CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208573Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208573 SUPPL # HFD # 161

Trade Name VENCLEXTA

Generic Name Venetoclax

Applicant Name AbbVie, Inc.

Approval Date, If Known April 11, 2016

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?

7-year Orphan Drug Exclusivity & 5-year New Chemical Entity Exclusivity

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: **Beatrice Kallungal**
Title: **Senior Regulatory Project Manager**
Date: **04/11/2016**

Name of Office/Division Director signing form: **Ann T. Farrell, MD**
Title: **Division Director**

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

APPEARS THIS WAY ON ORIGINAL

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

/s/

BEATRICE A KALLUNGAL
04/11/2016

ANN T FARRELL
04/11/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # **208573** BLA # **N/A**	NDA Supplement # **N/A** BLA Supplement # **N/A**	If NDA, Efficacy Supplement Type: **N/A** *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: **VENCLEXTA** Established/Proper Name: **Venetoclax** Dosage Form: **Tablets**		Applicant: **AbbVie, Inc.** Agent for Applicant (if applicable): **N/A**
RPM: **Beatrice Kallungal**		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 • User Fee Goal Date is June 29, 2016	☒ 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? 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): Type 1 New Molecular Entity (NME)
(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 ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other ASCO Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ 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 04/11/2016**
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)*	☐ Included
• Original applicant-proposed labeling	☒ Included
❖ 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 ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included
❖ 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
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	**Conditionally acceptable letter 12/16/2015** **Review 12/15/2015**
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 0**3/25/2016** DMEPA: **01/27/2016** DMPP/PLT (DRISK): 0**3/18/2016** OPDP: 0**3/17/2016** SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	**03/25/2016** ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

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

• This application is on the AIP
  ○ If yes, Center Director's Exception for Review memo *(indicate date)*
  ○ If yes, OC clearance for approval *(indicate date of clearance communication)*
	☐ Yes ☒ No
	
	☐ Not an AP action

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC N/A If PeRC review not necessary, explain: Orphan drug designation	
❖ Breakthrough Therapy Designation	☐ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	**Granted 04/27/2015; Denied 07/24/2013**
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	**N/A**
• 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)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	**Granted 04/09/2015; Denied 07/09/2013**
❖ 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)*	**04/08/2016; 04/07/2016; 04/04/2016; 04/01/2016 (2); 03/21/2016 (4); 03/18/2016 (3); 02/26/2016; 02/24/2016 (2); 02/11/2016; 02/09/2016; 01/28/2016; 01/20/2016; 01/11/2016; 12/23/2015; 12/14/2015; 11/24/2015; 11/23/2015; 11/12/2015; 11/09/2015; 11/05/2015; 11/04/2015; 11/03/2015; 09/30/2015**
❖ 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 (MPC) meeting minutes)	**MPC Meeting Minutes 04/14/2015 (Granted); 07/23/2013 (Denied)**
❖ 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)*	**09/22/2015**
• EOP2 meeting *(indicate date of mtg)*	**07/02/2014**
• Mid-cycle Communication *(indicate date of mtg)*	**02/08/2016**
• Late-cycle Meeting *(indicate date of mtg)*	**02/29/2016**
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	**N/A**

❖ 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)*	**04/11/2016**
Division Director Summary Review *(indicate date for each review)*	**04/08/2016**
Cross-Discipline Team Leader Review *(indicate date for each review)*	**04/04/2016**
PMR/PMC Development Templates *(indicate total number)*	**3**
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	**Cosigned integrated clinical & statistical primary review dated 03/14/2016**
• 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 OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	**See page 111 of clinical review dated 03/14/2016**
❖ 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 • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • 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)*	**N/A** **N/A** **03/15/2016**
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	**03/10/2016**
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
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	**Cosigned integrated clinical & statistical primary review dated 03/14/2016 (see clinical review)**

[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 Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review **Cosigned 03/14/2016 review**
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review **Cosigned 03/14/2016 review**
Clinical Pharmacology review(s) *(indicate date for each review)*	**03/14/2016**
❖ 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)*	**03/24/2016**
• Supervisory Review(s) *(indicate date for each review)*	**03/21/2016**
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**03/21/2016**
❖ 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 Included in P/T review, page
❖ 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)*	**04/04/2016**
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	**02/24/2016**
❖ 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 page 163 of integrated product quality review dated 04/04/2016**
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ 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: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☒ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • 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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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BEATRICE A KALLUNGAL
04/11/2016

From:	Kallungal, Beatrice
To:	Jenta, Tuah
Cc:	Kallungal, Beatrice
Subject:	NDA 208573, venetoclax - USPI and Medication Guide - FDA revisions 04/08/2016
Date:	Friday, April 08, 2016 2:00:46 PM
Attachments:	NDA208573_venetoclax_Medguide_04082016.pdf.doc NDA208573_venetoclax_uspi_04082016.pdf.doc

Hi Tuah,
Thank you for providing the response in a timely manner. We have accepted all of the Applicant changes to the PI and MedGuide and deleted the comments. We have included couple of minor edits in both documents. Please review these changes and if you agree, submit as final agreed upon labeling to the application by **4 pm EDT today**.

Please review the document for formatting. See *PLR Requirements for Prescribing Information internet site*

Thanks,

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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

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

/s/

BEATRICE A KALLUNGAL
04/08/2016

From:	Kallungal, Beatrice
To:	Jenta, Tuah
Cc:	Kallungal, Beatrice
Subject:	NDA 208573, venetoclax - USPI and Medication Guide - FDA revisions 04/07/2016
Date:	Thursday, April 07, 2016 3:08:11 PM
Attachments:	NDA 208573_Venclexta-medguide_04072016.doc NDA 208573_venclexta-uspi_04072016.doc

Hi Tuah,
Attached please find the Agency's further revisions to the USPI and medication guide. Please review the FDA's changes/comments and using the same draft, do the following:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition, please review the document for formatting. See *PLR Requirements for Prescribing Information internet site*

We request that you respond **by 8 am EDT, Friday April 8, 2016** via e-mail and officially submit to the NDA.

If you have any questions, please let me know. Also, please acknowledge the receipt of this communication.

Thanks,

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
04/07/2016

From:	Kallungal, Beatrice
To:	Jenta, Tuah
Cc:	Kallungal, Beatrice
Subject:	NDA 208573, venetoclax - additional FDA revisions to Med Guide - 04/04/2016
Date:	Monday, April 04, 2016 12:54:25 PM
Attachments:	NDA 208573_Venetoclax_MG_04042016.doc

Hi Tuah,
Attached please find the Agency's further revisions to the medication guide (med guide). Please review the FDA's changes/comments and using the same draft, do the following:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

We request that you respond **by 3 pm EDT, Tuesday April 5, 2016** via e-mail and officially submit to the NDA.

Also please note, the review team has indicated that the Applicant's explanations to the QSG are acceptable.

If you have any questions, please let me know. Also, please acknowledge the receipt of this communication.

Thanks,

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
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BEATRICE A KALLUNGAL
04/04/2016

Anderson, Alycia

From: Anderson, Alycia
Sent: Friday, April 01, 2016 9:59 AM
To: 'tuah.jenta@abbvie.com'
Cc: Kallungal, Beatrice
Subject: NDA 208573 - PI
Attachments: NDA 208573_Venetoclax_draft USPI_FDA edits_04012016.doc

Good morning, Dr. Jenta.

Attached is the PI for NDA 208573. Please review the changes/comments and do the following:

- Accept any changes that you agree with and delete the comments that apply to those agreed upon changes
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, feel free to send me the revised tracked change before you make your official submission electronically.

Please provide a revised PI to Mrs. Beatrice Kallungal by **COB (EST), Tuesday, April 4, 2016.**

Please confirm receipt of this e-mail.

Best Regards,

Alycia Anderson
~~~~~~~~~~~~~~~
Alycia Anderson, CCRP
Regulatory Project Manager
CDER/OND/OHOP/DHP
10903 New Hampshire Avenue
WO #22, Room 2379
Silver Spring, MD 20903
(240) 402-4270 (Desk)
alycia.anderson@fda.hhs.gov

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/s/

ALYCIA C ANDERSON
04/01/2016

From:	Kallungal, Beatrice
To:	Jenta, Tuah
Cc:	Kallungal, Beatrice; Fong, Maricel (maricel.fong@abbvie.com); Schary, William
Subject:	NDA 208573, Venetoclax USPI - FDA"s revisions dated 3/18/2016
Date:	Friday, March 18, 2016 4:26:41 PM
Attachments:	NDA 208573_Venetoclax_03182016.doc

Dear Tuah,
Attached is the draft package insert (PI) for NDA 208573, Venetoclax with FDA's revisions.

Please review the FDA's changes/comments and using the same draft, do the following:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition, please review the document for formatting. See *PLR Requirements for Prescribing Information internet site*

We request that you respond by **Noon EDT, Friday March 25, 2016** via e-mail and officially submit to the NDA.

If you have any questions, feel free to contact me.

Kind regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
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/s/

BEATRICE A KALLUNGAL
03/21/2016

From:	Kallungal, Beatrice
To:	Jenta, Tuah
Cc:	Kallungal, Beatrice
Subject:	RE: NDA 208573, Venetoclax USPI - FDA"s revisions dated 3/18/2016 - clarification and additional revisions
Date:	Monday, March 21, 2016 3:00:33 PM
Attachments:	image001.png

Hi Tuah,

Thank you for your question regarding the USPI that we sent on 3/18. We did intentionally delete [redacted] (b) (4) (however it was not our intention to "accept deletion"; we intended for you to see the edits).

The rationale for removing the information about [redacted] (b) (4) was per the "Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format" , [redacted] (b) (4) .

As your team work through the Agency's revisions to the USPI, please also incorporate the following addition/revision.

> *Upon further review of reproductive toxicology data, we have concluded that the embryocidal effects seen in animals may occur in humans. This is also supported by literature indicating involvement of BCL-2 in oocyte and embryonic development (see references below). Therefore, please include the following section under Warnings and Precautions of the label.*
>
> > *5.4 Embryo-Fetal Toxicity*
> > *Based on its mechanism of action and findings in animals, Venclexta may cause embryo-fetal harm when administered to a pregnant woman. In an embryo-fetal study conducted in mice, administration of venetoclax to pregnant animals at exposures equivalent to that observed in patients at the recommended dose of 400 mg daily resulted in post-implantation loss and decreased fetal weight. There are no adequate and well-controlled studies in pregnant woman using Venclexta. Advise females of reproductive potential to avoid pregnancy during treatment. If Venclexta is used during pregnancy or if the patient becomes pregnant while taking Venclexta, the patient should be apprised of the potential hazard to the fetus [see Use in Specific Populations (8.1)].*
>
> *Accordingly, please also include a bullet under W&P of the Highlights: "Embryo-Fetal toxicity: may cause embryo-fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment (5.4)".*
> *Delete the bullet* [redacted] (b) (4) *in the Highlights.*
>
> References:

http://www.reproduction-online.org/content/141/5/549.long
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1887292/pdf/amjpathol00055-0067.pdf
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1886804/pdf/amjpathol00075-0085.pdf
http://www.sciencedirect.com/science/article/pii/S0378432001001865
http://www.sciencedirect.com/science/article/pii/S0047637406000686

If you have any questions, please let me know.

Regards,

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

From: Jenta, Tuah [mailto:tuah.jenta@abbvie.com]
Sent: Friday, March 18, 2016 5:51 PM
To: Kallungal, Beatrice
Cc: Jenta, Tuah
Subject: RE: NDA 208573, Venetoclax USPI - FDA's revisions dated 3/18/2016

Hi Beatrice,

Thanks for returning my call earlier.

I'm requesting clarification of the deleted information (rather than lined out) on pages 22 and 23, specifically the previous (b) (4) (b) (4) Was the intent to completely remove this information?

Appreciate if you could obtain clarification of this.

Regards,

Tuah

TUAH JENTA, PHD, RAC
Associate Director, Regulatory Affairs
Global Regulatory Strategy

abbvie

AbbVie Inc

1 North Waukegan Road
Dept PA77, Bldg AP30-1
North Chicago, IL 60064
USA
OFFICE +1 847-937-2434
CELL (b) (6)
EMAIL tuah.jenta@abbvie.com

abbvie.com

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/s/

BEATRICE A KALLUNGAL
03/21/2016

From:	Kallungal, Beatrice
To:	Jenta, Tuah
Cc:	Kallungal, Beatrice
Subject:	NDA-208573, Venetoclax - Quick Start Guide and Medication Guide - FDA revisions - 03/21/2016
Date:	Monday, March 21, 2016 3:36:41 PM
Attachments:	NDA 208573 venetoclax (VENCLEXTA) MG FDA revisions 03212016.doc

Hi Tuah,
Please find below, the Agency's comments on the venetoclax Quick Start Guide (QSG).

Also attached is the Agency's revisions to the medication guide (med guide). Please review the FDA's changes/comments and using the same draft, do the following:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

Comments specific to each section of the QSG:

1) (b) (4)

2)

3)

4)

5)

(b) (4)

6)

7)

8)

We request that you respond **by Noon EDT, Friday March 25, 2016** via e-mail and officially submit to the NDA.

If you have any questions, please let me know. Also, please acknowledge the receipt of this communication.

Thanks,

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
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(301) 796-9845 (fax)
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BEATRICE A KALLUNGAL
03/21/2016

From: Kallungal, Beatrice
To: Jenta, Tuah
Cc: Kallungal, Beatrice
Subject: NDA 208573, Venetoclax PMR study
Date: Friday, March 18, 2016 4:44:51 PM

Dear Tuah,
Please refer to NDA 208573, Venetoclax. Please provide your response by **Noon EDT Tuesday March 22, 2016**.

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by telecon, if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that has already received full concurrence by FDA.

PMR #1 Description:	Submit the complete final report and data from trial GO28667, a randomized, phase 3 trial comparing venetoclax and rituximab with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia (CLL), including CLL with deletion 17p

PMR Schedule Milestones:	Final Protocol Submission:	Completed
	Study Completion:	MM//YYYY
	Final Report Submission:	MM//YYYY

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR or PMC designation numbers will be assigned later

Some things you can do to expedite this process:

1. For labeling and PMRs or PMCs reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs or PMCs as agreed upon. We ask the following:
   a. For any new study to address a PMR /PMC, it is necessary to submit the protocol for

DHP review and concurrence prior to initiating the study. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.

b. Send the RPM an email courtesy copy of the draft versions of the protocol, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.
c. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR or PMC NUMBER). This helps the document room and DHP to code the submission properly. All protocol submissions are made to the IND.

Regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
03/21/2016

From:	Kallungal, Beatrice
To:	Jenta, Tuah
Cc:	Kallungal, Beatrice
Subject:	NDA 208573, Venetoclax - Additional PMR studies
Date:	Monday, March 21, 2016 3:59:04 PM

Dear Tuah,
Please refer to NDA 208573, Venetoclax. Please provide your response by **Noon EDT Tuesday March 22, 2016**.

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by telecon, if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that has already received full concurrence by FDA.

PMR #2 Description:	Evaluate the effect of hepatic impairment on the pharmacokinetics and safety of venetoclax. Submit a complete final study report with all supporting datasets for trial [protocol #] entitled,"[protocol name]" .

PMR Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY

PMR #3 Description:	Evaluate the effect of venetoclax co-administration on pharmacokinetics of a probe substrate of P-gp. Submit a complete final study report with all supporting datasets.

PMR #3 Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR or PMC designation numbers will be assigned later

Some things you can do to expedite this process:

1. For labeling and PMRs or PMCs reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs or PMCs as agreed upon. We ask the following:
   a. For any new study to address a PMR /PMC, it is necessary to submit the protocol for DHP review and concurrence prior to initiating the study. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.
   b. Send the RPM an email courtesy copy of the draft versions of the protocol, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.
   c. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR or PMC NUMBER). This helps the document room and DHP to code the submission properly. All protocol submissions are made to the IND.

Regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
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E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
03/21/2016

From:	Kallungal, Beatrice
To:	Jenta, Tuah
Cc:	Kallungal, Beatrice
Subject:	NDA 208573, Venetoclax - Information Request - 3/21/2016
Date:	Monday, March 21, 2016 9:04:05 AM

Hello,
Please find below the information request for NDA 208573, Venetoclax. Please submit your response to this request via e-mail by **3 pm EDT today March 21, 2016** followed by officially submitting the response to the NDA. If you are unable to meet this response timeline, please let me know.
We have an issue requiring clarification - with regards to nonclinical study reports R&D/12/538 and R&D/10/1025. We note the pharmacology written summary states that venetoclax was equally potent against CLL samples bearing the 17p deletion, with an average EC50 of 8 nM (n = 5). Please clarify the data upon which this statement was based on, as we cannot determine which study report or even from which subjects this information is derived.

Please acknowledge receipt of this request.

Thanks,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
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E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
03/21/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208573

INFORMATION REQUEST

AbbVie Inc.
Attention: Tuah Jenta, PhD., RAC
Associate Director, Regulatory Affairs
1 N. Waukegan Road, AP30
North Chicago, IL 60064

Dear Dr. Jenta:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Venetoclax.

We also refer to your October 29, 2015 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.

For the (b) (4) and (b) (4) stages during drug product manufacturing, please address the following:

a) We note that (b) (4) are included in your current control strategy. We recommend that (b) (4) be included to mitigate the risk of (b) (4)

b) Confirm that (b) (4).

c) You have indicated that (b) (4) was monitored during development. Please provide the data to verify (b) (4).

For the (b) (4) stages during drug product manufacturing, please address the following:

a) We noticed the use of a (b) (4), which appears to be a change in equipment from development and exhibit batch manufacture. The process parameters (i.e. (b) (4)) are thereby different. Please provide verification that the (b) (4) obtained within the proposed operating ranges

are similar to those observed during development and that the (b) (4) is similar.

b) (b) (4)

c) We recommend that (b) (4) content uniformity testing. Provide analyses of (b) (4) content uniformity data discussed in section 2.4.4.2 of 3.2.P.2.3 for (b) (4) the tablet development.

d) Please commit to perform stratified content uniformity sampling during (b) (4) through validation and to submit the results as a CBE-30. Please evaluate your acceptance criteria and statistical properties (for example, confidence, coverage, ability for a future sample to pass the USP test [ASTM E2709], operating characteristic curves) and provide justification in your response. We recommend that your protocol also evaluate between and within location variances for your stratified sampling plan. Submit the protocol for evaluation. Please refer to the level II Q/A, published on FDA.gov - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124782.htm for more information regarding the agency's current thinking on (b) (4) content uniformity testing.

Please include (b) (4). In addition, no upper limit on (b) (4). Please add an upper limit which is supported by your development results.

We acknowledge the (b) (4) for the primary stability batches provided in your IR response received on 02/29/2016. For the 100 mg strength, please provide an explanation or rationale for the three individual tablet weights which failed the specification, and detail how risk for failures in future batches will be mitigated.

If you have any questions, please contact me, at (240) 402-6153. Please respond by March 25, 2016 with the exception of drug product information request.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Rabiya Laiq -A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -A, 0.9.2342.19200300.100.1.1=2001555007
Date: 2016.03.18 15:51:42 -04'00'

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208573

INFORMATION REQUEST

AbbVie Inc.
Attention: Tuah Jenta, PhD., RAC
Associate Director, Regulatory Affairs
1 N. Waukegan Road, AP30
North Chicago, IL 60064

Dear Dr. Jenta:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Venetoclax.

We also refer to your October 29, 2015 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.

Labeling:

Please make the following edits to all packaging labels:

Add NDC #s on each packaging presentation.
Add Trade name
Add parenthesis around nonproprietary (venetoclax) name.
Provide the color mock ups with indicated changes.

If you have any questions, please contact me, at (240) 402-6153. Please respond by March 5, 2016 with the exception of drug product information request.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Rabiya Laiq -A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -A, 0.9.2342.19200300.100.1.1=2001555007
Date: 2016.02.26 12:13:00 -05'00'

From: Kallungal, Beatrice
To: Jenta, Tuah
Cc: Kallungal, Beatrice
Subject: RE: NDA 208573, Venetoclax - Clinical Pharmacology proposed PMRs
Date: Wednesday, February 24, 2016 2:48:40 PM
Attachments: image001.png

Hi Tuah,
Please find below the responses from the team.

Regards,

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

From: Jenta, Tuah [mailto:tuah.jenta@abbvie.com]
Sent: Friday, February 19, 2016 4:01 PM
To: Kallungal, Beatrice
Cc: Jenta, Tuah
Subject: NDA 208573, Venetoclax - Clinical Pharmacology proposed PMRs

Dear Beatrice,

Following our Mid-Cycle Communication Meeting (telecon) on 2/8/2016, my Clinical Pharmacology team would like to clarify a couple of items with your review team related to the proposed post-marketing requirements (PMRs), as summarized below:

1. DDI Clinical Study with P-gp Substrate

As submitted in NDA 208573, the safety assessment of data from the DDI study of venetoclax co-administered with warfarin (Study M15-065) demonstrated that the administration of a single 400 mg dose of venetoclax alone was associated with transient decreases in CD19 B-cell lymphocyte counts in healthy volunteers. Accordingly, only three subjects received venetoclax in this study. (b) (4) (b) (4) (b) (4)

- Would the current proposed label language to (b) (4) be sufficient to address the potential interaction with P-gp substrates?

Agency Response: The proposed labeling language to [redacted] is not acceptable. [redacted]).

- Alternatively, would the Agency agree with conducting the [redacted] P-gp substrate DDI study [redacted] to minimize the risk for reductions in CD19 B-cell lymphocyte counts in healthy volunteers?

Agency Response: We agree.

2. Dedicated Hepatic Impairment Clinical Study

A clinical protocol for Study M15-342, entitled "*A Phase 1 Study to Evaluate the Safety and Pharmacokinetics of a Single Dose of Venetoclax in Female Subjects with Mild, Moderate, or Severe Hepatic Impairment*" was previously submitted to IND 110159 (Sequence/Serial 0405 on 12/16/2015).

- Does the Agency have any feedback on Study M15-342?

Agency Response: Mild hepatic impairment does not appear to have effect on venetoclax PK based on population PK analysis, [redacted] maybe reasonable. [redacted]

- Would the Agency also prefer the protocol for Study M15-342 to be submitted to NDA 208573?

Agency Response: There is no need to include the Study M15-342 protocol in the NDA 208573 submission.

Regards,

Tuah

TUAH JENTA, PHD, RAC
Associate Director, Regulatory Affairs
Global Regulatory Strategy

abbvie

AbbVie Inc
1 North Waukegan Road
Dept PA77, Bldg AP30-1
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OFFICE +1 847-937-2434
CELL (b) (6)
EMAIL tuah.jenta@abbvie.com

abbvie.com

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/s/

BEATRICE A KALLUNGAL
02/24/2016

From: Kallungal, Beatrice
To: Jenta, Tuah; Fong, Maricel (maricel.fong@abbvie.com); Schary, William
Cc: Kallungal, Beatrice
Subject: NDA 208573, Venetoclax - Information Request - 2/24/2016
Date: Wednesday, February 24, 2016 2:59:50 PM

Hello,
Please find below the information request for NDA 208573, Venetoclax. Please submit your response to this request via e-mail by **2 pm EST Friday March 11, 2016** followed by officially submitting the response to the NDA.

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

A. Monthly Blister Carton
   1. Ensure the NDC number is included on the carton. Currently the NDC is denoted by a place holder NDC. However, the NDC number is contained in the prescribing information.
   2. Wallet and blister pack labeling
      a. Inside flap of Week 1
         i. See A.1 and revise the wallet and blister pack labeling accordingly.
         ii. To enhance patient comprehension, consider use patient-friendly language. For example, instead of the word (b) (4) use the more patient friendly term, "before". This term is used consistently throughout the QSG.
   3. (b) (4) Please relocate the drug barcode to a visible location on carton labeling as it is often used as an additional verification during the pharmacy procurement process.

B. Weekly Wallet, Unit Dose Pack, and Bottle labeling
   1. See A.1 and revise the wallet, unit dose pack, and bottle labeling accordingly.
   2. Include the following cautionary statement on the PDP: "Dispense the accompanying Medication Guide to each patient."
   3. Please indicate where the required lot number and expiration date will appear as required per 21 CFR 201.17 and 21 CFR 201.10(i)(1).
   4. We recommend adding the NDC number in the top third of the principal display panel since it provides additional means of ensuring the correct product is selected.
   5. We note inconsistencies in the requirements for oral hydration in the prescribing information and the labeling. In the wallet system labeling, it states to (b) (4)

      In the PI it is recommended to drink 6-8 glasses of water each day. To mitigate the potential for administration errors, we recommend having

consistent instructions on oral hydration requirements across all labeling.

6. Inside the Week 1 and Week 4 wallet revise the statement "(b) (4) to "Push down on **both** tablets to remove" to ensure this important information is prominent.

C. Quick Start Guide

1. In the row: "Before 1st Dose"
    a. We recommend deleting the boxes that say (b) (4) Patients should be instructed to write in the day of the week and date for each Prep Day, and each day during Weeks 1 through 4. This will help ensure that patients do not inadvertently take a dose twice. (b) (4) add a reminder to patients that states, "Prep Day 1 and Prep Day 2 are the 2 days before the first dose of Venclexta, as directed by your healthcare provider."
2. In the box for each day, below the revised picture of the tablets, add the following bolded text:

    Each day of Week 1, add the statement: Take two 10 mg tablets
    Each day of Week 2, add the statement: Take one 50 mg tablet
    Each day of Week 3, add the statement: Take one 100 mg tablet
    Each day of Week 4, add the statement: Take two 100 tablets
3. For consistency with the packaging of the product
    a. Some information has been carried over from the Quick Start Guide to the packaging, for example, the inside flaps for each weekly pack of tablets and cardboard pull tabs for each daily dose. We recommend revising this information to be consistent with the revisions to the QSG, to the extent possible.

Please acknowledge receipt of this request. If you have any questions, please let me know.

Regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue

Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
02/24/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208573

MID-CYCLE COMMUNICATION

AbbVie, Inc.
Attention: Tuah Jenta, PhD, RAC
Associate Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, IL 60064

Dear Dr. Jenta:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for venetoclax tablets; 10, 50, and 100 mg.

We also refer to the teleconference between representatives of your firm and the FDA on February 8, 2016. 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 Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, MS, ACNP-BC
Clinical 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: February 8, 2016 at 9:30 AM – 10:30 AM EST

Application Number: NDA 208573

Product Name: Venetoclax
Indication: For the treatment of patients with relapsed or refractory chronic lymphocytic leukemia (R/R CLL) who have received at least one prior therapy, including patients with 17p deletion

Applicant Name: AbbVie, Inc.

Meeting Chair: Virginia Kwitkowski, MS, ACNP-BC
Meeting Recorder: Beatrice Kallungal, BS

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Ann Farrell, MD, Director
Virginia Kwitkowski, MS, ACNP-BC, Clinical Team Leader
Lori Ehrlich, MD, Clinical Reviewer
Aviva Krauss, MD, Clinical Reviewer
Qin Ryan, MD, PhD, Safety Medical Officer
Rachel Ershler, MD, Clinical Reviewer
Theresa Carioti, MPH, Chief Project Management Staff
Diane Leaman, BS, Safety Regulatory Project Manager
Beatrice Kallungal, BS, Senior Regulatory Project Manager

Office of Biostatistics/Division of Biometrics V
Qing Xu, PhD, Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Bahru Habtemariam, PharmD, Acting Team Leader
Guoxiang (George) Shen, PhD, Clinical Pharmacology Reviewer
Lian Ma, PhD, Pharmacometrics Reviewer

Office of Pharmaceutical Quality (OPQ)/Office of Process and Facilities
Peter Guerrieri, PhD, Reviewer

Office of Surveillance and Epidemiology (OSE), Division of Epidemiology I (DEPI I)
Carolyn McCloskey, MD, MPH, Epidemiologist

OSE/Division of Pharmacovigilance (DPV)
Wana Manitpisitkul, PharmD, Reviewer

OSE/Office of Medication Error Prevention & Risk Management (OMEPRM)/Division of Medication Error Prevention and Analysis (DMEPA)
Nicole Garrison, PharmD, Reviewer

OSE/Office of Medication Error Prevention & Risk Management (OMEPRM)/Division of Risk Management (DRISK)
Mona Patel, PharmD, Reviewer

Office of Medical Policy Initiatives/Division of Medical Policy Programs (DMPP)/Labeling & Patient Labeling
Rowe Medina, PharmD, Reviewer
Nisha Patel, PharmD, Reviewer

Center for Devices and Radiological Health (CDRH)

Office of In vitro Diagnostics and Radiological Health (OIR)
Division of Immunology and Hematology Devices
Reena Philip, PhD, Deputy Director
Donna Roscoe, PhD, Branch Chief

EASTERN RESEARCH GROUP ATTENDEE
Chris Sese, independent Assessor

APPLICANT ATTENDEES

AbbVie, Inc.
Gary Gordon, MD, VP Oncology Development
Rod Humerickhouse, MD, PhD, Global Project Director
Maria Verdugo, MD, Senior Medical Director, Oncology Development
Andrea Best, MD, Group Therapeutic Area Head, Pharmacovigilance
Monali Desai, MD, MPH, Senior Medical Director, Product Safety
James Duhig, PhD, Head Risk Communications & Behavioral Science
Todd Busman, MS, Assistant Director, Statistics
Ahmed Salem, PhD, Assistant Director, Clinical PK/PD
Sherry Ralston, PhD, Director, Preclinical Safety
Dan Kim, PhD, Associate Director, CMC Regulatory Affairs
David Ross, PharmD, Senior Director, Global TA Head, Regulatory Affairs
David Breines, PhD, Senior Director, Global Regulatory Leader
William Schary, PhD, RAC, Director, Global Regulatory Affairs
Tuah Jenta, PhD, RAC, Associate Director, Global Regulatory Affairs

Genentech/Roche
Mehrdad Mobasher, MD, Global Development Team Leader
Kathryn Humphrey, MD, Medical Director
Wei Dong, MD, PhD, Senior Group Director, Safety Science Oncology
Dale Miles, PhD, Senior Scientist, Clinical Pharmacology
Smita Kshirsagar, PhD, Senior Scientist, Clinical Pharmacology
Michelle Byrtek, PhD, Senior Statistical Scientist
Sofia Khan, PharmD, MPH, Director, Global Regulatory Leader
Emily Trinh, MS, Regulatory Program Manager

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. We reiterate that should your application receive an accelerated approval, you will be subject to the following post-marketing requirement:

   Complete and submit the final results of the ongoing randomized, open-label, Phase 3 clinical trial (GO28667) of venetoclax in combination with rituximab versus bendamustine in combination with rituximab in relapsed/refractory CLL. Enrollment of approximately (b) (4) patients is expected. The primary endpoint is progression-free survival as assessed by investigators.

2. (b) (4)

Statistical:
The Sponsor claimed that the (b) (4) . However, the Agency noticed that the (b) (4)

(b) (4)

3.0 INFORMATION REQUESTS

There are no information requests; however, we are considering the following post marketing requirements (PMRs):

Clinical Pharmacology

1. Conduct a drug-drug interaction (DDI) clinical study with a P-gp substrate
   - Both venetoclax and M27 has inhibition potential on P-gp at therapeutic dose and/or concentrations. IC50 for P-gp was approximately 0.8 μM for both venetoclax and M27, ratios of clinical exposure/IC50 are greater than the threshold values defined in Figure A2 of the FDA Drug Interaction Studies Guidance.
   - As previously communicated on a Type C meeting package (submission date October 14, 2014), the effect of single-dose venetoclax on the P-gp substrate should be planned as a post-approval requirement.
2. Conduct a dedicated hepatic impairment clinical study
   - As mentioned in the NDA submission package, conduct a dedicated post-approval study to evaluate the pharmacokinetics of venetoclax in subjects with varying degree of hepatic impairment.

Please submit the study protocols for FDA review before the start of both trials.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At this time, there are no major safety concerns identified and currently, there is no need for a Risk Evaluation and Mitigation Strategy (REMS).

5.0 ADVISORY COMMITTEE MEETING

At this time, there are no plans for an Advisory Committee meeting.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

As communicated earlier, the user fee goal date for NDA 208573 is June 29, 2016. But as we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting between you and the review team is currently scheduled for February 29, 2016 at 3:00 PM EST. We intend to send the briefing package to you approximately 2 days in advance of the meeting. We plan to communicate proposed labeling and, if necessary, any post-marketing requirement/commitment requests by March 14, 2016. If these timelines change, we will communicate updates to you during the course of review.

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/s/

VIRGINIA E KWITKOWSKI
02/12/2016

From:	Kallungal, Beatrice
To:	"Jenta, Tuah"; Schary, William; Fong, Maricel (maricel.fong@abbvie.com)
Cc:	Kallungal, Beatrice
Subject:	NDA 208573, Venetoclax - Information Request - 2/11/2016
Date:	Thursday, February 11, 2016 8:30:31 AM

Hello,
Please find below the information request for NDA 208573, Venetoclax. Please submit your response to this request via e-mail by **2 pm EST Wednesday February 17, 2016** followed by officially submitting the response to the NDA.

Please conduct analyses and provide your results for the following based upon n=106 defined as all patients with 17p del from M13982.
-Baseline patient characteristics (b) (4)
-Baseline disease status (b) (4)
-Efficacy Results (b) (4)

Please acknowledge receipt of this request. If you have any questions, please let me know.

Regards,

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
02/11/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208573

INFORMATION REQUEST

AbbVie Inc.
Attention: Tuah Jenta, PhD., RAC
Associate Director, Regulatory Affairs
1 N. Waukegan Road, AP30
North Chicago, IL 60064

Dear Dr. Jenta:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Venetoclax.

We also refer to your October 29, 2015 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.

Biopharmaceutics:

Based on our review of dissolution profiles from the pivotal and supportive clinical trials and the proposed commercial batches at the time of release and/or during stability testing, we recommend the following dissolution acceptance criteria for venetoclax tablets. Submit the revised drug product specification table with the recommended changes to the dissolution acceptance criteria as an amendment to the NDA.

	Specification Timepoint	
Tablet Strength	When Q = (b)(4)% of labeled amount	When Q = (b)(4)% of labeled amount
10 mg	1.5 h	2 h
50 mg	2 h	3 h
100 mg	3 h	4 h

*Evaluated per USP <711> Acceptance Table 1

Drug Product:

1. *Provide an update on the stability data on the tablet drug product manufactured in North Chicago and in Ireland.* ***Submit the data by 17th February.***

Microbiology:

1. *You propose waiving microbial limits release testing for your drug product. This proposal may be acceptable provided that you address the following point:*
   -Provide the results of microbial limits testing performed on exhibit or stability batches of the drug product. We recommend testing on release and at 12 and 24 month stability. Test method suitability should be verified (if compendial methods are used) or validated. Alternatively, commit to performing microbial testing for at least the first three commercial batches on release and at 12 and 24 months on stability, and providing the results to the Agency.

Drug Substance:

1. *In Section 3.2.S.2.6, you provided a control strategy for potential genotoxic and carcinogenic impurities. Please address the following:*
   a. *In the Type C meeting held on 02-Dec-2014, the Division noted that for the carcinogenic impurity* (b) (4) *it was unclear how you calculated a PDE of* (b) (4) *mg/day and that a risk assessment should be developed for this impurity, as the* (b) (4) *designation is not appropriate for non-mutagenic carcinogens. Provide the risk assessment and the calculations used to determine the PDE for* (b) (4)
   b. *Provide the maximum daily exposure of the mutagenic impurity* (b) (4).

2. *Address the following regarding the drug substance specification in Section 3.2.S.4.1:*
   a. *Tighten the limit for residue on ignition. The current limit of NMT* (b) (4) *% is not justified based on data from 28 batches using the current manufacturing process (*(b) (4)*) showing levels of* (b) (4) *%.*
   b. *Re-establish limits for elemental impurities.* (b) (4)

3. *In your validation reports for RTM.C5319 (Determination of Assay and Identification of Venetoclax by HPLC) and RTM.C5320 (Determination of Impurities in Venetoclax by HPLC), you conducted stress studies under various conditions to determine method specificity. Provide a rationale for using* (b) (4) *in your stress studies. Also, explain why stress studies* (b) (4) *were not conducted.*

4. *Provide any additional drug substance stability data obtained to-date for the primary, site-specific, and process validation stability batches to support the proposed* (b) (4) *-month retest date.*

Drug Process:

(b) (4)

If you have any questions, please contact me, at (240) 402-6153. Please respond by March 1, 2016 with the exception of drug product information request.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Rabiya Laiq -A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -A, 0.9.2342.19200300.100.1.1=2001555007
Date: 2016.02.09 15:57:21 -05'00'

From:	Kallungal, Beatrice
To:	"Jenta, Tuah"; Schary, William; Fong, Maricel (maricel.fong@abbvie.com)
Cc:	Kallungal, Beatrice
Subject:	NDA 208573, Venetoclax - Information Request - 1/28/2016
Date:	Thursday, January 28, 2016 4:27:14 PM

Hello,
Please find below the information request for NDA 208573, Venetoclax. Please submit your response to this request via e-mail by **2 pm EST Friday February 5, 2016** followed by officially submitting the response to the NDA.

Using data from Venetoclax monotherapy studies:

- *Submit summary and tables comparing the serious TEAEs experienced by CLL/SLL patients among the full range of studied doses.*
- *Submit summary and tables compared serious TEAEs experienced by all patients who are treated with Venetoclax to date.*
- *Re-evaluate the exposure-response relationship for CR/CRi using IRC data. Submit related datasets and codes along with the results.*
- *Conducted integrated dose response analysis for safety (serious TEAEs) and efficacy (CR/CRi) for patients with CLL/SLL in order to understand the therapeutic window of Venetoclax at different dose levels.*

Please acknowledge receipt of this request. If you have any questions, please let me know.

Regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
01/28/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

METHOD VERIFICATION
MATERIALS RECEIVED

NDA 208573

January 20, 2016

AbbVie Inc.
Attention: Tuah Jenta, Ph.D.
RAC Associate Director Regulatory Affairs
1 N. Waukegan Road.
Dept. PA77/Bldg. AP30
North Chicago IL 60064

Dear Tuah Jenta, Ph.D.:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Venetoclax Tablets 10mg, 50mg, 100mg and to our January 11, 2016, letter requesting sample materials for methods validation testing.

We acknowledge receipt on January 15, 2016, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

LAURA POGUE
01/20/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

REQUEST FOR METHODS VERIFICATION MATERIALS

NDA 208573

January 11, 2016

AbbVie Inc.
Attention: Tuah Jenta, Ph.D.
RAC Associate Director Regulatory Affairs
1 N. Waukegan Road.
Dept. PA77/Bldg. AP30
North Chicago IL 60064

Dear Tuah Jenta, Ph.D.:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Venetoclax Tablets 10mg, 50mg, 100mg.

We will be performing methods validation studies on Venetoclax Tablets 10mg, 50mg, 100mg, as described in NDA 208573.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

3.2.S.4.2	Determination of Assay of Venetoclax by HPLC (RTM.C5319)
3.2.S.4.2	Determination of Impurities in Venetoclax by HPLC (RTM.C5320)
3.2.P.5.2	Determination of Assay of Venetoclax Tablets by HPLC (RTM.C5477)
3.2.P.5.2	Determination of Degradation Products in Venetoclax Tablets by HPLC (RTM.C5512)

Samples and Reference Standards

2	x	(b) (4) mg of Venetoclax drug substance
2	x	(b) (4) mg of Venetoclax drug reference standard
2	x	(b) (4) Venetoclax tablets (10 mg)
2	x	Venetoclax tablets (50 mg)
2	x	Venetoclax tablets (100 mg)
(b) (4)	mg	All impurities and degradants (as available)

Equipment

1	(b) (4)
1	

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: **MVP Sample Custodian**
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this email. You may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

LAURA POGUE
01/11/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208573

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

AbbVie, Inc.
Attention: Tuah Jenta, PhD, RAC
Associate Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, IL 60064

Dear Dr. Jenta:

Please refer to your New Drug Application (NDA) dated October 29, 2015, received October 29, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Venetoclax Tablets 10, 50, and 100 mg.

We also refer to your amendments dated November 17, 20, 23, December 3, and 11, 2015.

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 June 29, 2016**.** 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.

However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

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 March 31, 2016. This date conforms to the 21st Century Review timeline for your application. If our review

continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests. In addition, the planned date for our internal mid-cycle review meeting is January 27, 2016. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Benefit/Risk Assessment.
2. Rationale for assuming the applicability of foreign data to U.S. population/practice of medicine.
3. Per the financial disclosure guidance (21 CFR § 54.4), submit a list of all investigators who are full-time or part-time employees.
4. In future submissions provide footnotes under the tables indicating which datasets were used to generate the tables.

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 *PLLR Requirements for Prescribing Information* websites including:

- 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.

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

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (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), Medication Guide, and patient PI. 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 a request for advisory comments 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), Medication Guide, and patient PI, 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 product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

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

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/s/

EDVARDAS KAMINSKAS
12/23/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208573

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

AbbVie Inc.
1 N. Waukegan Road
Dept PA77/Bldg. AP30
North Chicago, IL 60064

ATTENTION: Tuah Jenta, Ph.D., RAC
Associate Director, Regulatory Affairs

Dear Dr. Jenta:

Please refer to your New Drug Application (NDA) dated and received October 29, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Venetoclax Tablets, 10 mg, 50 mg, and 100 mg.

We also refer to your correspondence dated and received October 29, 2015, requesting review of your proposed proprietary name, Venclexta.

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

If any of the proposed product characteristics as stated in your October 29, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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 Kevin Wright, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Beatrice Kallungal, Regulatory Project Manager in the Office of New Drugs, at (301) 796-9304.

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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/s/

TODD D BRIDGES
12/16/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208573

INFORMATION REQUEST

AbbVie Inc.
Attention: Tuah Jenta, PhD., RAC
Associate Director, Regulatory Affairs
1 N. Waukegan Road, AP30
North Chicago, IL 60064

Dear Dr. Jenta:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Venetoclax.

We also refer to your October 29, 2015 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:

In order for us to adequately assess the quality controls proposed for the commercial manufacture of drug product, please provide the intended batch records for the commercial manufacture of all three strengths; alternatively, provide an updated commercial process description for the three strengths in 3.2.P3 with comprehensive stepwise details. The batch record or updated process description should include the following:

1. Material amounts added for each unit operation, including (b) (4) .
2. Determination of yield and associated limits for individual stages, as applicable.
3. Detailed description of the in-process controls for each stage including, as appropriate, sampling procedures, sample quantity, sampling frequency and acceptance criteria.
4. Proposed target and operating ranges for all process parameters, in addition to those assigned as "critical".

Biopharmaceutics:

1. To facilitate our review of the proposed strength dependent dissolution acceptance criteria for venetoclax tablets, provide the individual vessel dataset in .xpt format for all lots used in the pivotal clinical trial (Study M13-982) and the supportive clinical trial (Study M12-175), as well as all lots included in 3.2.P.5.4 Batch Analyses, and 3.2.P.8.3 Stability Data (i.e, under long term storage) that were generated using the proposed dissolution method. The dataset columns should include dosage strength, lot/batch number, batch use [clinical trial number, stability test conditions], uncoated/film-coated, debossed/unmarked, tablet manufacturing site, stability timepoint, vessel number, dissolution timepoint, and cumulative drug release.

If you have any questions, please contact me, at (240) 402-6153. Please respond by January 4, 2016.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Rabiya Laiq -A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -A, 0.9.2342.19200300.100.1.1=2001555007
Date: 2015.12.14 14:47:56 -05'00'

From:	Kallungal, Beatrice
To:	"Jenta, Tuah"; Schary, William; Fong, Maricel (maricel.fong@abbvie.com)
Cc:	Kallungal, Beatrice
Subject:	NDA 208573, Venetoclax - Information Request - 11//23/2015
Date:	Monday, November 23, 2015 12:46:37 PM

Hello,
Please find below the information request for NDA 208573, Venetoclax. Please submit your response to this request via e-mail by **4 pm EST November 30, 2015** followed by officially submitting the response to the NDA.

Please provide the following patient data listing information for Study Protocol M12-175 or M13-982 for the clinical study sites listed below, as applicable:

a) Subject discontinuations (per treatment group: site, subject number, screening visit date, randomization date, date of first dose, date of last dose, date of discontinuation, and reason for discontinuation).

b) Subject assignment per treatment arm.

c) Primary study efficacy endpoint (including patient laboratory values, or relevant diagnostic/imaging results).

d) Concomitant medication list (i.e., non-study medications).

e) All adverse events (per treatment group: preferred term or investigator entry, date start, date stopped, severity and/or resolution, and serious adverse event (SAE [yes/no], death [yes/no]).

f) Protocol deviations and/or violations (if applicable).

This information (a-f) should be grouped and presented by study site as a single pdf file.

Clinical study sites:

1. *Dr. Matthew Davids, (Site# 43157, Boston, MA, USA)*
2. *Dr. William Wierda (Site# 35505, Houston, TX, USA)*
3. *Dr. Steven Coutre (Site# 38961, Stanford, CA, USA)*

Please acknowledge receipt of this request. If you have any questions, please let me know.

Regards,

Beatrice

Beatrice Kallungal

Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
11/24/2015

From:	Kallungal, Beatrice
To:	Jenta, Tuah
Cc:	Schary, William; Fong, Maricel; Kallungal, Beatrice
Subject:	RE: NDA 208573, Venetoclax - Information Request - 11/24/2015
Date:	Tuesday, November 24, 2015 2:16:45 PM

Hi Tuah,
In the top paragraph of the study report M12-175, the Applicant mentioned that "the ECG statistical analysis will be included in a separate QT report (R&D/15/0254). Accumulation ratio assessment was performed on the Arm A dose escalation subjects between the multiple dose visit (Week 3/6 Day 1) and the single dose visit (Week 1 Day –7/–3)". We are not able to locate that study report.

Please submit that report (and its dataset) by **4 pm EST Monday November 30, 2015**. If it has already been submitted, please provide its location.

Thanks,

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
11/24/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208573

NDA ACKNOWLEDGMENT

AbbVie, Inc.
Attention: Tuah Jenta, PhD, RAC
Associate Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, IL 60064

Dear Dr. Jenta:

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: Venetoclax; 10, 50, and 100 mg Tablet

Date of Application: October 29, 2015

Date of Receipt: October 29, 2015

Our Reference Number: NDA 208573

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 December 28, 2015 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, call me at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Beatrice Kallungal, BS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

BEATRICE A KALLUNGAL
11/12/2015

From:	Kallungal, Beatrice
To:	"Jenta, Tuah"; Schary, William; Fong, Maricel (maricel.fong@abbvie.com)
Cc:	Kallungal, Beatrice
Subject:	NDA 208573, Venetoclax - Information Request - 11/09/2015
Date:	Monday, November 09, 2015 4:07:55 PM
Attachments:	Highlights_ClinPharm_and_Cardiac_Safety.doc

Hi Tuah,
Please find the enclosed information request for NDA 208573, Venetoclax. Please submit your response to this request via e-mail by **4 pm EST Monday November 23, 2015** followed by officially submitting the response to the NDA.

- *Please complete the attached ClinPharm and Cardiac Safety Table*

Please acknowledge the receipt of this request.

Regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

Table 1. Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose and exposure	Include maximum proposed clinical dosing regimen Mean (%CV) Cmax and AUC at the single maximum proposed clinical dose 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 • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t½	• Mean (%CV) for parent • 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/

BEATRICE A KALLUNGAL
11/09/2015

From:	Kallungal, Beatrice
To:	"Jenta, Tuah"
Cc:	Schary, William; Fong, Maricel; Kim, Daniel W; Kallungal, Beatrice
Subject:	RE: NDA 208573, Venetoclax - Information Request
Date:	Thursday, November 05, 2015 9:34:24 AM
Attachments:	image003.png

Hi Tuah,

The samples are requested by CMC and DMEPA teams. From a CMC stand point the request for the blister pack is for physical review of the blister container closure. Couple of [Week 1: 7-day weekly wallet (10 mg x 14)] with placebo would be acceptable.

DMEPA would like to receive 2 samples of the blister cards for weeks 1-4.

Feel free to extend the deadline for response of this request until Wednesday of next week (11/12/15).

Regards,

Beatrice

From: Jenta, Tuah [mailto:tuah.jenta@abbvie.com]
Sent: Wednesday, November 04, 2015 1:43 PM
To: Kallungal, Beatrice
Cc: Schary, William; Fong, Maricel; Kim, Daniel W; Jenta, Tuah
Subject: RE: NDA 208573, Venetoclax - Information Request
Importance: High

Hi Beatrice,

My CMC and Packaging teams would like clarification, regarding bullet point #2 in your information request email below:

AbbVie would like to clarify the FDA Information Request of "Please provide samples of the blister container closure system and packaging".

AbbVie's interpretation of this request are for the samples used during the Human Factors Summative Testing described in the Packaging Human Factors Report provided in Section 1.14.1.4. Is

AbbVie's interpretation correct? If so, AbbVie can provide samples from the 4 Week Starting Pack that contain:

- Week 1: 7-day weekly wallet (10 mg x 14)
- Week 2: 7-day weekly wallet (50 mg x 7)
- Week 3: 7-day weekly wallet (100 mg x 7)
- Week 4: 7-day weekly wallet (100 mg x 14)
- Quick Start Guide
- Outer monthly carton (the components listed above are all housed within this outer monthly carton)

While these samples are comparable to the final commercial configurations, some minor design adjustments may be made. In addition, the final commercial artwork will be slightly different.

Unit dose configurations will also be available commercially, however these configurations were not used during the Human Factors Summative Testing, and therefore samples are not available at this time. Prototypes of these configurations can be provided at a future date if needed.

In addition, to help us provide the exact samples needed, can further clarification please be provided:

- Are these samples intended for physical review of the container closure and packaging or for functionality testing, or for another purpose?
- The blister samples will contain placebo tablets. Will this be acceptable?
- How many of each sample is required?

Please assist in getting answers to our questions above from your reviewer, so my team can provide an appropriate response to you by the deadline.

Appreciate your help with this, Beatrice.

Regards,

Tuah

TUAH JENTA, PHD, RAC
Associate Director, Regulatory Affairs
Area & Affiliate Strategy (US/Canada)

abbvie

AbbVie Inc
1 North Waukegan Road
Dept PA77, Bldg AP30-1
North Chicago, IL 60064
USA
OFFICE +1 847-937-2434
CELL (b) (6)
EMAIL tuah.jenta@abbvie.com

From: Kallungal, Beatrice [mailto:Beatrice.Kallungal@fda.hhs.gov]
Sent: Tuesday, November 03, 2015 2:12 PM
To: Jenta, Tuah; Schary, William; Fong, Maricel
Cc: Kallungal, Beatrice
Subject: NDA 208573, Venetoclax - Information Request

Hi Tuah,
Please find below the information request for NDA 208573, Venetoclax. Please submit your response to this request via e-mail (and shipment) by **4 pm EST Friday November 6, 2015** followed by officially submitting the response to the NDA.

- *Please submit (or identify the location in the NDA) the site-level dataset "clinsite.xpt" as referenced in Attachment 1: Technical Instructions, Submitting Bioresearch Monitoring Clinical Data in eCTD Format of the preNDA meeting minutes*
- *Please provide samples of the blister container closure system and packaging*

Please acknowledge the receipt of this request.

Regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
11/05/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110159

MEETING MINUTES

AbbVie, Inc.
Attention: Tuah Jenta, PhD, RAC
Associate Director, Regulatory Affairs
1 N. Waukegan Road
Dept PA77/Bldg. AP30
North Chicago, IL 60064

Dear Dr. Jenta:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Venetoclax, ABT-199 (A-1195425.0; GDC-0199).

We also refer to the telecon between representatives of your firm and the FDA on September 22, 2015. The purpose of the meeting was to discuss the submission plan and proposed content and format for the proposed NDA for venetoclax in order to align with the Agency's expectations for informational content and timelines.

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

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, MS, ACNP-BC
Clinical Team Leader
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:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	September 22, 2015; 3:00 PM – 4:00 PM EDT
Meeting Location:	Teleconference
Application Number:	IND 110159
Product Name:	Venetoclax, ABT-199 (A-1195425.0; GDC-0199)
Indication:	For the treatment of patients with chronic lymphocytic leukemia (CLL), including those with 17p deletion, who have received at least one prior therapy
Sponsor/Applicant Name:	AbbVie, Inc.
Meeting Chair:	Virginia Kwitkowski, MS, ACNP-BC
Meeting Recorder:	Beatrice Kallungal, BS

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Ann Farrell, MD, Director
Virginia Kwitkowski, MS, ACNP-BC, Clinical Team Lead
Lori Ehrlich, MD, PhD, Clinical Reviewer
Beatrice Kallungal, BS, Senior Regulatory Project Manager

OHOP/Division of Hematology, Oncology, Toxicology
Christopher Sheth, PhD, Team Lead
Ramadevi Gudi, PhD, Reviewer

Office of Biostatistics/Division of Biometrics V
Lei Nie, PhD, Team Leader

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Bahru Habtemariam, PharmD, Acting Team Lead
Vicky Hsu, PharmD, Clinical Pharmacology Reviewer

CDER eData Management Solutions/Office of Business Informatics
Rui Li, MD, MS, Computer Scientist

EASTERN RESEARCH GROUP ATTENDEES
Christopher A. Sese, Independent Assessor

AbbVie Attendees
Andrew Storey, MS, Vice President, US Regulatory Affairs
Rod Humerickhouse, MD, PhD, Global Project Director
Maria Verdugo, MD, Senior Medical Director, Oncology Development
Monali Desai, MD, MPH, Senior Medical Director, Product Safety
Jane Qian, PhD, Director, Statistics
Todd Busman, MS, Assistant Director, Statistics
Shekman Wong, PhD, Director, Clinical PK/PD
Ahmed Salem, PhD, Assistant Director, Clinical PK/PD
Myra Herrle, PhD, RPh, RAC, Senior Director, Regulatory Affairs
David Breines, PhD, Senior Director, Global Regulatory Leader
William Schary, PhD, RAC, Director, Regulatory Affairs
Tuah Jenta, PhD, RAC, Associate Director, Regulatory Affairs

Genentech/Roche Attendees
Bea Lavery, MS, Global Franchise Head, Hematology, Regulatory Affairs
Michael Wenger, MD, Global Development Team Leader
Dale Miles, PhD, Senior Scientist, Clinical Pharmacology
Smita Kshirsagar, PhD, Senior Scientist, Clinical Pharmacology
Coen Bernaards, PhD, Principal Statistical Scientist
Sofia Khan, PharmD, MPH, Director, Global Regulatory Leader
Emily Trinh, MS, US Regulatory Partner

1.0 BACKGROUND

Venetoclax is a selective, potent, orally bioavailable, small molecule, B-cell lymphocyte-2 (Bcl-2) inhibitor that restores programmed cell death (apoptosis) in cancer cells. Bcl-2 over-expression is a major contributor to the pathogenesis of some types of lymphoid malignancies, such as CLL.

AbbVie and Genentech/Roche (the Sponsors) are jointly developing venetoclax under IND 110159 and IND 115045 for the potential treatment of patients with hematologic malignancies.

The purpose of this Type B meeting request was to discuss the submission plan and proposed content and format for the New Drug Application (NDA) for venetoclax (ABT-199, GDC-0199) for the single agent treatment of (b) (4) patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) who specifically harbor the 17p deletion (17p del) mutation; (b) (4) . Pertinent regulatory and administrative topics related to the proposed NDA were also identified for discussion. The first module of the NDA was submitted on 09/15/15 and the final module is expected on 10/29/15.

FDA sent Preliminary Comments to AbbVie on September 16, 2015.

2. DISCUSSION

Clinical

Question 1: Proposal to Assess Differences Between IRC- and Investigator-Assessed Response Rates from Studies M13-982 and M12-175

Does the Agency agree with the Sponsors' proposal to provide an overview and tabular presentation of subjects that were CR/CRi/nPR/PR per investigator-assessed but not in the same category per Independent Review Committee (IRC)-assessed for Studies M13-982 and M12-175?

FDA Response:
Yes, this is acceptable. However please plan to fully discuss discrepancies going in either direction.

Meeting Discussion:
No discussion.

Safety

Question 2: Postmarketing Pharmacovigilance Plan for Venetoclax

(2a) Does the Agency agree that the Pharmacovigilance (PV) Plan is appropriate for the postmarketing use of venetoclax?

FDA Response:
Yes, your plan appears appropriate, however, whether additional measures are required to ensure the safe and effective use of venetoclax will be a review issue upon review of the NDA.

Meeting Discussion:
No discussion.

(2b) Can the Agency provide any feedback or comment on the proposed routine risk minimization measures for the safe use of venetoclax in the postmarketing setting?

FDA Response:
We have no additional comments regarding the proposed risk minimization measures.

Meeting Discussion:
No discussion.

Question 3: Safety Narrative Format and Content

Does the FDA consider the format and content of the safety narratives to be adequate to permit an accurate understanding of the clinical course of the pertinent clinical events?

FDA Response:
The format of the safety narratives is acceptable.

Meeting Discussion:
No discussion.

Regulatory
Question 4: Content and Format of the NDA
Regarding the NDA for single agent venetoclax for the treatment of patients with R/R CLL, including patients with the 17p del:

(4a) Does the FDA agree that the proposed content and format of the planned NDA for venetoclax as outlined in the Table of Contents (Appendix C) is adequate and could constitute a complete NDA to support the proposed indication (Section 4.0) under the provisions for Accelerated Approval (21 CFR 314 Subpart H)?

FDA Response
From a technical standpoint (not content related) yes, the proposed format for the planned NDA is acceptable. However, please see additional comments below.

- **If you are utilizing m1 v3.3 DTD, then FDA Form 3397 can be placed in m1.1.3 otherwise, please provide it in m1.2 cover letter section, with a clear leaf title.**
- **For archival purposes, also submit a pdf file of any document submitted in word (e.g. labeling). When you submit word documents, make sure the leaf title includes "word", so reviewers could quickly identify the word version of the document.**
- **The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6, should be provided in tabular format and linked to the referenced studies in m5.**
- **Do not provide duplicate heading element (e.g.m3.2.s.2.3) for sections that have more than one document. Instead, a single m3.2.s.2.3. section should be provided and referenced documents should have clear leaf title, that is indicative of the content**
- **Providing Table of Contents in m3.1 and 4.1, is not necessary in the eCTD structure.**

Cross referencing information – eCTD section m1.4.4

Sponsors options of cross referencing information submitted to another application (if any), would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

1. **To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (non- eCTD or paper) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the**

submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.,) of the referenced document.

2. **To use the second option (cross application links), both applications would need to be in eCTD format. The applications need to include the appropriate prefix in the href links (e.g. (e.g. xlink:href="../../ind000000/0009/m2/24-nonclin-over/nonclinical-overview.pdf">)). In the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference to" and the application number (e.g. Cross Ref to ind104405). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.**

   Prior to using cross application linking in an application, it is recommended that sponsor submits an "eCTD cross application links" sample, to ensure successful use of cross application links.

   To submit an eCTD cross application links sample, sponsor would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. For more information on eCTD sample, please refer to the Sample Process web page which is located at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf

Meeting Discussion:
No discussion.

(4b) Does the FDA have any comments on the modules and summaries that were submitted as part of the rolling submission on September 15, 2015?

FDA Response:

Please see instructions below for submitting rolling submissions to CDER.

- **The initial US Regional.xml file should be coded as "presubmission"**
- **Cover letter and form should state "presubmission to rolling submission – part 1 of XXX (depending on how many parts before the final submission)**
- **The subsequent sequences prior to the final sequence should also be coded as "presubmission"**
- **The US Regional of the final submission that makes everything complete and kicks off the clock, should be coded as the "original-application" to start the clock**
- **Cover letter and form of the final submission should state "original application - part XXX of XXX of rolling submission" – this starts the clock for review.**

Please refer to the study data technical conformance guide for data submission. http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

Meeting Discussion:
No discussion.

Question 5: Priority Review Consideration
Does the FDA agree that the proposed data for venetoclax for the treatment of patients with (b) (4) with 17p del R/R CLL can meet the criteria for Priority Review?

FDA Response:
Yes, the submitted topline data could meet the criteria for Priority Review; however, this will not be determined until the application is filed.

Meeting Discussion:
No discussion.

Question 6: Clinical Site Inspections
Does the FDA agree that the Subject Level Data by Clinical Site for Studies M13-982 and M12-175 are sufficient for the Agency's purposes of site inspection selection?

FDA Response:
We agree. Additional Information Requests may be sent during the course of the application review, to prepare for clinical site audits.

Meeting Discussion:
No discussion.

Question 7: Postmarketing Requirements
Does the Agency agree with the Sponsors' initial assessments for postmarketing requirements?

FDA Response:
Yes, we agree.

Please clarify when the final clinical results for the hepatic impairment study will be available.

Meeting Discussion:
The Sponsor stated that as a provisional estimate (although they are still finalizing the vendor to perform the study), the anticipated availability of the final Clinical Study Report is December 2017. The Agency noted this response.

Administrative
Question 8: Applicant Orientation Meeting
Does the FDA agree to the Sponsors' proposal on having a meeting and timing for an applicant orientation meeting for the venetoclax NDA?

FDA Response:
Your proposal and timing for an application orientation meeting are acceptable.

Meeting Discussion:
No discussion.

Question 9: Other Considerations
In light of agreements reached with the FDA during the development of venetoclax in R/R CLL and information provided in the Pre-NDA information package, does the FDA agree with the Sponsors' assessment that there are no major unresolved issues regarding the proposed supportive studies and proposed content and format of the venetoclax NDA?

FDA Response:
We have not identified any major unresolved issues in the review of this pre-NDA meeting package.

Additional Clinical Pharmacology Comments
In the appropriate clinical pharmacology sections of the eCTD, include the following:

- **An evaluation of the effects of covariates such as age, weight, gender, race, etc. on the PK (pharmacokinetics) of venetoclax.**

Meeting Discussion:
The Sponsor confirms that an evaluation of the effects of covariates such as age, weight, gender, race, etc. will be provided as part of the venetoclax population PK report in the NDA.

- **Datasets for clinical pharmacology and biopharmaceutics studies should be complete and not be limited to PK/PD. For example, domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology-related causes of clinical safety outcomes.**

Meeting Discussion:
The Agency stated that the Sponsor's proposal appears acceptable. However, this will be a review issue.

- **Provide all concentration-time and derived PK parameter datasets for all studies. In the study reports, present the PK parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.**

Meeting Discussion:
The Sponsor confirmed that all concentration-time and derived PK parameter datasets for all studies will be provided in the NDA. In the study reports, PK parameter data such as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range will be listed.

- **Provide a table listing of patients with renal or hepatic impairment who have received venetoclax, 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.**

Meeting Discussion:
The Sponsor stated that in accordance with the FDA request above, the Sponsors will provide two table listings (in PDF) of CLL/SLL and NHL subjects with renal and/or hepatic impairment who were treated with venetoclax (from studies M13-982, M12-175, M14-032, M13-365), organized by study number. The renal impairment listing includes: 192 subjects with mild renal impairment (CLCr ≥ 60 and < 90 mL/min) and 80 subjects with moderate renal impairment (CLCr ≥ 30 and < 60 mL/min. The hepatic impairment listing includes: 69 subjects with mild hepatic impairment (total bilirubin less than or equal to ULN [1mg/dL] and AST greater than ULN [40 IU/L], or total bilirubin greater than 1.0 to 1.5 times ULN [>1-1.5mg/dL] and any AST) and 7 subjects with moderate hepatic impairment (total bilirubin greater than 1.5 to 3 times ULN [>1.5-3 mg/dL] and any AST). Hepatic function was defined based on National Cancer Institute Organ Dysfunction Working Group Classification of Hepatic Dysfunction.

The available renal and hepatic function parameters of CLCr calculated by the Cockcroft-Gault equation, AST, ALT, level of impairment (mild, moderate) and total bilirubin will be provided for each subject in the listing.
As a summary of each subject's PK, PD, safety, and clinical efficacy, the Sponsors propose to provide for each subject with mild and moderate renal and hepatic impairment:

- ***Individual apparent clearance;***
- ***Individual apparent volume of central compartment;***
- ***AUC_{24} at the best response (CLL/SLL subjects only);***
- ***AUC_{24} at the worst grade of neutropenia;***
- ***AUC_{24} at the worst grade of infection;***
- ***Minimum total lymphocyte count (CLL/SLL subjects only);***
- ***Minimum tumor size (CLL/SLL patients only),***
- ***Best response (CLL/SLL patients only);***
- ***Worst grade of neutropenia; and***
- ***Worst grade of infection.***

The complete time course of each subject's PK, PD, safety, and clinical efficacy will be part of the analysis ready dataset for the exposure-response report.

The Sponsor provided the example tables below to illustrate the proposed listings:

LISTING OF SUBJECTS WITH HEPATIC IMPAIRMENT AND THEIR AVAILABLE RENAL AND HEPATIC FUNCTION

Study	Subject No.	Cancer Type	Renal Impairment Status	Hepatic Impairment Status	Creatinine Clearance (mL/min)	AST (IU/L)	ALT (IU/L)	Bilirubin (mg/dL)
12175	103	CLL/SLL*	Moderate	Mild	55.61	26	18	1.05
	106	CLL/SLL*	Mild	Mild	70.15	43	32	0.58
	107	CLL/SLL*	Normal	Mild	114.64	46	14	0.35
	115	CLL/SLL*	Normal	Mild	102.04	48	31	0.6
	124	CLL/SLL*	Moderate	Mild	50.04	84	75	0.4
	133	CLL/SLL*	Normal	Mild	121.35	44	33	0.4
	139	CLL/SLL*	Mild	Mild	86.1	26	16	1.23
	141	CLL/SLL*	Mild	Mild	81.15	29	20	1.1
	146	CLL/SLL*	Mild	Mild	74.09	41	53	0.4
	150	CLL/SLL*	Moderate	Mild	46.83	42	21	0.47
	166	CLL/SLL*	Mild	Mild	79.3	54	9	0.76
	202	NHL*	Mild	Mild	71.82	20	28	1.05
	226	NHL*	Mild	Mild	77.38	43	34	0.4

SUMMARY OF PK, PD, EFFICACY AND SAFETY FOR SUBJECTS WITH RENAL AND HEPATIC IMPAIRMENT

Study	Subject No.	Cancer Type	Renal Impairment Status	Hepatic Impairment Status	CL/F (L/day)	V2/F (L)	Variable	Time (days)	AUC** (µg*hr/mL)	Response
12175	103	CLL/SLL*	Moderate	Mild	207	168	Best Tumor Response	79.0	38.6	PR
							Minimum Total Lymphocytes (10**9/L)	136.0	38.0	0.2
							Minimum Tumor Size (cm**2)	161.0	38.0	2.38
							Worst Grade of Infection	11.0	59.5	2
							Worst Grade of Neutropenia	10.0	21.1	4
	104	CLL/SLL*	Mild	Normal	194	136	Best Tumor Response	84.9	49.5	PR
							Minimum Total Lymphocytes (10**9/L)	43.1	78.1	0.2
							Minimum Tumor Size (cm**2)	84.9	49.5	17.35
							Worst Grade of Infection	41.9	78.1	3
							Worst Grade of Neutropenia	27.9	36.2	3
	106	CLL/SLL*	Mild	Mild	405	218	Best Tumor Response	43.0	10.8	SD
							Minimum Total Lymphocytes (10**9/L)	105.0	10.4	7.2
							Minimum Tumor Size (cm**2)	74.0	10.4	40.03
							Worst Grade of Infection	0.0	2.0	0
							Worst Grade of Neutropenia	0.0	2.0	0

The Agency stated that the Sponsor's proposal is acceptable. In addition to listings of individual patients, please provide summary of safety by organ impairment category (e.g, Mild Hepatic Impairment, Moderate hepatic impairment, etc). The summary should include rates severe adverse events per organ impairment category.

The Sponsor asked whether given the lack of renal excretion of venetoclax (<0.1% excreted in urine), does the Agency still require the listings for normal/mild/moderate renal impaired patients? The Agency stated that yes, using available data the Sponsor should provide listing and summary of rates of adverse events by renal impairment category.

- **We encourage you to refer to the Guidance for Industry *Population Pharmacokinetics*. For any population PK models all datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/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 should be provided for all major model building steps (e.g., base structural model, covariates models, final model, and validation model). These files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which give an overview of modeling steps should be included. For the population analysis reports, we request that you submit, in addition to the 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. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.**

Meeting Discussion:
The Sponsor confirmed that a venetoclax population PK analysis that meets the guidance above will be provided in the NDA. The FDA noted the Sponsor's response.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Sponsor stated that they intend to submit a complete application and therefore, there are no agreements for late submission of application components.

- 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. The Sponsor stated that the list of manufacturing facilities was submitted with the initial module that was submitted on 09/15/15. The Sponsor stated that the clinical sites listing will be submitted with the final module on 10/29/15.

- A preliminary discussion on the need for a REMS was held and it was concluded that at this time, the Agency does not see the need for REMS, however the Agency reserves a final decision on the need for a REMS until after the review team has fully reviewed the data that is to be submitted.

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. 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 *PLLR Requirements for Prescribing Information* websites including:

- 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 in the PI for human drug and biological products
- 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 42 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.

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

MANUFACTURING FACILITIES

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

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

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI) Requests

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

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

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

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

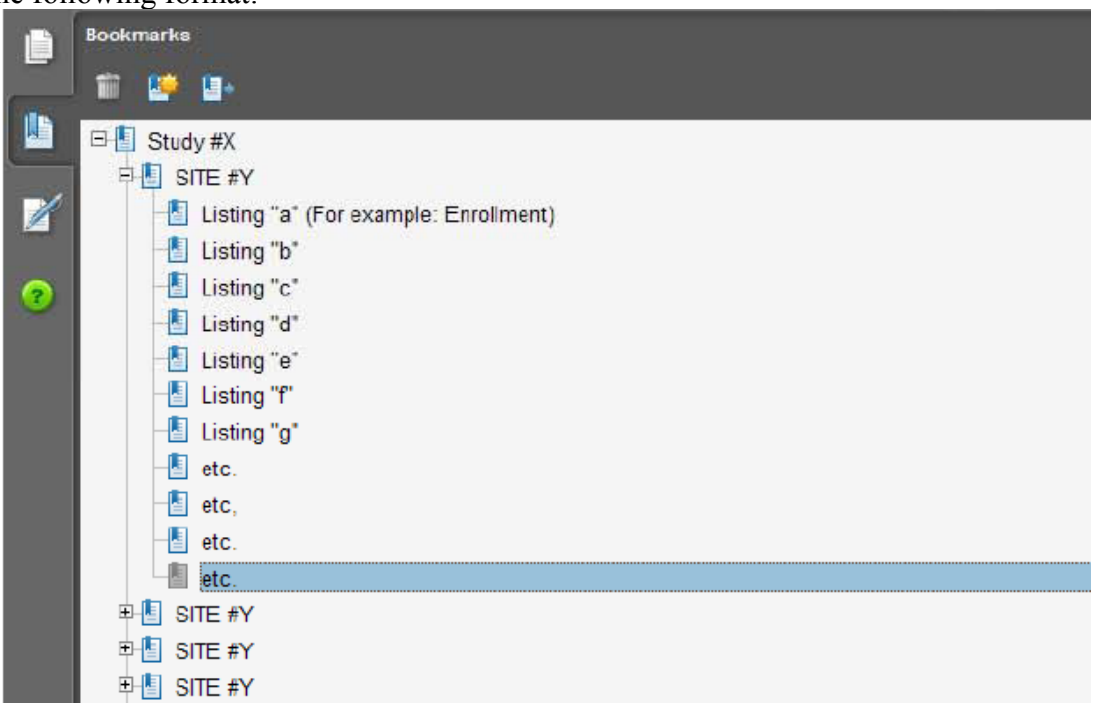
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

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

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

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

Attachment 1

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

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

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

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

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

[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

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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/s/

VIRGINIA E KWITKOWSKI
09/30/2015

From:	Kallungal, Beatrice
To:	"Jenta, Tuah"; Schary, William; Fong, Maricel (maricel.fong@abbvie.com)
Cc:	Kallungal, Beatrice
Subject:	NDA 208573, Venetoclax - Information Request - 11//04/2015
Date:	Wednesday, November 04, 2015 4:02:45 PM

Hello,
Please find below the information request for NDA 208573, Venetoclax. Please submit your response to this request via e-mail by **4 pm EST November 9, 2015** followed by officially submitting the response to the NDA. If this information is already included in the NDA submission, please help us identify the location of this document in the NDA.

- *Submit all versions of the informed consent form documents (U.S. or ex-US, as applicable) in Study Protocols M13982 and M12175.*

Please acknowledge receipt of this request.

Regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
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E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
11/04/2015

From:	Kallungal, Beatrice
To:	"Jenta, Tuah"; Schary, William; Fong, Maricel (maricel.fong@abbvie.com)
Cc:	Kallungal, Beatrice
Subject:	NDA 208573, Venetoclax - Information Request
Date:	Tuesday, November 03, 2015 3:11:39 PM

Hi Tuah,
Please find below the information request for NDA 208573, Venetoclax. Please submit your response to this request via e-mail (and shipment) by **4 pm EST Friday November 6, 2015** followed by officially submitting the response to the NDA.

- *Please submit (or identify the location in the NDA) the site-level dataset "clinsite.xpt" as referenced in Attachment 1: Technical Instructions, Submitting Bioresearch Monitoring Clinical Data in eCTD Format of the preNDA meeting minutes*
- *Please provide samples of the blister container closure system and packaging*

Please acknowledge the receipt of this request.

Regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
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/s/

BEATRICE A KALLUNGAL
11/03/2015

From: Kallungal, Beatrice
To: "Jenta, Tuah"
Cc: Kallungal, Beatrice
Subject: NDA 208573, Venetoclax - Non-clinical Information request
Date: Wednesday, September 30, 2015 4:37:13 PM

Hi Tuah,
Please find below the information request for NDA 208573, Venetoclax. Please submit your response to this request via e-mail by **4 pm EDT Wednesday October 14, 2015** followed by officially submitting the response to the NDA.

In reference to Abbott report number, R&D/10/421 (Abbott study number TX09-236), Study title: "Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes With A-195425", we have noted some issues in the report (R&D/10/421) submitted to the NDA 208573, involving the interpretation of the study data for the S9-activated 3 hour treatment group. Please see below and address the inconsistencies in the study report.

In the 3 hour S9-activated treatment group, the high dose selected (50 µg/mL) for chromosome aberrations analysis did not meet the acceptance criteria required to justify the high dose (page16 of the report). (b) (4) [redacted] *None of these issues or changes from the original protocol was discussed in a protocol deviation or an amendment.*

1. *Amend the final report to address the acceptability of the high dose selected for chromosome aberration analysis for the 3 hour S9-activated treatment.*
2. *Amend the final report to address the errors in the text and the tables.*

Please acknowledge receipt of this request.

Regards,

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
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10903 New Hampshire Avenue
Silver Spring, MD 20993
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E-Mail: beatrice.kallungal@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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/s/

BEATRICE A KALLUNGAL
09/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110159

GRANT –
BREAKTHROUGH THERAPY DESIGNATION

AbbVie, Inc.
Attention: Tuah Jenta, PhD, RAC
Associate Director, Regulatory Affairs
1 N. Waukegan Road
Dept PA77/Bldg. AP30
North Chicago, IL 60064

Dear Dr. Jenta:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Venetoclax (ABT-199).

We also refer to your February 27, 2015 request for Breakthrough Therapy designation. We have reviewed your request and have determined that Venetoclax (ABT-199) for the treatment of patients with relapsed or refractory (R/R) chronic lymphocytic leukemia who harbor the 17p deletion (17p del) cytogenetic abnormality (17p del CLL), meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of Venetoclax (ABT-199) for the treatment of patients with relapsed or refractory chronic lymphocytic leukemia (R/R CLL) who harbor the 17p deletion cytogenetic abnormality to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.*[1]

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics,* Attachment 1, for potential topics for discussion at this initial

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

breakthrough therapy meeting[2]. Please refer to the *Guidance for Industry: Formal Meetings between FDA or Sponsors and Applicants*[3] for procedures on requesting a meeting. If you feel that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project Manager noted below to discuss the timing of this meeting.

If the breakthrough therapy designation for Venetoclax (ABT-199) for the treatment of patients with relapsed or refractory (R/R) chronic lymphocytic leukemia who harbor the 17p deletion (17p del) cytogenetic abnormality (17p del CLL) is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

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

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[2] http://www fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm

[3] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

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/s/

ANN T FARRELL
04/27/2015

Benton, Sandra J

From: Benton, Sandra J
Sent: Thursday, April 09, 2015 8:08 AM
To: Jarow, Jonathan; Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Griebel, Donna; Mahoney, Karen M (Deputy DD, DNDP); Hinton, Denise; Sacks, Leonard V
Cc: Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Moscicki, Richard; Throckmorton, Douglas C; Kallungal, Beatrice; Kwitkowski, Virginia; Kaminskas, Edvardas; Farrell, Ann T; Ehrlich, Lori (Lori.Ehrlich@fda.hhs.gov); Kwitkowski, Virginia
Subject: RE: April 10, 2015 - Medical Policy Council – Breakthrough Therapy Designation - IND 110159

As the Council agrees with DHP's recommendation to grant AbbVie's breakthrough therapy designation request and does not believe a Council discussion is needed, this request will be cancelled from the April 10, 2015 meeting agenda.

Please let me know if you have any questions. Thanks!

Sandy Benton
Senior Policy Analyst
CDER/Office of Medical Policy
301-796-1042
sandra.benton@fda.hhs.gov

From: Benton, Sandra J
Sent: Monday, March 30, 2015 8:10 AM
To: Jarow, Jonathan; Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Griebel, Donna; Mahoney, Karen M (Deputy DD, DNDP); Hinton, Denise; Sacks, Leonard V
Cc: Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Moscicki, Richard; Throckmorton, Douglas C; Kallungal, Beatrice; Kwitkowski, Virginia; Kaminskas, Edvardas; Farrell, Ann T; Ehrlich, Lori (Lori.Ehrlich@fda.hhs.gov); Kwitkowski, Virginia
Subject: April 10, 2015 - Medical Policy Council – Breakthrough Therapy Designation - IND 110159

Hi! OMP has scheduled a Medical Policy Council discussion on April 10, 2015 regarding the breakthrough therapy designation request from AbbVie, Inc. for its IND 110159, Venetoclax (ABT-199) for the treatment of patients with relapsed or refractory (R/R) chronic (b) (4) leukemia who harbor the 17p deletion (17p del) cytogenetic abnormality (17p del CLL).

DHP recommends that this breakthrough therapy request be granted. Attached is DHP's background on the breakthrough therapy designation with its rationale for granting the request.

DHP has asked if this request can be reviewed by email.

Would you please review DHP's recommendation and let me know by COB Friday, April 3 if –

- You agree with DHP's recommendation regarding this breakthrough therapy request and you do not believe a Council discussion is needed.
- You agree with DHP's recommendation regarding this breakthrough therapy request. However, you would like a Council discussion regarding any questions you have.

- You disagree with DHP's recommendation regarding this breakthrough therapy request.

If the Council agrees with bullet 1, I will cancel the discussion for this IND.

Please let me know if you have any questions. Thank you.

Sandy Benton
Senior Policy Analyst
CDER/Office of Medical Policy
301-796-1042
sandra.benton@fda.hhs.gov

<< File: IND 110159 ABT-199 BTDR MPC Ehrlich.ppt >> << File: IND 110159 MPC BTD Brief.doc >> << File: 110159BTDR.PDF >>

CDER Medical Policy Council Brief
Breakthrough Therapy Designation
Division of Hematology Products
April 10, 2015

Summary Box

1. IND 110159
2. Sponsor: AbbVie, Inc.
3. Drug: Venetoclax (ABT-199)
4. Indication: For the treatment of patients with relapsed or refractory (R/R) chronic (b) (4) leukemia who harbor the 17p deletion (17p del) cytogenetic abnormality (17p del CLL)
5. Is the drug intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition? Yes.
6. Does the preliminary clinical evidence indicate that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints? Yes, Ventoclax has the potential to provide a substantial improvement over available therapies for the treatment of patients with 17p del CLL with preliminary evidence of complete disease responses.

Division: Division of Hematology Products
Medical officer: Lori Ehrlich
Clinical Team Leader: Virginia Kwitkowski

1. Brief description of the drug

Venetoclax is a Bcl-2 family protein inhibitor. Bcl-2 is an oncogenic protein that is overexpressed in some lymphoid malignancies and is associated with increased resistance to chemotherapy. CLL cells are almost universally dependent on Bcl-2; therefore, inhibition of Bcl-2 could restore apoptosis in CLL cells. Because Bcl-2 is downstream of other survival signals such as p53, it is anticipated that cells with p53 dysfunction or those resistant to other therapies will remain responsive to venetoclax.

2. Brief description of the disease and intended population

CLL is a neoplasm composed of monomorphic small, round to slightly irregular, mature B cell lymphocytes in the peripheral blood, bone marrow or lymphatic tissue. CLL is the most common leukemia of adults in Western countries. Based on SEERS data from 2004-2008 the age adjusted incidence rate of CLL is approximately 4.2 per 100,000 men and women per year with the rate in men being approximately twice that of women. From 2004-2008 the median age of diagnosis was 72 years of age with approximately 70% of patients being diagnosed at age 65 or later.

The clinical course of CLL varies depending on risk stratification by the Rai staging system or Binet classification but it is typically a slowly progressing disease. Chromosomal abnormalities such as del 17p and 11q are associated with a significantly poorer prognosis. 17p del is present in 5-7% of patients with early stage CLL[1] and has been correlated in multiple clinical studies to have higher tumor burden, shorter progression-free survival, and shorter overall survival[2]. Higher rates of refractoriness to standard chemotherapies have been seen in this population. The median overall survival for patients with the 17p deletion mutation has been consistently observed as less than 24 months[2].

3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area

In support of their Breakthrough Therapy Designation Request, the Sponsor reports the best overall response rate with rates of complete responses and partial responses. They have provided supporting information on minimal residual disease and safety.

For their ongoing phase 2 trial, M13-982, the primary endpoint is overall response rate. The secondary endpoints are complete response rate, partial response rate, duration of response, progression free survival, time to progression, overall survival, and percent of subjects proceeding to allogenic stem cell transplant.

In CLL, the ultimate clinical benefit endpoint is overall survival, but the long duration of studies needed to reach median overall survival is often limiting in this disease. The division has previously accepted progression free survival for regular approval or overall response rate with a long duration of response for accelerated approval. Rate of complete responses and evidence of negative minimal residual disease have been provided as supporting information.

4. Brief description of available therapies (if any)

Only one agent, ibrutinib, has been approved in the US specifically for the 17p del subset of patients with CLL. The overall response rate for ibrutinib in the trial that led to its approval was 47.6% (vs. 4.7% in the control arm) with all responses categorized as partial and no complete responses. Idelalisib is approved in combination with rituximab for the treatment of patients with relapsed CLL for whom rituximab alone would be considered appropriate therapy due to other co-morbidities. Though not approved specifically for the treatment of patients with 17p del, this regimen is recommended for these patients in the NCCN guidelines and approved in Europe for first line treatment for patients with 17p del or TP53 mutations unsuitable for chemo-immunotherapy. The response rate for idelalisib in combination with rituximab was 78.3% with no complete responses. Common standard therapies of fludarabine + cyclophosphamide + rituximab or bendamustine + rituximab have historically low response rates of 35% and 7%, respectively. See Table 1 for a summary of the currently available therapies for 17p del CLL.

Table 1: Treatment Options for 17p del CLL

Trial	Product (s)	N	Response Rate in del17p CLL	% Complete Response
Ibrutinib vs. ofatumumab	Ibrutinib*	127 (63 on ibrutinib)	47.6% vs. 4.7%	0%
Rituximab ± idelalisib	Idelalisib + Rituximab	46	78.3%	0%
Single arm (Badoux 2011 Blood)[3]	Fludarabine + Cyclophosphamide + Rituximab	20	35%	0%
Single arm (Fischer 2011 JCO)[4]	Bendamustine + Rituximab	14	7%	7%

* FDA approved specifically for patients with 17p del CLL

5. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation

Ibrutinib (Imbruvica) was previously granted Breakthrough Therapy Designation for 17p del CLL, and has since been approved for that indication. Obinutuzumab (Gazyva), ofatumumab (Arzerra), and idelalisib (Zydelig) have been granted BTD for CLL.

6. Description of preliminary clinical evidence

Patient information was submitted from two ongoing trials of venetoclax in relapsed and refractory CLL. The first was a phase 1 trial, M12-175, for determination of the recommended phase 2 dosing. This trial enrolled 56 patients with CLL in the dose-finding portion and 60 patients in a safety expansion cohort. Of those, 8 patients had 17p del CLL and were treated at the target dose of 400 mg daily. The second trial was a phase 2 study, M13-982, open-label single-arm trial of single-agent venetoclax for the treatment of relapsed/refractory 17p del CLL with a planned enrollment of 107 patients in the main study and 50 in an safety expansion cohort. Of those enrolled on that trial, 25 patients have completed the 36-week response assessment or have discontinued the study. For the total 33 patients, the median time on study was 10.1 months (range 1.3-17.0 months) with a median number of prior treatment regimens of 4, and 37.5% of patients were fludarabine refractory.

A summary of the best responses for these patients are shown in Table 2. An overall response rate of 82% was seen with 9% complete responses and 6% complete responses with incomplete marrow recovery (CRi). Partial responses were seen in an additional 67% of patients, and stable disease was seen in 18%. At the time of reporting, of the 25 subjects in Study M13-982, 19 remain on study, 4 discontinued for progressive disease, 1 discontinued for an adverse event, and 1 proceeded to allogeneic transplant after achieving a nodular PR and is still disease-free 6 months after transplant. For the 8 subjects in Study M12-175, 5 remain on study and 3 discontinued for progressive disease.

Table 2: Best Response for Patients with 17p del CLL Treated with Venetoclax

Response Category	M13-982 N=25	M12-175 N=8	Total N=33
ORR	84%	75%	82%
CR	12%	0	9%
CRi	8%	0	6%
nodular PR	8%	0	6%
PR	56%	75%	61%
SD	16%	25%	18%
PD	0	0	0

Of the 25 patients from trial M13-982, 8 had testing for minimal residual disease (MRD) at the time of complete remission. Two of the 8 patients achieved MRD negativity with a sensitivity of <10-4 cells. Three of the remaining patients have had sequential MRD assessments, and the MRD level continues to decrease.

The Sponsor submitted a summary of safety information for 279 patients who have received venetoclax as monotherapy or in combination with rituximab. The most common adverse reactions were nausea (36%), diarrhea (36%), neutropenia (30%), fatigue (25%), and anemia (24%).

The serious safety risks identified to date are neutropenia and tumor lysis syndrome (TLS). Tumor lysis syndrome was identified as an on-target effect that occurred soon after initiating therapy with venetoclax and in subjects with high tumor burden. The TLS rate from the initial dose-ranging studies was 19.6%, including two deaths and one occurrence of acute renal failure requiring dialysis. Upon intensification of monitoring and prophylactic treatments, the rate of TLS has been reduced to 9.3% and 1.7%, in the main cohort of study M13-982 and the safety expansion cohort of study M12-275, respectively. No further deaths or events requiring dialysis have occurred. The Division believes that the current dose escalation, intensive monitoring, and prophylactic measures for patients to be treated with venetoclax is adequate at this time.

Severe (grade 3-4) neutropenia is reported in 42% of patients with relapsed/refractory CLL receiving venetoclax. Neutropenia with venetoclax appears to be responsive to dose interruptions and granulocyte colony stimulating factor. The rate of grade ≥3 infections in this R/R CLL population at the 400 mg proposed dose of venetoclax was approximately 16%, which is consistent with the historical rates for patients in this setting[5].

Deaths due to adverse events in studies of venetoclax range from 0-8.4%. This compares with 4.6% in the ibrutinib CLL trial (PCYC-1112-CA) and 2.7% in the idelalisib CLL trial (312-0116).

7. Division's recommendation and rationale

DHP recommends that venetoclax be granted Breakthrough Therapy Designation for Relapsed or Refractory CLL harboring the 17p deletion mutation. The disease is a serious condition, and preliminary clinical evidence indicates a substantial improvement over available therapy for the following reasons:

- New mechanism of action, targets Bcl-2
- Venetoclax provides Complete Responses in patients with 17p del CLL (other therapies do not)
- Venetoclax provides a higher Overall Response Rate than available therapies
- Safety profile appears different than available therapies (possibly better)

8. Division's next steps and sponsor's plan for future development

AbbVie intends to submit an application for accelerated approval in August 2015 based on 107 patients with CLL that harbor the 17p deletion mutation. They are developing a companion diagnostic for the assay to determine 17p del status in CLL patients.

They have (b) (4) planned Phase 3 trial (b) (4)

- R/R CLL (incl. 17p del): Venetoclax/rituximab vs. bendamustine/rituximab (Trial MURANO)

(b) (4)

9. References (if any)

1. Zenz, T., et al., *Chronic lymphocytic leukemia and treatment resistance in cancer: the role of the p53 pathway.* Cell Cycle, 2008. **7**(24): p. 3810-4.
2. Stilgenbauer, S. and T. Zenz, *Understanding and managing ultra high-risk chronic lymphocytic leukemia.* Hematology Am Soc Hematol Educ Program, 2010. **2010**: p. 481-8.
3. Badoux, X.C., et al., *Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL.* Blood, 2011. **117**(11): p. 3016-24.
4. Fischer, K., et al., *Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group.* J Clin Oncol, 2011. **29**(26): p. 3559-66.
5. Thurmes, P., et al., *Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic leukemia.* Leuk Lymphoma, 2008. **49**(1): p. 49-56.

IND 110159 Venetoclax (ABT-199) Breakthrough Therapy Designation Request by AbbVie, Inc.

Proposed Indication:

Venetoclax for the treatment of patients with relapsed or refractory chronic lymphocytic leukemia (R/R CLL) who harbor the 17p deletion (17p del) cytogenetic abnormality.

Lori A. Ehrlich, MD, PhD
OHOP/DHP

Reference ID: 3728920

Breakthrough Therapy Designation
FDASIA § 902 requirements

- The disease is serious and life-threatening
- Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

Mechanism of Action: Venetoclax

- Oral, small molecule
- Inhibitor of Bcl-2 protein family
- Restores apoptosis in cancer cells
- Target downstream of other signaling pathways important in CLL cell propagation

Background of 17p del CLL

- 17p includes *TP53*
  - deletion results in loss of p53-dependent apoptosis
- Correlates in multiple clinical studies, with higher tumor burden, shorter PFS, and OS
- Median OS <24 mos.
- High rates of refractoriness to standard chemotherapy (FC and FCR)
- Considered "ultra high risk"

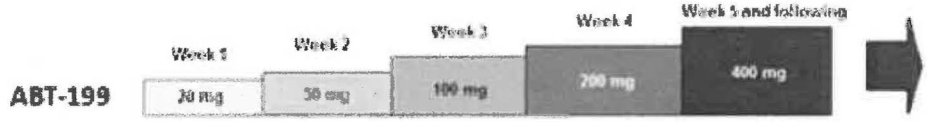
Available Therapy for 17p del CLL

Trial	Product (s)	N	Response Rate in del17p CLL	% Complete Response
Ibrutinib vs. ofatumumab	Ibrutinib*	127 (63 on ibrutinib)	47.6% vs. 4.7%	0%
Rituximab ± idelalisib	Idelalisib + Rituximab	46	78.3%	0%
Single arm (Badoux 2011 Blood)	Fludarabine + Cyclophosphamide + Rituximab	20	35%	0%
Single arm (Fischer 2011 JCO)	Bendamustine + Rituximab	14	7%	7%

*Approved specifically for 17p del CLL population

Phase 2 Trial: M13-982

- Design: Open-label, single arm, venetoclax monotherapy (400 mg)
- Relapsed/refractory 17p del CLL
- Primary endpoint: ORR
- Exploratory endpoint: MRD
- Planned enrollment 107 patients + 50 in safety expansion cohort
- **25 patients** completed the 36-week response assessment or discontinued the study



Phase 1 Trial: M12-175

- Design: Safety and PK of venetoclax monotherapy
- Relapsed/refractory CLL (56 patients) and NHL (70 patients) + 60 patient expansion cohort in R/R CLL
- Primary objectives: safety, PK, MTD, RP2D
- Included **8 patients** with 17p del CLL

Patients with 17p del CLL Treated at 400 mg Venetoclax

25 patients from M13-982

8 patients from M12-175

= **33 patients with 17p del r/r CLL**

Median time on study 10.1 months (range 1.3-17.0)

Median # of prior regimens = 4

Best Response For Patients with 17p del CLL (per INV)

Response Category	M13-982 N=25	M12-175 N=8	Total N=33
ORR	84%	75%	82%
CR	12%	0	9%
CRi	8%	0	6%
nodular PR	8%	0	6%
PR	56%	75%	61%
SD	16%	25%	18%
PD	0	0	0

Minimal Residual Disease

- Among the first 25 patients in M13-982, 8 patients had MRD assessments
- No detectable MRD was reported in 2 out of the 8 patients (sensitivity $<10^{-4}$)
- 3 of 8 had serial MRD assessments, and continued reduction observed in all 3

Comparison of Venetoclax to Available Therapies in 17p del CLL

	Venetoclax	Ibrutinib	Idelalisib + Rituximab	Ofatumumab	FCR regimen
CR/CRi rate	15%	0	0	---	0
ORR	82%	48%	78%	14%	35%

Safety Profile

- 279 patients with R/R CLL have received venetoclax

- The most frequent AEs are:
  - nausea (36%)
  - diarrhea (36%)
  - neutropenia (30%)
  - fatigue (25%)
  - anemia (24%)

Safety Issues

- Tumor lysis syndrome (including fatal) occurred early in the development
  - TLS signal has declined since initiating a stepped-up dosing and prophylaxis
  - Now 9% (down from 20%)
- Neutropenia occurs at grade 3-4 in 42%; responds to G-CSF

Safety Concerns with Available Therapies Not Evident with Venetoclax

Ibrutinib is associated with:

- Atrial fibrillation (6-9%)
- Bleeding events (6% ≥grade 3)

Idelalisib is associated with:

- Hepatitis (14%)
- Colitis (14%)
- Pneumonitis (3.6%)
- Severe cutaneous reactions

Future Development Plans for Venetoclax

- Plan to submit data on 107 patients with 17p del CLL for Accelerated Approval in August 2015
- Planned Phase 3 Trials
  - R/R CLL (incl. 17p del): *Venetoclax*/Ritux vs. Bendamustine/Ritux

Summary

- New mechanism of action, targets Bcl-2
- Venetoclax provides a higher Overall Response Rate than available therapies
- Venetoclax provides Complete Responses in patients with 17p del CLL (other therapies do not)
- Safety profile appears different than available therapies (possibly better)

Regulatory Recommendations

DHP recommends that venetoclax be granted Breakthrough Therapy Designation for Relapsed or Refractory CLL harboring the 17p deletion mutation

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/s/

SANDRA J BENTON
04/09/2015

ANN T FARRELL
04/14/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110159

DENY -
BREAKTHROUGH THERAPY DESIGNATION

AbbVie Inc.
Attention: Tuah Jenta, Ph.D.
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, IL 60064

Dear Dr. Jenta:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABT-199, A-1995425, Bcl-2 Family Protein Inhibitor.

We also refer to your June 3, 2013 request for Breakthrough Therapy designation for the treatment of patients with previously treated 17p deletion mutation-positive chronic lymphocytic leukemia (CLL), as detected by an FDA-approved test.

We have reviewed your request and while we have determined that ABT-199 for the treatment of patients with previously treated 17p deletion mutation-positive CLL as detected by an FDA-approved test meets the criteria for a serious or life-threatening disease or condition, the preliminary clinical evidence you submitted does not indicate that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Therefore, designation as a Breakthrough Therapy cannot be granted at this time.

The rationale for our determination is as follows:

1. There is limited data with which to conclude that ABT-199 may demonstrate substantial improvement over existing therapies.
2. Data on activity at the dose/schedule that you propose to take forward is not available.
3. It is unclear whether the changes to the dose/schedule made in response to the cases of tumor lysis syndrome will improve safety and/or reduce activity.

You may submit a new request if you obtain new clinical evidence that demonstrates a substantial improvement in treatment of patients with previously treated 17p deletion mutation-positive CLL as detected by an FDA-approved test over existing therapies for ABT-199.

If you submit a new request, include the following information:

- *Data on activity and safety at the dose/schedule that you propose to take forward in development.*

For further information regarding Breakthrough Therapy designation, refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the draft Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf).

For further information regarding Fast Track, refer to the guidance for industry *Fast Track Drug Development Programs – Designation, Development, and Application Review.*

If you have any questions, contact Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Division Director
Division of Hematology Products
Office of Drug Evaluation and Research
Center for Drug Evaluation and Research

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

/s/

ANN T FARRELL
07/24/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110159

MEETING MINUTES

AbbVie, Inc.
Attention: Tuah Jenta, Ph.D., RAC
Associate Director, Regulatory Affairs
1 N. Waukegan Road
Dept PA77/Bldg. AP30
North Chicago, IL 60064

Dear Dr. Jenta:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABT-199 (A-1195425.0; GDC-0199).

We also refer to the meeting between representatives of your firm and the FDA on July 02, 2014. The purpose of the meeting was to discuss with the FDA the proposed expedited registration plan for ABT-199 in a subset of R/R CLL patients harboring the 17p deletion cytogenetic mutation and to gain concurrence on the sponsor's proposal to confirm the risk/benefit profile of ABT-199.

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 Beatrice Kallungal, Regulatory Project Manager at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, M.S., RN, ACNP-BC
Lead Clinical Analyst, Clinical Team Leader
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: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: July 02, 2014 2:00 PM – 3:00 PM EDT
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: IND 110159
Product Name: ABT-199 (A-1195425.0; GDC-0199)
Indication: ABT-199 as a single agent for the treatment of adult patients with 17p deletion positive (CLL), as determined by an FDA-approved test, who have received at least one prior therapy.

Sponsor/Applicant Name: AbbVie, Inc.

Meeting Chair: Virginia Kwitkowski, MS, RN, ACNP-BC
Meeting Recorder: Beatrice Kallungal, BS

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)
Jonathan Jarow, MD, Associate Director for Regulatory Science (Acting)

Division of Hematology Products
Ann Farrell, MD, Division Director
Edvardas Kaminskas, MD, Deputy Division Director
Virginia Kwitkowski, MS, RN, ACNP-BC Clinical Team Lead
Adam George, PharmD, Clinical Reviewer
Beatrice Kallungal, BS, Senior Regulatory Project Manager

Office of Biostatistics
Lei Nie, PhD, Team Leader

Center for Devices and Radiological Health (CDRH)

Molecular Genetics Branch (MGB) &
Division of Molecular Genetics and Pathology (DMGP)
Donna Roscoe, PhD, Branch Chief, MGB, DMGP, OIR
Jennifer Dickey, PhD, RAC, Reviewer, MGB, DMGP, OIR

SPONSOR ATTENDEES
Rod Humerickhouse, MD, PhD, Global Project Director, AbbVie
Sari Heitner-Enschede, MD, Medical Director, AbbVie
Monali Desai, MD, MPH, Senior Medical Director, Product Safety, AbbVie
Todd Busman, MS, Assistant Director, Statistics, AbbVie
Shekman Wong, PhD, Director, Clinical PK, AbbVie
David Breines, PhD., Director, GRL, AbbVie
Tuah Jenta, PhD., Associate Director, US RA, AbbVie
Nancy Valente, MD, Vice President, Head, Global Hematology Dept., Genentech/Roche
Beatrice Lavery, MS, Global Franchise Head, Hematology, RA, Genentech/Roche
Jane Huang, MD, Global Development Team Leader, Genentech/Roche
Coen Bernaards, PhD, Principal Statistical Scientist, Genentech/Roche
Sofia Khan, PharmD, MPH, Director, GRL, Genentech/Roche
Thomas Haberberger, Associate Director, US Regulatory Partner, Genentech/Roche

1.0 BACKGROUND

ABT-199 is indicated for the treatment of patients with relapsed or refractory chronic lymphocytic leukemia (R/R CLL) harboring the 17p deletion cytogenetic mutation, as detected by an FDA-approved diagnostic test.

The purpose of this meeting is to gain clarity on the FDA's application of the broader accelerated approval provisions (21 CFR 314.500 Subpart H) as these pertain to ABT-199; secondarily, the sponsors wish to understand the FDA's requirements for demonstrating a meaningful advantage over available therapies (per the FDA's recent draft guidance on "*Expedited Programs for Serious Conditions – Drugs and Biologics*," released June 2013).

The Sponsors' objective for the meeting is to discuss and gain concurrence with the FDA on the proposed expedited registration plan for ABT-199 in a subset of R/R CLL patients harboring the 17p deletion cytogenetic mutation and to gain concurrence on the Sponsors' proposal to confirm the risk/benefit profile of ABT-199.

2. DISCUSSION

Introductory Comments: ***Virginia Kwitkowski stated that because there has been rapid development in the treatment of CLL (as well as 17p del CLL), the Sponsor should be prepared for new drug approvals in these indications to potentially block an accelerated approval for ABT-199. Should that occur, the Sponsor should make every possible argument as to why ABT-199 provides an improvement over available therapy, in their NDA submission.***

Clinical/Medical

1. Does the FDA agree that the design of the single-arm Phase 2 Study M13-982 is appropriate for registration of ABT-199 for the treatment of patients with R/R CLL harboring the 17p del mutation under accelerated approval?

FDA Response:
No. The proposal to conduct the primary analysis when 70/100 patients have been enrolled is not acceptable as it would be considered an interim analysis. It is unlikely that data from 70 patients in a single arm trial would be adequate to support an NDA. You should conduct the primary analysis on at least 100 patients.

At this time it appears that you have adequately identified a population of patients with no available therapies. The acceptability of trial M13-982 to support accelerated approval of ABT-199 will be a review issue at the time of NDA action that will be influenced by therapies which are available to the population of patients with relapsed/refractory CLL harboring the 17p deletion.

Discussion:
In their written response, the Sponsor clarified that the planned analysis will occur once the 70th patient has completed 36 weeks of therapy. IRC confirmation on these first 70 patients would be submitted with the NDA. The remaining 30 patients (beyond 70) will have early response data (prior to 36 week response assessment). Therefore, for the NDA filing, they will have early responses prior to the 36-week time point on all 100 patients. The Sponsor proposes to submit the IRC confirmation for the remaining 30 patients after the NDA submission. The Sponsor added that they also expect to submit with the NDA, data on 25 additional patients (10 dosed at 400 mg) from Study M12-175.

The Agency stated that this approach appears reasonable. The Sponsor was asked to provide clarification on the proposed timeline for submission of the IRC data on the additional 30 patients. The Agency clarified that this data should come in early in the review cycle in order to avoid a major amendment and extension of the review clock. The Sponsor plans to submit a proposed timeline at a later date.

2. Does the FDA agree that the expected results from the Phase 2 Study M13-982 (based on the current data from the R/R CLL subject arm with 17p del from the FIH Study M12-175 [Table 1]) would be sufficient to allow an adequate assessment of benefit/risk at the time the NDA is submitted?

FDA Response: The results projected may be sufficient to allow an assessment of benefit/risk in this population, as long as, durability of response and acceptable safety profile are demonstrated. See FDA response to question 1.

Discussion:
The Sponsor requested clarification on how large a treatment effect and how durable a response would need to be. The Agency stated that the magnitude of response and duration of response that would be considered adequate would be data driven and a review issue.

3. Does the FDA agree that the proposed safety database is adequate to support registration of ABT-199 under accelerated approval conditions?

FDA Response:
It is unclear as to the number of patients that you intend to include in the safety data base to support the NDA. At the meeting, or in your responses, please provide the number of patients with 17p del CLL treated at the proposed dose and schedule that will be available for the safety population at the time of NDA submission. See FDA response to question 1.

Discussion:
The Agency received clarification from the Sponsor that at least interim study reports and data sets for studies M12-175, M13-365, GP28331, G028440, M13-982, and M14-032 would be available and submitted to the NDA to support the safety evaluation. The Agency stated that (b) (4) ***patients in the safety population appeared robust, but would be a review issue at the time of NDA submission.***

Regulatory

4. (b) (4)

FDA Response:
Possibly, however this will be a review issue at the time of NDA action. See FDA introductory comments and response to question 1.

Discussion:
The Agency encouraged the Sponsor to provide an argument in the NDA based on as many characteristics of ABT-199 that may provide evidence of an improvement over available therapy. The Agency would encourage the Sponsor to request a preliminary review of updated data prior to a formal breakthrough therapy designation request (via the Project Manager), once more data is available on the 17 p deletion population. The Sponsor asked whether they would have to pre-specify the analysis conducted for the breakthrough therapy request in the protocol. The Agency stated that they would not request that this be done, given the single-arm design of the trial.

5. Does the FDA agree that the successful completion of the ongoing Phase 3 study GO28667 could convert the initial accelerated approval of ABT-199 to full approval (i.e., that Study GO28667 can be used to confirm the risk/benefit profile of ABT-199 for the treatment of R/R CLL patients harboring the 17p del mutation)?

FDA Response:
Yes, if ABT-199 receives accelerated approval.

Discussion:
No discussion.

6. The Sponsors plan to submit a registration package in mid-2015 based on Study M13-982 that should be sufficient to determine the overall benefit/risk of ABT-199 and inclusive of data supportive of key differentiators from other targeted therapies. Additionally, Study GO28667 (the confirmatory study) will be ongoing. Is there additional advice that the FDA can provide to the Sponsors regarding the projected NDA submission for ABT-199 in mid-2015 targeting an indication for 17p deletion R/R CLL patients under a broader use of the accelerated approval provisions afforded by FDASIA section 506(c) and as codified in 21 CFR 314.500 Subpart H?

FDA Response:
See FDA response to question 1. We recommend that you continue discussion with CDRH with regard to approval of the Vysis test for patient selection. An FDA-approved test for selection of patients with the 17p del will be required for approval in a 17p del population. In preparation for the possibility of a coordinated review of a PMA companion diagnostic to align with your NDA, we suggest a pre-PMA meeting be held with the device Sponsor (Abbott Molecular) and AbbVie as soon as possible so that alignment can be reached on coordinated submission and review of the applications.

You should consider broader exploration of other doses in CLL, given that this will be a chronically administered drug, where low grade long-term toxicities may not be tolerable.

Discussion:
No discussion.

Additional comments:

Clinical

- **In reviewing the synopsis of trial M13-982 provided in the meeting package as well as the latest version of trial M13-982 amendment 1 submitted to the IND on May 29, 2013 it does not appear that the current version of the protocol includes the 50 patient dose expansion phase proposed in the meeting package. Please submit a protocol amendment for trial M13-982 and state in the cover letter for the submission that you are requesting comments on the protocol.**

Discussion:
No discussion.

- **For the upcoming Type B meeting on July 2nd, please provide topline efficacy and safety data on the number of patients with CLL harboring the 17p deletion currently enrolled in trials with ABT-199 at the 400 mg dose.**

Discussion:
The Sponsor provided a summary of the efficacy results to date. The ORR in 7 patients with 17p del CLL dosed at 400 mg was 86% (1 CR and 5 PRs). (b) (4)

The Sponsor stated that 107 patients have been enrolled to study M13-982 (Phase 2 single agent trial in patients with 17p del); that no analyses have been conducted, but they shared preliminary information with the Agency. The Agency had no further questions.

Clinical pharmacology
Please submit your clinical pharmacology plan for 2015 NDA submission in a separate submission. We will provide comments on your dose selection rationale with comments on your clinical pharmacology plan.

Discussion:
No discussion.

3.0 PREA REQUIREMENTS

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 this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor used the attached presentation to enhance the discussions during the meeting.

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

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/s/

VIRGINIA E KWITKOWSKI
07/08/2014

CDER Medical Policy Council
Decisions/Action Items – Breakthrough Designation Request
July 8, 2013

Council Members:
Rachel Sherman, Chair
Gerald Dal Pan, OSE
John Jenkins, OND
Pamela Horn, OND/ODEII/DAAAP
Robert Temple, CDER
Sandra Benton, Executive Secretary

Attendees:
George Adam, OND/OHOP/DHP
Ann Farrell, OND/OHOP/DHP
Joseph Griffin, OMP
Beatrice Kallungal, OND/OHOP/DHP
Virginia Kwitkowski, OND/OHOP/DHP
Diane Maloney, CBER
Peter Marks, CBER
Miranda Raggio, OND
Jennifer Ross, CBER
Leonard Sacks, OMP
Rose Tiernan, OMP/OMPI
Ellis Under, OND/ODEI
Issam Zineh, OTS/OCP

Topic: To discuss Abbvie's breakthrough therapy designation request for IND 110159, ABT-199 for the treatment of patients with previously treated 17p deletion mutation-positive chronic lymphocytic leukemia (CLL) as detected by an FDA-approved test. Please see background and PowerPoint presentation.

Discussion: DHP agreed that 17p deletion mutation-positive CLL is a serious and life-threatening disease.

ABT-199 is an orally available, small molecule inhibitor of the Bcl-2 family protein. In an ongoing Phase 1 trial (M12-175), the sponsor is attempting to determine the safest dose and schedule for ABT-199. The IND was placed on partial clinical hold [halting enrollment and dose-escalation to M12-175 and M13-365 and halting enrollment of any new CLL patients] on December 18, 2012 due to the death of 2 patients with CLL from tumor lysis syndrome (TLS). Deaths from TLS are usually dose related; in the case of ABT-199, 4/5 cases of clinical TLS occurred after the first [and lowest] dose. Please see slide 2 that included the dosing schedule investigated prior to and after the clinical hold. DHP noted that it is unusual to see fatalities due to TLS in successful CLL development programs.

Although there are no drugs approved specifically to treat patients with previously treated 17p deletion mutation-positive CLL, slide 3 listed published results from broad CLL trials that enrolled subsets of patients with 17p deletion CLL. The 17p deletion mutation is usually an

acquired mutation from drug treatment but can also be present de novo in newly diagnosed patients.

To support the breakthrough therapy designation request, the sponsor submitted data from the Phase 1, first-in-human, dose-escalation trial, M12-175. The results can be seen on slides 4 and 5. DHP was unsure of the credibility of the median duration of response rate (b) (4) (b) (4)

The sponsor's drug development plans included two trials (see slide 6). The phase 2 trial will include CLL patients with the 17p deletion (b) (4) (b) (4). DHP noted that if the sponsor can find a safe dose and the phase 2 trial was successful, DHP would be willing to grant accelerated approval based on the phase 2 trial. (b) (4) (b) (4)

(b) (4)

(b) (4)

Slides 7 and 8 showed the safety profile of ABT-199. Slide 7 described the two deaths from TLS. One patient (b) (6) did not harbor the 17p deletion while the other (b) (6)) did. The patient with the 17p deletion had a reaction after the first dose of 50 mg of ABT-199. However, the most frequently observed adverse events described on slide 8 are consistent with adverse events seen with other treatments for CLL.

DHP recommended denying the sponsor's request. Specifically, the presented data do not currently indicate that ABT-199 may demonstrate substantial improvement over existing therapies given the absence of a safe dose/schedule to take forward. The Council agreed. A (b) (4)

(b) (4) However, it was hard to review the sponsor's development plans regarding CLL patients with the 17p deletion as DHP has yet to receive the complete clinical trial protocol for the proposed randomized phase 3 trial.

Update – The sponsor did submit a phase 3 study proposal. The sponsor plans to enroll CLL patients with the 17p deletion [redacted] (b) (4). [redacted] (b) (4) [redacted].

Action Items: DHP will draft a letter denying Abbvie's breakthrough therapy designation request for IND 110159, ABT-199 for the treatment of patients with previously treated 17p deletion mutation-positive chronic lymphocytic leukemia (CLL) as detected by an FDA-approved test.

Attachment: Background Document and Presentation

Draft: S Benton 7/10/2013
R/D: I Zineh 7/11/2013
V Kwitkowski 7/11/2013
A George 7/11/2013
A Farrell 7/11/2013
Final: S Benton 7/22/2013

Briefing Document
Breakthrough Therapy Designation request for ABT-199 under IND# 110159
Adam George Pharm.D., Clinical Reviewer
Division of Hematology Products
Office of Hematology and Oncology Products
June XX, 2013

1. Executive Summary

AbbVie Inc. has submitted a request for Breakthrough Therapy designation for ABT-199 for the treatment of patients with previously treated 17p deletion mutation-positive CLL as detected by an FDA-approved test. ABT-199 is an orally available, small molecule Bcl-2 family protein inhibitor. This reviewer concludes that the Sponsor has not met one of the two key requirements (FDASIA § 902) for Breakthrough Therapy designation. The Sponsor has met the requirement that the disease is serious and life-threatening. The Sponsor has not met the requirement for preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

2. Rationale for the use of drug for proposed indication

ABT-199 is a Bcl-2 family protein inhibitor. The Bcl-2 protein family includes both proapoptotic and antiapoptotic proteins, and the interplay between these 2 groups regulates the intrinsic apoptotic pathway. Bcl-2 overexpression is commonly found in some lymphoid malignancies and is associated with increased resistance to chemotherapy.

3. Background: in proposed indication

CLL is a neoplasm composed of monomorphic small, round to slightly irregular, mature B cell lymphocytes in the peripheral blood, bone marrow or lymphatic tissue. Immunophenotyping is critical in diagnosing CLL as B cells typically express CD5, CD20, and CD23. CLL is the most common leukemia of adults in Western countries. Based on SEERS data from 2004-2008 the age adjusted incidence rate of CLL is approximately 4.2 per 100,000 men and women per year with the rate in men being approximately twice that of women. It is estimated that 15,680 men and women will be diagnosed with CLL in 2013.[1] From 2004-2008 the median age of diagnosis was 72 years of age with approximately 70% of patients being diagnosed at age 65 or later.

The clinical course of CLL varies depending on risk stratification by the Rai staging system or Binet classification but it is typically a slowly progressing disease. Chromosomal abnormalities such as del 17p and 11q are associated with a significantly poorer prognosis. An article by Dohner reported that in 325 patients with various stages of CLL 7% (23) had a 17p chromosomal aberration. Dohner evaluated the clinical implications of this chromosomal aberration compared to patients with a normal karyotype and found that at a median follow-up of 70 months patients

1. Cancer Statistics Reference for 2013: Siegel R, Naishadham D, Jemal A. Cancer Statistics, 2013. CA Cancer J Clin. 2013; 63: 11-30.

with del 17p had a median survival of 32 months compared to 111 months for patients with normal karyotype.[2]

Currently there are no drugs approved specifically for the treatment of patients that have received prior treatment for CLL and who harbor deletion 17p. There are, however regimens commonly used for the treatment of patients with CLL which are also used to treat patients with 17p deletion CLL (Table 1~~Table 1~~). The rates of overall response are variable mainly due to the fact that the results are based on small subgroups of 17p deletion patients that were included in the broader trial population.

Table 1 Treatment options for relapsed/refractory CLL with 17p deletion

Trial	Regimen	Response Data in 17p deletion CLL	Response Data in broad CLL population
Single arm, open label (Wierda 2010, JCO) n=59 FA, n=79 BF n=17, 17p del FA group n=14, 17p del BF group	Ofatumumab	ORR 41% (FA) ORR 14% (BF) CR rate not published	ORR 58% (FA) ORR 47% (BF) CR rate 0%(FA) CR rate 1% (BF)
Single arm, open label (Fischer 2011, JCO) n=78 r/r CLL n=14, 17p del	Bendamustine + rituximab (BR)	ORR 7% CR rate 7%	ORR 59% CR rate 9%
Single arm, open label (Badoux 2011, Blood) n=80 r/r CLL n=14, 17p del	Cyclophosphamide, fludarabine, alemtuzumab and rituximab (CFAR)	ORR 29% CR rate 14%	ORR 65% CR rate 29%
Single arm, open label (Stilgenhauer 2009, JCO) n=103 fludarabine refractory CLL n= 31, 17p del	Alemtuzumab	ORR 39% CR rate not published	ORR 34% CR rate not published
Single arm, open label (Pettitt 2012, JCO) n=39, 1st line and prior tx. 17p del n=22, prior tx CLL 17p del	Alemtuzumab + methylprednisolone	ORR 77% CR rate 14%	ORR 82% CR rate 36%

FA=fludarabine and alemtuzumab refractory, BF=fludarabine refractory only due to bulky disease (>5 cm)

4. Clinical trial experience with drug

Dosing of ABT-199

At this phase of the development process the Sponsor is trying to determine the safest dose and schedule to administer ABT-199 in order to mitigate the risk of a serious toxicity of tumor lysis syndrome (TLS) which has lead to the death of 2 patients with relapsed/refractory CLL. As a result of these fatal events the IND was put on partial clinical hold. This serious toxicity is discussed in greater detail in the safety section of the briefing document.

[2] Dohner et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343(26):1910-6.

Prior to clinical hold ABT-199 was administered at a starting test dose of 50 mg and the dose was increased incrementally using a step-up approach until the patient reached the final cohort assigned dose.

- 50 mg x 1 day → no dosing x 6 days → 50 mg x 7 days → 100 mg x 7 days → dose ~25% of final assigned cohort dose x 7 days → final cohort assigned dose (max 1,200 mg daily)

Following the partial clinical hold the Sponsor proposed a revised step-up approach for administering ABT-199.

- [redacted] (b) (4)

Efficacy

To support the request for Breakthrough Therapy designation the Sponsor provided preliminary data for the ongoing first in human trial M12-175 titled "A Phase 1 Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma." Currently, there were 17 patients enrolled with relapsed or refractory CLL that have the 17p deletion mutation. As of a data cut-off of April 4, 2013 16 of the 17 patients were evaluable for efficacy. The one patient who is not evaluable for efficacy did not yet have the first (Week 6) tumor evaluation conducted at the time of the data cut-off. The ORR (CR+CRi+PR) rate in the 16 patients evaluable for efficacy was 81% (13/16) [Table 2~~Table 2~~].

Table 2 Disposition and response information for 17p deletion CLL patients M12-175

Subject Disposition	No. of Subjects
Achieved a Partial Response (PR)	11
Achieved a Complete Response (CR)	1
Achieved a Complete Response with incomplete bone marrow recovery (CRi)	1
Achieved a response of Stable Disease (SD)	1
Achieved a response of Progressive Disease (PD)	1
Discontinued prior to the Week 6 assessment	1
Had not reached Week 6 assessment and therefore non-evaluable at time of reporting	1

The median duration of response in the 16 evaluable patients receiving ABT-199 monotherapy and expressing the 17p deletion mutation is 13 months. The median time on trial for 17 patients (includes responders and non-responders) is approximately 7 months with 4 of the 17 being on trial for > 1 year. Twelve subjects remain active on trial. Given the available information we are unable to confirm the Sponsor's claimed duration of response [redacted] (b) (4) We suspect there is an error in the duration of response.

Safety

In December of 2012 the IND was put on partial clinical hold, prohibiting further enrollment of patients with CLL. This was due to the fact that the Division of Hematology Products (DHP) received reports of fatal events of tumor lysis syndrome (TLS) which occurred in 2 patients with relapsed/refractory CLL. In addition to the 2 fatal events of TLS, there were 7 serious events of TLS which required the patient's to be hospitalized. Of these 7 serious events 5 met the Cairo-Bishop criteria for clinical TLS. Clinical TLS is a serious medical condition that even if treated can result in death. In 4 out of the 5 cases of clinical TLS 4 occurred after the patient received their first dose of ABT-199. Of the 5 cases of clinical TLS 2 occurred in patients that harbor the 17p deletion mutation.

Subject #(b) (6) in Study M12-175

On (b) (6) a 55 year old male patient with relapsed CLL enrolled in trial M12-175 suffered a fatal event. Based on the information provided by the Sponsor this patient did not harbor the 17p deletion, This patient had bulky disease (a 10 cm nodal mass). The patient received his first dose of ABT-199 at 50 mg on (b) (6). The patient then received 7 days of dosing with 50 mg and 7 days of dosing on 150mg ABT-199. He received his first dose of 1200mg on (b) (6). The following laboratory abnormalities suggestive of TLS were observed at 8 hours and 24 hours after receiving the 1200 mg dose; elevated serum phosphate, elevated uric acid and an increase in serum creatinine (observed at 24 hours). These laboratory changes met Cairo-Bishop criteria for TLS. The subject received a second dose of 1200mg on (b) (6). Subsequently, the subject was found dead that night at home. The cause of death was not confirmed.

Subject # (b) (6) in Study M13-365

On (b) (6) a 58 year old male patient with relapsed CLL enrolled in trial M13-365 with bulky abdominal lymphadenopathy (14 x 18 cm) developed clinical tumor lysis syndrome (TLS) with elevations in potassium and phosphate following his first dose of 50 mg of ABT-199. The subject died of cardiac arrest secondary to hyperkalemia. The subject had a cardiac history of atrial flutter with subsequent cardioversion. Based on the information provided by the Sponsor in the response to clinical hold, this patient harbored the 17p deletion.

The Sponsor submitted a response to clinical hold which made changes to the protocols under partial clinical hold that may mitigate the risk of tumor lysis syndrome in patients with CLL. These changes were acceptable and the IND was removed from partial clinical hold in May 2013. To date the Agency does not yet have any data to determine if these changes mitigate risk of TLS.

The Sponsor submitted combined safety data for the broad population of patients with relapsed/refractory CLL enrolled in trial M12-175. As of a data cutoff of April 4, 2013 there were 56 patients enrolled in this trial which includes the patients with 17p deletion. The most commonly reported treatment emergent adverse events are diarrhea (23 patients, 41%); neutropenia (22 patients, 39%); nausea (21 patients, 37%); fatigue (16 patients, 29%); and upper respiratory tract infection (15 patients, 27%). The most common Grade $\geq$3 adverse events $\geq$10% are neutropenia 37% (n=21) and tumor lysis syndrome 11% (n=6). A total of 3 patients with

CLL/SLL in Study M12-175 have experienced adverse events that led to death: multi-organ failure, sudden death and mental status change each occurring in one patient.

5. Regulatory Considerations

Relapsed/refractory CLL is a serious and life threatening disease. Clinical outcomes in patients with CLL that harbor the 17p deletion mutation is significantly worse than the outcomes compared to the broader population of patients with CLL that do not harbor the 17p deletion. Currently there are no drugs that have FDA approval for the treatment of patients with relapsed/refractory CLL with 17p deletion. There are however drugs which are approved for the treatment of lymphoma that are used off label which have activity in patients with 17p deletion. In analyses of small subsets of patients with 17p deletion included in clinical trials in patients with CLL, ORRs ranged from 7-77% (Table 1~~Table 1~~). In clinical trial M12-175 investigating the use of ABT-199 in patients with relapsed or refractory CLL the ORR in 16 patients with the 17p deletion evaluable for efficacy was 81%. While this response rate indicates that ABT-199 maybe highly active in patients with CLL that harbor the 17p deletion, the number of patients (n=16) included in this analysis is too small to reliably conclude that ABT-199 may demonstrate substantial improvement over existing therapies.

Drug development plan

Under IND 110159 AbbVie is currently conducting multiple early stage Phase 1 trials evaluating the maximum tolerated dose of ABT-199 in various hematologic malignancies. At this time the Sponsor has the following later stage clinical trials planned for the development of ABT-199:

- A Phase 2 single-arm trial of ABT-199 monotherapy in subjects with a diagnosis of relapsed/refractory CLL with chromosome 17p deletion (Study M13-982)
- A randomized Phase 3 trial investigating ABT-199 combined with rituximab versus a combination of bendamustine with rituximab in subjects with a diagnosis of relapsed/refractory CLL (Study GO28667).

Both studies are anticipated to be initiated in 2013.

Recommendation

At this time DHP is recommending that the request for Breakthrough therapy designation for ABT-199 for the treatment of patients with previously treated 17p deletion mutation-positive CLL as detected by an FDA-approved test be denied for the following reasons:

- There is limited data with which to conclude that ABT-199 may demonstrate substantial improvement over existing therapies.
- Data on activity at the dose/schedule that the Sponsor proposes to take forward is not available.
- It is unclear whether the changes to the dose/schedule will improve safety and/or reduce activity.

References: provided throughout document

Breakthrough Therapy Request
ABT-199 IND 110159

Proposed indication: ABT-199 for the treatment of patients with previously treated 17p deletion mutation-positive chronic lymphocytic leukemia (CLL) as detected by an FDA-approved test.

Adam George, Pharm.D., Clinical Reviewer
Division of Hematology Products
Office of Hematology and Oncology Products

ABT-199

- Orally available, small molecule Bcl-2 family protein inhibitor.
- In the ongoing Phase 1 trial (M12-175) ABT-199 is administered daily as followed:

  Prior to clinical hold

  – 50 mg x 1 day → no dosing x 6 days → 50 mg x 7 days → 100 mg x 7 days → dose ~25% of final assigned cohort dose x 7 days → final cohort assigned dose (max 1,200 mg daily)

  Post clinical hold

(b) (4)

Treatments for 17p deletion Chronic Lymphocytic Leukemia

Trial	Regimen	Response Data in 17p deletion CLL	Response Data in broad CLL population
Single arm, open label (Wierda 2010, JCO) n=59 FA, n=79 BF n=17, 17p del FA group n=14, 17p del BF group	Ofatumumab	ORR 41% (FA) ORR 14% (BF) CR rate not published	ORR 58% (FA) ORR 47% (BF) CR rate 0%(FA) CR rate 1% (BF)
Single arm, open label (Fischer 2011, JCO) n=78 r/r CLL n=14, 17p del	Bendamustine + rituximab (BR)	ORR 7% CR rate 7%	ORR 59% CR rate 9%
Single arm, open label (Badoux 2011, Blood) n=80 r/r CLL n=14, 17p del	Cyclophosphamide, fludarabine, alemtuzumab and rituximab (CFAR)	ORR 29% CR rate 14%	ORR 65% CR rate 29%
Single arm, open label (Stilgenhauer 2009, JCO) n=103 fludarabine refractory CLL n= 31, 17p del	Alemtuzumab	ORR 39% CR rate not published	ORR 34% CR rate not published
Single arm, open label (Pettitt 2012, JCO) n=39, 1st line and prior tx. 17p del n=22, prior tx CLL 17p del	Alemtuzumab + methylprednisolone	ORR 77% CR rate 14%	ORR 82% CR rate 36%

Reference ID: 3345360

Efficacy

- The Sponsor submitted data from a Phase 1 first-in-human, dose-escalation trial, M12-175, in relapsed/refractory chronic lymphocytic leukemia (CLL) to support designation
  - 17 patients with relapsed/refractory CLL 17p deletion
  - 16 patients evaluable for response
- Overall Response Rate is 81% (13/16)
- Complete Response rate is 13% (2/16)
- Median duration of response (b) (4)

Disposition and Response Data 17p Deletion Chronic Lymphocytic Leukemia Patients

Subject Disposition	No. of Subjects
Achieved a Partial Response (PR)	11
Achieved a Complete Response (CR)	1
Achieved a Complete Response with incomplete bone marrow recovery (CRi)	1
Achieved a response of Stable Disease (SD)	1
Achieved a response of Progressive Disease (PD)	1
Discontinued prior to the Week 6 assessment	1
Had not reached Week 6 assessment and therefore non-evaluable at time of reporting	1

Drug Development Plan in Chronic Lymphocytic Leukemia (CLL)

- Phase 2 trial (M13-982)
  - Single-arm trial of ABT-199 monotherapy in patients with relapsed/refractory CLL with chromosome 17p deletion
- Phase 3 trial (GO28667)
  - Randomized trial of ABT-199 combined with rituximab versus a combination of bendamustine with rituximab in patients with relapsed/refractory CLL

Significant Toxicity Issue

- December of 2012 the IND was put on partial clinical hold due to 2 fatal events of tumor lysis syndrome (TLS) in patients with CLL
  - PT# (b) (6) in trial M12-175
  - PT# (b) (6) in trial M13-365 (17p deletion +)
  - 7 serious events requiring hospitalization
  - 5 met Cairo-Bishop criteria for clinical TLS
    - 4/5 cases occurred after 1st dose
    - 2/5 patients reported as harboring 17p deletion

Safety Data from M12-175

- Data from broad relapsed/refractory Chronic Lymphocytic Leukemia (CLL) population N=56
  - Common treatment emergent adverse events include diarrhea (41%), neutropenia (39%), nausea (37%), fatigue (29%), and upper respiratory tract infection (27%)
  - Grade $\geq$3 adverse events include neutropenia 37% and tumor lysis syndrome 11% (n=6).
  - 3 patients with CLL/SLL in Study M12-175 have experienced adverse events that led to death: multi-organ failure, sudden death (a.k.a tumor lysis syndrome) and mental status change.

Recommendation

DHP recommends request for BT designation be denied.

- Sponsor has not provided adequate data to support that ABT-199 may demonstrate substantial improvement over existing therapies
  - Data on activity at the dose/schedule that the Sponsor proposes to take forward is not available
    - It is unclear whether the changes to the dose/schedule will improve safety and/or reduce activity.

Back-up slides

Breakthrough Therapy Designation
FDASIA § 902 requirements

- The disease is serious and life-threatening
- Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

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/s/

SANDRA J BENTON
07/23/2013

ANN T FARRELL
07/23/2013

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208573

LATE-CYCLE MEETING MINUTES

AbbVie, Inc.
Attention: Tuah Jenta, PhD, RAC
Associate Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, IL 60064

Dear Dr. Jenta:

Please refer to your New Drug Application (NDA) dated October 29, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Venclexta (venetoclax) tablets; 10, 50, and 100 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on February 29, 2016.

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, call Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, MS, ACNP-BC
Clinical Team Leader
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: February 29, 2016; 3:00 PM – 4:00 PM EST
Meeting Location: Teleconference

Application Number: NDA 208573

Product Name: Venclexta (venetoclax)
Indication: For the treatment of patients with relapsed or refractory chronic lymphocytic leukemia (R/R CLL) who have received at least one prior therapy, including patients with 17p deletion

Meeting Chair: Virginia Kwitkowski, MS, ACNP-BC
Meeting Recorder: Beatrice Kallungal, BS

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Ann Farrell, MD, Director
Virginia Kwitkowski, MS, ACNP-BC, Clinical Team Leader
Lori Ehrlich, MD, Clinical Reviewer
Qin Ryan, MD, PhD, Safety Medical Officer
Rachel Ershler, MD, Clinical Reviewer
Theresa Carioti, MPH, Chief, Project Management Staff
Beatrice Kallungal, BS, Senior Regulatory Project Manager

OHOP/Division of Hematology, Oncology, Toxicology
Ramadevi Gudi, PhD, Reviewer

Office of Biostatistics/Division of Biometrics V
Yuan-Li Shen, DrPh, Team Leader
Qing Xu, PhD, Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Nitin Mehrotra, PhD, Pharmacometrics Team Leader
Lian Ma, PhD, Pharmacometrics Reviewer
Rosane Charlab Orbach, PhD, Pharmacogenomics Team Leader
Sarah Dorff, PhD, Pharmacogenomics Reviewer

Office of New Drug Products/Division of New Drug Products I Branch II
Anamitro Banerjee, PhD, Branch Chief
Tracey Rogers, PhD, Application Technical Lead

Office of Surveillance and Epidemiology (OSE)/Division of Epidemiology I (DEPI I)
Carolyn McCloskey, MD, MPH, Epidemiologist

Office of Medical Policy Initiatives/Division of Medical Policy Programs (DMPP)/Labeling & Patient Labeling
Sharon Mills, BSN, RN, CCRP, Team Leader
Rowe Medina, PharmD, Reviewer

EASTERN RESEARCH GROUP ATTENDEE
Chris Sese, independent Assessor

APPLICANT ATTENDEES

AbbVie, Inc.
Rod Humerickhouse, MD, PhD, Global Project Director
Maria Verdugo, MD, Senior Medical Director, Oncology Development
Andrea Best, MD, Group Therapeutic Area Head, Pharmacovigilance
Monali Desai, MD, MPH, Senior Medical Director, Product Safety
Todd Busman, MS, Assistant Director, Statistics
Ahmed Salem, PhD, Assistant Director, Clinical PK/PD
James Duhig, PhD, Director, Risk Communications and Behavioral Systems
Geeta Thakkar, PhD, Senior Manager, Strategic Labeling
David Ross, PharmD, Senior Director, Global TA Head, Regulatory Affairs
David Breines, PhD, Senior Director, Global Regulatory Leader
William Schary, PhD, RAC, Director, Global Regulatory Affairs
Dan Kim, PhD, Associate Director, CMC Regulatory Affairs
Tuah Jenta, PhD, RAC, Associate Director, Global Regulatory Affairs

Genentech/Roche, Inc.
Nancy Valente, MD, Global Franchise Head, Hematology Development
Mehrdad Mobasher, MD, Global Development Team Leader
Kathryn Humphrey, BS, Principal Scientist
Sofia Khan, PharmD, MPH, Director, Global Regulatory Leader
Nathan Winslow, BA, Franchise Head, Product Development Regulatory
Emilie Trinh, MS, Regulatory Program Manager
Wei Dong, MD, PhD, Senior Group Director, Safety Science Oncology
Martina Wollenhaupt, MD, MSc, Senior Safety Science Leader, Safety Science Oncology
Dale Miles, PhD, Senior Scientist, Clinical Pharmacology
Jamie Robinson, MBA, RAC, Regulatory Program Director, Pharma Technical Regulatory
Michelle Byrtek, PhD, Senior Statistical Scientist, Biostatistics

1.0 BACKGROUND

NDA 208573 was submitted on October 29, 2015 for Venclexta (venetoclax).

Proposed indication: For the treatment of patients with relapsed or refractory chronic lymphocytic leukemia (R/R CLL) who have received at least one prior therapy, including patients with 17p deletion

PDUFA goal date: June 29, 2016

FDA issued a Background Package in preparation for this meeting on February 25, 2016.

2.0 DISCUSSION

1. Introductory Comments – 5 minutes (RPM/CDTL)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 20 minutes

   - (b) (4)

   MEETING DISCUSSION

   Question from Applicant:
   The Applicant acknowledges the FDA's remarks on Study M12-175 and Study M14-032. Can the FDA confirm that the application for venetoclax is still on track for accelerated approval in 17p del R/R CLL?

   Discussion
   The Agency stated that they are not able to comment on approval decisions prior to action on an application. The Agency stated that the review is ongoing and that the indication currently being considered is for the 17p del CLL population.

   (b) (4)

3. Information Request (IR) – 5 minutes

   A CMC mid-cycle IR was sent – response outstanding (due March 1, 2016).

   - Drug Product Process and Microbiology (minor issues) – requests for in-process controls/data/justification.

MEETING DISCUSSION

Question from Applicant:
The Applicant is working on the information request related to the packaging configurations and Quick Start Guide (QSG), received on February 24, 2016, and will provide our responses by the deadline of March 11, 2016. Can the FDA confirm this information request represents the collective remarks from both DMEPA and DMPP?

Discussion
The Agency clarified that the IR was generated by DMEPA and that DMPP's review is ongoing. Both groups will review your response to the IR.

4. Postmarketing Requirements/Postmarketing Commitments – 15 minutes

   - Confirmatory Trial—G028667 (MURANO) Phase 3 trial in patients with relapsed/refractory CLL (including 17p del) comparing Venetoclax + Rituximab vs. Bendamustine + Rituximab
   - Drug-drug Interaction Study with a P-gp Substrate: To investigate the effect of single-dose venetoclax on the pharmacokinetics of a P-gp substrate
   - Hepatic Impairment Study: To evaluate the pharmacokinetics of venetoclax in subjects with varying degree of hepatic impairment

MEETING DISCUSSION

No discussion

5. Major labeling issues – 5 minutes

   The (b) (4) will be removed from the labeling because (b) (4) . Revised labeling will be sent to the Applicant on approximately March 14, 2016.

MEETING DISCUSSION

Question from Applicant:
The Applicant notes that Section 6.1 in the proposed USPI contains pooled safety data from subjects dosed at 400 mg QD from Studies M13-982, M12-175, and M14-032. Can the FDA confirm that (b) (4) the proposed safety data tables will remain unchanged in Section 6.1?

Discussion
At this time, the Agency plans to include M12-175 safety data in section 6 of the US Prescribing Information (USPI).

6. Review Plans – 5 minutes

   Clinical

   - Confirmation of IRC-assessed response rates are ongoing.
   - Exploratory safety analyses are ongoing.

   Inspection Status Update

   - Two of the three scheduled clinical site inspections have been conducted.

   MEETING DISCUSSION

   Discussion:
   The Agency stated that, at this time, no manufacturing site inspections are scheduled.

   The user fee goal date is June 29, 2016. The Agency stated that an action earlier than this date may occur.

7. Wrap-up and Action Items – 5 minutes

   MEETING DISCUSSION

   No discussion

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.

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/s/

VIRGINIA E KWITKOWSKI
03/02/2016