penny,

I have an additional information request that is also due on **Monday, June 5th, 2017 COB**. Kindly confirm receipt of both sets of information requests.

Thank you,
Jennie

***FDA Information Request***

*No updated adeff2 data or analysis results by using adeff2 data have been submitted as a response to our information request sent on May 12 , 2017.*

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- *Exclude responses that occurred only after other therapy given after IDHIFA (e.g., HSCT).*

*Specifically, exclude the CRs that occurred in subjects 110-006 and 111-046.*

*Provide the datasets and SAS programs used to generate the above analyses.*

---

**From:** Lee, Jennifer (CDER)
**Sent:** Friday, June 02, 2017 6:39 AM
**To:** 'Penny Ng'
**Cc:** 'Paul McInulty'
**Subject:** NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB

Good morning Penny,

I have the following information request from the FDA review team for NDA 209606 enasidenib. Please send a response to #1 and #2 to me via email by **COB Monday, June 5th, 2017,** and then follow up with a formal submission to your NDA file**.**

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

***FDA Information Request***

1. *The dataset for Study AG221-C-001 (combined parts I and II) submitted electronically to the NDA on 5/10/17 is missing the ADPDPV (protocol violations) dataset. Please clarify if there have been any new protocol violations, and if so, provide the APPDPV dataset updated with a data cut date of October 15, 2016.*

2. *For the file ADSL, please explain why subjects 101-007 and 111-037 have STDIS = blank but death dates are prior to the October 15, 2016 data cut-off date.*

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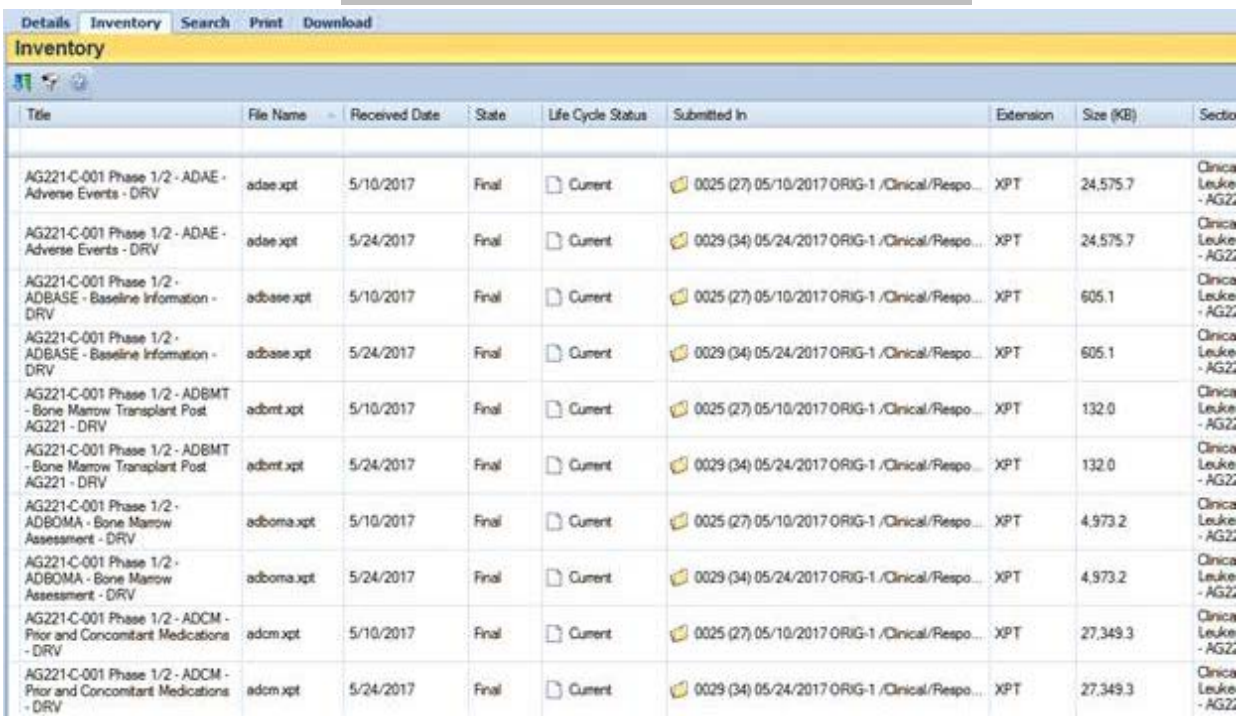
APPEARS THIS WAY ON ORIGINAL



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**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

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**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov


FDA U.S. FOOD & DRUG ADMINISTRATION

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

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/s/

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JENNIFER J LEE
06/05/2017

**From:** Lee, Jennifer (CDER)
**To:** "Penny Ng"
**Cc:** "Paul McInulty"
**Subject:** RE: NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB
**Date:** Friday, June 02, 2017 8:02:00 AM
**Attachments:** image002.png

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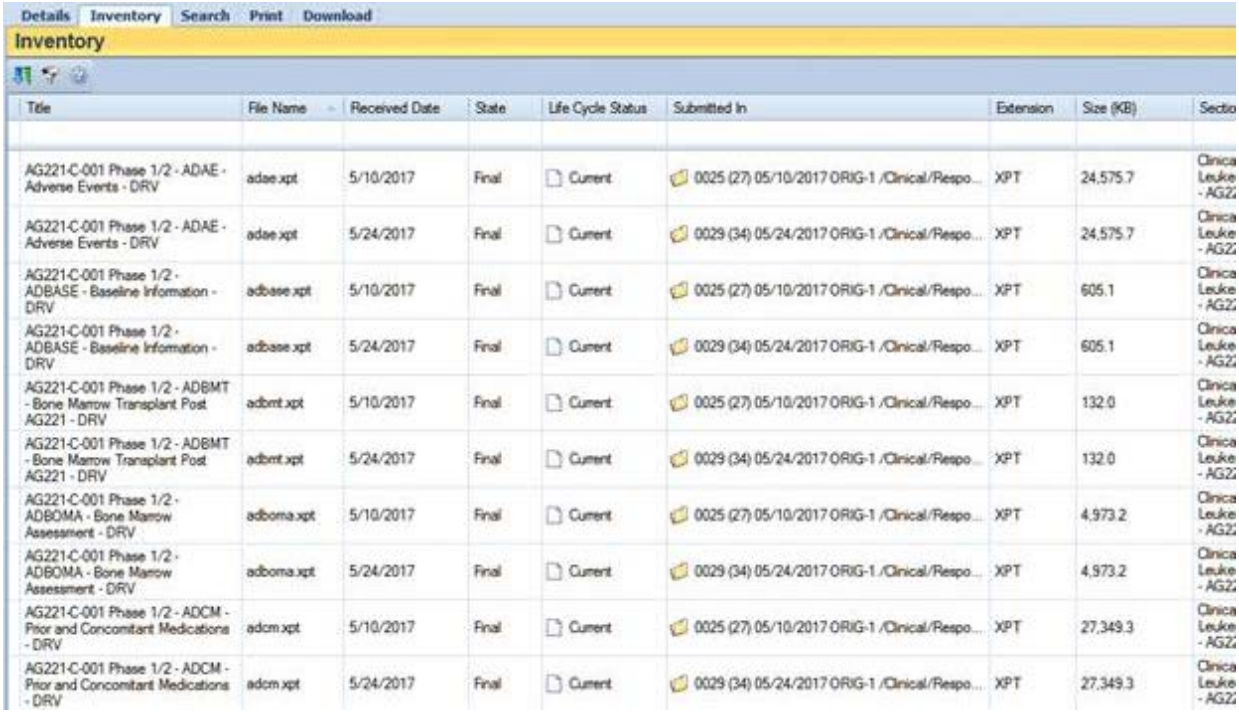

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**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
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Tel: 240-402-4622
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/s/

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JENNIFER J LEE
06/02/2017

| | |
|---|---|
| **From:** | Lee, Jennifer (CDER) |
| **To:** | "Penny Ng" |
| **Cc:** | "Paul McInulty" |
| **Subject:** | NDA 209606 enasidenib -- FDA Information Request Response Due 6/5 COB |
| **Date:** | Friday, June 02, 2017 6:38:00 AM |
| **Attachments:** | image014.png |

Good morning Penny,

I have the following information request from the FDA review team for NDA 209606 enasidenib.

Please send a response to #1 and #2 to me via email by **COB Monday, June 5th, 2017,** and then follow up with a formal submission to your NDA file**.**

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Thank you,
Jennie

***FDA Information Request***

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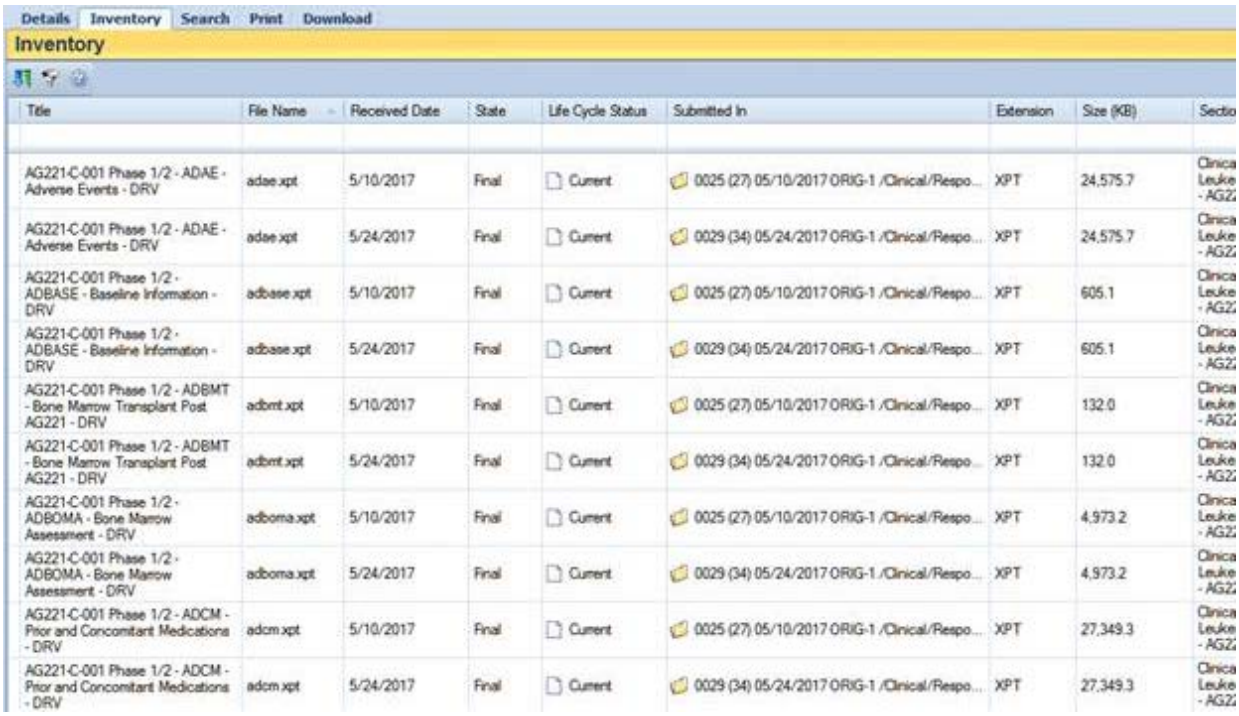

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**Jennifer J. Lee, PharmD**

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/s/

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JENNIFER J LEE
06/02/2017

## Lee, Jennifer (CDER)

| | |
|---|---|
| **From:** | Lee, Jennifer (CDER) |
| **Sent:** | Tuesday, May 30, 2017 12:33 PM |
| **To:** | 'Penny Ng' |
| **Cc:** | 'Paul McInulty' |
| **Subject:** | NDA 209606 enasidenib -- FDA Labeling and PMR/PMC Comments Response Due 6/6 Noon EST |
| **Attachments:** | NDA 209606 enasidenib -- FDA Revisions 5-30-2017.docx; NDA 209606 Idhifa -- PMRs.docx |

Dear Penny,

Please refer to the attached FDA labeling revisions to the prescribing information (PI) for NDA 209606 enasidenib.

Please review the FDA revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

After you have made any necessary changes, please send the revised tracked changes labeling documents to me via email before you make your official submission electronically to the NDA file. **Any edits you make should be in tracked changes.**

In addition, we are also providing you with proposed post marketing studies. Please review the attached FDA proposed PMR/PMCs and provide your response. Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR/PMC studies/trials description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial.

Please submit your responses to the labeling and PMR/PMC comments by **Tuesday, June 6th, 2017, Noon EST.**

Kindly confirm receipt of this correspondence and do not hesitate to contact me should you have any questions.

Kind regards,
Jennie

_____

**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov

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/s/

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JENNIFER J LEE
05/30/2017

| | |
|---|---|
| **From:** | Lee, Jennifer (CDER) |
| **To:** | "Penny Ng" |
| **Subject:** | NDA 209606 enasidenib -- FDA Information Request Response Due 5/22 Noon EST |
| **Date:** | Friday, May 12, 2017 1:38:00 PM |
| **Attachments:** | image013.png |

Dear Penny,

I have the following information request for NDA 209606 enasidenib. Please provide a response by **Monday, May 22nd, 2017 Noon EST** via email and also follow up with a formal submission to your NDA file.

Kindly confirm receipt of this email.

Thank you,
Jennie

***FDA Information Request***

1. ***Please submit the following analysis results in patients with R/R AML who were assigned enasidenib at 100 mg total daily dose (combined phase 1 and phase 2) for the primary and key secondary efficacy endpoints of ORR, CR, DOR, RBC/Platelet transfusion, OS, etc. as well as important subgroup analyses of these endpoints (i.e., forest plots of subgroup analysis) based on following requirements.***

    - ***Use Oct 14, 2016 as the data cutoff date***
    - ***Exclude patients from the numerator and denominator who did not have IDH2 mutation identified in either their blood or marrow based on the companion diagnostic. Provide a list of the subject ID excluded for this reason.***
    - ***Exclude responses that occurred only after other therapy given after IDHIFA (e.g., HSCT). Specifically, exclude the CRs that occurred in subjects 110-006 and 111-046.***

2. ***Submit a revised table of patient demographics and important baseline characteristics based on the new denominator established by the above requirements.***

3. ***Provide the datasets and SAS programs used to generate the above analyses.***

4. ***We are having trouble locating the DSRC charter in the CSR. Please provide a screen shot of the file structure identifying its location.***

**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov


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/s/

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JENNIFER J LEE
05/12/2017

**From:** Lee, Jenn fer (CDER)
**To:** "Penny Ng"
**Subject:** NDA 209606 enasidenib -- Additional Comment Regarding Information Request Due 5/8 Noon EST
**Date:** Friday, May 05, 2017 6:42:00 PM
**Attachments:** image001.png

Dear Penny

The FDA would like to provide an additional comment related to our clinical information request dated 25-April-2017 and updated 03-May-2017 regarding the AG221-C-001 datasets.

When an updated dataset (.xpt file) is submitted to the NDA it should be submitted as a replacement file (not a new file) and should have the same name as the dataset it is replacing. The updated datasets (Phase 1+Phase 2 with October 14 data cut date) for study AG221-C-001 submitted in eCTD 0023 were submitted as new files. This means that we now have duplicate files in eCTD (see image below rows 2 and 4 for an example) which creates data integrity problems. Please delete the data files submitted in eCTD 0023 and resubmit the entire dataset for AG221-C-001 (Phase 1+Phase 2 with Oct 14 cut date) as requested in the 25-April-2017 and 03-May-2017 communications to the AG221-C-001 (phase 1) folder as replacement files to the ones submitted in eCTD 0001. It is okay that the phase 1+phase 2 datasets are in the phase 1 folder.

To further clarify there may be some confusion as to why we requested datasets in the 25-April-2017 and 03-May-2017 communications that are identical to those that you already provided in the 4-month safety update (in the Integrated Summary of Safety folder). This stems from the fact that your ISS currently "integrates" data from only one trial. But as this may change in the future datasets provided to the ISS folder in support of the ISS (which may one day integrate data from several studies) have to be kept distinct from the datasets provided for an individual clinical trial. A complete set of datasets from each individual study that is the basis of an NDA submission review must be submitted to that study s folder in eCTD.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 3221-C-001 Phase 1/2 - Analysis ogram - ADAE | 0001 (1) 12/30/2016 ORIG-1 ... | Current | | Analysis Program | adae.txt | TXT | Clinical Study Reports\Reports of Efficacy and Safety Studies [Indication]\Acute Myeloid Leukemia\Study Reports of Uncor Studies [Study ID - Study Title]\ag221-c-001-phase-1 - AG221 |
| 3221-C-001 Phase 1/2 - ADAE - dverse Events - DRV | 0001 (1) 12/30/2016 ORIG-1 ... | Current | | Analysis Dataset Legacy | adae.xpt | XPT | Clinical Study Reports\Reports of Efficacy and Safety Studies [Indication]\Acute Myeloid Leukemia\Study Reports of Uncor Studies [Study ID - Study Title]\ag221-c-001-phase-1 - AG221 |
| 3221-C-001 - AML - 4-Month Safety pdate - ADAE - Adverse Events - RV | 0020 (20) 04/25/2017 ORIG-... | Current | | Analysis Dataset Legacy | adae.xpt | XPT | Clinical Study Reports\Reports of Efficacy and Safety Studies [Indication]\Acute Myeloid Leukemia\Reports of Analyses of I than One Study [Study ID - Study Title]\integrated-summary-of |
| 3221-C-001 Phase 1/2 - ADAE - dverse Events - DRV | 0023 (25) 05/04/2017 ORIG-... | Current | | Analysis Dataset Legacy | adae.xpt | XPT | Clinical Study Reports\Reports of Efficacy and Safety Studies [Indication]\Acute Myeloid Leukemia\Study Reports of Uncor Studies [Study ID - Study Title]\ag221-c-001-phase-1 - AG221 |

APPEARS THIS WAY ON ORIGINAL

BEST AVAILABLE COPY

Kindly confirm receipt of this correspondence. We look forward to your response on **May 8, 2017 Noon EST**.

Thank you
Jennie

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**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Wednesday, May 03, 2017 12:23 PM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: Enasidenib NDA_209606_IR received on 28 Apr

Hello Jennie

Thank you again for the very prompt and helpful reply I am acknowledging the receipt of this correspondence.

Kind regards,
Penny

---

**From:** Lee Jennifer (CDER) [mailto Jennifer.Lee1@fda.hhs.gov]
**Sent:** Wednesday May 03 2017 11 09 AM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** RE Enasidenib NDA_209606_IR received on 28 Apr

Hello Penny

Thank you for the tables of data files. We are most interested in the analysis data files. Please do submit the updated versions of the files identified as "can be provided" (ADPAT ADTRAH ADRATH ADCP ADPTRT ADPTS ADPTANT ADPBMT ADBMT) but we will also need ADEDRT2 ADEDRT3 ADEFF2 ADPDPV and ADTRAN2.

Please also update and submit your ad hoc efficacy analyses for all patients in Phase 1 and Phase 2 using ADEDRT2 ADEDRT3 ADEFF2 ADPDPV and ADTRAN2 as applicable. Your response is requested no later than **May 8, 2017 Noon EST** (via email and a formal submission to your NDA file).

Kindly confirm receipt of this correspondence.

Thank you
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Wednesday, May 03, 2017 11:30 AM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: Enasidenib NDA_209606_IR received on 28 Apr

Good morning Jennie

Thanks again for the feedback from your team.

I have shared the feedback with my stats. colleague and we have prepared the tables below identifying the raw and analysis datasets (analysis and tabulation) of Study AG221-C-001 with a data cut-off date of 14 Oct 2016 that have been provided to the Agency (within the 4-Month Safety Update Report submission on 25 Apr 2017 or the response to IR submitted yesterday) and the ones that have not yet been provided.

Datasets not previously submitted to the NDA (in the 4MSU Report submission or the 02 May response to IR) was because they were not used for the analyses included in both submissions; but can be provided per FDA s request.

Please kindly confirm if submitting the dataset marked in green below would adequately addresses the IR sent on 4/28/2017.

**Raw Data:**

x dataset already provided
*same dataset as the 4MSU submission dataset
As noted below in green fonts the dataset has not been submitted to the NDA but can be provided upon request.

| | | Data -cut of Study AG221-C-001 Phase 1 and 2 data | | |
|---|---|---|---|---|
| **Raw Data** | | **15-Apr-16** | **14-Oct-16** | **14-Oct-16** |
| **Dataset name** | **Dataset Description** | **NDA Submission** | **4MSU** | **FDA IR (response submitted on 02 May** |
| AE | ADVERSE EVENTS | x | x | * |
| AE2 | ADVERSE EVENTS REPORTS | x | x | * |
| AE2AER | AE2 CODED TERM | x | x | * |
| AEAER | AE CODED TERM | x | x | * |
| ANTH2C | PRIOR ANTICANCER THERAPY INVESTIGATION 2 | x | x | * |

| | | | | |
|---|---|---|---|---|
| BMT | BONE MARROW TRANSPLANT POST AG221 | x | x | * |
| BOMA | BONE MARROW ASSESSMENTS (ASPIRATE) | x | x | * |
| BOMA1 | BONE MARROW BIOPSY | x | x | * |
| CM | CONCOMITANT MEDICATIONS | x | x | * |
| CMCMR | CM CODED TERM | x | x | * |
| CP | CONCOMITANT PROCEDURES | x | can be provided | |
| CPCPR | CP CODED TERM | x | can be provided | |
| DISP | AG-221 RETURN AND DISPENSATION | x | can be provided | |
| DISP2 | AG-221 RETURN AND DISPENSATION 2 | x | can be provided | |
| DM | DEMOGRAPHY | x | x | * |
| DORE | DOSING RECORD | x | x | * |
| DTC | DEATH FORM | x | x | * |
| ECG | CENTRAL ECG | x | x | * |
| ECHO | ECHOCARDIOGRAM / MUGA | x | x | * |
| ECOG | ECOG PERFORMANCE STATUS | x | x | * |
| EDRT | EXTENT OF DISEASE AND RESPONSE TO TREAT | x | x | * |
| ENTR | SUBJECT TERMINATION SUMMARY | x | x | * |
| FU | FOLLOW-UP VISIT | x | can be provided | |
| GEMU | GENE MUTATION ANALYSIS | x | x | * |
| IE | INCLUSION / EXCLUSION CRITERIA | x | x | * |
| IE2 | INCLUSION / EXCLUSION CRITERIA 2 | x | x | * |
| LAB | LAB TESTS | x | x | * |
| LABO | LAB TESTS - OTHER | x | x | * |
| LEEG | 12-LEAD ECG | x | can be provided | |
| MADI2 | UNDERLYING MALIGNANCY DIAGNOSIS 2 | x | x | * |
| MH | MEDICAL / SURGICAL HISTORY | x | x | * |
| MHMHR | MH CODED TERM | x | x | * |
| PBDC3 | PERIPHERAL BLOOD DRAW / CYTOGENETICS 3 | x | x | * |
| PBMT | POST BONE MARROW TRANSPLANT POST AG221 | x | can be provided | |
| PE | PHYSICAL EXAM | x | x | * |
| PTANTC | POST TREATMENT ANTI NEOPLASTIC THERAPY | x | x | * |
| PTHP | POST TREATMENT THERAPIES FOR DISEASE | x | can be provided | |
| PTRT | POST TREATMENT RADIATION THERAPY | x | x | * |
| PTSC | POST TREATMENT SURGERIES | x | x | * |
| Q2 | Q2 MUTATION DATA | x | x | * |
| RATH | PRIOR RADIOTHERAPY | x | can be provided | |
| RIC | INFORMED RE-CONSENT | x | x | * |
| SDIS | STUDY DISCONTINUATION | x | x | * |
| SEVS | SERIAL VITAL SIGNS | x | can be provided | |
| SFP | SURVIVAL FOLLOW-UP | x | can be provided | |
| SLEG | SERIAL 12-LEAD ECG | x | x | * |
| SM | STUDY MEDICATION | x | x | * |
| SM2 | STUDY MEDICATION 2 | x | x | * |
| SPRG | SERUM PREGNANCY TEST | x | can be provided | |
| SUBJ | SUBJECT ENROLLMENT | x | x | * |
| TERM | TREATMENT DISCONTINUATION | x | x | * |
| TLEG | TRIPLICATE SERIAL ECG | x | can be provided | |
| TLEG1 | TRIPLICATE ECG | x | can be provided | |
| TRAH | TRANSPLANT HISTORY | x | x | * |
| TRAN | PRIOR AND CONCURRENT TRANSFUSIONS | x | x | * |
| UPRG | URINE PREGNANCY TEST | x | can be provided | |
| VD | VISIT DATE | x | x | * |
| VS | VITAL SIGNS | x | x | * |

**Analysis Data**

X dataset already provided
x* provided in FDA IR same datasets as provided in 4-Month Safety Update Submission
As noted below in green fonts the dataset has not been submitted to the
NDA but can be provided upon request.

| | **Analysis Data** | **Data -cut of Study AG221-C-001 Phase 1 and 2 data** | | |
|---|---|---|---|---|
| | | **15-Apr-16** | **14-Oct-16** | **14-Oct-16** |
| **Dataset Name** | **Dataset Description** | **NDA Submission** | **4MSU** | **FDA IR (response submitted on 02 May** |
| ADDOSE | DOSING RECORD - DRV | x | x | x* |
| ADCYC | CYCLE RECORD - DRV | x | x | x* |
| ADSL | SUBJECT CHARACTERISTICS - DRV | x | x | x* |
| ADCM | PRIOR AND CONCOMITANT MEDICATIONS - DRV | x | x | x* |
| ADMH | MEDICAL HISTORY - DRV | x | x | x* |
| ADPAT | PRIOR ANTI CANCER THERAPY - DRV | x | can be provided | |
| ADECHO | ECHOCARDIOGRAM / MUGA - DRV | x | x | x* |
| ADBOMA | BONE MARROW ASSESSMENT - DRV | x | x | x* |
| ADEG | ECG - DRV | x | x | x* |
| ADTRAH | TRANSPLANT HISTORY - DRV | x | can be provided | |
| ADRATH | PRIOR RADIOTHERAPY - DRV | x | can be provided | |
| ADECOG | ECOG PERFORMANCE STATUS - DRV | x | x | x* |
| ADLB | LAB - DRV | x | x | x* |

| | | | | |
|---|---|---|---|---|
| ADVS | VITAL SIGNS - DRV | x | x | x* |
| ADEX | STUDY DRUG EXPOSURE - DRV | x | x | x* |
| ADBASE | BASELINE INFORMATION - DRV | x | x | x* |
| ADAE | ADVERSE EVENTS - DRV | x | x | x* |
| ADCP | CONCOMITANT PROCEDURES - DRV | x | can be provided | |
| ADPTRT | POST TREATMENT RADIATION THERAPY - DRV | x | can be provided | |
| ADPTS | POST TREATMENT SURGERY - DRV | x | can be provided | |
| ADPTANT | POST TREATMENT ANTINEOPLASTIC THER - DRV | x | can be provided | |
| ADPBMT | POST BONE MARROW TRANSPLANT POST AG221 | x | can be provided | |
| ADBMT | BONE MARROW TRANSPLANT POST AG221 - DRV | x | can be provided | |
| ADEDRT | INV ASSESSED RESPONSE BY VISIT - DRV | x | X | x* |
| ADEDRT2 | DRV RSP BY VISIT BY FDA CRh DEFI - DRV | x | No conducted | No conducted |
| ADEDRT3 | DRV RSP BY VISIT BY mIWG - DRV | x | No conducted | No conducted |
| ADEFF | EFFICACY ENDPOINTS (INV/DRV mIWG) - DRV | x | X | Provided. Different from dataset Updated with OS data |
| ADEFF2 | EFFICACY ENDPOINTS (FDA CRh) - DRV | x | No conducted | No conducted |
| ADGEMU | GENE MUTATION ANALYSIS - DRV | x | X | x* |
| ADDT | DEATH - DRV | x | X | x* |
| ADPDPV | PROTOCOL DEVIATION VIOLATION - DRV | x | No conducted | No conducted |
| ADIE | INCLUSION EXCLUSION - DRV | x | X | x* |
| ADTRAN | BLOOD TRANSFUSION (INV RESPONSE) - DRV | x | X | x* |
| ADTRAN2 | BLOOD TRANSFUSION (FDA DEF RESP) - DRV | x | No conducted | No conducted |

As always we appreciate the guidance and clarification from the Agency and will submit the information to meet the Agency s request.

Kind regards,
Penny

---

**From:** Lee Jennifer (CDER) [mailto Jennifer.Lee1@fda.hhs.gov]
**Sent:** Tuesday May 02 2017 1 26 PM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** RE Enasidenib NDA_209606_IR due on 02May_datasets (Zip files) - w/o attachment

Hi Penny

The team has taken a look at your response submitted today and has the following comment in regards to whether it adequately addresses the IR sent on 4/28/2017.

***No. Please provide the full data set (Analysis and Tabulations) for Phase 1 and Phase 2 combined for Study AG221-C-001 with the data cut-off date of 14 Oct 2016.***

Kindly confirm receipt of this correspondence and I look forward to your response to be submitted no later than **May 8, 2017 Noon EST**.

Thank you
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Tuesday, May 02, 2017 1:48 PM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: Enasidenib NDA_209606_IR due on 02May_datasets (Zip files) - w/o attachment

Hi Jennie
Thanks for the confirmation appreciated! I look forward hearing back from you.

Kind regards,
Penny

---

**From:** Lee Jennifer (CDER) [mailto Jennifer.Lee1@fda.hhs.gov]
**Sent:** Tuesday May 02 2017 12 35 PM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** RE Enasidenib NDA_209606_IR due on 02May_datasets (Zip files) - w/o attachment

Hi Penny

I confirm receipt of the zip file. I will have to get back to you on your question whether your response addresses the IR from 4/28. I will circle back with my team and let you know.

Thank you
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Tuesday, May 02, 2017 1:33 PM
**To:** Lee, Jennifer (CDER)
**Subject:** Enasidenib NDA_209606_IR due on 02May_datasets (Zip files) - w/o attachment

Dear Jennie

The attachment was quite bit (as it took a while to download and zip) so I am sending this note without any attachments to confirm if you have received the zip file from my earlier e-mail (sent at 12 23 pm CT/1 23 pm ET).

I have also included a question to confirm if the datasets submitted (with a data cut of 14 Oct 2016) have addressed the IR received on 28 Apr.

Please kindly confirm receipt of the zip file. If you have not received it I will download the datasets into 2 separate zip files and retry. Thank you again and my apologies for the technical difficulties again.

Kind regards,
Penny

---

**From:** Penny Ng
**Sent:** Tuesday May 02 2017 12 23 PM
**To:** Lee Jennifer (CDER) <Jennifer Lee1@fda hhs gov>
**Subject:** Enasidenib NDA_209606_IR due on 02May_datasets (Zip files)

Dear Jennie

My apologies again for sending all in different e-mails. Please find attached zip files with a total of 34 individual files.

We are also formally submitting these files to the NDA on Thursday (04 May).

Regarding the IR received on 28 April evening "*We acknowledge your plan to submit the Clinical Study Report for AG221-C-001 at a later date. Please submit the updated data set for this study with the data cut-off of 14 Oct 2016*".

The attached zip file includes datasets for Study AG221-C-001 with the data-cut of 14 Oct 2016. Datasets with the same data-cut for safety analysis (and efficacy analysis per request from the Agency) included in the 4-Month Safety Update Report were submitted with the report to the NDA (submitted on 25 April 2017).

Please kindly advice if the provided datasets have addressed the IR from 28 April.

Kind regards
Penny

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Your message is ready to be sent with the following file or link attachments

New_Archive_20170502T130531.zip

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message Thank You

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/s/

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JENNIFER J LEE
05/05/2017

**From:** Lee, Jenn fer (CDER)
**To:** "Penny Ng"
**Subject:** RE: Enasidenib NDA_209606_IR received on 28 Apr
**Date:** Wednesday, May 03, 2017 12:09:00 PM

Hello Penny

Thank you for the tables of data files. We are most interested in the analysis data files. Please do submit the updated versions of the files identified as "can be provided" (ADPAT ADTRAH ADRATH ADCP ADPTRT ADPTS ADPTANT ADPBMT ADBMT) but we will also need ADEDRT2 ADEDRT3 ADEFF2 ADPDPV and ADTRAN2.

Please also update and submit your ad hoc efficacy analyses for all patients in Phase 1 and Phase 2 using ADEDRT2 ADEDRT3 ADEFF2 ADPDPV and ADTRAN2 as applicable. Your response is requested no later than **May 8, 2017 Noon EST** (via email and a formal submission to your NDA file).

Kindly confirm receipt of this correspondence.

Thank you
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Wednesday, May 03, 2017 11:30 AM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: Enasidenib NDA_209606_IR received on 28 Apr

Good morning Jennie

Thanks again for the feedback from your team.

I have shared the feedback with my stats. colleague and we have prepared the tables below identifying the raw and analysis datasets (analysis and tabulation) of Study AG221-C-001 with a data cut-off date of 14 Oct 2016 that have been provided to the Agency (within the 4-Month Safety Update Report submission on 25 Apr 2017 or the response to IR submitted yesterday) and the ones that have not yet been provided.

Datasets not previously submitted to the NDA (in the 4MSU Report submission or the 02 May response to IR) was because they were not used for the analyses included in both submissions; but can be provided per FDA s request.

Please kindly confirm if submitting the dataset marked in green below would adequately addresses the IR sent on 4/28/2017.

**Raw Data:**

x dataset already provided
*same dataset as the 4MSU submission dataset
As noted below in green fonts the dataset has not been submitted to the NDA but can be provided upon request.

| | | Data -cut of Study AG221-C-001 Phase 1 and 2 data | | |
|---|---|---|---|---|
| **Raw Data** | | **15-Apr-16** | **14-Oct-16** | **14-Oct-16** |
| **Dataset name** | **Dataset Description** | **NDA Submission** | **4MSU** | **FDA IR (response submitted on 02 May** |
| AE | ADVERSE EVENTS | x | x | * |
| AE2 | ADVERSE EVENTS REPORTS | x | x | * |
| AE2AER | AE2 CODED TERM | x | x | * |
| AEAER | AE CODED TERM | x | x | * |
| ANTH2C | PRIOR ANTICANCER THERAPY INVESTIGATION 2 | x | x | * |
| BMT | BONE MARROW TRANSPLANT POST AG221 | x | x | * |
| BOMA | BONE MARROW ASSESSMENTS (ASPIRATE) | x | x | * |
| BOMA1 | BONE MARROW BIOPSY | x | x | * |
| CM | CONCOMITANT MEDICATIONS | x | x | * |
| CMCMR | CM CODED TERM | x | x | * |
| CP | CONCOMITANT PROCEDURES | x | can be provided | |
| CPCPR | CP CODED TERM | x | can be provided | |
| DISP | AG-221 RETURN AND DISPENSATION | x | can be provided | |
| DISP2 | AG-221 RETURN AND DISPENSATION 2 | x | can be provided | |
| DM | DEMOGRAPHY | x | x | * |
| DORE | DOSING RECORD | x | x | * |
| DTC | DEATH FORM | x | x | * |
| ECG | CENTRAL ECG | x | x | * |
| ECHO | ECHOCARDIOGRAM / MUGA | x | x | * |
| ECOG | ECOG PERFORMANCE STATUS | x | x | * |
| EDRT | EXTENT OF DISEASE AND RESPONSE TO TREAT | x | x | * |
| ENTR | SUBJECT TERMINATION SUMMARY | x | x | * |
| FU | FOLLOW-UP VISIT | x | can be provided | |
| GEMU | GENE MUTATION ANALYSIS | x | x | * |
| IE | INCLUSION / EXCLUSION CRITERIA | x | x | * |
| IE2 | INCLUSION / EXCLUSION CRITERIA 2 | x | x | * |
| LAB | LAB TESTS | x | x | * |
| LABO | LAB TESTS - OTHER | x | x | * |
| LEEG | 12-LEAD ECG | x | can be provided | |
| MADI2 | UNDERLYING MALIGNANCY DIAGNOSIS 2 | x | x | * |
| MH | MEDICAL / SURGICAL HISTORY | x | x | * |
| MHMHR | MH CODED TERM | x | x | * |
| PBDC3 | PERIPHERAL BLOOD DRAW / CYTOGENETICS 3 | x | x | * |
| PBMT | POST BONE MARROW TRANSPLANT POST AG221 | x | can be provided | |
| PE | PHYSICAL EXAM | x | x | * |
| PTANTC | POST TREATMENT ANTI NEOPLASTIC THERAPY | x | x | * |
| PTHP | POST TREATMENT THERAPIES FOR DISEASE | x | can be provided | |
| PTRT | POST TREATMENT RADIATION THERAPY | x | x | * |
| PTSC | POST TREATMENT SURGERIES | x | x | * |
| | | | | |

| | | | | |
|---|---|---|---|---|
| Q2 | Q2 MUTATION DATA | x | x | * |
| RATH | PRIOR RADIOTHERAPY | x | can be provided | |
| RIC | INFORMED RE-CONSENT | x | x | * |
| SDIS | STUDY DISCONTINUATION | x | x | * |
| SEVS | SERIAL VITAL SIGNS | x | can be provided | |
| SFP | SURVIVAL FOLLOW-UP | x | can be provided | |
| SLEG | SERIAL 12-LEAD ECG | x | x | * |
| SM | STUDY MEDICATION | x | x | * |
| SM2 | STUDY MEDICATION 2 | x | x | * |
| SPRG | SERUM PREGNANCY TEST | x | can be provided | |
| SUBJ | SUBJECT ENROLLMENT | x | x | * |
| TERM | TREATMENT DISCONTINUATION | x | x | * |
| TLEG | TRIPLICATE SERIAL ECG | x | can be provided | |
| TLEG1 | TRIPLICATE ECG | x | can be provided | |
| TRAH | TRANSPLANT HISTORY | x | x | * |
| TRAN | PRIOR AND CONCURRENT TRANSFUSIONS | x | x | * |
| UPRG | URINE PREGNANCY TEST | x | can be provided | |
| VD | VISIT DATE | x | x | * |
| VS | VITAL SIGNS | x | x | * |

**Analysis Data:**

X dataset already provided
x* provided in FDA IR same datasets as provided in 4-Month Safety Update Submission
As noted below in green fonts the dataset has not been submitted to the
NDA but can be provided upon request.

| | **Analysis Data** | **Data -cut of Study AG221-C-001 Phase 1 and 2 data** | | |
|---|---|---|---|---|
| | | **15-Apr-16** | **14-Oct-16** | **14-Oct-16** |
| **Dataset Name** | **Dataset Description** | **NDA Submission** | **4MSU** | **FDA IR (response submitted on 02 May** |
| ADDOSE | DOSING RECORD - DRV | x | x | x* |
| ADCYC | CYCLE RECORD - DRV | x | x | x* |
| ADSL | SUBJECT CHARACTERISTICS - DRV | x | x | x* |
| ADCM | PRIOR AND CONCOMITANT MEDICATIONS - DRV | x | x | x* |
| ADMH | MEDICAL HISTORY - DRV | x | x | x* |
| ADPAT | PRIOR ANTI CANCER THERAPY - DRV | x | can be provided | |
| ADECHO | ECHOCARDIOGRAM / MUGA - DRV | x | x | x* |
| ADBOMA | BONE MARROW ASSESSMENT - DRV | x | x | x* |
| ADEG | ECG - DRV | x | x | x* |
| ADTRAH | TRANSPLANT HISTORY - DRV | x | can be provided | |
| ADRATH | PRIOR RADIOTHERAPY - DRV | x | can be provided | |
| ADECOG | ECOG PERFORMANCE STATUS - DRV | x | x | x* |
| ADLB | LAB - DRV | x | x | x* |
| ADVS | VITAL SIGNS - DRV | x | x | x* |
| ADEX | STUDY DRUG EXPOSURE - DRV | x | x | x* |
| ADBASE | BASELINE INFORMATION - DRV | x | x | x* |
| ADAE | ADVERSE EVENTS - DRV | x | x | x* |
| ADCP | CONCOMITANT PROCEDURES - DRV | x | can be provided | |
| ADPTRT | POST TREATMENT RADIATION THERAPY - DRV | x | can be provided | |
| ADPTS | POST TREATMENT SURGERY - DRV | x | can be provided | |
| ADPTANT | POST TREATMENT ANTINEOPLASTIC THER - DRV | x | can be provided | |
| ADPBMT | POST BONE MARROW TRANSPLANT POST AG221 | x | can be provided | |
| ADBMT | BONE MARROW TRANSPLANT POST AG221 - DRV | x | can be provided | |
| ADEDRT | INV ASSESSED RESPONSE BY VISIT - DRV | x | X | x* |
| ADEDRT2 | DRV RSP BY VISIT BY FDA CRh DEFI - DRV | x | No conducted | No conducted |
| ADEDRT3 | DRV RSP BY VISIT BY mIWG - DRV | x | No conducted | No conducted |
| ADEFF | EFFICACY ENDPOINTS (INV/DRV mIWG) - DRV | x | X | Provided. Different from dataset Updated with OS data |
| ADEFF2 | EFFICACY ENDPOINTS (FDA CRh) - DRV | x | No conducted | No conducted |
| ADGEMU | GENE MUTATION ANALYSIS - DRV | x | X | x* |
| ADDT | DEATH - DRV | x | X | x* |
| ADPDPV | PROTOCOL DEVIATION VIOLATION - DRV | x | No conducted | No conducted |
| ADIE | INCLUSION EXCLUSION - DRV | x | X | x* |
| ADTRAN | BLOOD TRANSFUSION (INV RESPONSE) - DRV | x | X | x* |
| ADTRAN2 | BLOOD TRANSFUSION (FDA DEF RESP) - DRV | x | No conducted | No conducted |

As always we appreciate the guidance and clarification from the Agency and will submit the information to meet the Agency s request.

Kind regards,
Penny

**From:** Lee Jennifer (CDER) [mailto Jennifer.Lee1@fda.hhs.gov]
**Sent:** Tuesday May 02 2017 1 26 PM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** RE Enasidenib NDA_209606_IR due on 02May_datasets (Zip files) - w/o attachment

Hi Penny

The team has taken a look at your response submitted today and has the following comment in regards to whether it adequately addresses the IR sent on 4/28/2017.

***No. Please provide the full data set (Analysis and Tabulations) for Phase 1 and Phase 2 combined for Study AG221-C-001 with the data cut-off date of 14 Oct 2016.***

Kindly confirm receipt of this correspondence and I look forward to your response to be submitted no later than **May 8, 2017 Noon EST**.

Thank you
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Tuesday, May 02, 2017 1:48 PM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: Enasidenib NDA_209606_IR due on 02May_datasets (Zip files) - w/o attachment

Hi Jennie
Thanks for the confirmation appreciated! I look forward hearing back from you.

Kind regards,
Penny

---

**From:** Lee Jennifer (CDER) [mailto Jennifer.Lee1@fda.hhs.gov]
**Sent:** Tuesday May 02 2017 12 35 PM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** RE Enasidenib NDA_209606_IR due on 02May_datasets (Zip files) - w/o attachment

Hi Penny

I confirm receipt of the zip file. I will have to get back to you on your question whether your response addresses the IR from 4/28. I will circle back with my team and let you know.

Thank you
Jennie

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Tuesday, May 02, 2017 1:33 PM
**To:** Lee, Jennifer (CDER)
**Subject:** Enasidenib NDA_209606_IR due on 02May_datasets (Zip files) - w/o attachment

Dear Jennie

The attachment was quite bit (as it took a while to download and zip) so I am sending this note without any attachments to confirm if you have received the zip file from my earlier e-mail (sent at 12 23 pm CT/1 23 pm ET).

I have also included a question to confirm if the datasets submitted (with a data cut of 14 Oct 2016) have addressed the IR received on 28 Apr.

Please kindly confirm receipt of the zip file. If you have not received it I will download the datasets into 2 separate zip files and retry. Thank you again and my apologies for the technical difficulties again.

Kind regards,
Penny

---

**From:** Penny Ng
**Sent:** Tuesday May 02 2017 12 23 PM
**To:** Lee Jennifer (CDER) <Jennifer.Lee1@fda.hhs.gov>
**Subject:** Enasidenib NDA_209606_IR due on 02May_datasets (Zip files)

Dear Jennie

My apologies again for sending all in different e-mails. Please find attached zip files with a total of 34 individual files.

We are also formally submitting these files to the NDA on Thursday (04 May).

Regarding the IR received on 28 April evening "*We acknowledge your plan to submit the Clinical Study Report for AG221-C-001 at a later date. Please submit the updated data set for this study with the data cut-off of 14 Oct 2016*".

The attached zip file includes datasets for Study AG221-C-001 with the data-cut of 14 Oct 2016. Datasets with the same data-cut for safety analysis (and efficacy analysis per request from the Agency) included in the 4-Month Safety Update Report were submitted with the report to the NDA (submitted on 25 April 2017).

Please kindly advice if the provided datasets have addressed the IR from 28 April.

Kind regards
Penny

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/s/

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JENNIFER J LEE
05/03/2017

**From:** Lee, Jennifer (CDER)
**To:** "Penny Ng"
**Subject:** RE: Enasidenib NDA_209606_IR due on 02May_datasets (Zip files) - w/o attachment
**Date:** Tuesday, May 02, 2017 2:26:00 PM

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Hi Penny,

The team has taken a look at your response submitted today and has the following comment in regards to whether it adequately addresses the IR sent on 4/28/2017.

***No. Please provide the full data set (Analysis and Tabulations) for Phase 1 and Phase 2 combined for Study AG221-C-001 with the data cut-off date of 14 Oct 2016.***

Kindly confirm receipt of this correspondence and I look forward to your response to be submitted no later than **May 8, 2017 Noon EST**.

Thank you,
Jennie

---

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**Sent:** Tuesday, May 02, 2017 1:48 PM
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Kind regards,
Penny

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**Sent:** Tuesday, May 02, 2017 12:35 PM
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**Subject:** RE: Enasidenib NDA_209606_IR due on 02May_datasets (Zip files) - w/o attachment

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Thank you,
Jennie

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Penny

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Dear Jennie,

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The attached zip file includes datasets for Study AG221-C-001 with the data-cut of 14 Oct 2016. Datasets with the same data-cut for safety analysis (and efficacy analysis per request from the Agency) included in the 4-Month Safety Update Report were submitted with the report to the NDA (submitted on 25 April 2017).

Please kindly advice if the provided datasets have addressed the IR from 28 April.

Kind regards,
Penny

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/s/

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JENNIFER J LEE
05/02/2017

| | |
|---|---|
| **From:** | Lee, Jennifer (CDER) |
| **To:** | "Penny Ng" |
| **Subject:** | NDA 209606 enasidenib -- FDA Information Request Response Due 5/8 Noon EST |
| **Date:** | Friday, April 28, 2017 7:46:00 PM |
| **Attachments:** | image013.png |

Dear Penny,

I have the following FDA information request for NDA 209606 enasidenib. Please provide a response via email by **Monday, May 8, 2017 Noon EST** and also follow-up with a formal submission to the NDA file.

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

_____

***FDA Information Request***

***We acknowledge your plan to submit the Clinical Study Report for AG221-C-001 at a later date. Please submit the updated data set for this study with the data cut-off of 14-Oct-2016.***


_____

**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov

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/s/

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JENNIFER J LEE
04/28/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209606

**MID-CYCLE COMMUNICATION**

Celgene Corporation
Attention: Penny Ng, MSc, MBA, RAC
Director, Regulatory Affairs
9225 Indian Creek Parkway, Suite 900
Overland Park, KS 66210

Dear Ms. Ng:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IDHIFA™ (enasidenib) tablets, 50 and 100mg.

We also refer to the teleconference between representatives of your firm and the FDA on April 28, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Jennifer Lee, Regulatory Project Manager, at (240) 402-4622.

Sincerely,

*{See appended electronic signature page}*

Donna Przepiorka, MD, PhD
Cross-Discipline Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# MID-CYCLE COMMUNICATION

**Meeting Date and Time:** April 28, 2017; 10:00 AM – 11:00 AM (ET)

**Application Number:** NDA 209606
**Product Name:** IDHIFA™ (enasidenib)
**Indication:** Relapsed or refractory acute myeloid leukemia (AML) with an IDH2 mutation
**Applicant Name:** Celgene Corporation

**Meeting Chair:** Donna Przepiorka, MD, PhD
**Meeting Recorder:** Jennifer J. Lee, PharmD

## FDA ATTENDEES

*Office of Hematology and Oncology Products/Division of Hematology Products*
Ann T. Farrell, MD, Director
Al Deisseroth, MD, PhD, Supervisory Associate Division Director
Donna Przepiorka, MD, PhD, Clinical Team Leader
Ashley Ward, MD, Clinical Reviewer
Theresa Carioti, MPH, Chief Project Management Staff
Jennifer Lee, PharmD, Regulatory Project Manager
Wanda Nguyen, PharmD, Regulatory Project Manger
Quyen Tran, PharmD, Regulatory Project Manger

*Office of Hematology and Oncology Products/Division of Hematology Oncology Toxicology*
Chris Sheth, PhD, Supervisory Pharmacologist
Rama Gudi, PhD, Pharmacologist Reviewer

*Office of Biostatistics/Division of Biometrics V*
Thomas Gwise, PhD, Deputy Division Director
Yuan-Li Shen, DrPh, Biometrics Team Leader
Qing Xu, PhD, Biometrics Reviewer

*Office of Clinical Pharmacology/Division of Clinical Pharmacology V*
Stacy Shord, PharmD, Clinical Pharmacology Team Leader
Walt Cao, PhD, Pharmacometrics Reviewer

*Office of Clinical Pharmacology/Genomics and Targeted Therapy Group*
Rosane Charlab Orbach, PhD, Team Leader
Sarah Dorff, PhD, Pharmacogenomics Reviewer

*Office of Product Quality/Office of New Drug Products/Division of New Drug Products 1*
Sherita McLamore-Hines, PhD, Regulatory Review Chemist
Banu Zolnik, PhD, Product Quality Reviewer
David Anderson, PhD, Product Quality Reviewer

*Office of In Vitro Diagnostics and Radiological Health/Division of Molecular Genetics and Pathology*
Aaron Schetter, PhD, MPH, Scientific Reviewer
Reena Philip, PhD, Supervisory Biologist

*Office of Medication Error Prevention and Risk Mangement/Division of Risk Management*
Till Olickal, PhD, PharmD, Risk Management Analyst
Ingrid Chapman, PharmD, Risk Management Analyst

*Office of Pharmacovigilance and Epidemiology/Division of Epidemiology I*
Carolyn McCloskey, MD, MPH, Medical Officer Epidemiologist

**APPLICANT ATTENDEES:**

*Celgene Corporation*
Jay Backstrom, MD, MPH, Chief Medical Officer/Global Head of Regulatory Affairs
Ira Gupta, MD, Executive Medical Director, Clinical R&D
Irina Kline, MD, Senior Director, Lead Product Safety Physician
Paul McInulty, Vice President, Regulatory Affairs
Penny Ng, MSc, MBA, RAC, Director, Regulatory Affairs
Anjan Thakurta, MSc MTech PhD, Executive Director, Translational Development
Krishnan Viswanadhan, PharmD, MBA, Executive Director, Global Project Leadership
Robert Wildman, Senior Director, Global CMC
Qiang (Casey) Xu, PhD, Associate Director, Biostatistics
Simon Zhou, PhD, Executive Director, Clinical Pharmacokinetics

*Agios Pharmaceuticals, Inc.*
Sam Agresta, MD, MPH &TM, MS CI & TR

## 1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## 2.0 SIGNIFICANT ISSUES

Clinical

1. You have evidence that patients who achieve complete remission (CR) after enasidenib monotherapy may uniformly have persistence of minimal residual disease (MRD), which appears to distinguish enasidenib from cytotoxic agents used in this setting. It is not clear, therefore, whether CR as produced by enasidenib monotherapy is a surrogate endpoint "reasonably likely to predict clinical benefit" as it has been considered for cytotoxic agents. Additional endpoints, such as conversion to transfusion independence, may be needed to support a demonstration of clinical benefit.

2. The pivotal portion of Study AG221-C-001 enrolled only 106 of a planned 125 patients. The early termination of the accrual to AG221-C-001 will be taken into consideration during the review of the adequacy of the trial and interpretation of the trial results.

3. While the literature is conflicting regarding the prognostic impact of IDH2 mutations, there is some evidence that patients with IDH2-mutated acute myeloid leukemia (AML) respond more frequently to salvage therapy in first relapse (e.g., DiNardo et al, 2015 showed a CR/CRi rate for IDH2+ patients in first relapse of 50% compared to 41% in IDH WT patients) and have prolonged survival (e.g., Patel et al, NEJM 2012). It is not clear that you have established that AG-221 is better than available therapy in the IDH2+ relapsed/refractory AML population.

Clinical Pharmacology

Safety in patients with organ impairment and the potential for interaction with drugs used commonly in this population are concerns for the postmarketing period. The following studies will likely be requested as postmarketing requirements.

1. Conduct a clinical pharmacokinetic trial to determine an appropriate dose of enasidenib (b) (4) in patients with hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.*"

2. Conduct clinical pharmacokinetic trials 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. Design and conduct the trials in accordance with the FDA Guidance for Industry entitled "*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.*"

## 3.0 INFORMATION REQUESTS

Regulatory

1. Please clarify the status of your supply of to-be-marketed drug.

*Meeting Discussion:* Celgene confirmed that drug supply is available, and they indicated that they intend to launch product within a week of the approval. Celgene stated that they will work with the Agency to be prepared to launch as soon as possible after approval. Celgene also inquired about the status of the manufacturing facility inspections, and the Agency noted that it is not able to provide further details at this time.

Clinical

*The following information request was sent on April 26, 2017, with a requested response date of April 27, 2017.*

1. In your response to an earlier information request, you indicated that 3 of the 106 patients enrolled on Phase 2 of AG221-C-001 had NOT either completed 6 months of AG-221 or discontinued as of the data cut-off date for the safety update (14-Oct-2016). However, in the ADEFF.xpt file submitted with the safety update, it appears that the treatment start dates for the three patients from Phase 2 without the 6m follow up flag (FU6MFL; 109-017, 111-049 and 112-006) are 04/18/16, 08/25/15 and 07/22/15, respectively, and the last off treatment date of the 3 is 08/25/16, which suggests that all three discontinued prior to the data cutoff date. Please explain this apparent discrepancy, and provide the subject ID numbers for the 3 subjects on Phase 2 who did not complete 6 months of AG-221 or discontinue as of the data cut for the safety update.

2. Please clarify when you will be submitting the interim Clinical Study Report for AG221-C-001 that includes the prespecified analyses through the 14-Oct-2016 cut-off date (at least 6 months of follow-up for all subjects on Phase 1 and Phase 2).

*The following information request was sent on April 25, 2017, with a requested response date of May 8, 2017.*

1. We are not able to fully confirm the incidence of "differentiation syndrome" in the patients treated with enasidenib. Because a differentiation-like syndrome induced by enasidenib was first recognized while Study AG221-C-001 was on-going, it is not clear how best to identify affected patients with the current adverse event data file. Please address the following:

    a. Provide a summary and timeline of formal and informal communications to study investigators regarding how to recognize and treat differentiation syndrome. Provide the screening criteria used to define Differentiation Syndrome (as

mentioned on p.75 of Module 2.7.4) and explain how and when these were used on Study AG221-C-001.

b. Provide a summary and timeline of formal and informal communications to study investigators regarding how to report symptoms that may be consistent with "differentiation syndrome" or code them as "retinoic acid syndrome" or code them in other ways.

c. Explain how the 72 cases of possible differentiation syndrome (p.78 of Module 2.7.4) were selected for DSRC review, and describe the procedures used by the external DSRC to adjudicate these events.

2. In Module 2.7.1, you provided data showing differences in dissolution for the different formulations of enasidenib used in AG221-C-001. The PK analysis in Section 3 of Module 2.7.1 only partially allays concerns regarding the potential differences between the formulations. For the patients treated with the 100 mg dose in Phase 1 and Phase 2 of AG221-C-001, address the following:

   a. Provide an .xpt dataset that includes one line per patient per formulation received. Include patient ID, formulation, first dose date of that formulation, and last dose date of that formulation.

   b. Provide an analysis of safety (adverse events, serious adverse events, adverse events of special interest) by formulation.

   c. Provide an analysis of efficacy (response and duration of response) by formulation.

3. We have not been able to confirm the findings of conversion from transfusion-dependent to transfusion-independent, maintenance of transfusion independence, or duration of transfusion independence. For the patients treated with the 100 mg dose in Phase 1 and Phase 2 of AG221-C-001, provide an .xpt file with at least the following variables: subject ID, a flag for your adjudication of RBC transfusion dependence at baseline (Y/N), a flag for your adjudication of PLT transfusion dependence at baseline (Y/N), date of start of RBC transfusion independence, date of end of RBC transfusion independence, date of start of PLT transfusion independence, date of end of PLT transfusion independence. If you collected the data based on study visit rather than actual date between study visits, you may provide the visit number and date of visit in lieu of the actual date for transfusion-dependence or transfusion-independence.

4. On page 42 of Module 2.7.3, you explain that 2 of the 34 subjects identified as having a CR achieved only a PR with enasidenib and then converted to CR after HSCT. Identify these two patients. For all patients treated on Phase 1 or Phase 2 of AG221-C-001, provide an .xpt file with at least the following variables: subject ID, best response with enasidenib alone, date of start of first alternate or additional therapy (including HSCT) after enasidenib. How many of the patients that you called CR actually achieved CR only

after receiving additional therapy? How does this alter your conclusions about the efficacy of enasidenib?

5. On page 33 of Module 2.7.3, you explain that 4 subjects had less than 5% blasts on the screening marrow aspirate. Identify these 4 subjects and any other subjects in Phase 1 or Phase 2 of AG221-C-001 for whom you do not have documentation of relapse at study entry. Once these subjects are removed from the efficacy analysis, is your conclusion about the efficacy of enasidenib altered?

6. We have not been able to confirm the results of your analyses in AG221-C-001-TD-IDH2VAF. Please address the following:

    a. Provide an .xpt data set containing the data used to generate the study report for AG221-C-001-TD-IDH2VAF. This should include subject ID, IDH2 mutation (specify whether this is by LDT or CDx), results of MRD testing, method used (digital PCR, FoundationOne, MSKCC mutational panel), date of sample collection, and clinical response at the time of sample collection. Explain how patients were selected for MRD testing, and provide an analysis of any bias that may have been introduced on the basis of patient selection.

    b. If you have collected MRD data on additional patients from AG-221-C-001 that were not included in the NDA submission, please include that data in the aforementioned .xpt file and provide a summary of the results.

7. We are unable to confirm the conclusions you stated from your analysis in AG-221-C-001-TD. Please address the following:

    a. Clarify where in the NDA the data can be found for the cytogenetics and molecular data such as is listed in Appendix B and Appendix C of Drug Discovery Report AG221-C-001-TD-CoMut. Identify also the data file with the risk classification by ELN, Grimwade and Papaemmanuil. If the data are not in the NDA, please submit them.

    b. Explain how the n=100 patients tested with FoundationOne mutation analysis were selected, and specify whether you have analyzed co-occurring mutations in additional patients beyond those described in the submission. If you have, please provide the data and analysis results.

    c. Provide further explanation for why Table 13 of Module 2.7.3 is incomplete; specifically, which data are missing in which patients, and why the analysis was conducted in only 72 of the 80 patients with complete data.

8. Please submit a summary of efficacy data from all patients who have received AG-221 in combination with chemotherapy on AG120-221-C-001 to date. Your summary should include patient identification #, date treatment was initiated, date of each response

assessment, and response determination. Also indicate which of the patients have had testing for MRD, the type of test, the date of the test, and the result.

9. Please submit a Letter of Authorization with the correct PMA number to cross-reference the PMA for the companion diagnostic.

Biometrics

*The following information request was sent on April 25, 2017, with a requested response date of May 2, 2017.*

Please submit the following analysis results for the primary efficacy endpoint (ORR), key secondary endpoints (i.e., CR, DOR, RBC/Platelet transfusion, OS…etc.), and important subgroup analyses of these endpoints (i.e., forest plots of subgroup analysis results for the ORR and CR). The datasets and SAS programs should also be included.

- Phase 2 subjects as of 28 Oct 2016

- Combined Phase I and Phase 2 subjects who received 100 mg QD of enasidenib as of 28 Oct 2016

Clinical Pharmacology

*The following information request was sent on April 24, 2017, with a requested response date of May 1, 2017.*

- Please provide a table of the pharmacokinetic data for study AG221-C-001 including geometric mean and 90% CI for $C_{max}$ and AUC to compare the F2 and F3 formulations. Submit a dataset with the subject level pharmacokinetic data for the F2 and F3 formulations used to generate the table from this study.

- Please clarify if "(b) (4)" as indicated in Tables 10 and 11 of the AG221-N-027-R study report is referring to the active metabolite "AGI-0016903".

## 4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no need for a REMS.

## 5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an AC meeting.

## 6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late-Cycle Meeting between you and the review team is currently scheduled for Friday, June 16, 2017. We intend to send the Agency background package to you approximately 12 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of the review.

APPEARS THIS WAY ON ORIGINAL

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/s/

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DONNA PRZEPIORKA
05/01/2017

# NDA 209606 IDHIFA™ (enasidenib) Mid-Cycle Agenda

**Friday, April 28, 2017**

**10:00 – 11:00 AM EST**

## 1. Applicant/FDA Review Team/ERG Independent Assessor Introductions

## 2. Introductory Comments

We are providing these comments to you before we complete our review of the entire application to give you **preliminary** notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## 3. Significant Review Issues

*Clinical*

1. You have evidence that patients who achieve complete remission (CR) after enasidenib monotherapy uniformly have persistence of minimal residual disease (MRD), which appears to distinguish enasidenib from cytotoxic agents used in this setting. It is not clear, therefore, whether CR as produced by enasidenib monotherapy is a surrogate endpoint "reasonably likely to predict clinical benefit" as it has been considered for cytotoxic agents. Additional endpoints, such as conversion to transfusion independence, may be needed to support a demonstration of clinical benefit.

2. The pivotal portion of Study AG221-C-001 enrolled only 106 of a planned 125 patients. The early termination of the accrual to AG221-C-001 will be taken into consideration during the review of the adequacy of the trial and interpretation of the trial results.

3. While the literature is conflicting regarding the prognostic impact of IDH2 mutations, there is some evidence that patients with IDH2-mutated acute myeloid leukemia (AML) respond more frequently to salvage therapy in first relapse (e.g., DiNardo et al, 2015 showed a CR/CRi rate for IDH2+ patients in first relapse of 50% compared to 41% in IDH WT patients) and have prolonged survival (e.g., Patel et al, NEJM 2012). It is not

clear that you have established that AG-221 is better than available therapy in the IDH2+ relapsed/refractory AML population.

*Clinical Pharmacology*

Safety in patients with organ impairment and the potential for interaction with drugs used commonly in this population are concerns for the postmarketing period. The following studies will likely be requested as postmarketing requirements.

1. Conduct a clinical pharmacokinetic trial to determine an appropriate dose of enasidenib (b) (4) in patients with hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

2. Conduct clinical pharmacokinetic trials to evaluate the effect of multiple doses of enasidenib on the single dose pharmacokinetics of a sensitive substrates of CYP3A4, CYP2D6, CYP2C19, CYP2C9, UGTs, P-gp, and BCRP to address the potential for excessive drug toxicity. Design and conduct the trials in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

## 4. Information Requests

*Regulatory*

1. Please clarify the status of your supply of to-be-marketed drug.

*Clinical*

*The following information request was sent on April 26, 2017, with a requested response date of April 27, 2017.*

1. In your response to an earlier information request, you indicated that 3 of the 106 patients enrolled on Phase 2 of AG221-C-001 had NOT either completed 6 months of AG-221 or discontinued as of the data cut-off date for the safety update (14-Oct-2016). However, in the ADEFF.xpt file submitted with the safety update, it appears that the treatment start dates for the three patients from Phase 2 without the 6m follow up flag (FU6MFL; 109-017, 111-049 and 112-006) are 04/18/16, 08/25/15 and 07/22/15, respectively, and the last off treatment date of the 3 is 08/25/16, which suggests that all three discontinued prior to the data cutoff date. Please explain this apparent discrepancy, and provide the subject ID numbers for the 3 subjects on Phase 2 who did not complete 6 months of AG-221 or discontinue as of the data cut for the safety update.

2. Please clarify when you will be submitting the interim Clinical Study Report for AG221-C-001 that includes the prespecified analyses through the 14-Oct-2016 cut-off date (at least 6 months of follow-up for all subjects on Phase 1 and Phase 2).

*The following information request was sent on April 25, 2017, with a requested response date of May 8, 2017.*

1. We are not able to fully confirm the incidence of "differentiation syndrome" in the patients treated with enasidenib. Because a differentiation-like syndrome induced by enasidenib was first recognized while Study AG221-C-001 was on-going, it is not clear how best to identify affected patients with the current adverse event data file. Please address the following:

   a. Provide a summary and timeline of formal and informal communications to study investigators regarding how to recognize and treat differentiation syndrome. Provide the screening criteria used to define Differentiation Syndrome (as mentioned on p.75 of Module 2.7.4) and explain how and when these were used on Study AG221-C-001.

   b. Provide a summary and timeline of formal and informal communications to study investigators regarding how to report symptoms that may be consistent with "differentiation syndrome" or code them as "retinoic acid syndrome" or code them in other ways.

   c. Explain how the 72 cases of possible differentiation syndrome (p.78 of Module 2.7.4) were selected for DSRC review, and describe the procedures used by the external DSRC to adjudicate these events.

2. In Module 2.7.1, you provided data showing differences in dissolution for the different formulations of enasidenib used in AG221-C-001. The PK analysis in Section 3 of Module 2.7.1 only partially allays concerns regarding the potential differences between the formulations. For the patients treated with the 100 mg dose in Phase 1 and Phase 2 of AG221-C-001, address the following:

   a. Provide an .xpt dataset that includes one line per patient per formulation received. Include patient ID, formulation, first dose date of that formulation, and last dose date of that formulation.

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4. On page 42 of Module 2.7.3, you explain that 2 of the 34 subjects identified as having a CR achieved only a PR with enasidenib and then converted to CR after HSCT. Identify these two patients. For all patients treated on Phase 1 or Phase 2 of AG221-C-001, provide an .xpt file with at least the following variables: subject ID, best response with enasidenib alone, date of start of first alternate or additional therapy (including HSCT) after enasidenib. How many of the patients that you called CR actually achieved CR only after receiving additional therapy? How does this alter your conclusions about the efficacy of enasidenib?

5. On page 33 of Module 2.7.3, you explain that 4 subjects had less than 5% blasts on the screening marrow aspirate. Identify these 4 subjects and any other subjects in Phase 1 or Phase 2 of AG221-C-001 for whom you do not have documentation of relapse at study entry. Once these subjects are removed from the efficacy analysis, is your conclusion about the efficacy of enasidenib altered?

6. We have not been able to confirm the results of your analyses in AG221-C-001-TD-IDH2VAF. Please address the following:

   a. Provide an .xpt data set containing the data used to generate the study report for AG221-C-001-TD-IDH2VAF. This should include subject ID, IDH2 mutation (specify whether this is by LDT or CDx), results of MRD testing, method used (digital PCR, FoundationOne, MSKCC mutational panel), date of sample collection, and clinical response at the time of sample collection. Explain how patients were selected for MRD testing, and provide an analysis of any bias that may have been introduced on the basis of patient selection.

b. If you have collected MRD data on additional patients from AG-221-C-001 that were not included in the NDA submission, please include that data in the aforementioned .xpt file and provide a summary of the results.

7. We are unable to confirm the conclusions you stated from your analysis in AG-221-C-001-TD. Please address the following:

a. Clarify where in the NDA the data can be found for the cytogenetics and molecular data such as is listed in Appendix B and Appendix C of Drug Discovery Report AG221-C-001-TD-CoMut. Identify also the data file with the risk classification by ELN, Grimwade and Papaemmanuil. If the data are not in the NDA, please submit them.

b. Explain how the n=100 patients tested with FoundationOne mutation analysis were selected, and specify whether you have analyzed co-occurring mutations in additional patients beyond those described in the submission. If you have, please provide the data and analysis results.

c. Provide further explanation for why Table 13 of Module 2.7.3 is incomplete; specifically, which data are missing in which patients, and why the analysis was conducted in only 72 of the 80 patients with complete data.

8. Please submit a summary of efficacy data from all patients who have received AG-221 in combination with chemotherapy on AG120-221-C-001 to date. Your summary should include patient identification #, date treatment was initiated, date of each response assessment, and response determination. Also indicate which of the patients have had testing for MRD, the type of test, the date of the test, and the result.

9. Please submit a Letter of Authorization with the correct PMA number to cross-reference the PMA for the companion diagnostic.

*Biometrics*

*The following information request was sent on April 25, 2017, with a requested response date of May 2, 2107.*

Please submit the following analysis results for the primary efficacy endpoint (ORR), key secondary endpoints (i.e., CR, DOR, RBC/Platelet transfusion, OS…etc.), and important subgroup analyses of these endpoints (i.e., forest plots of subgroup analysis results for the ORR and CR). The datasets and SAS programs should also be included.

- Phase 2 subjects as of 28 Oct 2016

- Combined Phase I and Phase 2 subjects who received 100 mg QD of enasidenib as of 28 Oct 2016

*Clinical Pharmacology*

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- Please provide a table of the pharmacokinetic data for study AG221-C-001 including geometric mean and 90% CI for $C_{max}$ and AUC to compare the F2 and F3 formulations. Submit a dataset with the subject level pharmacokinetic data for the F2 and F3 formulations used to generate the table from this study.

- Please clarify if "(b) (4)" as indicated in Tables 10 and 11 of the AG221-N-027-R study report is referring to the active metabolite "AGI-0016903".

## 5. Major Safety Concerns

There are no major safety concerns identified at this time.

## 6. Risk Management Update

There is no need for a REMS identified at this time.

## 7. Advisory Committee Meeting Plans

There are no plans at this time for an AC meeting.

## 8. Proposed Date and Format for Late-Cycle Meeting/Other Projected Milestones

The Late-Cycle Meeting between you and the review team is currently scheduled for Friday, June 16, 2017. We intend to send the Agency background package to you approximately 12 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of the review.

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JENNIFER J LEE
04/27/2017

| | |
|---|---|
| **From:** | Lee, Jennifer (CDER) |
| **To:** | "Penny Ng" |
| **Subject:** | NDA 209606 enasidenib -- FDA Information Request Response Due 4/27 3PM EST |
| **Date:** | Wednesday, April 26, 2017 6:18:00 PM |
| **Attachments:** | image002.png |

Dear Penny,

I have the following FDA information request from the review team for NDA 209606 enasidenib. Please provide a response via email by **tomorrow, Thursday, April 27, 2017 3PM EST** and follow up with a formal submission to your NDA file.

Kindly confirm receipt of this email.

Thank you,
Jennie

***FDA Information Request***

1. ***In your response to an earlier information request, you indicated that 3 of the 106 patients enrolled on Phase 2 of AG221-C-001 had NOT either completed 6 months of AG-221 or discontinued as of the data cut-off date for the safety update (14-Oct-2016). However, in the ADEFF.xpt file submitted with the safety update, it appears that the treatment start dates for the three patients from Phase 2 without the 6m follow up flag (FU6MFL; 109-017, 111-049 and 112-006) are 04/18/16, 08/25/15 and 07/22/15, respectively, and the last off treatment date of the 3 is 08/25/16, which suggests that all three discontinued prior to the data cutoff date. Please explain this apparent discrepancy, and provide the subject ID numbers for the 3 subjects on Phase 2 who did not complete 6 months of AG-221 or discontinue as of the data cut for the safety update.***

2. ***Please clarify when you will be submitting the interim Clinical Study Report for AG221-C-001 that includes the prespecified analyses through the 14-Oct-2016 cut-off date (at least 6 months of follow-up for all subjects on Phase 1 and Phase 2).***


**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov

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JENNIFER J LEE
04/26/2017

**From:** Lee, Jennifer (CDER)
**To:** "Penny Ng"
**Subject:** RE: NDA 209606 enasidenib -- Clinical Information Request Response due COB 5/8
**Date:** Wednesday, April 26, 2017 11:42:00 AM
**Attachments:** image001.png

Dear Penny,

The team has discussed your request regarding the data cutoff date of 14 Oct 2016. While we will accept a data cutoff date of 14 Oct 2016 for the IRs sent to you on Tuesday, the efficacy data analysis should be based on the intention-to-treat principle.

Please confirm receipt of this correspondence.

Thank you,
Jennie

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Tuesday, April 25, 2017 10:06 AM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- Clinical Information Request Response due COB 5/8

Dear Jennie,

I would like to acknowledge receipt of this Information Request. I will work with my team to provide a response per the requested timeline below.

Regarding the IR received earlier this morning, I had a discussion with my team regarding the IR received this morning. The 4-Month Safety Update report being submitted today included both safety and efficacy updates as of 14 Oct 2016, a 2 weeks difference versus the Agency's request received today for a 28 Oct 2016 data-cut. Given the availability of data with 14 Oct 2016 cut-off for the 4MSU report, our team would like to propose to provide the Agency's requested information with the 14 Oct 2016 data-cut date, please kindly confirm if this is acceptable.

We also received acknowledgment that the 4MSU Report has been submitted via the gateway. Please do not hesitate to contact me if you have any problems receiving it.

As always, I appreciate your guidance and look forward to you reply to our proposal above. Thank you again.

Kind regards,
Penny

**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Tuesday, April 25, 2017 8:55 AM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** NDA 209606 enasidenib -- Clinical Information Request Response due COB 5/8

**Importance:** High

Dear Penny,

I have the following clinical information requests for NDA 209606 enasidenib. Please provide a response via email by **COB Monday, May 8, 2017** and then follow up with a formal submission to your NDA file.

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

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**FDA Information Request**

1. We are not able to fully confirm the incidence of "differentiation syndrome" in the patients treated with enasidenib. Because a differentiation-like syndrome induced by enasidenib was first recognized while Study AG221-C-001 was on-going, it is not clear how best to identify affected patients with the current adverse event data file. Please address the following:

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    c. Explain how the 72 cases of possible differentiation syndrome (p.78 of Module 2.7.4) were selected for DSRC review, and describe the procedures used by the external DSRC to adjudicate these events.

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between the formulations. For the patients treated with the 100 mg dose in Phase 1 and Phase 2 of AG221-C-001, address the following:

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9. Please submit a Letter of Authorization with the correct PMA number to cross-

reference the PMA for the companion diagnostic.

_____

**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov


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/s/

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JENNIFER J LEE
04/26/2017

**From:** Lee, Jennifer (CDER)
**To:** "Penny Ng"
**Subject:** NDA 209606 enasidenib -- Container Labels Response Due 5/12 noon EST
**Date:** Tuesday, April 25, 2017 3:50:00 PM
**Attachments:** image002.png

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Hello Penny,

Reference is made to NDA 209606 enasidenib and the container labels submitted on December 30, 2016. The review team has completed their review of the container labels and have the following comments. Please provide the revised container labels to me via email by **Friday, May 12, 2017 noon EST** and also follow up with a formal submission to your NDA file.

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

**FDA Comments Regarding NDA 209606 enasidenib Container Labels:**

1. The proprietary name and the 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.

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**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**

Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov


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JENNIFER J LEE
04/25/2017

**From:** Lee, Jennifer (CDER)
**To:** "Penny Ng"
**Subject:** NDA 209606 enasidenib -- Clinical Information Request Response due COB 5/8
**Date:** Tuesday, April 25, 2017 9:54:00 AM
**Attachments:** image002.png
**Importance:** High

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Dear Penny,

I have the following clinical information requests for NDA 209606 enasidenib. Please provide a response via email by **COB Monday, May 8, 2017** and then follow up with a formal submission to your NDA file.

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

---

**FDA Information Request**

1. We are not able to fully confirm the incidence of "differentiation syndrome" in the patients treated with enasidenib. Because a differentiation-like syndrome induced by enasidenib was first recognized while Study AG221-C-001 was on-going, it is not clear how best to identify affected patients with the current adverse event data file. Please address the following:

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    a. Provide an .xpt dataset that includes one line per patient per formulation received. Include patient ID, formulation, first dose date of that formulation, and last dose date of that formulation.

    b. Provide an analysis of safety (adverse events, serious adverse events, adverse events of special interest) by formulation.

    c. Provide an analysis of efficacy (response and duration of response) by formulation.

3. We have not been able to confirm the findings of conversion from transfusion-dependent to transfusion-independent, maintenance of transfusion independence, or duration of transfusion independence. For the patients treated with the 100 mg dose in Phase 1 and Phase 2 of AG221-C-001, provide an .xpt file with at least the following variables: subject ID, a flag for your adjudication of RBC transfusion dependence at baseline (Y/N), a flag for your adjudication of PLT transfusion dependence at baseline (Y/N), date of start of RBC transfusion independence, date of end of RBC transfusion independence, date of start of PLT transfusion independence, date of end of PLT transfusion independence. If you collected the data based on study visit rather than actual date between study visits, you may provide the visit number and date of visit in lieu of the actual date for transfusion-dependence or transfusion-independence.

4. On page 42 of Module 2.7.3, you explain that 2 of the 34 subjects identified as having a CR achieved only a PR with enasidenib and then converted to CR after HSCT. Identify these two patients. For all patients treated on Phase 1 or Phase 2 of AG221-C-001, provide an .xpt file with at least the following variables: subject ID, best response with enasidenib alone, date of start of first alternate or additional therapy (including HSCT) after enasidenib. How many of the patients that you called CR actually achieved CR only after receiving additional therapy? How does this alter your conclusions about the efficacy of enasidenib?

5. On page 33 of Module 2.7.3, you explain that 4 subjects had less than 5% blasts on the screening marrow aspirate. Identify these 4 subjects and any other subjects in Phase 1 or Phase 2 of AG221-C-001 for whom you do not have documentation of

relapse at study entry. Once these subjects are removed from the efficacy analysis, is your conclusion about the efficacy of enasidenib altered?

6. We have not been able to confirm the results of your analyses in AG221-C-001-TD-IDH2VAF. Please address the following:

    a. Provide an .xpt data set containing the data used to generate the study report for AG221-C-001-TD-IDH2VAF. This should include subject ID, IDH2 mutation (specify whether this is by LDT or CDx), results of MRD testing, method used (digital PCR, FoundationOne, MSKCC mutational panel), date of sample collection, and clinical response at the time of sample collection. Explain how patients were selected for MRD testing, and provide an analysis of any bias that may have been introduced on the basis of patient selection.

    b. If you have collected MRD data on additional patients from AG-221-C-001 that were not included in the NDA submission, please include that data in the aforementioned .xpt file and provide a summary of the results.

7. We are unable to confirm the conclusions you stated from your analysis in AG-221-C-001-TD. Please address the following:

    a. Clarify where in the NDA the data can be found for the cytogenetics and molecular data such as is listed in Appendix B and Appendix C of Drug Discovery Report AG221-C-001-TD-CoMut. Identify also the data file with the risk classification by ELN, Grimwade and Papaemmanuil. If the data are not in the NDA, please submit them.

    b. Explain how the n=100 patients tested with FoundationOne mutation analysis were selected, and specify whether you have analyzed co-occurring mutations in additional patients beyond those described in the submission. If you have, please provide the data and analysis results.

    c. Provide further explanation for why Table 13 of Module 2.7.3 is incomplete; specifically, which data are missing in which patients, and why the analysis was conducted in only 72 of the 80 patients with complete data.

8. Please submit a summary of efficacy data from all patients who have received AG-221 in combination with chemotherapy on AG120-221-C-001 to date. Your summary should include patient identification #, date treatment was initiated, date of each response assessment, and response determination. Also indicate which of the patients have had testing for MRD, the type of test, the date of the test, and the

result.

9. Please submit a Letter of Authorization with the correct PMA number to cross-reference the PMA for the companion diagnostic.


**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov



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/s/

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JENNIFER J LEE
04/25/2017

| | |
|---|---|
| **From:** | Lee, Jennifer (CDER) |
| **To:** | "Penny Ng" |
| **Subject:** | NDA 209606 enasidenib -- FDA Information Request Response Due 5/2 Noon EST |
| **Date:** | Tuesday, April 25, 2017 7:47:00 AM |
| **Attachments:** | image002.png |

Good morning Penny,

I have the following FDA information request for NDA 209606 enasidenib. Please provide your response via email by **Tuesday, May 2nd, 2017 Noon EST** and also follow up with a formal submission to your NDA file.

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

***FDA Information Request***

***Please submit the following analysis results for the primary efficacy endpoint (ORR), key secondary endpoints (i.e., CR, DOR, RBC/Platelet transfusion, OS…etc.), and important subgroup analyses of these endpoints (i.e., forest plots of subgroup analysis results for the ORR and CR). The datasets and SAS programs should also be included.***

- ***Phase 2 subjects as of 28 Oct 2016***
- ***Combined Phase I and Phase 2 subjects who received 100 mg QD of enasidenib as of 28 Oct 2016***


**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
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JENNIFER J LEE
04/25/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209606

**INFORMATION REQUEST**

Celgene Corporation
Attention: Robert E. Wildman, Senior Director, Global Regulatory CMC
556 Morris Avenue
Summit, NJ 07901

Dear Mr. Wildman:

Please refer to your New Drug Application (NDA) dated December 30, 2016, received December 30, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Idhifa (enasidenib) Tablets, 50 mg and 100 mg.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. 21 CFR 211.186(b)(7) requires that master production and control records include a statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation is required. Percentage of theoretical yield as defined in the preamble to 21 CFR parts 210 and 211 means the ratio of the actual yield to the theoretical yield stated as a percentage where the actual yield means the quantity that is actually produced and the theoretical yield is the quantity that would be produced based on the quantity of components to be used in the absence of any loss or error in actual production. In your information request response #2 from 30 Mar 2017, you have stated that you have established total accountable yield limits only instead of actual yield limits. This does not satisfy 21 CFR 211.186(b)(7). Furthermore, total accountable yields are not a sufficient indicator of actual manufacturing process performance. Provide tentative percentage of theoretical yield acceptance criteria (lower and upper bound) for the individual processing steps with justification as required per 21 CFR 211.186(b)(7).

2. Provide the data from the hold time studies that was used to support the maximum manufacturing processing times and hold time acceptance criteria provided in information request response #3 from 30 Mar 17. Discuss how the data justifies the current hold time acceptance criteria and control strategy. (b) (4) .

3. [redacted] (b) (4)

We request a response to these requests no later than **May 5, 2017**.

If you have any questions, please contact me, at (301) 796-1649.

Sincerely,

*{See appended electronic signature page}*

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, USPHS, Quality Assessment Lead (Acting)
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Teshara Bouie

Digitally signed by Teshara Bouie
Date: 4/24/2017 09:13:05AM
GUID: 508da7230002a24fd4abdd8018af2a08

| | |
|---|---|
| **From:** | Lee, Jennifer (CDER) |
| **To:** | "Penny Ng" |
| **Subject:** | NDA 209606 enasidenib -- FDA Information Request Response Due May 1st Noon EST |
| **Date:** | Monday, April 24, 2017 7:04:00 AM |
| **Attachments:** | image002.png |

Good morning Penny,

I have the following FDA information requests for NDA 209606 enasidenib. Please provide a response via email by **Monday, May 1st, 2017 Noon EST** and also follow up with a formal submission to your NDA file.

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

***FDA Information Requests***

1. ***Please provide a table of the pharmacokinetic data for study AG221-C-001 including geometric mean and 90% CI for Cmax and AUC to compare the F2 and F3 formulations. Submit a dataset with the subject level pharmacokinetic data for the F2 and F3 formulations used to generate the table from this study.***

2. ***Please clarify if "(b) (4)" as indicated in Tables 10 and 11 of the AG221-N-027-R study report is referring to the active metabolite "AGI-0016903".***


**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov

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JENNIFER J LEE
04/24/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209606

**INFORMATION REQUEST**

Celgene Corporation
Attention: Robert Wildman, Director, Global Regulatory CMC
556 Morris Avenue
Summit, NJ 07901

Dear Mr. Wildman:

Please refer to your New Drug Application (NDA) dated December 30, 2016, received December 30, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Idhifa (enasidenib) Tablets, 50 mg and 100 mg.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

**Drug Substance:**

1. Provide the synthetic scheme for [redacted] (b) (4).

2. Provide relative response times (RRTs) and relative response factors (RRFs) for the impurities, [redacted] (b) (4).

3. It is noted that [redacted] (b) (4) was included for method development purpose based on the information provided in the analytical method and validation of the DS and DP. However, impurity [redacted] (b) (4) is not described in the "Impurities" section of the AG-221 DS. Please clarify why this is the case and provide the fate and purge data for this impurity if it is an observed process impurity in the drug substance.

4. It is noted that AG-221 DS [redacted] (b) (4). Please provide the detailed protocol for this study.

**Drug Product:**

1. Provide justification for the inconsistent relative response factors for impurities [redacted] and [redacted] between the drug substance and drug product HPLC analytical methods for related substances.

2. Provide the acceptance criteria for all of the validation parameters for the HPLC analytical methods used for the release and stability testing of the drug substance and the drug product.

3. On page 44 of Drug Product in Section 3.2.P.2, in Tables 37, 39, and 44 etc., you have indicated in your footnote1: due to presence of multiple crystalline forms, the amorphous content is estimated by the relative position of sample spectrum to the spectra of calibration standards. However, in the column of "unintended crystalline forms", you have reported either as "not detected" or "<LOD". Please clarify if there are no unintended crystalline forms observed, why the amorphous content in the same sample has to be estimated per your footnote.

4. On page 47, you have indicated that "the drug product tablets were [redacted] ranging from approximately [redacted] at 25°C for 2 or 4 weeks and analyzed for % amorphous free base using the XRPD method described in Section 2.5.1.2." Please clarify which method you have used to analyze for % amorphous free base, XRPD or ssNMR?

5. In the CoA for the site specific lots of VYNV and VYNW, there are several testing results missing in the CoA, including: content uniformity, [redacted], and microbial limits. Please provide all missing data accordingly.

6. [redacted] is controlled in your provided drug product release and stability specifications. However, in both Sections 3.2.P.5.4 and 3.2.P.8.3, [redacted] data are missing for all batches. Please provide all missing data accordingly.

7. Provide information on how to release the packaging components for use in house.

We request a response to these requests no later than **April 27, 2017**.

If you have any questions, please contact me, at (301) 796-1649.

Sincerely,

*{See appended electronic signature page}*

Teshara G. Bouie, MSA, RAC, OTR/L

CDR, USPHS, Quality Assessment Lead (Acting)
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Teshara Bouie

Digitally signed by Teshara Bouie
Date: 4/06/2017 08:02:40AM
GUID: 508da7230002a24fd4abdd8018af2a08

**From:** Lee, Jennifer (CDER)
**To:** "Penny Ng"
**Subject:** NDA 209606 enasidenib -- Additional Clinical Pharmacology Information Request Response Due 4/6 Noon EST
**Date:** Tuesday, April 04, 2017 2:29:00 PM
**Attachments:** image013.png

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Dear Penny,

Reference is made to "Celgene Response to FDA Information Request Received on 09 MAR 2017" submitted on April 3, 2017 (Seq No. 0015) to NDA 209606 enasidenib. Please submit the model codes and analysis datasets used in the exposure–response analysis by **Thursday, April 6, 2017 Noon EST**. Please submit your response via email and also follow-up with a formal submission to your NDA file.

Kindly confirm receipt of this information request.

Thank you,
Jennie


**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov

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JENNIFER J LEE
04/04/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209606

**PROPRIETARY NAME REQUEST**
**CONDITIONALLY ACCEPTABLE**

Celgene Corporation
9225 Indian Creek Parkway
Suite 900
Overland Park, KS 66210

ATTENTION: Penny Ng, M.Sc., MBA, RAC
Director, Regulatory Affairs

Dear Ms. Ng:

Please refer to your New Drug Application (NDA) dated and received December 30, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Enasidenib Tablets, 50 mg and 100 mg.

We also refer to your correspondence, dated and received January 4, 2017, requesting review of your proposed proprietary name, Idhifa.

We have completed our review of the proposed proprietary name, Idhifa and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your January 4, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Jennifer Lee, Regulatory Project Manager, in the Office of New Drugs at (240) 402-4622.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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DANIELLE M HARRIS on behalf of TODD D BRIDGES
03/30/2017

| | |
|---|---|
| **From:** | Lee, Jennifer (CDER) |
| **To:** | "Penny Ng" |
| **Subject:** | NDA 209606 enasidenib -- FDA Information Request Response Due 4/3 Noon EST |
| **Date:** | Thursday, March 30, 2017 11:13:00 AM |
| **Attachments:** | image002.png |

Hello Penny,

I have the following information request from our review team regarding NDA 209606 enasidenib. Please provide a response via email by **Monday, April 3, 2017 Noon EST** and also follow-up with a formal submission to your NDA file.

***FDA Information Request***

***We could not locate the study on enasidenib (AG-221) reversal of DNA-hypermethylation in AML cells in vitro. Please submit this study by Monday, April 3, 2017 Noon EST.***

Kindly confirm receipt of this information request.

Thank you,
Jennie


**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov

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JENNIFER J LEE
03/30/2017

## Vora, Neil

**From:** Penny Ng <PNg@celgene.com>
**Sent:** Monday, March 27, 2017 12:55 PM
**To:** Vora, Neil
**Subject:** RE: NDA 209606 (enasidenib)

Hi Neil,
Thanks for the guidance! I will amend the document and submit to the NDA this week. Thanks again!

Kind regards,
*Penny*

---

**From:** Vora, Neil [mailto:Neil.Vora@fda.hhs.gov]
**Sent:** Monday, March 27, 2017 12:53 PM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** RE: NDA 209606 (enasidenib)

Hi Penny,

No problem at all! Sorry we had to contact you while you were travelling. Please submit an amendment to update the name review submission when you are able to.

Thanks so much,
Neil

**Neil Vora, Pharm.D, MBA, PMP**
*Safety Regulatory Project Manager (SRPM)*

**Center for Drug Evaluation and Research (CDER)**
**Office of Surveillance and Epidemiology (OSE)**
**U.S. Food and Drug Administration**
Tel: 240-402-4845
Neil.Vora@fda.hhs.gov

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Monday, March 27, 2017 8:01 AM
**To:** Vora, Neil
**Subject:** RE: NDA 209606 (enasidenib)

Good morning Neil,

Thanks for confirmation. My sincere apologies again for the late response when I was away from the country last week. I am back to the office.

Would you kindly advise if I should update the name review submission [redacted] (b) (4)) and submit as a formal submission? Thanks again for your guidance. Upon your confirmation, I will proceed accordingly.

Kind regards,
*Penny*

---

**From:** Vora, Neil [mailto:Neil.Vora@fda.hhs.gov]
**Sent:** Friday, March 24, 2017 10:01 AM
**To:** Penny Ng <PNg@celgene.com>
**Cc:** Paul McInulty <pmcinulty@celgene.com>
**Subject:** RE: NDA 209606 (enasidenib)

Hi good morning Penny,

I spoke with our review team and they confirmed that only the two strengths (50 mg and 100 mg) relevant to the current NDA submission will be included in the name review.

Please let us know if you have any further questions.

Thanks,
Neil

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Thursday, March 23, 2017 7:19 PM
**To:** Vora, Neil
**Cc:** Paul McInulty
**Subject:** Re: NDA 209606 (enasidenib)

Dear Neil,

My apologies for the late reply as I am away from the country.

I would like to confirm that the NDA has the 2 strengths only (50 mg and 100 mg).

[redacted] (b) (4)

Would you kindly advice if we can [redacted] (b) (4) ?

Thanks in advance for your guidance.

Kind regards,
Penny

-sent from my iPhone

On Mar 24, 2017, at 2:05 AM, Vora, Neil <Neil.Vora@fda.hhs.gov> wrote:

Hi Penny,

Reference is made to your January 4, 2017 proprietary name submission for the proposed name, Idhifa. The Agency is requesting clarification on whether Celgene is requesting review of (b) (4) only two strengths (50 mg and 100 mg.) Based on the 356h form submitted, only two strengths of 50 mg and 100 mg are stated (b) (4) in your "Request for Proprietary Name Review" document under Section 1.18.

We are requesting clarification by **COB today (March 23, 2017)** followed by a submission with a formal amendment reflecting the clarification point.

If you have any questions, please do not hesitate to contact me.

Thank you,
Neil

**Neil Vora, Pharm.D, MBA, PMP**
*Safety Regulatory Project Manager (SRPM)*

**Center for Drug Evaluation and Research (CDER)**
**Office of Surveillance and Epidemiology (OSE)**
**U.S. Food and Drug Administration**
Tel: 240-402-4845
Neil.Vora@fda.hhs.gov

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sender to notify us of the error and delete the original message. Thank You.

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/s/

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NEIL VORA
03/28/2017

## Vora, Neil

**From:** Vora, Neil
**Sent:** Friday, March 24, 2017 10:01 AM
**To:** 'Penny Ng'
**Cc:** Paul McInulty
**Subject:** RE: NDA 209606 (enasidenib)

Hi good morning Penny,

I spoke with our review team and they confirmed that only the two strengths (50 mg and 100 mg) relevant to the current NDA submission will be included in the name review.

Please let us know if you have any further questions.

Thanks,
Neil

---

**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Thursday, March 23, 2017 7:19 PM
**To:** Vora, Neil
**Cc:** Paul McInulty
**Subject:** Re: NDA 209606 (enasidenib)

Dear Neil,

My apologies for the late reply as I am away from the country.

I would like to confirm that the NDA has the 2 strengths only (50 mg and 100 mg).

(b) (4)

Would you kindly advice if we can (b) (4) ?

Thanks in advance for your guidance.

Kind regards,
Penny

-sent from my iPhone

On Mar 24, 2017, at 2:05 AM, Vora, Neil <Neil.Vora@fda.hhs.gov> wrote:

> Hi Penny,
>
> Reference is made to your January 4, 2017 proprietary name submission for the proposed name, Idhifa. The Agency is requesting clarification on whether Celgene is requesting review of (b) (4) only two strengths (50 mg and 100 mg.) Based on the

356h form submitted, only two strengths of 50 mg and 100 mg are stated [redacted] (b) (4) in your "Request for Proprietary Name Review" document under Section 1.18.

We are requesting clarification by **COB today (March 23, 2017)** followed by a submission with a formal amendment reflecting the clarification point.

If you have any questions, please do not hesitate to contact me.

Thank you,
Neil

**Neil Vora, Pharm.D, MBA, PMP**
*Safety Regulatory Project Manager (SRPM)*

**Center for Drug Evaluation and Research (CDER)**
**Office of Surveillance and Epidemiology (OSE)**
**U.S. Food and Drug Administration**
Tel: 240-402-4845
Neil.Vora@fda.hhs.gov



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NEIL VORA
03/24/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209606

**INFORMATION REQUEST**

Celgene Corporation
Attention: Robert Wildman
Sr. Director, Global Regulatory CMC
86 Morris Avenue
Summit, NJ 07901

Dear Mr. Wildman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IDHIFA (Enasidenib) Tablets 50mg, 100mg.

We also refer to your December 30, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

**Drug Process**

1. (b) (4)
2.
3.
4.

5. (b) (4)

6.

If you have any questions, please contact me, at (240) 402-6153. Please respond by **April 7, 2017**.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Laiq -S

Digitally signed by Rabiya Laiq -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -S, 0.9.2342.19200300.100.1.1=2001555007
Date: 2017.03.15 17:12:29 -04'00'

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Thursday, March 09, 2017 3:24 PM
**To:** 'Penny Ng'
**Subject:** NDA 209606 enasidenib -- Pharmacometrics Information Request Response Due 3/31 Noon EST

Dear Penny,

Reference is made to "Population PK and Exposure-Response Analysis Report of AG-221" in Module 5.3.3.5 of NDA 209606, submitted on December 30, 2016, in Sequence 0001. Please conduct the following analysis and submit the datasets, codes and reports, accordingly.

For general expectations on submitting pharmacometric data and models, please refer to the following website, https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm

1. Since the first dose and steady state PK data are available in patients, please evaluate the time-dependent clearance model in the population PK analysis:
    a. Further evaluate the effect of covariates including renal and hepatic function measures and categories, healthy vs patient, gene mutations status (IDH2) and other concomitant medications on AG-221 PK.
    b. Analyze and summarize the contribution of time-dependent PK to the accumulation of the exposures at steady state after multiple doses.
    c. Submit the model diagnostic plots including the individual plots with observed concentrations overlaid with individual and population predictions.
    d. Submit the individual post-hoc estimates of PK parameters, steady state AUC and Cmax estimates from the final model for each subject.

2. Conduct exposure-response analysis for efficacy end points of ORR, PR and CR rates:
    a. Using steady state $AUC_{0\text{-}24hrs}$ as the exposure metrics
    b. Adjusted with potential prognostic factors (for e.g., ECOG).
    c. Do separate analysis for
    (a) all patients combining phase 1 and 2 data, stratified by gene mutations status for IDH2
    (b) patients with relapsed or refractory AML with an IDH2 mutation stratified by gene mutations status for IDH2.

3. Conduct exposure-response analysis with logistic regression for safety endpoints using the steady state AUC derived by the dose at the time of event as the exposure metrics. Perform the analysis (a) for all subjects and (b)subjects with R/R AML. The safety endpoints should include all grade and ≥ grade 3 TEAES including anemia, febrile neutropenia, leukocytosis, tumor lysis syndrome, IDH differentiation syndrome, hepatic safety (TEAEs from the SMQ Biliary System Related Investigations), and total bilirubin elevation from the liver function tests. Category and criteria of each TEAE in the ER analysis should be specified. Submit the final analysis datasets including the time of event for each individual for each type of safety event.

Please provide a response via email by **March 31, 2017 Noon EST** and also follow up with a formal submission to your NDA file.

Kindly confirm receipt of this correspondence.

Thank you,

Jennie

_____

**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov


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/s/

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JENNIFER J LEE
03/09/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209606

**INFORMATION REQUEST**

Celgene Corporation
Attention: Penny Ng, M.Sc., MBA, RAC
Director, Regulatory Affairs
86 Morris Avenue
Summit, NJ 07901

Dear Ms. Ng:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IDHIFA (Enasidenib) Tablets 50mg, 100mg.

We also refer to your December 30, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

**Facilities**

1. Please update Module 3.2.S.2.1 ***and*** 356h form for the information about the facility(ies) that is (are) responsible for the manufacture of the primary stability batches in support of NDA 209606. Include the site information in the 3.2.S.2.1. section of the submission.

**Drug Product**

1. Provide confirmation that all compendial analytical methods for the drug substance and drug product have been verified to be suitable under actual conditions of use.
2. Provide representative copy of the manufacture's certificate of analysis for each excipient used in the proposed commercial drug product.
3. Provide representative copy of the manufacture's certificate of analysis for your selected primary packaging system for the proposed commercial drug product.
4. Provide statement of compliance to pertinent CFR regulations for indirect food additives for each component used in the primary packaging system.

If you have any questions, please contact me, at (240) 402-6153. Please respond by **March 20, 2017**.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Laiq -S

Digitally signed by Rabiya Laiq -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -S, 0.9.2342.19200300.100.1.1=2001555007
Date: 2017.03.02 19:24:46 -05'00'

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209606

**FILING COMMUNICATION -**
**FILING REVIEW ISSUES IDENTIFIED**

Celgene Corporation
Attention: Penny Ng, MSc, MBA, RAC
Director, Regulatory Affairs
9225 Indian Creek Parkway, Suite 900
Overland Park, KS 66210

Dear Ms. Ng:

Please refer to your New Drug Application (NDA) dated December 30, 2016, received December 30, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for IDHIFA™ (enasidenib) Tablets, 50 and 100 mg.

We also refer to your amendments dated January 27 and February 3, 17, and February 23, 2017.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is August 30, 2017. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: *Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 30, 2017.

In addition, the planned date for our internal mid-cycle review meeting is April 21, 2017, and the scheduled mid-cycle teleconference meeting is April 28, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

1. You have evidence that patients who achieve complete remission (CR) after enasidenib monotherapy have persistence of minimal residual disease (MRD). You have hypothesized that enasidenib is a differentiating agent and as such it may not eradicate measurable MRD. It is not clear, therefore, whether CR as produced by enasidenib monotherapy is a surrogate endpoint "reasonably likely to predict clinical benefit" as it has been considered for cytotoxic agents.

2. Your proposed data cut-off date (October 14, 2016) for the follow-up analysis of Study AG221-C-001to be submitted with the safety update does not reflect the pre-specified criteria described in your protocol. Section 12.5.1 of the protocol states that the study data will be analyzed and reported when all subjects have completed at least 6 cycles of treatment or discontinued study drug. As of October 15, 2016, 3 of the 106 enrolled patients did not meet these criteria. The FDA intends to include these 3 patients in the evaluable population for both safety and efficacy analyses using the data available as of the cut-off date.

3. You have not explained why the pivotal portion of Study AG221-C-001 enrolled only 106 of a planned 125 patients. The early termination of the accrual will be taken into consideration during the review of the adequacy of the trial and interpretation of the trial results.

4. You have not provided a subgroup analysis of the activity of enasidenib for Study AG221-C-001 by specific isocitrate dehydrogenase-2 (IDH2) amino acid change as detected by the companion diagnostic, which makes it difficult to determine if the diagnostic appropriately selects the population most likely to benefit from enasidenib.

5. It is not clear whether you have selected the appropriate historical comparator population (Roboz et al, 2014). The patients on Study AG221-C-001 were generally less heavily pretreated than those on the Roboz study, and the Roboz study was not conducted in patient population having IDH2 mutations alone. While the literature is conflicting regarding the prognostic impact of IDH2 mutations, there is some evidence that patients with IDH2-mutated acute myeloid leukemia (AML) respond more frequently to salvage therapy in first relapse (e.g., DiNardo et al, 2015) and have prolonged survival (e.g., Patel et al, NEJM 2012). The impact of co-occurring mutations (e.g., FLT3, NPM1) may explain some of the discrepancies reported in the literature, but in the absence of data regarding co-occurring mutations that are known to influence prognosis in patients enrolled on Study AG221-C-001, it is difficult to know how comparable the patients in Study AG221-C-001 are to those selected as the historical control.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded

upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. Of the 106 patients that received at least one dose of AG-221 on the Phase 2 portion of study AG-221-C-001, how many were selected for the study on the basis of a local lab-developed test (LDT), and how many were selected for the study using the In Vitro Diagnostic (IVD) companion diagnostic device under development by Abbott Molecular? If any subjects were selected for participation in the study using the IVD companion diagnostic device, please state how many were screened, how many tested positive, and how many tested negative. Please provide a response by March 3, 2017.

2. Please explain why enrollment of the Phase 2 portion of AG-221-C-001 was stopped at n=106, rather than the planned n=125. Please provide a response by March 3, 2017.

3. We remind you of your commitment to submit updated safety and efficacy data from all subjects on Study AG-221-C-001 (including all subjects who have enrolled on Phase 2 and with a data cutoff date of October 14, 2016).

**PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

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

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

Highlights (HL)

1. The HL has some sections that have bullets when only one item is listed in that section. Use bullets when there is more than one item (e.g., piece of information) under each heading in HL.

2. The different strengths of tablets under the subsection *Dosage Forms and Strengths* should appear on the same line and not separate bullet points. Use bullet points for products that have more than one dosage form (e.g., capsules, tablets, injection).

3. Replace the (b) (4) statement with the following verbatim statement: "**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**".

Full Prescribing Information (FPI)

4. (b) (4) .

5. (b) (4)

6. Replace the statement in section *17 Patient Counseling Information* with the following verbatim statement: "Advise the patient to read the FDA-approved patient labeling (Patient Information)".

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by March 21, 2017. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. The checklist is available at the following link: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

**PROMOTIONAL MATERIAL**

We will review this application under the provisions of 21 CFR 314 Subpart H – *Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 314.550, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient information. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf ).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient information, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of

administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, please call Jennifer Lee, Regulatory Project Manager, at (240) 402-4622.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, MD
Director
Division of Hematology
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

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ANN T FARRELL
02/28/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Friday, February 17, 2017 1:16 PM
**To:** 'Penny Ng'
**Subject:** NDA 209606 enasidenib -- FDA Information Request Response Due 5PM EST Today

Hi Penny,

I have the following FDA information request from our review team. Please provide a response by **5PM EST today** and also follow-up with a formal submission to the NDA file.

Kindly confirm receipt of this email.

Thank you,
Jennie

---

Please provide an enrollment update for Phase 2 of AG221-C-001. Please complete the table below and also confirm: has the study completed enrollment? If so, when did the last patient enroll, and what is the total number of patients enrolled on Phase 2 of the study? If not when do you expect to complete enrollment (provide number of patients and approximate date on which you expect the last patient to enroll)?

| Date | Number enrolled on Phase 2 portion of AG221-C-001 | Number of enrolled who have completed 6 months of AG-221 or discontinued |
|---|---|---|
| 15-April-2016 (data cutoff date for NDA) | | |
| 14-Oct-2016 (data cutoff date proposed for 90- or 120 day update) | | |
| 28-Oct-2016 (“dirty” cutoff date described in interim CSR) | | |
| 17-Feb-2017 (today) | | |
| Anticipated or actual date of last patient enrollment | | |


**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**

Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov


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/s/

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JENNIFER J LEE
02/17/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Tuesday, February 14, 2017 5:03 PM
**To:** 'Penny Ng'
**Subject:** NDA 209606 enasidenib -- FDA Information Request Response Due

Hello Penny,

I have the following information requests from the FDA review team for NDA 209606 enasidenib. Please provide a response by **Friday, February 17, 2017, Noon EST** and also follow up with a formal submission to the NDA file.

Kindly confirm receipt of this correspondence and do not hesitate to contact me should you have any questions.

Kind regards,
Jennie

**FDA Information Request**

1. The unplanned analyses of data from Study AG-221-C-001 that were conducted to support the NDA submission were performed in a different patient population (Phase I, selected patients) than the planned analyses (Phase I and II, all patients who received at least one dose). In addition, justification for the timing of the unplanned analysis has not been provided. Please provide justification for the timing of the unplanned and the post-hoc nature of the selected patient population. In addition, please discuss whether or not bias may be introduced into the unplanned analysis compared to the planned analysis. Specifically, your responses should:

    a. Clarify the timing of the planned analyses for Study AG-221-C-001 through the end of the protocol as well as provide a justification for the proposed data cut-off date (e.g., X patients followed for X amount of time or until X event) used for the unplanned analysis submitted with the NDA. A justification that requires retrospective analysis, such as “when the response rate stabilizes”, is not sufficient. Provide explanation for any discrepancy between the timing of the pre-planned efficacy analyses and the timing of the analyses in this NDA submission. Your response should address in detail the maturity of the data that were submitted with the NDA.

    b. Provide explanation for any discrepancy between the pre-planned efficacy analysis population and the proposed analysis population submitted in this NDA.

2. For the purposes of obtaining accelerated approval, you need to provide data showing that your drug provides meaningful therapeutic benefit to patients over existing treatments, and that clinical trials should show that the drug product has an effect on a surrogate endpoint reasonably likely to predict clinical benefit. CR is the endpoint used to predict clinical benefit with duration of CR being supportive. Please identify where in the NDA you show that the effect of enasidenib on CR and durability of CR represents a meaningful advantage over available therapy (i.e., combination chemotherapy) for patients with relapsed or refractory IDH2-mutated AML.

3. Please plan to submit updated efficacy data from Study AG-221-C-001 at the time of your 90- or 120- day safety update. This analysis should include data from Phase 2 patients, and the patient population and data cutoff date should be described and justified as outlined in #1 above.

4. From the information submitted in Module 1.3.4, it is not possible to tell whether there were any investigators for whom financial disclosure information could not be obtained, or whether any investigators on the study are full- or part-time employees of the study sponsor. In Module 1.3.4, please provide a table listing all investigators on Study AG221-C-001, and indicate which had financial interests or arrangements to disclose. Please also state whether there are any investigators for which financial disclosure information could not be obtained, and whether any investigators on the study are full-time or part-time employees of the study sponsor.

5. To assist reviewers in locating expected NDA contents, please provide a hyperlink to the SCE (which is located in Module 2.7.3) in Module 5.3.5.3, where the ISE would be expected, and provide a hyperlink to the SCS (which is located in Module 2.7.4) in Module 5.3.5.3, where the body of the ISS would be expected.

6. Please submit a .xpt dataset including IDH2 mutation with changes at the DNA level and at the protein level (amino acid substitution) as determined by both local testing and the proposed companion diagnostic test for all patients in Study AG221-C-001.

---

**Jennifer J. Lee, PharmD**
*Regulatory Project Manager*

**Center for Drug Evaluation and Research**
**Office of Hematology and Oncology Products**
**Division of Hematology Products**
**U.S. Food and Drug Administration**
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov

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/s/

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JENNIFER J LEE
02/14/2017

## Lee, Jennifer (CDER)

**From:** Penny Ng <PNg@celgene.com>
**Sent:** Tuesday, February 07, 2017 8:38 AM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: NDA 209606 enasidenib -- Carton Labels

Good morning Jennie,

I have just confirmed with my team that there are no carton labels to review, only the bottle labels as the bottles will contain only a bottle label and PI.

Please do not hesitate to let me know if you have further questions.

Kind regards,
*Penny*

---

**From:** Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
**Sent:** Tuesday, February 07, 2017 6:52 AM
**To:** Penny Ng <PNg@celgene.com>
**Subject:** NDA 209606 enasidenib -- Carton Labels

Good morning Penny,

I have a question for you regarding draft labeling. I noticed that there were no carton labels included in the draft labeling folder in your NDA 209606 submission. I wanted to follow up and see if they were inadvertently left out or if there are no carton labels to review?

Thanks for clarifying,
Jennie

_____

**Jennifer J. Lee, PharmD**
Regulatory Project Manager
Division of Hematology Products | OHOP | CDER | FDA
10903 New Hampshire Ave
WO22, Room 3209
Silver Spring, MD 20993
Office: (240) 402-4622
Email: jennifer.lee1@fda.hhs.gov

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JENNIFER J LEE
02/07/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209606

**INFORMATION REQUEST**

Celgene Corporation
Attention: Penny Ng, M.Sc., MBA, RAC
Director, Regulatory Affairs
86 Morris Avenue
Summit, NJ 07901

Dear Ms. Ng:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IDHIFA (Enasidenib) Tablets 50mg, 100mg.

We also refer to your December 30, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

**Please provide executed batch records for the manufacturing of the drug product registration stability lots.**

If you have any questions, please contact me, at (240) 402-6153. Please respond **ASAP**.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Laiq -S

Digitally signed by Rabiya Laiq -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -S, 0.9.2342.19200300.100.1.1=2001555007
Date: 2017.02.01 15:22:36 -05'00'

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Friday, January 27, 2017 2:18 PM
**To:** 'Penny Ng'
**Subject:** NDA 209606 enasidenib -- FDA Information Request Response Due 1/31 Noon EST

Hello Penny,

I have the following FDA information request for NDA 209606 enasidenib.

- *Identify the location of all versions of the Study Protocol AG221-C-001 submitted in NDA 209606. If not, please submit pdfs of all the versions.*

Please send a response to the following information request via email by **Tuesday, January 31, 2017 Noon EST** and also follow up with a formal submission to the NDA file.

Kindly confirm receipt of this email.

Thank you,
Jennie

---

**Jennifer J. Lee, PharmD**
Regulatory Project Manager
Division of Hematology Products | OHOP | CDER | FDA
10903 New Hampshire Ave
WO22, Room 3209
Silver Spring, MD 20993
Office: (240) 402-4622
Email: jennifer.lee1@fda.hhs.gov

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JENNIFER J LEE
01/27/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Tuesday, January 24, 2017 3:17 PM
**To:** 'Penny Ng'
**Subject:** NDA 209606 enasidenib -- Late Cycle Meeting Date and QT Information Request Due 1/26 Noon EST
**Attachments:** NDA 209606 enasidenib -- Highlights_ClinPharm_and_Cardiac_Safety.doc

Hello Penny,

Could you please respond back regarding the following two items for NDA 209606 enasidenib?

1. The FDA review team is available on **Friday, June 16, 2017 from 11:00 AM – 12:00 PM** for the Late Cycle Meeting. Could you please confirm that your team is available at the scheduled date and time for the Late Cycle Meeting and whether a teleconference would be suitable?

2. I have attached a 'Highlights of Clinical Pharmacology and Cardiac Safety' table to this email. Could you please have your team fill out the table and return it to me no later than **Thursday, January 26, 2017 Noon EST**? Please also submit the completed table as a formal submission to the NDA file.

Kindly confirm receipt of this email and please let me know if you have any questions regarding the above items.

Thank you,
Jennie

---

**Jennifer J. Lee, PharmD**
Regulatory Project Manager
Division of Hematology Products | OHOP | CDER | FDA
10903 New Hampshire Ave
WO22, Room 3209
Silver Spring, MD 20993
Office: (240) 402-4622
Email: jennifer.lee1@fda.hhs.gov

**Table 1. Highlights of Clinical Pharmacology and Cardiac Safety**

| | | |
|---|---|---|
| Therapeutic dose and exposure | Include maximum proposed clinical dosing regimen<br>Mean (%CV) Cmax and AUC at the single maximum proposed clinical dose<br>Mean (%CV) Cmax and AUC at the steady state with the maximum proposed clinical dosing regimen | |
| Maximum tolerated dose | Include if studied or NOAEL dose | |
| Principal adverse events | Include most common adverse events; dose limiting adverse events | |
| Maximum dose tested | Single Dose | Specify dose |
| | Multiple Dose | Specify dosing interval and duration |
| Exposures Achieved at Maximum Tested Dose | Single Dose | Mean (%CV) Cmax and AUC |
| | Multiple Dose | Mean (%CV) Cmax and AUC |
| Range of linear PK | Specify dosing regimen | |
| Accumulation at steady state | Mean (%CV); specify dosing regimen | |
| Metabolites | Include listing of all metabolites and activity | |
| Absorption | Absolute/Relative Bioavailability | Mean (%CV) |
| | Tmax | • Median (range) for parent<br>• Median (range) for metabolites |
| Distribution | Vd/F or Vd | Mean (%CV) |
| | % bound | Mean (%CV) |
| Elimination | Route | • Primary route; percent dose eliminated<br>• Other routes |
| | Terminal t½ | • Mean (%CV) for parent<br>• Mean (%CV) for metabolites |
| | CL/F or CL | Mean (%CV) |
| Intrinsic Factors | Age | Specify mean changes in Cmax and AUC |
| | Sex | Specify mean changes in Cmax and AUC |
| | Race | Specify mean changes in Cmax and AUC |
| | Hepatic & Renal Impairment | Specify mean changes in Cmax and AUC |
| Extrinsic Factors | Drug interactions | Include listing of studied DDI studies with mean changes in Cmax and AUC |
| | Food Effects | Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat) |
| Expected High Clinical Exposure Scenario | Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose. | |
| Preclinical Cardiac Safety | Summarize *in vitro* and *in vivo* results per S7B guidance. | |
| Clinical Cardiac Safety | Describe total number of clinical trials and number of subjects at different drug exposure levels. 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). | |

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/s/

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JENNIFER J LEE
01/24/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Thursday, January 19, 2017 1:40 PM
**To:** 'Penny Ng'
**Subject:** NDA 209606 enasidenib -- FDA Information Request Response Due 1/20 10AM EST

Hello Penny,

We have an additional information request for NDA 209606 enasidenib from the review team. Please provide a response to this information request by **10:00 AM tomorrow, January 20, 2017,** and also follow up with a formal submission to the NDA file.

> Table 5 of the submission in Module 5.3.5.4 titled "AG221-C-001 – General Study and Investigator Related Information" specifies the location of specific pieces of clinical trial documentation. Please confirm whether the physical address for all portions of the eTMF (except drug accountability records), even those not specifically listed in the table, is at 86 Morris Avenue Summit, NJ 07901. If any portions of the clinical trial data or trial master file are physically located elsewhere, please provide the address.

Kindly confirm receipt of this correspondence.

Thank you,
Jennie

_____

**Jennifer J. Lee, PharmD**
Regulatory Project Manager
Division of Hematology Products | OHOP | CDER | FDA
10903 New Hampshire Ave
WO22, Room 3209
Silver Spring, MD 20993
Office: (240) 402-4622
Email: jennifer.lee1@fda.hhs.gov

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/s/

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JENNIFER J LEE
01/19/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Thursday, January 19, 2017 8:41 AM
**To:** 'Penny Ng'
**Cc:** Carioti, Theresa
**Subject:** NDA 209606 enasidenib -- FDA Information Request Response Due 1/24 3PM EST

Good morning Penny,

We have the following information request for NDA 209606 enasidenib from the review team. To expedite review, please provide a response to the following clinical site inspection information request via email by **3:00 PM EST on Tuesday, January 24, 2017** and also follow-up with a formal submission to the NDA file.

Kindly confirm receipt of this email and please do not hesitate to contact me should you have any questions.

**Information Request**

1. Submit the following study subject data listing information as grouped together as pdf files, sorted by the Phase of the study, for Site 201 (France), Stephane De Botton, M.D., in Study AG221-C-001.
   a. Study eligibility
   b. Subject assignment per treatment arm (enrolled, randomized as applicable)
   c. Subject discontinuations (If applicable per treatment group: subject number, screening visit date, randomization date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation)
   d. Concomitant medication list (i.e., non-study medications)
   e. Protocol deviation and violations
   f. Primary study efficacy endpoint data (e.g., calendar dates for time to relapse or progression, as applicable)
   g. All adverse events (If applicable, per treatment group: preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event (SAE [yes/no], death [yes/no])

2. Submit also similar above information for Site 111 (Texas), Hagop M. Kantarjian, M.D.

3. Submit also similar above information for Site 104 (MSKCC, New York), Eytan M. Stein, M.D.

4. Submit all versions of the informed consent form documents used for U.S. and French study sites as above.

Kind regards,
Jennie

_____

**Jennifer J. Lee, PharmD**
Regulatory Project Manager
Division of Hematology Products | OHOP | CDER | FDA
10903 New Hampshire Ave
WO22, Room 3209
Silver Spring, MD 20993
Office: (240) 402-4622
Email: jennifer.lee1@fda.hhs.gov

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JENNIFER J LEE
01/19/2017

## Lee, Jennifer (CDER)

**From:** Lee, Jennifer (CDER)
**Sent:** Tuesday, January 17, 2017 7:11 AM
**To:** 'Penny Ng'
**Subject:** RE: Enasidenib (AG-221) NDA 209606: ECG Warehouse Notification for Upload 20161212140528 - paper ECG data

Good morning Penny,

It will be fine for the paper ECGs to be scanned in as PDF files and submitted to the NDA. Also, in regards to your question regarding the number of Celgene guests to attend the AOM on February 10th, we will accommodate twelve, but no more due to size limitations of the conference room.

Kind regards,
Jennie

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**From:** Penny Ng [mailto:PNg@celgene.com]
**Sent:** Friday, January 13, 2017 12:38 PM
**To:** Lee, Jennifer (CDER)
**Subject:** RE: Enasidenib (AG-221) NDA 209606: ECG Warehouse Notification for Upload 20161212140528 - paper ECG data

Good afternoon Jennie,

Follow-up to the e-mail notification below regarding FDA access to ECG warehouse of ECG data from Study AG221-C-001, I would also like to notify you that some ECG data was only available in paper format and was not able to be uploaded to the ECG Warehouse.

The paper ECGs are available electronically as scanned pdfs. If agreed, the pdfs can be submitted to the NDA application (as an NDA Amendment) as part of the eCTD structure under the study folder.

Please kindly advise if you agree with this approach (or if you have other suggestions) and we will plan to submit the information by end-Jan to the NDA.

Thanks again.

Kind regards,
*Penny*

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**From:** Penny Ng
**Sent:** Thursday, January 05, 2017 12:43 PM
**To:** 'Lee, Jennifer (CDER)'
**Subject:** Enasidenib (AG-221) NDA 209606: ECG Warehouse Notification for Upload 20161212140528

Hello Jennie,

As shared in the NDA submission cover letter, we are submitting/uploading ECG data via the ECG Warehouse for FDA access in parallel with the NDA. Please see notification below indicating that: The study designated as "AG221-C-

001" that is part of FDA application "NDA 209606" has been imported into the ECG Warehouse. The study includes 5680 ECGs from 374 subjects. FDA has been granted access to this study for regulatory review.

Please do not hestiate to contact me if you have any questions.

Kind regards,
*Penny*

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**From:** support@ecgwarehouse.com [mailto:support@ecgwarehouse.com]
**Sent:** Wednesday, January 04, 2017 2:16 PM
**To:** (b) (4); Penny Ng; Natasha.Kormanik@fda.hhs.gov; CDERDCRPQT@fda.hhs.gov; support@ecgwarehouse.com
**Subject:** ECG Warehouse Notification for Upload 20161212140528

| ECG Warehouse Notification | | Upload ID: | 20161212140528 |
|---|---|---|---|
| Sponsor: | Celgene Corporation | Status: | FDA Access Granted |
| Study: | NDA 209606 / AG221-C-001 | Action: | None (Ready For Regulatory Review) |

Attention: (b) (4), Penny Ng, Natasha Kormanik, FDA Reviewers, and ECG Warehouse Administrators

The study designated as "AG221-C-001" that is part of FDA application "NDA 209606" has been imported into the ECG Warehouse. The study includes 5680 ECGs from 374 subjects. FDA has been granted access to this study for regulatory review.

If you have any questions, please reply to this message.

Regards,
The ECG Warehouse
www.ecgwarehouse.com

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JENNIFER J LEE
01/18/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209606

**PROPRIETARY NAME ACKNOWLEDGEMENT**

Celgene Corporation
9225 Indian Creek Parkway
Suite 900
Overland Park, KS 66210

ATTENTION: Penny Ng, M.Sc., MBA, RAC
Director, Regulatory Affairs

Dear Ms. Ng:

Please refer to your New Drug Application (NDA) dated and received December 30, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Enasidenib Tablets, 50 mg, 100 mg, (b) (4)

We acknowledge receipt of your correspondence, dated and received January 4, 2017, requesting a review of your proposed proprietary name, Idhifa.

If the application is filed, the user fee goal date will be April 4, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact me in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Jennifer Lee, Regulatory Project Manager, in the Office of New Drugs at (240) 402-4622.

Sincerely,

*{See appended electronic signature page}*

Neil Vora, PharmD, MBA
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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NEIL VORA
01/11/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209606

**NDA ACKNOWLEDGMENT**

Celgene Corporation
Attention: Penny Ng, MSc, MBA, RAC
Director, Regulatory Affairs
9225 Indian Creek Parkway, Suite 900
Overland Park, KS 66210

Dear Ms. Ng:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: IDHIFA™ (enasidenib)

Date of Application: December 30, 2016

Date of Receipt: December 30, 2016

Our Reference Number: NDA 209606

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 28, 2017, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please contact me at (240) 402-4622.

Sincerely,

*{See appended electronic signature page}*

Jennifer J. Lee, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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JENNIFER J LEE
01/06/2017

## Vora, Neil

**From:** Penny Ng <PNg@celgene.com>
**Sent:** Friday, December 30, 2016 11:00 AM
**To:** Vora, Neil
**Cc:** Kormanik, Natasha; Carioti, Theresa
**Subject:** Re: NDA 209606 Product Name: AG-221

**Follow Up Flag:** Follow up
**Flag Status:** Flagged

Dear Neil,
Thank you for the e-mail.

We are planning to submit the proposed proprietary name for review to the NDA as a amendment to the NDA on 04 Jan. I have also notified Theresa and Natasha on this planned submission.

I will send you a notification once the submission is made to/accepted by the gateway.

Have a wonderful New Year!

Kind regards,
Penny

-sent from my iPhone

On Dec 30, 2016, at 10:50 AM, Vora, Neil <Neil.Vora@fda.hhs.gov> wrote:

> Hi good morning Penny,
>
> Reference is made to your December 30, 2016 submission for NDA 209606. Upon review, Celgene will need to resubmit their proposed proprietary name for review under NDA 209606 under SDN 1. Please resubmit your proposed proprietary name under the newly filed NDA. Please see the Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf
>
> Please include the following information:
>
> - Cover Letter for proposed proprietary name reviews, include the statement "**REQUEST FOR PROPRIETARY NAME REVIEW**" in bold, capital letters on the first page of the submission
> - Submit all labels and labeling or refer to the date and eCTD sequence where the labels and labeling can be found.
>
> The PNR review clock will start on the date we receive your new submission.
>
> If you have any questions, please do not hesitate to reach out.
>
> Kind regards,

**Neil Vora, Pharm.D, MBA**
*Safety Regulatory Project Manager (SRPM)*

**Center for Drug Evaluation and Research (CDER)**
**Office of Surveillance and Epidemiology (OSE)**
**U.S. Food and Drug Administration**
Tel: 240-402-4845
Neil.Vora@fda.hhs.gov

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NEIL VORA
12/30/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 117631

**MEETING MINUTES**

Celgene Corporation
Attention: Penny Ng, MSc, RAC
Director, Regulatory Affairs
9225 Indian Creek Parkway, Suite 900
Overland Park, KS 66210

Dear Ms. Ng:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AG-221.

We also refer to the meeting between representatives of your firm and the FDA on July 26, 2016. The purpose of the meeting was to discuss the AG-221 drug development program, specifically to obtain 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.

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

If you have any questions, call Natasha Kormanik, Regulatory Project Manager at (240) 402-4227.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# MEMORANDUM OF MEETING MINUTES

| | |
|---|---|
| **Meeting Type:** | B |
| **Meeting Category:** | Pre-NDA |
| **Meeting Date and Time:** | July 26, 2016 from 10:00-11:00 AM (ET) |
| **Meeting Location:** | 10903 New Hampshire Avenue<br>White Oak Building 22, Conference Room: 1309<br>Silver Spring, Maryland 20903 |
| **Application Number:** | IND 117631 |
| **Product Name:** | AG-221 |
| **Indication:** | Advanced hematologic malignancies that harbor an isocitrate dehydrogenase-2 (IDH2) mutation |
| **Sponsor/Applicant Name:** | Celgene Corporation |
| **Meeting Chair:** | Ann T. Farrell, MD |
| **Meeting Recorder:** | Natasha Kormanik, MSN, RN, OCN® |

## FDA ATTENDEES

Office of Hematology Oncology Products (OHOP)/ Division of Hematology Products
Ann Farrell, MD – Director
Edvardas Kaminskas, MD – Deputy Director
R. Angelo de Claro, MD – Clinical Team Lead
Ashley Ward, MD – Clinical Reviewer
Bindu Kanapuru, MD – Clinical Reviewer
Theresa Carioti, MPH – Chief, Project Management Staff
Natasha Kormanik, MSN, RN, OCN® – Regulatory Health Project Manager

OHOP/ Division of Hematology Oncology Toxicology
Christopher Sheth, PhD – Team Lead
Ramadevi Gudi, PhD – Reviewer

Office of Pharmaceutical Quality/ Office of New Drug Products
Sherita D. McLamore-Hines, PhD – Reviewer

Office of Clinical Pharmacology
Stacy Shord, PharmD – Team Lead
George Shen, PhD – Reviewer

Office of Biostatistics/ Division of Biometrics V
Yuan-Li Shen, DrPH – Team Lead
Qing Xu, PhD – Reviewer

Center for Devices and Radiological Health/ Office of In Vitro Diagnostics
You Li, PhD – Reviewer

**SPONSOR ATTENDEES**

Celgene Corporation
Jay Backstrom, MD, MPH - Chief Medical Officer/Global Head of Regulatory Affairs
Ira Gupta, MD - Executive Medical Director, Clinical R&D
Robert Knight, MD - Corporate VP, Hematology/Oncology Clinical R&D
Paul McInulty - Executive Director, Regulatory Strategy Disease Leader
Penny Ng, MSc, MBA, RAC - Director, Regulatory Affairs
Anjan Thakurta, MSc, MTech, PhD - Executive Director, Translational Development
Krishnan Viswanadhan, PharmD, MBA - Executive Director, Global Project Leadership
Qiang (Casey) Xu, PhD - Principal Statistician, Biostatistics
Simon Zhou, PhD - Executive Director, Clinical Pharmacokinetics

Agios
Sam Agresta, MD, MPH & TM, MS CI & TR - Vice President, Clinical Development
Chris Bowden, MD - Chief Medical Officer

## 1.0 BACKGROUND

AG-221 is being developed jointly by Celgene Corporation and Agios Pharmaceuticals. The Sponsor states that AG-221 is a selective, oral, potent inhibitor of the IDH2 mutant protein, making it a highly targeted therapeutic candidate for the treatment of patients with IDH2 mutated AML.

On June 12, 2014, orphan-drug designation was granted for "treatment of AML that harbor IDH2 mutation."

On July 31, 2014, Fast Track Designation was granted for AG-221 for the treatment of patients with AML that harbor IDH2 mutation.

On May 26, 2016, the Sponsor requesting a type B Pre-NDA Meeting is 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 or full approval.

FDA sent Preliminary Comments to Celgene Corporation on July 24, 2016.

## 2.0 DISCUSSION

**Question 1:** Does the Agency agree that the AG-221 nonclinical toxicology program supports the registration of AG-221 for the treatment of patients with an IDH2 mutation positive relapsed or refractory AML (R/R AML)?

***FDA Response to Question 1:*** *Based on the information provided in the meeting package, the proposed nonclinical program appears reasonable to support the registration of AG-221 for the proposed indication. The adequacy of the nonclinical studies will be a review issue.*

**Discussion: No discussion.**

**Question 2:** Does the Agency agree that the R/R AML population enrolled into the dose escalation and Part 1 expansion portions of AG221-C-001 represent a population who have no established alternative efficacious therapies available?

***FDA Response to Question 2:*** *The FDA agrees that subjects with relapsed or refractory AML who relapse after allogeneic transplantation, are in second or later relapse, are refractory to initial induction or re-induction treatment, who relapse within 1 year of initial treatment, and/or have failed two or more cycles of first line therapy (consisting of an intermediate intensity chemotherapy, hypomethylating agent, or low dose cytarabine) represent a population with unmet medical need. Whether or not the subjects enrolled in dose escalation and part I expansion portion of AG221-C-001 fall into one or more of those categories would be a review issue.*

**Discussion: No discussion.**

**Question 3:** Does the Agency agree that the durable investigator assessed response rates and the Sponsor Derived CR + CRh rate are clinically meaningful in this R/R AML population with no alternative effective therapies available?

***FDA Response to Question 3:*** *The FDA agrees that the rate of complete response, in combination with duration of response, is a reasonable predictor of survival in AML. Whether other responses (CRi, CRp, CRh, PR, etc) also predict a survival benefit has not been established, and may depend on other factors (e.g. MRD status). However, the FDA agrees that durable CRh, particularly if it is associated with decreased transfusion dependency, and a deepening of response over time, would represent a clinically meaningful outcome in a R/R AML population with no alternative effective therapies available.*

*We strongly encourage you to provide all available data regarding minimal residual disease (MRD) in subjects enrolled on AG221-C-001.*

**Discussion: No discussion.**

**Question 4:** To define the clinical benefit of Partial Response (PR), Celgene intends to provide Overall Survival data and Grade 3/4 Infection, Grade 3/4 Bleeding, Febrile

Neutropenia, and transfusion data during the period of response from Study AG221-C-001 Phase 1.
Does the Agency agree that these data from AG221-C-001 Phase 1 could be used to support clinical benefit of PR achieved by AG-221 treatment?

***FDA Response to Question 4:*** *Partial response is not an established surrogate of survival in AML, and time-to-event variables such as overall survival cannot be interpreted in single arm studies. Establishment of a new surrogate endpoint reasonably likely to predict survival in AML would require using independent data (i.e., data external to AG221-C-001).*

*Decreased rates of infection, bleeding, and transfusions could potentially be used to support a claim of palliative benefit of AG-221. However, whether your data would support such label claims, particularly given the absence of randomized data, would be a review issue.*

*We suggest that you do a comprehensive literature search and provide a summary of published data in patient populations comparable to the population on AG221-C-001 with respect to duration of response, overall survival, rates of febrile neutropenia, rates of Grade 3/4 infections (broken down by subtype where possible: sepsis, pneumonia, etc), rates of Grade 3/4 bleeding, and transition to transfusion independence. Your analysis should break down these outcomes by best response (i.e. CR, CRh, CRi, CRp, PR) and include a side-by-side table comparing the results of your study with that of other studies in the literature with respect to these outcomes. You should provide your literature ascertainment plan and include all relevant publications in your analysis, including those whose results would not support your claims.*

*We also suggest that you provide any data (clinical or nonclinical) that you have that may help to determine whether the neutrophils arising from differentiation induced by AG-221 are functional.*

**Discussion:** **No discussion.**

**Question 5:** Does the Agency agree that a durable response rate combining CR + CRh + PR are clinically meaningful in this R/R AML population?

***FDA Response to Question 5:*** *No. See responses to questions 3 and 4.*

**Discussion:** **No discussion.**

**Question 6:** Does the Agency agree that the efficacy data for AG-221 obtained from the Dose Escalation and Expansion 1 cohorts of AG221-C-001 in 173 patients with R/R AML, and safety data from approximately 450 subjects (including approximately 230 R/R AML) support the submission of a marketing application for accelerated approval under 21 CFR 314 Subpart H or full approval?

***FDA Response to Question 6:*** *The FDA is encouraged by the data that have been presented in the pre-meeting package, but the adequacy of the data to support the submission of a*

*marketing application would be determined in the filing review. Trials in the r/r AML setting that are not randomized and that have a primary endpoint considered reasonably likely to predict clinical benefit (i.e., an endpoint other than survival) would typically be used to support accelerated approval under 21 CFR 314 Subpart H.*

*Please note that if your initial NDA submission is delayed, your proposed clinical data cut point of 15 April 2016 may not be appropriate. We encourage you to include as much data as possible in your initial submission.*

**Discussion: The Agency encourages the Sponsor to present data regarding transfusions in multiple ways, describing changes in transfusion dependence over time in the overall study population, by best response, and by interim response (e.g. transfusion dependence during period of PR, CRh, or CR). The Agency would like to see as much supportive data as possible in patients who do not achieve CR that demonstrates evidence of some benefit.**

**Question 7:** AG-221-AML-004 is a randomized, multicenter, open-label study comparing the efficacy and safety of AG-221 vs. conventional care regimens in patients with late stage acute myeloid leukemia with an IDH2 mutation with the primary endpoint of overall survival. Should a confirmatory study be required, does the Agency agree that the AG-221-AML-004 study is an acceptable confirmatory study to support full approval?

***FDA Response to Question 7:*** *Whether or not AG-221-AML-004 could be used to support traditional approval of AG-221 would be a review issue. The FDA reiterates its concern about excluding patients <60 years of age and with only one prior line of therapy from this study, as well as its concerns about adequate dose justification in patients with R172K mutations.*

*In your NDA, please include an enrollment update for study AG-221-AML-004, as well as an assessment of the impact that an accelerated approval of AG-221 in the United States would have on your ability to complete this study.*

*Please also be advised that two adequate and well-controlled studies are typically required for traditional approval. FDA would accept a single pivotal study to support traditional approval if the results show a highly statistically significant effect on survival that is internally consistent across relevant subgroups. The results of the single pivotal trial must be sufficiently robust and so compelling that it would be unethical to repeat the study.*

**Discussion: No discussion.**

**Question 8:** Efficacy data for the proposed NDA will be based on a single Celgene-sponsored study in the proposed indication, Study AG221-C-001, as outlined in Question 2. In lieu of an Integrated Summary of Efficacy (ISE) in Module 5, Celgene proposes to provide only a Clinical Summary of Efficacy in Module 2.7.3, which will include all relevant efficacy results. Is this acceptable to the Agency?

***FDA Response to Question 8:*** *We agree with your plan to submit an SCE with all required elements of the ISE in lieu of an ISE as long as the document does not exceed the page limitation. The adequacy of the content of the SCE will be assessed during the filing review of the NDA submission.*

**Discussion: No discussion.**

**Question 9:** Does the Agency agree with Celgene's plan to provide individual patient safety narratives?

***FDA Response to Question 9:*** *No. In addition to the listed categories, please also submit individual patient narratives for:*

- *all deaths that occurred on study, regardless of when the death occurred respective to the last dose of AG-221*
- *all discontinuations of study treatment for any reason other than progressive disease (i.e. include narratives for patients who withdrew for reasons of physician decision, patient decision, etc)*
- *all serious adverse events that occurred prior to documented progression and/or initiation of next/line therapy, whichever occurred first*

**Discussion: No discussion.**

**Question 10:** Based on the Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document and the fact that the safety information in this submission is based on a number of small studies, as listed below:

- one study in the proposed indication (Study AG221-C-001) with safety of Phase 1 and Phase 2 included within separate interim CSRs;
- three completed single-dose healthy volunteer studies;
- Four ongoing studies (with data-cut of 01 Jul 2016) – Serious Adverse Events only to be provided.

In lieu of an Integrated Summary of Safety (ISS) in Module 5, Celgene proposes to provide only a Clinical Summary of Safety in Module 2.7.4, which will include all relevant safety results. Is this acceptable to the Agency?

***FDA Response to Question 10:*** *We agree with your plan to submit an SCS with all required elements of the ISS in lieu of an ISS as long as the document does not exceed the page limitation. The adequacy of the content of the SCS will be assessed during the filing review of the NDA submission.*

*For all ongoing studies, please include in your submission a detailed analysis of all deaths and adverse events that occurred prior to the data cut point (not just Serious Adverse Events as you proposed).*

**Discussion: No discussion.**

**Question 11:** Per 21 CFR 314.50, Celgene intends to submit a 4 month safety update (or a 3 month safety update if priority review is granted) during the review of the NDA as outline below. Does the Agency agree with the proposed information to be included in the safety update?

***FDA Response to Question 11:*** *Yes. However, please be advised that the safety update should include an update on deaths and all adverse events from all ongoing studies, not just SAEs.*

**Discussion:** **No discussion.**

**Question 12:** Based on the safety profile observed in AG221-C-001, does the Agency agree with the proposal to not submit a Medication Guide or a REMS for the use of AG-221 in the proposed indication of relapsed/refractory AML?

***FDA Response to Question 12:*** *The FDA has preliminary concerns that the risk of differentiation syndrome and appropriate management guidelines may need to be communicated effectively to physicians in some manner. However, at this time, there is insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.*

**Discussion:** **No discussion.**

**Question 13:** Does the Agency agree that the current clinical PK studies are adequate to support the initial NDA submission, and the proposed clinical pharmacology studies are adequate after NDA approval?

***FDA Response to Question 13:*** *No. Our expectation is that all of the appropriate clinical pharmacology studies should be conducted before filing your NDA. We recommend you address the following:*

1) *Based on in vitro assessment, AG221 and its major metabolite AGI-16903 have drug-drug interaction (DDI) risk at clinical exposure as an inhibitor on concomitant medications that are sensitive substrates of multiple CYPs (CYP1A2, 2C8, 2C9, 2C19 and 2D6), UGT1A1 or human transporters P-gp, BCRP and OATP1B1; therefore, corresponding clinical DDI studies should be conducted to assess the risk and provide dose adjustment recommendation in the label. Refer to the Drug Interaction Studies Guidance for more information regarding DDI study design.*
2) *AG221 has pH-dependent solubility; therefore, clinical studies to assess pH-dependent PK interaction with gastric acid reducing agents (antacids, H2 blockers, or proton pump inhibitors) should be conducted.*
3) *Positive food effect was observed with early formulation of AG221. Please conduct a food effect trial using the final marketing formulation per Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies.*

4) *Please explain the apparent 5-fold exposure difference between healthy subjects and AML patients.*

5) *Since AG-221 has 5-fold faster clearance in healthy subjects than patients with AML, the systemic exposure of AG-221 at a given dose will be much lower (5-fold lower) than in patients. Therefore, DDI study findings that used 100 mg AG-221 in healthy subjects may not predict clinical DDI in patients with AML treated with 100 mg of AG-221. To be meaningful, DDI studies may need to be conducted in patients with AML.*

*The Agency will respond to the request for waiver of thorough QTc study separately in a post-meeting correspondence.*

**Discussion: The Agency recommends that you develop a detailed population pharmacokinetic analysis plan to evaluate the potential for drug-drug interactions with cytochrome P450 modulators and acid-reducing agents and include the plan in the NDA submission. The adequacy of the population analysis will be reviewed as part of the NDA submission.**

**Question 14:** Does the Agency agree that the rationale provide below supports the inclusion of the intended commercial formulation in the NDA, without conducting an in vivo bioequivalence study?

***FDA Response to Question 14:*** *Based on available information, it is unclear whether in vivo BE study can be waived.*

1) *Using available data, conduct comparative exposure (AUC and Cmax) analysis to assess the effect of formulation on the PK of AG-221.*
2) *If there is meaningful PK difference between formulations, you will need to assess the impact of altered exposure on safety and efficacy of your drug.*

**Discussion: The Agency recommends that you provide comparative analysis of the exposure and safety data at the proposed dose of 100 mg and that you include the formulation as a covariate in the population pharmacokinetic analysis in the NDA submission. For the cross-study comparative analysis, provide the geometric mean ratio and 90% confidence interval.**

**Question 15:** Per the guidance on the FDA website, "Providing Regulatory Submissions In Electronic Format – Standardized Study Data", datasets for studies initiated prior to December 17, 2016 are not required to be presented in standard format. As the studies supporting the initial NDA were all initiated prior to December 17, 2016, raw clinical datasets and derived analysis datasets will be provided in the structure used for the analysis of each individual study, not in standard SDTM/ADaM format. Does the Agency agree with this approach?

***FDA Response to Question 15:*** *While the raw clinical datasets and derived analysis datasets may provide legitimate structure for the analysis of each individual study, we*

*encourage you to submit data in SDTM/ADaM format, since the use of this common model will support more efficient data-sharing among the sponsor and the Agency.*

*Comments regarding datasets and SAS programs:*

a. *Datasets should have one and only one unique ID for each patient among all trials. One record should contain all data for one patient.*
b. *Variables used in the define datasets should be the same for all datasets so that sets can be combined or sorted as needed for cross study evaluations (i.e., one definition, well-annotated, per one variable).*
c. *Please provide a simple and all-containing "Statistical Efficacy Analysis Data Set" for statistical reviewers, in SAS transport. There should be a reviewer-friendly dataset without the necessity to merge datasets: on demographics, baseline status, and other prognostic variables, and efficacy on which the statistical analyses were performed, along with patient and site/investigator identifications. We prefer one row of data for each patient, time, and treatment combination.*
d. *There should be an instruction for the reviewer for the use of variables and flags to identify the set of patients on which the primary analysis was performed. Please provide flags to identify different analysis population*
e. *The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the NDA submission. All programs should be thoroughly commented and have passed Sponsor's validation procedures.*
    - *Ensure the SAS dataset file name are consistent with those in the SAS programs that call them, so that the Agency can run the programs smoothly to verify the results/figures/tables reported in the submission.*
    - *Annotations for all efficacy and safety tables and figures should be included in the main text portion of the CSR. The annotations should indicate which analysis dataset variables were used to produce the table or figure.*

**Discussion:** **No discussion.**

**Question 16:** As outlined in Question 6 above, clinical efficacy and safety data supporting the initial NDA will be based on Study AG221-C-001 Phase 1( Dose Escalation Phase and Part 1 Expansion) CSR and preliminary data from Phase 2 (Part 2 Expansion) CSR. Based on a data from a data-cut of 15 April 2016 , an NDA is being planned for submission in December 2016.
As Fast-Track Designation has been granted for AG-221 in the proposed indication, Celgene proposes to submit the NDA in a rolling basis. Does the Agency agree with the plan of rolling submission for the initial NDA? And also please comment if the Agency would consider rolling review of the NDA.

***FDA Response to Question 16:*** *Please submit a formal request for rolling submission.*

*The planned review timeline will be communicated to you early in the review.*

*See also the Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics:* **http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm358301.pdf**

**Discussion: No discussion.**

**Question 17:** Relapsed or refractory AML is a serious condition in need of safe and effective therapies. Based on the efficacy and safety data presented, would the Agency comment if the AG-221 NDA for R/R AML would qualify for priority review designation at the time of the submission of the NDA?

***FDA Response to Question 17:*** *Priority review designation, if appropriate, will be determined at the time of filing review.*

**Discussion: No discussion.**

**Question 18:** The Sponsor will submit the NDA in electronic format using the electronic common technical document (eCTD) specifications as described in the FDA Guidance for Industry "*Providing Regulatory Submissions in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*" (June 2008, electronic submissions, Revision 2). In this eCTD submission, the individual document format will follow the CTD guideline. Is this acceptable to the Agency?

***FDA Response to Question 18:*** *Yes.*

**Discussion: No discussion.**

**Question 19:** Does the Agency agree with the proposed PMA plan for the CDx, including the timeline and the proposed bridging plan?

***FDA Response to Question 19:*** *The proposed timeline of contemporaneous filing of a PMA with the NDA accelerated approval is acceptable.*

*You did not provide any statistical analysis plans for the bridging study and therefore we are unable to determine if the plan is acceptable. Please provide the information requested in the feedback provided for the pre-submission so that we may make this determination.*

**Discussion: No discussion.**

## Additional Clinical Pharmacology Comments

In addition to the comments regarding your clinical pharmacology studies to support the initial NDA submission, we remind you to include the following in your NDA application:

1. Address the following clinical pharmacology questions in Summary of Clinical Pharmacology (Module 2.7.2):
    a. What are the exposure-response relationships (dose-response, exposure-response) for efficacy and for safety?
    b. What influence do intrinsic and extrinsic factors have on exposure, efficacy, or safety?
    c. What dose and administration modifications are recommended for these factors?
2. Provide complete datasets for the pharmacokinetic data. A subjects' unique ID number in the pharmacokinetic dataset should be consistent to those presented in the clinical safety and efficacy datasets.
3. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
4. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range, as appropriate in the study reports.
5. Identify individual subjects with dose reduction, interruption or discontinuation; the time to the first dose reduction, interruption or discontinuation; the reasons for dose reduction, interruption or discontinuation within the exposure-response datasets. Provide the relevant descriptive statistics for each of these variables.
6. Submit the following information and data to support the population pharmacokinetic analysis:
    - SAS transport files (*.xpt) for all datasets used for model development and validation.
    - A description of each data item provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
    - Model codes or control streams and output listings for all major model building steps, (e.g., base structural model, covariates models, final model, and validation model). Submit these files as ASCII text files with *.txt extension.
    - A model development decision tree or table which gives an overview of modeling steps.

    Submit the following for the population analysis report:
    - Standard model diagnostic plots.
    - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.
    - Model parameter names and units in tables. For example, oral clearance should be presented as CL/F (L/h), not as THETA(1).
    - A summary of the report describing the clinical application of modeling results.
7. Provide a table listing of patients with renal or hepatic impairment who have received AG-221, organized by trial number. Include available renal and hepatic function

parameters such as SCr, CLCr calculated by the Cockcroft Gault equation (or eGFR calculated by MDRD), AST/ALT, T. Bili, platelet count, etc. for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.

**Discussion: No discussion.**

**Post Meeting Addendum**

We reviewed your protocols submitted under the IND and cannot find a statistical analysis plan for AG-221-C-001 which tests a hypothesis and allows the study report to conclude that the data reflect AG-221 is better than available therapy. Please address this.

For the patients whom you have enrolled in your trials do you have information on the coexistent mutations? This is not for a regulatory decision but to understand the utility of AG-221 better.

## 3.0 OTHER IMPORTANT INFORMATION

**DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed.
  - Late CMC stability data submission to be discussed at the CMC focused pre-NDA meeting.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that
  - The Sponsor believes that no REMS is needed. DHP is in agreement.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

**PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.
Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of

your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

## PRESCRIBING INFORMATION

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

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

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

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

## Office of Scientific Investigations (OSI) Requests

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

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

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

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

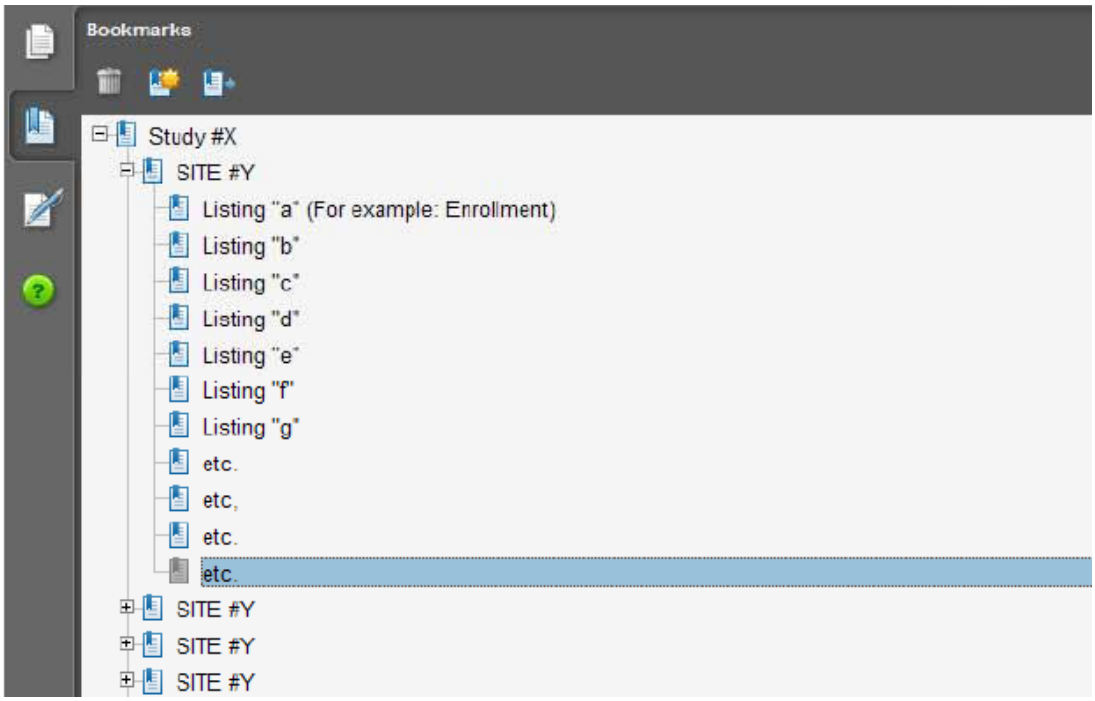
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

## II. Request for Subject Level Data Listings by Site

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

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:




## III. Request for Site Level Dataset:

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

**Attachment 1**

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

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

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

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


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

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

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

## 4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues identified.

## 5.0 ACTION ITEMS

None

## 6.0 ATTACHMENTS AND HANDOUTS

Sponsor's PowerPoint presentation.

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/s/

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ANN T FARRELL
08/08/2016

# LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209606

**LATE-CYCLE MEETING MINUTES**

Celgene Corporation
Attention: Penny Ng, MSc, MBA, RAC
Director, Regulatory Affairs
9225 Indian Creek Parkway, Suite 900
Overland Park, KS 66210

Dear Ms. Ng:

Please refer to your New Drug Application (NDA) dated December 30, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Idhifa® (enasidenib) tablets, 50 and 100mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 16, 2017.

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

If you have any questions, please contact Jennifer Lee, Regulatory Project Manager at (240) 402-4622.

Sincerely,

*{See appended electronic signature page}*

Donna Przepiorka, MD, PhD
Cross-Discipline Team Lead
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# MEMORANDUM OF LATE-CYCLE MEETING MINUTES

**Meeting Date and Time:** June 16, 2017; 11:00 AM – 12:00 PM (ET)
**Meeting Location:** 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

**Application Number:** NDA 209606
**Product Name:** Idhifa® (enasidenib)
**Applicant Name:** Celgene Corporation

**Meeting Chair:** Donna Przepiorka, MD, PhD
**Meeting Recorder:** Jennifer Lee, PharmD

## FDA ATTENDEES

*Office of Hematology and Oncology Products/Division of Hematology Products*
Ann Farrell, MD – Director
Al Deisseroth, MD, PhD – Supervisory Associate Division Director
Donna Przepiorka, MD, PhD – Cross-Discipline Team Leader
Ashley Ward, MD – Clinical Reviewer
Theresa Carioti, MPH – Chief Project Management Staff
Jennifer Lee, PharmD – Regulatory Project Manager
Rosa Lee-Alonzo, PharmD – Regulatory Project Manger
Ashley Lucci Vaughn, MS – Regulatory Project Manager

*Office of Hematology and Oncology Products/Division of Hematology Oncology Toxicology*
Chris Sheth, PhD – Supervisory Pharmacologist
Rama Gudi, PhD – Pharmacologist

*Office of Biostatistics/Division of Biometrics V*
Yuan Li Shen, DrPh – Biometrics Team Leader
Qing Xu, PhD – Biometrics Reviewer

*Office of Clinical Pharmacology*
Stacy Shord, PharmD, BCOP, FCCP –Team Leader
Rosane Charlab Orbach, PhD – Pharmacogenomics Team Leader
Sarah Dorff, PhD – Clinical Pharmacology & Pharmacogenomics Reviewer

*Office of Product Quality/Office of New Drug Products/Division of New Drug Products 1*
Sherita Mclamore-Hines, PhD – Regulatory Review Chemist

*Office of Product Quality/Office of New Drug Products/Division of Biopharmaceutics*
Banu Zolnik, PhD – Product Quality Reviewer

*Office of In Vitro Diagnostics and Radiological Health/Division of Molecular Genetics and Pathology*
Aaron Schetter, PhD, MPH – Scientific Reviewer

*Office of Medication Error Prevention and Risk Mangement/Division of Risk Management*
Till Olickal, PhD, PharmD – Risk Management Analyst

*Office of Pharmacovigilance and Epidemiology/Division of Epidemiology I*
Carolyn McCloskey, MD, MPH – Medical Officer Epidemiologist

*Office of Pharmacovigilance and Epidemiology/Division of Pharmacovigilance II*
Regina Lee, PharmD – Safety Evaluator

*Office of Medical Policy Initiatives/Division of Medical Policy Programs*
Susan Redwood, MPH, BSN, RN – Patient Labeling Reviewer

**APPLICANT ATTENDEES**

*Celgene Attendees*
Jay Backstrom, MD, MPH – Chief Medical Officer/Global Head of Regulatory Affairs
Rick Couch – Vice President, Regulatory Affairs, CMC
Ira Gupta, MD – Executive Medical Director, Clinical R&D
Irina Kline, MD – Senior Director, Lead Product Safety Physician
Yan Li, PhD – Senior Principal Scientist, Clinical Pharmacokinetics
Paul McInulty – Vice President, Global Regulatory Affairs
Penny Ng, MSc, MBA, RAC – Director, Regulatory Affairs
Anjan Thakurta, MSc MTech PhD – Executive Director, Translational Development
Steve Songer, PharmD – Director, Clinical R&D
Krishnan Viswanadhan, PharmD, MBA – Executive Director, Global Project Leadership
Qiang (Casey) Xu, PhD – Associate Director, Biostatistics

*Agios Attendees*
Sam Agresta, MD, MPH & TM, MS CI & TR – Vice President, Clinical Development
Jamie Cohen – Regulatory Affairs

## 1.0 BACKGROUND

NDA 209606 was submitted on December 30, 2016 for Idhifa® (enasidenib).

Proposed indication: *Treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation*

PDUFA goal date: *August 30, 2017*

FDA issued a Background Package in preparation for this meeting on June 14, 2017.

## 2.0 DISCUSSION

1. *Introductory Comments*

   This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL), and therefore, this meeting did not address the final regulatory decision for the application.

2. *Discussion of Substantive Review Issues*

   *Clinical*

   a. The Applicant's method of identifying patients with differentiation syndrome may underestimate the frequency of the adverse event in patients treated with enasidenib. 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 proposed product label are still not clear. Diagnostic criteria need to be clarified, and the effectiveness of the proposed management guidelines must be confirmed. A PMR to this effect will be required.

   b. Follow-up time on Study AG221-C-001 is limited, and thus limited information has been generated with respect to the long-term safety of enasidenib in the proposed indication. A PMR to characterize the long-term safety of enasidenib will be required.

   c. Insufficient information is available to verify the responses of some patients with investigator-assessed CR. As some of patients with investigator-assessed CR do not actually meet the protocol-specified criteria based on laboratory and other data provided in the submission, only responses verifiable by the FDA will be included in the product label.

   *Clinical Pharmacology*

   d. Safety in patients with organ impairment and the potential for interaction with drugs used commonly in this population are concerns for the postmarketing period.

***Discussion:*** *Celgene required no additional discussion regarding 2a, 2b and 2d. In reference to 2c, Celgene indicated that they have additional documentation that would support the investigator's finding of CR in additional patients in Cohort 2. FDA agreed to*

*review this new information if provided in a timely fashion and re-iterated that only responses verified by FDA would be included in the label. Celgene agreed to provide final pathology report data to the Agency on June 16, 2017.*

3. *Discussion of Minor Review Issues*

*Biometrics*

a. The investigator assessed CR rate and the sponsor assessed CR rate are different. In the pooled analysis, the investigator assessed that the response rate was 19.3% with a 95% CI of (14.2, 25.4); the sponsor assessed CR rate was 14.5% with a 95% CI of (10.0, 20.0).

b. Even though the demographic and baseline disease characteristics of the trial populations between the Phase I and Phase II studies are consistent, the sponsor assessed CR rate was different across the two trials. In the Phase I study, the sponsor assessed CR rate was 16.5% with a 95% CI of (9.9, 25.1); while in Phase II study, the sponsor assessed CR rate was 12.5% with a 95% CI of (6.8, 20.4).

c. There were more deaths in the Phase I population (63.1% compared to those from the Phase II population 54.8%). The median overall survival (OS) time in the Phase 2 population of 6.6 months was shorter in comparison than the Phase I population of 9.1 months.

d. Due to the variation of response rates across the two trials, the interpretation of the pooled analysis should be taken with caution.

***Discussion:*** *No discussion occurred for 3a-3c. Celgene acknowledged the caution provided in 3d and indicated that with an update on CRs using the new pathology reports, there may be less difference in response rates between the two cohorts.*

4. *Additional Applicant Data*

***Discussion:*** *Celgene does not plan on submitting any additional new data at this time other than the pathology reports as discussed for Agenda Item #2c.*

5. *Information Requests*

*Clinical/Biometrics*

a. A revised ADPVPD.xpt data file with a data cutoff date of October 14, 2016, which was requested June 5, 2017.

*Clinical Pharmacology*

b. A summary of the review of the found.xpt file conversion (if any discrepancies are noted) as outlined in Celgene's response submitted to the Agency on June 8, 2017.

c. A response to the information request sent by the Agency on June 12, 2017: Based on the dataset CDXMAY17.xpt, the IDH2 genotyping results of 3 patients (subject IDs 101-007, 111-029, 112-004) varied across the biospecimens tested with the proposed companion diagnostic assay. Please clarify the rules for how these 3 patients were assigned to one of the two IDH2 mutation groups (i.e., R140 or R172) in the efficacy dataset.

***Discussion:*** *FDA acknowledged recent receipt of the responses to the Information Requests listed in 5a and 5c. Celgene intends to provide a response to 5b on June 16, 2017.*

6. *Postmarketing Requirements/Postmarketing Commitments*

i. **PMR-1:** Conduct a study to characterize enasidenib-related differentiation syndrome, specifically incidence, appropriate diagnostic criteria, and effective treatment based on data and pooled analysis from trials in patients with acute myeloid leukemia: AG-221-C-001, AG-120-221-C-001, AG-221-AML-004, and AG-221-AML-005.

ii. **PMR-2:** Characterize the long-term safety of enasidenib in patients with relapsed or refractory acute myeloid leukemia (AML). Submit the final study report and data (b) (4) with 3 years of follow-up from Study AG-221-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 (b) (4) patients with relapsed or refractory AML.

iii. **PMR-3:** 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 data (b) (4) with 3 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.

iv. **PMR-4:** Conduct clinical pharmacokinetic trials 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*."

v. **PMR-5:** 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*."

vi. **PMC-1:** Develop and report a control strategy for the drug product to minimize the risk of (b) (4) .

***Discussion:*** *Celgene acknowledged receipt of the FDA comments on the proposed revisions to the PMRs and PMC, and they required no additional clarifications. Celgene intends to provide their responses to the FDA comments by the requested date, Wednesday, June 21, 2017.*

7. *Major Labeling Issues*

***Discussion:*** *Celgene proposed to use only the pooled response analysis in the USPI. FDA indicated that the proposal should be included in Celgene's response to the FDA comments on the USPI as this would need to be reviewed carefully.*

*Celgene also requested clarification on whether enasidenib could be considered for regular approval based on achievement of transfusion independence. FDA suggested that Celgene* (b) (4) *provide their rationale for regular approval. Celgene will include their proposed revisions with the next round of USPI revisions.*

(b) (4)

8. *Review Plans*

The Agency plans to complete the review within the PDUFA timeline.

***Discussion:*** *Celgene plans to bring enasidenib to market the day after approval and intends to submit a Pre-Launch Activities Importation Request (PLAIR) within 60 days prior to the PDUFA goal date. FDA indicated that with the new pathology report data, it was not clear that an earlier action date would be possible and recommended that Celgene request an update on the agreed-upon labeling at a later date pending the approval decision. FDA also confirmed the intent to approve enasidenib and the companion diagnostic on the same date.*

*9. Wrap-up and Action Items*

***Discussion:*** *Celgene intends to provide final pathology reports on June 16, 2017 and the next set of USPI revisions and PMR/PMC comments by Wednesday, June 21, 2017.*

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/s/

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DONNA PRZEPIORKA
06/20/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209606

**LATE CYCLE MEETING**
**BACKGROUND PACKAGE**

Celgene Corporation
Attention: Penny Ng, MSc, MBA, RAC
Director, Regulatory Affairs
9225 Indian Creek Parkway, Suite 900
Overland Park, KS 66210

Dear Ms. Ng:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IDHIFA® (enasidenib) tablets, 50 and 100mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for June 16, 2017. Attached is our background package, including our agenda, for this meeting.

Please email a final list of your attendees at jennifer.lee1@fda.hhs.gov by June 15, 2017.

If you have any questions, call Jennifer Lee, Regulatory Project Manager, at (240) 402-4622.

Sincerely,

*{See appended electronic signature page}*

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

| | |
|---|---|
| **Meeting Date and Time:** | June 16, 2017, 11:00 AM – 12:00 PM (ET) |
| **Meeting Location:** | 10903 New Hampshire Avenue<br>White Oak Building 22, Conference Room: 1315<br>Silver Spring, Maryland 20903 |
| **Application Number:** | NDA 209606 |
| **Product Name:** | IDHIFA® (enasidenib) |
| **Indication:** | Treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an IDH2 mutation |
| **Applicant Name:** | Celgene Corporation |

**FDA ATTENDEES (tentative)**

*Office of Hematology and Oncology Products/Division of Hematology Products*
Ann Farrell, MD - Director
Ed Kaminskas, MD - Deputy Director
Al Deisseroth, MD, PhD - Supervisory Associate Division Director
Donna Przepiorka, MD, PhD - Cross-Discipline Team Lead
Ashley Ward, MD - Clinical Reviewer
Theresa Carioti, MPH - Chief Project Management Staff
Jennifer Lee, PharmD - Regulatory Project Manager

*Office of Hematology and Oncology Products/Division of Hematology Oncology Toxicology*
Chris Sheth, PhD - Supervisory Pharmacologist
Rama Gudi, PhD – Pharmacologist

*Office of Biostatistics/Division of Biometrics V*
Yuan Li Shen, DrPh - Biometrics Team Leader
Qing Xu, PhD - Biometrics Reviewer

*Office of Clinical Pharmacology/Division of Clinical Pharmacology V*
Stacy Shord, PharmD - Clinical Pharmacology Team Leader
Walt Cao, PhD, Pharmacometrics Reviewer

*Office of Clinical Pharmacology/Division of Pharmacometrics*
Nitin Mehrotra - Pharmacometrics Team Leader

*Office of Clinical Pharmacology/Genomics and Targeted Therapy Group*
Rosane Charlab Orbach, PhD, Team Leader
Sarah Dorff, PhD - Clinical Pharmacology and Pharmacogenomics Reviewer

*Office of Product Quality/Office of New Drug Products/Division of New Drug Products 1*
Sherita Mclamore-Hines, PhD - Regulatory Review Chemist

## INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

## BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

### 1. Discipline Review Letters

No Discipline Review letters have been issued to date.

### 2. Substantive Review Issues

The following substantive review issues have been identified to date:

*Clinical*

a. The Applicant's method of identifying patients with differentiation syndrome may underestimate the frequency of the adverse event in patients treated with enasidenib. 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 proposed product label are still not clear. Diagnostic criteria need to be clarified, and the effectiveness of the proposed management guidelines must be confirmed.

b. Follow-up time on Study AG221-C-001 is limited, and thus limited information has been generated with respect to the long-term safety of enasidenib in the proposed intended population.

c. Insufficient information is available to verify the responses of some patients with investigator-assessed CR. As some of patients with investigator-assessed CR do not actually meet the protocol-specified criteria based on laboratory and other

data provided in the submission, only responses verifiable by the FDA will be included in the product label.

*Clinical Pharmacology*

d. Safety in patients with organ impairment and the potential for interaction with drugs used commonly in this population are concerns for the postmarketing period.

## ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

## REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

## LCM AGENDA

1. ***Introductory Comments – 5 minutes (RPM/CDTL)***

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. ***Discussion of Substantive Review Issues – 10 minutes***

   Each issue will be introduced by FDA and followed by a discussion.

   *Clinical*

   a. The Applicant's method of identifying patients with differentiation syndrome may underestimate the frequency of the adverse event in patients treated with enasidenib. 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 proposed product label are still not clear. Diagnostic criteria need to be clarified, and the effectiveness of the proposed management guidelines must be confirmed. A PMR to this effect will be required.

   b. Follow-up time on Study AG221-C-001 is limited, and thus limited information has been generated with respect to the long-term safety of enasidenib in the proposed indication. A PMR to characterize the long-term safety of enasidenib will be required.

   c. Insufficient information is available to verify the responses of some patients with investigator-assessed CR. As some of patients with investigator-assessed CR do

not actually meet the protocol-specified criteria based on laboratory and other data provided in the submission, only responses verifiable by the FDA will be included in the product label.

*Clinical Pharmacology*

d. Safety in patients with organ impairment and the potential for interaction with drugs used commonly in this population are concerns for the postmarketing period.

3. ***Discussion of Minor Review Issues – 10 minutes***

*Biometrics*

a. The investigator assessed CR rate and the sponsor assessed CR rate are different. In the pooled analysis, the investigator assessed that the response rate was 19.3% with a 95% CI of (14.2, 25.4); the sponsor assessed CR rate was 14.5% with a 95% CI of (10.0, 20.0).

b. Even though the demographic and baseline disease characteristics of the trial populations between the Phase I and Phase II studies are consistent, the sponsor assessed CR rate was different across the two trials. In the Phase I study, the sponsor assessed CR rate was 16.5% with a 95% CI of (9.9, 25.1); while in Phase II study, the sponsor assessed CR rate was 12.5% with a 95% CI of (6.8, 20.4).

c. There were more deaths in the Phase I population (63.1% compared to those from the Phase II population 54.8%). The median overall survival (OS) time in the Phase 2 population of 6.6 months was shorter in comparison than the Phase I population of 9.1 months.

d. Due to the variation of response rates across the two trials, the interpretation of the pooled analysis should be taken with caution.

***4. Additional Applicant Data – 5 minutes (Applicant)***

***5. Information Requests – 5 minutes***

*Clinical/Biometrics*

a. A revised ADPVPD.xpt data file with a data cutoff date of October 14, 2016, which was requested June 5, 2017.

*Clinical Pharmacology*

b. A summary of the review of the found.xpt file conversion (if any discrepancies are noted) as outlined in Celgene's response submitted to the Agency on June 8, 2017.

c. A response to the information request sent by the Agency on June 12, 2017: Based on the dataset CDXMAY17.xpt, the IDH2 genotyping results of 3 patients (subject IDs 101-007, 111-029, 112-004) varied across the biospecimens tested with the proposed companion diagnostic assay. Please clarify the rules for how these 3 patients were assigned to one of the two IDH2 mutation groups (i.e., R140 or R172) in the efficacy dataset.

6. ***Postmarketing Requirements/Postmarketing Commitments – 10 minutes***

i. **PMR-1:** Conduct a study to characterize enasidenib-related differentiation syndrome, specifically incidence, appropriate diagnostic criteria, and effective treatment based on data and pooled analysis from trials in patients with acute myeloid leukemia: AG-221-C-001, AG-120-221-C-001, AG-221-AML-004, and AG-221-AML-005.

ii. **PMR-2:** Characterize the long-term safety of enasidenib in patients with relapsed or refractory acute myeloid leukemia (AML). Submit the final study report and data (b) (4) with 3 years of follow-up from Study AG-221-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 (b) (4) patients with relapsed or refractory AML.

iii. **PMR-3:** 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 data (b) (4) with 3 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.

iv. **PMR-4:** Conduct clinical pharmacokinetic trials 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*."

v. **PMR-5:** 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.*"

vi. **PMC-1:** Develop and report a control strategy for the drug product to minimize the risk of (b) (4) .

7. ***Major labeling issues – 5 minutes***

8. ***Review Plans – 5 minutes***

The Agency plans to complete the review within the PDUFA timeline.

9. ***Wrap-up and Action Items – 5 minutes***

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/s/

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ALBERT B DEISSEROTH
06/14/2017