

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209394Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 209394

SUPPL # N/A

HFD # 530

Trade Name Mavyret™

Generic Name Glecaprevir and Pibrentasvir

Applicant Name AbbVie Inc.

Approval Date, If Known August 17, 2017

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☒ NO ☐

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

N/A

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:

N/A

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5-years of Hatch-Waxman 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.

N/A

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 ☐
Explain:

!
!
! NO ☐
! Explain:

Investigation #2
YES ☐
Explain:

!
!
! NO ☐
! 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: Alicia Moruf, PharmD, MPH
Title: Regulatory Project Manager
Date: 03/14/2017

Name of Division Director signing form:
Title:

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

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

/s/

ALICIA MORUF
07/26/2017

JEFFREY S MURRAY
07/27/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 209394	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: MAVYRET™ Established/Proper Name: glecaprevir/pibrentasvir Dosage Form: Tablets		Applicant: AbbVie Inc. Agent for Applicant (if applicable): N/A
RPM: Alicia Moruf, PharmD, MPH		Division: Antiviral Products
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: N/A BLA Application Type: N/A Efficacy Supplement: N/A <u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Review the information in the 505(b)(2) Assessment and submit the draft² 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: <i>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.</i>		
❖ Actions		
- Proposed action - User Fee Goal Date is August 14, 2017		☒ AP ☐ TA ☐ CR
Previous actions (specify type and date for each action taken)		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? 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 _____		N/A
❖ 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): Antivirals
(confirm chemical classification at time of approval)

☐ Fast Track
Note: FT was granted to the individual INDs for GLE (IND 116169) and PIB (IND 116170), (b) (4) IND for GLE/PIB (IND 127416)

☐ 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)	N/A
❖ 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
❖ 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 (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval; August 3, 2017
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☒ Included July 27, 2017
• Original applicant-proposed labeling	☒ Included December 14, 2016
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☒ Included July 27, 2017
• Original applicant-proposed labeling	☒ Included December 14, 2016
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	☒ Included June 30, 2017
❖ Proprietary Name	Letters: May 31, 2017 (granted) March 9, 2017 (denied) Reviews: May 31, 2017 March 9, 2017
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: None (NME) RPM: PLR Format Review: January 31, 2017 DMEPA: June 23, 2017 DMPP/PLT (DRISK): June 27, 2017 OPDP: June 27, 2017 SEALD: None CSS: None Product Quality March 22, 2017 (primary review) ; May 23, 2017 (secondary review) ; digitally signed May 25/26, 2017 Human Factors: May 15, 2017
Administrative / Regulatory Documents	

❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	January 19, 2017
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
o If yes, Center Director's Exception for Review memo (<i>indicate date</i>)	
o If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	
❖ Pediatrics (<i>approvals only</i>)	
• Date reviewed by PeRC	June 21, 2017
If PeRC review not necessary, explain: N/A	
❖ Breakthrough Therapy Designation	
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	Granted: April 21, 2016 (IND 127416)
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	Template included. Note: A meeting was not held as MPC was in agreement with DAVP
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	N/A
(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>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</i>)	Labeling PMR/PMC Discussion Comments: July 27, 2017 Labeling PMR/PMC Discussion Comments: July 25, 2017 Labeling PMR/PMC Discussion Comments: July 21, 2017 Labeling PMR/PMC Discussion Comments: July 14, 2017 Labeling PMR/PMC Discussion Comments: July 12, 2017 Labeling PMR/PMC Discussion Comments: July 7, 2017 Labeling PMR/PMC Discussion Comments: July 5, 2017 Information Request: June 26, 2017 Information Request: June 19, 2017 Labeling PMR/PMC Discussion Comments: June 13, 2017 Late Cycle Meeting Background Package: June 13, 2017 Labeling PMR/PMC Discussion Comments: May 26, 2017 Information Request: May 25, 2017 Information Request: May 25, 2017 Information Request: May 18, 2017 CMC Information Request: May 12, 2017

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

	Information Request: May 2, 2017 Information Request: April 27, 2017 Information Request: April 14, 2017 Information Request: April 14, 2017 Information Request: April 12, 2017 CMC Information Request: April 11, 2017 Information Request: April 10, 2017 Information Request: April 7, 2017 Information Request: April 3, 2017 Information Request: March 24, 2017 Proprietary name Acknowledgment Letter: March 21, 2017 Information Request: March 14, 2017 CMC Information Request: March 14, 2017 Information Request: March 9, 2017 Information Request: March 9, 2017 Information Request: March 7, 2017 Information Request: March 2, 2017 CMC Information Request: February 23, 2017 Information Request: February 17, 2017 Information Request: February 13, 2017 (b) (4) CMC Information Request: February 1, 2017 No Filing Review Issues Identified: January 30, 2017 Information Request: January 24, 2017 Information Request: January 12, 2017 Information Request: January 10, 2017 Proprietary Name Acknowledgement Letter: January 4, 2017 Acknowledge NDA: December 21, 2016
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	❖ PREA Waiver/Deferral/Assessment Template: July 26, 2017 ❖ Medical Policy Council Minutes: April 11, 2017 (under IND 127416)
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	November 3, 2016
• EOP2 meeting (<i>indicate date of mtg</i>)	Preliminary Comments letter dated November 16, 2015 (IND 116169/116170) Note: Preliminary Comments serve as meeting minutes as meeting was cancelled per AbbVie request (see November 30, 2015 cancellation letter)
• Mid-cycle Communication (<i>indicate date of mtg</i>)	March 15, 2017
• Late-cycle Meeting (<i>indicate date of mtg</i>)	June 22, 2017
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	• CMC EOP2: Preliminary comments letter dated (IND 116169/116170) Note: Preliminary comments serve as meeting minutes as meeting was cancelled per AbbVie request • Type C WRO: 4/8/2016; 5/26/2016

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	August 3, 2017 (Combined review)
Division Director Summary Review (<i>indicate date for each review</i>)	August 2, 2017 (Combined review)
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	August 2, 2017 (Combined review); July 17, 2017
PMR/PMC Development Templates (<i>indicate total number</i>)	1 PREA PMR 4 PMCs
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	June 12, 2017
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	N/A
❖ 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 (<i>indicate date of review/memo</i>)	June 12, 2017 (Appendix B; page 179)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	N/A
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	N/A
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	May 14, 2017
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	Review: April 28, 2017 OSI Letters: OSI Staff Letter NAI: June 8, 2017 OSI Staff Letter NAI Foreign: June 6, 2017 OSI Staff Letter NAI Foreign: June 5, 2017 OSI Staff Letter NAI: June 2, 2017 OSI Staff Letter NAI: June 2, 2017 OSI Staff Letter VAI: April 25, 2017

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

Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☒ No separate review
Clinical Microbiology Review(s) (indicate date for each review)	July 18, 2017 May 11, 2017 (2 separate reviews)
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)	May 18, 2017
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology review(s) (indicate date for each review)	May 26, 2017
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	May 15, 2017
• Supervisory Review(s) (indicate date for each review)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	May 15, 2017
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	☒ None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	Executive Summary by ATL: June 6, 2017 Drug Substance: May 24, 2017 (primary and secondary reviews); digitally signed May 25, 2017 (primary) and May 24, 2017 (secondary) Drug Product: May 25, 2017 (primary and secondary reviews); digitally signed May 26, 2017 Process Review: April 25, 2017 (primary review); May 2, 2017 (secondary review); digitally signed May 5, 2017 (primary) and May 4, 2017 (secondary) Facilities Review Interim: May 15, 2017 Biopharmaceutics: May 11, 2017 (primary review); May 22, 2017 (secondary review); digitally signed May 22, 2017 Final Risk Assessment: June 6, 2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	May 24, 2017 (primary review) May 26, 2017 (secondary) Digitally signed May 25, 2017
☐ Review & FONSI (<i>indicate date of review</i>)	N/A
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
❖ Facilities Review/Inspection	
☒ Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ Acceptable: August 3, 2017 ☐ 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 <i>(Notify CDER OND IO)</i>
Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: Notify the CDER BT Program Manager	☒ Done <i>(Send email to CDER OND IO)</i>
❖ 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 <i>Application Product Names</i> 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
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	☒ Done

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

/s/

ELIZABETH G THOMPSON
08/03/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: July 27, 2017

To: Sejal Emerson, PharmD, Director, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Labeling Comments

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

The Division has reviewed your proposed labeling for the above referenced application, and at this time we have the following comments and proposed edits in the attached documents.

Please review and provide revised labeling **(clean and tracked changes versions)** by **today July 27th, 2017**. When you provide updated labeling for Division review, please only include any new proposed edits **(accept any changes you agree with)**.

Please confirm receipt of this email.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
07/27/2017

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: ☐ Full Waiver ☒ Partial Waiver ☐ Pediatric Assessment ☒ Deferral/Pediatric Plan

BLA/NDA#: NDA 209394

PRODUCT PROPRIETARY NAME: Mavyret

ESTABLISHED/GENERIC NAME: glecaprevir and pibrentasvir film coated tablets

APPLICANT/SPONSOR: AbbVie Inc.

PREVIOUSLY APPROVED INDICATION/S: N/A; this is an NME

(1) _____
(2) _____
(3) _____
(4) _____

PROPOSED INDICATION/S:

(1) *Chronic Hepatitis C* _____
(2) _____
(3) _____
(4) _____

BLA/NDA STAMP DATE: December 14, 2016

PDUFA GOAL DATE: August 14, 2017

SUPPLEMENT TYPE: N/A

SUPPLEMENT NUMBER: N/A

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ☒ **active ingredient(s)** (includes new combination); ☒ **indication(s)**; ☒ **dosage form**; ☒ **dosing regimen**; or ☐ **route of administration**?

Did the sponsor submit an Agreed iPSP? Yes ☒ No ☐ **IND 127416**

Are there any changes to the Agreed iPSP that are different than the sponsor's current pediatric plan? Yes ☒ No ☐

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ☒ No ☐

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ No ☒

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes ☐ No ☐

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

APPEARS THIS WAY ON ORIGINAL

WAIVER REQUEST

Please attach:

- ☒ **Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.**
- ☐ **Pediatric Record**

1. Pediatric age group(s) to be waived. Patients younger than 3 years of age.
2. Reason(s) for waiving pediatric assessment requirements (**Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.**)
 - ☒ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.
 - ☐ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
 - ☐ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
 - ☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. **(This reason is for Partial Waivers Only)**

3. *Provide justification for Waiver:* The number of patients under age 3 requiring treatments is very small. A diagnosis of chronic HCV infection is difficult to establish definitively in patients younger than 3 to 4 years of age. In approximately 55%, spontaneous resolution of HCV infection may occur in pediatric patients, generally up to age 4, depending on the mode of transmission and HCV genotype; and, the risk of progression of liver disease in HCV-infected patients prior to age 3 is very low. Infection early in life is usually asymptomatic; treatment for signs or symptoms of hepatic disease or extrahepatic manifestations is not usually required. The risk of advanced fibrosis and of cirrhosis or other complications among young children is also low.

4. *Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:* N/A

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis	digestive disorders (gallstones)
acute bacterial exacerbations of chronic bronchitis (a complication of chronic obstructive pulmonary disease)	dry eye syndrome (keratoconjunctivitis sicca)
adjunctive treatment of major depressive disorder	dupuytren's disease and manifestations
age-related macular degeneration	erectile dysfunction essential thrombocytosis
Alzheimer's disease	giant cell arteritis
amyloidosis	gout
amyotrophic lateral sclerosis	heavy menstrual bleeding associated with uterine fibroids
androgenic alopecia	Huntington's chorea
ankylosing spondylitis	idiopathic pulmonary fibrosis
atherosclerotic cardiovascular disease	infertility & reproductive technology
benign monoclonal gammopathy	juvenile psoriatic arthritis
benign prostatic hyperplasia	memory loss
cancer:	menopause and perimenopausal disorders
basal cell and squamous cell skin cancer	mesothelioma
bladder	microscopic polyangiitis
breast	myelodysplasia
cervical	myelofibrosis & myeloproliferative disorders
colorectal	opioid induced constipation in chronic, non-cancer pain
cholangiocarcinoma	osteoarthritis
endometrial	overactive bladder
esophageal	Parkinson's disease
fallopian tube	paroxysmal nocturnal hemoglobinuria
follicular lymphoma	persistent facial erythema assoc. with rosacea in adult
gastric	plasma cells and antibody production disorders
hairy cell leukemia	polycythemia vera
hepatocellular	polymyalgia rheumatica (PMR)
indolent non-Hodgkin lymphoma	postmenopausal osteoporosis
liposarcoma	prevention of stroke and systemic embolic events in atrial fibrillation
lung (small & non-small cell)	psoriatic arthritis
multiple myeloma	reduction of thrombotic cardiovascular events in patients with coronary artery disease
oropharynx (squamous cell)	retinal vein occlusions stress
ovarian (non-germ cell)	urinary incontinence
pancreatic	Sjogren's Syndrome
peritoneal	temporary improvement in the appearance of caudal lines
prostate	treatment of heavy uterine bleeding associated with uterine leiomyomata
refractory advanced melanoma	treatment of Hypoactive Sexual Desire Disorder (HSDD) in postmenopausal women
renal cell	treatment of incompetent great saphenous veins and varicosities
uterine	type 2 diabetic mellitus with cardiovascular disease
chronic lymphocytic leukemia	type 2 diabetic nephropathy
chronic obstructive pulmonary disease	vascular dementia/vascular cognitive disorder/impairment
cryoglobulinemia	
degenerative intervertebral disc disease	
diabetic peripheral neuropathy/macular edema	
diabetic foot infections	
diabetic retinopathy	

DEFERRAL REQUEST

Please attach:

☒ *Pediatric Record*

1. **Age groups included in the deferral request:** pediatric patients ≥ 3 to < 18 years
2. **Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:**
Pediatric patients younger than 3 years, because the number of patients requiring treatment is very small.
3. **Reason/s for requesting deferral of pediatric studies in pediatric patients with disease: (Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.)**
 - a. **Adult studies are completed and ready for approval- YES**
 - b. Additional safety or effectiveness data needed (**describe**)
 - c. Other (**specify**):
4. **Provide projected date for the submission of the pediatric assessment (deferral date):** January 2023
5. **Did applicant provide certification of grounds for deferring assessments?** ☒ Yes ☐ No
6. **Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?** ☒ Yes ☐ No

(b) (4)

(b) (4)

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL

(b) (4)

Division comments on product safety:

Are there any safety concerns currently being assessed? ☐ Yes ☒ No Adult formulation/data are currently under NDA review, and has favorable benefit risk profile.

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? ☐ Yes ☒ No

Will a DSMB be required? ☒ Yes ☐ No

Other comments:

Division comments on product efficacy:

GLE/PIB has demonstrated SVR12 rates ranging from 91-100% for treatment durations of 8-16 weeks. SVR rates varied depending on the regimen, patients' HCV GT, and patients' prior treatment history. Efficacy was similar in patients with or without cirrhosis, with or without HCV/HIV coinfection, and with moderate and severe CKD, with or without hemodialysis. GLE/PIB represents the first DAA therapy recommended for a duration of as little as 8 weeks for HCV GT 1 -4 treatment-naïve patients without cirrhosis and the first IFN-free regimen for treatment of HCV GTs 2, 3, 5 and 6 in patients with severe CKD patients, including those receiving hemodialysis. GLE/PIB is also an effective option for HCV GT 1 infected patients with prior DAA treatment experience with NS5A inhibitors or NS3/4A protease inhibitors.

Division comments on sponsor proposal to satisfy PREA:

DAVP generally agrees with the planned proposals to satisfy PREA. We are negotiating with the Sponsor regarding the language regarding the primary efficacy endpoint; however, the appropriate data are planned for collection and will be available for analysis.

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/s/

ALICIA MORUF
07/26/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: July 25, 2017

To: Sejal Emerson, PharmD, Director, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Labeling Comments

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

The Division has reviewed your proposed labeling for the above referenced application, and at this time we have the following comments and proposed edits in the attached documents.

Please review and provide revised labeling **(clean and tracked changes versions)** by **July 26th, 2017**. When you provide updated labeling for Division review, please only include any new proposed edits **(accept any changes you agree with)**. Please note that the PPI changes are in a separate word document due to formatting constraints.

Please confirm receipt of this email.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
07/25/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: July 21, 2017

To: Sejal Emerson, PharmD, Director, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Labeling Comments

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

The Division has reviewed your proposed labeling for the above referenced application, and at this time we have the following comments and proposed edits in the attached documents.

Please review and provide revised labeling **(clean and tracked changes versions)** by **July 25th, 2017**. When you provide updated labeling for Division review, please only include any new proposed edits **(accept any changes you agree with)**. Please note that the PPI changes are in a separate word document due to formatting constraints.

Please confirm receipt of this email.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
07/21/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: Mavyret™ (Glecaprevir and Pibrentasvir) film-coated tablets, 100 mg/40 mg

Date: July 14, 2017

To: Sejal Emerson, PharmD, Director, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Container Labels- Requests for information

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg. Please also reference your submissions dated April 13, 2017, June 09, 2017, and June 30, 2017 wherein draft carton and container labels were submitted.

We have the following requests for information.

Container Label

- 1) Please clarify whether there is any printing on the blister foil itself, and if so provide an image of that printing.
- 2) Please provide a few samples of the daily dose pack containing active or placebo tablets.
- 3) Please provide printed mock-ups (which can be empty) of the various cartons which are intended to be part of the commercial packages.

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 301-796-3953.

Alicia Moruf, PharmD, MPH

Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

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ALICIA MORUF
07/14/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: Mavyret™ (Glecaprevir and Pibrentasvir) film-coated tablets, 100 mg/40 mg

Date: July 12, 2017

To: Sejal Emerson, PharmD, Director, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Information Request- PMR/PMC Schedule Milestones

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg. Please also refer to your submission dated July 7, 2017 wherein you provided the schedule milestones for the planned PMR/PMCs.

We have the following requests for information.

Clinical

1. The Division agrees with all proposed milestones and timelines.
2. The Division concurs with the use of the data generated from the ongoing Study (b) (4)
[REDACTED] to fulfill the following post-marketing commitment:
PMC: Conduct a study evaluating the efficacy of glecaprevir/pibrentasvir in HCV genotype 1 infected subjects with prior treatment experience with an NS5A inhibitor plus sofosbuvir regimen.
3. The Division requests submission (b) (4)
[REDACTED] for the following post-marketing commitment:

PMC: Submit the final report and datasets, including drug resistance datasets, for the ongoing clinical trial M16-126, evaluating glecaprevir/pibrentasvir in patients with HCV genotype 5 or 6 infection.

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 301-796-3953.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
07/12/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: July 7, 2017

To: Sejal Emerson, PharmD, Director, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Labeling Comments

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

The Division has reviewed your proposed labeling for the above referenced application, and at this time we have the following comments and proposed edits in the attached documents.

Please review and provide revised labeling **(clean and tracked changes versions)** by **July 12, 2017**. When you provide updated labeling for Division review, please only include any new proposed edits **(accept any changes you agree with)**. Please note that the PPI changes are in a separate word document due to formatting constraints.

Please confirm receipt of this email.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
07/07/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: Glecaprevir and Pibrentasvir film-coated tablets, 100 mg/40 mg

Date: July 5, 2017

To: Sejal Emerson, PharmD, Director, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Information Request- PMR/PMC Schedule Milestones

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We have the following requests for information.

Please confirm the schedule milestone dates for the following PREA PMR:

1. PMR Description: Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of glecaprevir and pibrentasvir in pediatric subjects 3 through less than 18 years of age with chronic hepatitis C infection
-

PMR Schedule Milestones:	<u>Final Protocol Submission:</u>	<u>January 2017</u>
	Study/Trial Completion:	<u>January 2022</u>
	Final Report Submission:	<u>January 2023</u>
	Other: _____	<u>MM/DD/YYYY</u>

Please provide the schedule milestone dates for the following proposed PMCs:

Please note we plan to request (b) (4) for the M16-126 data in the approval letter.

2. PMC Description: Submit the final report and datasets, including drug resistance datasets, for the ongoing clinical trial M16-126, evaluating glecaprevir/pibrentasvir in patients with HCV genotype 5 or 6 infection.
-
- PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: MM/DD/YYYY
Other: MM/DD/YYYY
3. PMC Description: Submit the final clinical study report and datasets for the ongoing trial M14-730 (EXPEDITION-2) to provide additional efficacy and safety data in HIV/HCV co-infected subjects receiving glecaprevir and pibrentasvir.
-
- PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: MM/DD/YYYY
Other: MM/DD/YYYY
4. PMC Description: Conduct a study evaluating the efficacy of glecaprevir/pibrentasvir in HCV genotype 1 infected subjects with prior treatment experience with an NS5A inhibitor plus sofosbuvir regimen.
-
- PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: MM/DD/YYYY
Other: MM/DD/YYYY
5. PMC Description: Conduct a study to characterize the phenotypic effect of the following individual NS3/4A or NS5A substitutions on the cell culture anti-HCV activity of glecaprevir or pibrentasvir, respectively: genotype 1a NS3_I18V, NS3_N77S, NS3_V116A, NS3_I354V and NS4A_V23A, genotype 3a NS3_I366V, and genotype 1a NS5A_A61T.
-
- PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: MM/DD/YYYY
Other: MM/DD/YYYY

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Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
07/05/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: June 26, 2017

To: Sejal Emerson, PharmD, Director, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Carton and Daily Dose Wallet Container Labels- Comments and Recommendations

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We have the following recommendations. **Please provide a response by Friday June 30th, 2017**

Carton and Container Labeling

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

1. Remove the statement “ (b) (4) ” from each container label and carton labeling to mitigate possible confusion surrounding the administration of the tablets and to be consistent with the DOSAGE AND ADMINISTRATION section of the Mavyret prescribing information.

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 301-796-3953.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

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/s/

ALICIA MORUF
06/26/2017

PeRC Meeting Minutes
June 21, 2017

PeRC Members Attending:

Lynne Yao
Jacqueline Yancey
Gettie Audain
Donna Snyder
Lily Mulugeta
Wiley Chambers
Gerri Baer
Adrienne Hornatko-Munoz
Jinging Ye
Donna Katz
Rachel Tapia
Skrikant Pagay
Kevin Krudys
Dionna Green
Harri Cheryl Sachs
Ikram Elayan
Skip Nelson
Mark Rodmann
Kristiana Brugger
Barbara Buch

Agenda

NON-RESPONSIVE

9:00	NON-RESPONSIVE				
9:15					
10:05					
10:15					
10:35					
10:55					
11:05					
11:15	NDA 209394	Glecaprevir and pibrentasavir film coated tablets Partial Waiver/Deferral/Plan with Agreed iPSP	DAVP	Alicia Moruf/Su zanne Strayhorn	Treatment of HCV (genotypes 1,2,3,4,5 or 6)
11:45	NON-RESPONSIVE				

4 Page(s) has been Withheld in Full as NON-RESPONSIVE immediately following this page

Glecaprevir and pibrentasavir film coated tablets Partial Waiver/Deferral/Plan with Agreed iPSP

- Proposed indication: Treatment of HCV (genotypes 1,2,3,4,5 or 6)
- The PREA trigger is new active ingredient, dosing regimen, dosage form, and indication with a PDUFA date of August 14, 2017. The sponsor has an Agreed iPSP to IND 127416.
- The division noted that there is difference between the Agreed iPSP and the proposed PREA PMR. (b) (4)

- *PeRC Recommendations:*

- o The PeRC concurs with the division to grant a partial waiver from birth to less than 3years of age because the studies are impossible or highly impractical and a deferral of pediatric studies for ages 3 to <18 years.

- o (b) (4)

NON-RESPONSIVE

NON-RESPONSIVE

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/s/

MESHAUN L PAYNE
06/30/2017

From: Moruf, Alicia
To: "Gandhi, Virajkumar B"; "Emerson, Sejal"
Subject: RE: IND 127416 - FDA Feedback regarding Study (b) (4)
Date: Monday, June 19, 2017 10:04:00 AM
Attachments: [image001.png](#)
Importance: High

Dear Viraj and Sejal-

We acknowledge the prior discussion of the endpoints, (b) (4). However, DAVP, after consultation with the Pediatric Review Committee (PeRC) has determined that the primary efficacy endpoint for pediatric trials, (b) (4) is SVR12. In an effort to appropriately guide your fulfillment of the Pediatric Requirement in the US, we recommend that you submit a country specific protocol (US), in which the primary efficacy endpoint remains SVR 12 for study (b) (4).

Please refer to Section II the following guidance documents for further reference.

<https://www.fda.gov/ohrms/dockets/98fr/980265gd.pdf>

From: Gandhi, Virajkumar B [mailto:viraj.b.gandhi@abbvie.com]
Sent: Thursday, May 18, 2017 3:23 PM
To: Moruf, Alicia
Subject: RE: IND 127416 - FDA Feedback regarding Study (b) (4)

Alicia,

Thank you for the update.

Would you have any update on the sponsor/monitor inspection email sent earlier (April 28)?

Kind regards,

Viraj

VIRAJ GANDHI, MS MBA, RAC (US)

Senior Manager
Global Regulatory Strategy

abbvie

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OTHER

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From: Moruf, Alicia [<mailto:Alicia.Moruf@fda.hhs.gov>]
Sent: Thursday, May 18, 2017 1:41 PM
To: Gandhi, Virajkumar B
Subject: RE: IND 127416 - FDA Feedback regarding Study (b) (4)

Viraj-

Thank you for your email. These responses are still under review. I will provide an update from the team as soon as one is available.

Kind Regards,
Alicia

From: Gandhi, Virajkumar B [<mailto:viraj.b.gandhi@abbvie.com>]
Sent: Wednesday, May 17, 2017 11:53 AM
To: Moruf, Alicia
Subject: IND 127416 - FDA Feedback regarding Study (b) (4)

Dear Dr. Moruf,

In response to FDA's clinical comment received March 17, 2017 regarding pediatric Study (b) (4), AbbVie submitted a response on April 14, 2017 (IND 127416, eCTD Seq 0085).

Could you kindly confirm if FDA is in agreement with the rationale AbbVie provided regarding primary and secondary endpoints for Study (b) (4)? The endpoints proposed in this study is consistent with the agreed iPSP (b) (4).

(b) (4)

Please let me know if you would like to have a brief call to further discuss this or have any questions.

Kind regards,

Viraj

VIRAJ GANDHI, MS MBA, RAC (US)
Senior Manager
Global Regulatory Strategy

abbvie

One North Waukegan Rd

Dept. PA72/Bldg. AP30-1
North Chicago, Illinois 60064

OFFICE: +1 847-938-1967

CELL: (b) (6)

FAX: +1 847-935-5344

EMAIL: viraj.b.gandhi@abbvie.com

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abbvie.com

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/s/

ALICIA MORUF
06/19/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: June 13, 2017

To: Viraj Gandhi, MS MBA, RAC, Senior Manager, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Labeling Comments

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

The Division has reviewed your proposed labeling for the above referenced application, and at this time we have the following comments and proposed edits in the attached document.

Please review and provide revised labeling **(clean and tracked changes versions)** by **June 20, 2017**. When you provide updated labeling for Division review, please only include any new proposed edits **(accept any changes you agree with)**.

Please confirm receipt of this email.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
06/13/2017



NDA 209394

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Viraj Gandhi, MS, MBA, RAC (US)
Senior Manager, Regulatory Affairs

Dear Mr. Gandhi:

Please refer to your New Drug Application (NDA) dated and received December 14, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glecaprevir and Pibrentasvir Tablets, 100 mg/40 mg.

We also refer to your correspondence, dated and received, March 17, 2017, requesting review of your proposed proprietary name, Mavyret.

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

If any of the proposed product characteristics as stated in your March 17, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-3813. For any other information regarding this application, contact Alicia Moruf, Regulatory Project Manager in the Office of New Drugs, at 301-796-3953.

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/

AZEEM D CHAUDHRY
05/31/2017

DANIELLE M HARRIS on behalf of TODD D BRIDGES
05/31/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: May 26, 2017

To: Viraj Gandhi, MS MBA, RAC, Senior Manager, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Labeling Comments

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

The Division has reviewed your proposed labeling for the above referenced supplemental applications, and at this time we have the following comments and proposed edits in the attached document.

Please review and provide revised labeling **(clean and tracked changes versions)** by **June 2, 2017**. When you provide updated labeling for Division review, please only include any new proposed edits **(accept any changes you agree with)**.

Please confirm receipt of this email.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
05/26/2017

From: Moruf, Alicia
To: ["Gandhi, Virajkumar B"](#)
Subject: RE: NDA-209394 Information Request- Carton and Daily Dose Wallet Container Labels
Date: Thursday, May 25, 2017 2:54:00 PM
Attachments: [image001.png](#)

Hello Viraj- Please see responses in red below.

Kind Regards,

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Email: alicia.moruf@fda.hhs.gov
Phone: 301-796-3953

From: Gandhi, Virajkumar B [mailto:viraj.b.gandhi@abbvie.com]
Sent: Monday, May 22, 2017 3:36 PM
To: Moruf, Alicia
Subject: RE: NDA-209394 Information Request- Carton and Daily Dose Wallet Container Labels

Dear Dr. Moruf,

In response to the information request received last week on May 18 regarding carton and container labels, AbbVie agrees with FDA recommendations for carton labels and will submit revised artwork by June 9th. Will the revised carton samples need to be submitted prior to approval of the NDA or submission of artwork should suffice? **Submission of the artwork will suffice.**

For DSA recommendations on monthly carton and daily dose wallet container label [REDACTED] (b) (4) [REDACTED] regarding inclusion of expiration date and lot number, AbbVie confirms that the final container label will include expiration date and lot number. This information will be printed in the "black rectangle box" already included in the current design of the carton and daily wallet and are attached for your reference.

Additionally, could you kindly clarify if additional comments on carton/container labels will be forthcoming or these are the final comments? **A determination on additional forthcoming comments regarding the carton/container labels is dependent upon the revised carton/container label mockups that will be received by June 9, 2017.**

Kind regards,

Viraj

VIRAJ GANDHI, MS MBA, RAC (US)
Senior Manager
Global Regulatory Strategy



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From: Moruf, Alicia [<mailto:Alicia.Moruf@fda.hhs.gov>]

Sent: Thursday, May 18, 2017 10:50 AM

To: Gandhi, Virajkumar B

Subject: NDA-209394 Information Request- Carton and Daily Dose Wallet Container Labels- Comments and

Hello Viraj-

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg. Enclosed, please find an information request/comments for Carton and Daily Dose Wallet Container Labels.

Kind Regards,

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Email: alicia.moruf@fda.hhs.gov
Phone: 301-796-3953

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/s/

ALICIA MORUF
05/25/2017

From: Moruf, Alicia
To: ["Gandhi, Virajkumar B"](#)
Subject: NDA 209394 GLE/PIB Information Request please respond by COB today
Date: Thursday, May 25, 2017 2:38:00 PM
Importance: High

Viraj-

Please provide the number of healthy volunteers that received at least one dose of GLE/PIB (300/120mg).

Can you please provide this information by COB today?

Thank you

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Email: alicia.moruf@fda.hhs.gov
Phone: 301-796-3953

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/s/

ALICIA MORUF
05/25/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: May 18, 2017

To: Viraj Gandhi, MS MBA, RAC, Senior Manager, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Carton and Daily Dose Wallet Container Labels- Comments and Recommendations

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We have the following recommendations.

The human factors (HF) label comprehension validation study results show that “NextGen 4-Week” and “NextGen 8-Week” carton labeling are not sufficiently differentiable from one another. Therefore, we propose the following recommendations to mitigate selection errors between the two cartons. These changes will not require additional validation through another HF validation study. The following recommendations need to be implemented prior to approval of this NDA:

Carton Labeling

1. We are concerned the “8-WEEK (b) (4)” statement located on the outermost carton labeling may be misinterpreted by patients as the full therapy duration and subsequently take the medication for 8 weeks only when intended therapy duration is 12 or 16 weeks. Consider revising “8-WEEK (b) (4)” to state “8-WEEK SUPPLY (168 tablets).”
2. Include a similar statement (e.g. 4-WEEK SUPPLY (84 tablets)) on the “NextGen” 4-Week outermost carton labeling to provide an additional differentiating cue to users.

3. Enlarge the last two digits in the NDCs of the 4-week and 8-week cartons in a format such as xxxx-xxxx-XX to provide an additional visual cue to aid in differentiating the two cartons as both pharmacists and pharmacy technicians identified “checking NDCs” as a form of product verification during the HF validation study.
4. Consider duplicating the principle display panel of the 4-week and 8-week carton labeling to also appear on the top closure flap of each carton. To accommodate this placement, we recommend you move the area labeled as “Area for pharmacy label” on the top closure flap to the back panel of the carton labeling.

Daily Dose Wallet Container Label

5. A section for the expiration date and lot number has not been designated on the monthly carton labeling, 3ct daily wallet, (b) (4). The expiration date and lot number are required on the immediate container and carton labeling per 21 CFR 201.17 and 21 CFR 201.10(i)(1), respectively. Ensure the final container labels and carton labeling contains the lot number and expiration date.

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 301-796-3953.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
05/18/2017



NDA 209394

INFORMATION REQUEST

AbbVie Inc
Attention: Debra Webb
Director, Regulatory Affairs CMC
1 N. Waukegan Road, Dept. PA77/Bldg. AP50
North Chicago, IL 60064

Dear Ms.Webb:

Please refer to your New Drug Application (NDA) dated December 14, 2016, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- Glecaprevir/Pibrentasvir, 100 mg/40 mg, fixed dose combination film-coated tablets

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a written response by **Wednesday, May 17, 2017**, in order to continue our evaluation of your NDA.

1. Please amend your analytical procedures RTM.C5776 (Determination of Impurities in Glecaprevir and (b) (4) by HPLC) and RTM.C5730 (Assay for Pibrentasvir by HPLC), as follows.
 - a. For RTM.C5776: Include a description of the preparation of Glecaprevir (b) (4) Standard in the procedure. In addition, add RRT and RRF information to the table in section 7.1 (Peak Identification) for impurity compounds (b) (4). These compounds are part of (b) (4) but are currently not listed in the table in sec. 7.1.
 - b. For RTM.C5730: (b) (4). Please read the following comment which was generated by FDA's Division of Pharmaceutical Analysis (DPA) after performing this analytical procedure:

(b) (4)



- c. (b) (4) RTM.C5718, section 3.2P.5.2
Analytical Procedure for Degradation Products by HPLC

2. Please explain the origin (b) (4) in the drug product sample chromatograms, Analytical Procedure for Degradation Products by HPLC, RTM.C5718. Please see the DPA comment below:

3.2. P.5.2- RTM.C5718, *Degradation products by HPLC*: (b) (4)



A specimen chromatogram from DPA is provided below:

(b) (4)



If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov

Sincerely,

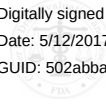
{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Luz
Rivera

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Date: 5/12/2017 03:22:27PM
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: May 2, 2017

To: Viraj Gandhi, MS MBA, RAC, Senior Manager, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Information Request

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We have the following requests for information. **Please respond by COB May 5, 2017.**

Pharmacology/Toxicology

Please clarify the data and calculations used in the following statement in the NDA 209394 label under **section 8.2**.

“Glecaprevir in milk was 13 times lower than in plasma and pibrentasvir in milk was 1.5 times higher than in plasma.”

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 301-796-3953.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
05/02/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: April 27, 2017

To: Viraj Gandhi, MS MBA, RAC, Senior Manager, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Information Request

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We have the following requests for information.

Clinical

Please inform DAVP as soon as possible if amylase or lipase were routinely collected for any of the studies in the Phase 2/3 pooled safety dataset.

If routine collection of amylase and/or lipase occurred for any studies and data are available, please complete the attached tables for amylase and lipase values in conventional units (as possible). Please provide the dataset used to create the table and create a flag allowing for the creation of tables listing subject counts by the highest toxicity grade for Amylase and Lipase (as was done in the LDBGRD database for other laboratory values).

In addition, for all subjects in the Phase 2/3 Safety Dataset excluding Trial M15-462 (N=2,265) who experienced a Treatment Emergent **Gastrointestinal Disorders** Body System Organ Class Event or Treatment Emergent Dictionary Derived Term Event of **Back Pain, Flank Pain, Pancreatitis, Pleural Effusion** or reported **hypocalcemia** (either as a dictionary derived term or laboratory abnormality), please provide a table with subject identification, all adverse events

experienced (with start and end dates) and **all lipase and amylase values** (with dates). Please also include both routinely and non-routinely collected Grade 2 or higher laboratories that were reported in association with, or related to, the reported AE (i.e. AE associated laboratories).

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 301-796-3953.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
04/27/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: April 14, 2017

To: Viraj Gandhi, MS MBA, RAC, Senior Manager, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Information Request

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We have the following requests for information.

Clinical

1. There were 6 de-novo cases of hepatocellular carcinoma in the safety population, which included approximately 300 cirrhotics with mild liver impairment. For all cirrhotic subjects, and as available for non-cirrhotic subjects, please complete the table below. Please also include grades, if these data are available.
2. In an inspection of principal investigator Reem Ghalib (Site 37759), it was found that Subject #612516 had a gastrointestinal bleeding event 2 weeks into the study. This was considered an SAE, but not related to the study drug according to Dr. Ghalib. We cannot find this event in the submitted data. Only two gastrointestinal bleeding events were reported in the safety dataset (Subjects #203507 and #8405). Please clarify this discrepancy.

Alpha Fetal Protein in (IU/ml)

Alpha Fetal Protein in (IC/ml)	ENDURANCE-2		ENDURANCE -3			Pooled studies, excluding subjects with renal impairment	
	M15-464 (Placebo Controlled)		Study M13-594 (Active Controlled)				
	Placebo 12 weeks (N=100)	GLE/PIB 12 weeks (N=202)	SOF/DCV 12 weeks (N=115)	GLE/PIB 12 weeks (N=233)	GLE/PIB 8 weeks (N=157)	GLE/PIB All Durations No Cirrhosis (n=1,977)	GLE/PIB All Durations Cirrhosis (n=288)
Baseline AFP n Mean (SD) Median Min, Max							
Maximum change from baseline AFP on treatment (within 30 days before last dose day) n Mean (SD) Median Min, Max							
AFP treatment Week 4 n Mean (SD) Median Min, Max							
Time to maximum AFP Levels (days) N Mean (SD) Median Min, Max							

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 301-796-3953.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
04/14/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: April 14, 2017

To: Viraj Gandhi, MS MBA, RAC, Senior Manager, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Information Request

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We have the following requests for information.

Clinical

Tables 1-2 Hypertension

We have noted approximately 44 subjects with reported treatment-emergent **Hypertension, Hypertensive Crisis or Hypertensive Heart Disease**, amongst the 2,265 subjects in the pooled Phase 2/3 safety dataset (excluding those with severe renal disease). Several of these events were labelled as possibly related to study drug. In addition, 34 subjects had a “Criterion 2 Evaluation Result Flag” indicating a Diastolic BP ≥ 105 mmHg AND ≥ 15 mmHg increase from baseline and 34 subjects had Systolic BP ≥ 180 mmHg AND ≥ 20 mmHg increase from baseline. For all of these subjects, and separately for subjects meeting this criteria in the severe renal population, please complete the below table and comment on possible mechanisms, drug-drug interactions or other etiologies that might account for these findings (feel free to add columns as necessary). Please summarize overall changes from baseline in these subjects including mean and maximum changes in systolic and diastolic blood pressure and time to maximum systolic and diastolic blood pressure. Please also comment on any on treatment differences or patterns in changes from baseline in systolic and diastolic blood pressures between subjects having met a BP flag and those who did not while accounting for treatment duration and renal impairment status.

Unique Subject ID	Age/Gender/Race	Pre-existing hypertension diagnosis (Y/N)	Hypertension Dictionary Derived Term(s)(Day Onset- Day End)	Grade	Causality	Criterion 2 Flag Systolic (Y/N)	Criterion 2 Flag Diastolic (Y/N)	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events (Day Onset- Day End)	Other Past Medical History	Concomitant Medications

Tables 3-4 Hypotension

Amongst the Phase 2/3 safety population, excluding those with renal failure, we also note that 7 subjects reported **Hypotension** or **Orthostatic Hypotension**, 28 subjects had Criterion 1 Flags indicating Diastolic BP ≤ 50 mmHg AND ≥ 15 mmHg decrease from baseline and 36 subjects had Systolic BP ≤ 90 mmHg AND ≥ 20 mmHg decrease from baseline. For all of these subjects, and separately for subjects meeting this criteria in the severe renal population, please complete the below table and comment on possible mechanisms, drug-drug interactions or other etiologies that might account for these findings (feel free to add columns as necessary). Please summarize overall changes from baseline in these subjects including mean and maximum changes in systolic and diastolic blood pressure and time to minimum systolic and diastolic blood pressure. Please also comment on any on treatment differences or patterns in changes from baseline in systolic and diastolic blood pressures between subjects who met a BP flag and those who did not while accounting for treatment duration and renal impairment status.

Unique Subject ID	Age/Gender/Race	Hypotension Dictionary Derived Term(s)(Day Onset- Day End)	Grade	Causality	Criterion 1 Flag Systolic (Y/N)	Criterion 1 Flag Diastolic (Y/N)	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events (Day Onset- Day End)	Other Past Medical History	Concomitant Medications

Tables 5-6 Cardiac, Vascular Adverse and Potential Blood Pressure Related Events

In separate tables for the pooled Phase 2/3 dataset (2,265) and for those with severe renal impairment, for each subject experiencing a Body System or Organ Class **Cardiac Disorder** or Dictionary Derived Term **Chest Pain, Chest Discomfort, Dyspnea, Dyspnea Exertional, Edema, Edema Peripheral, Cerebral Hemorrhage, Facial paresis, Transient Ischemic Attack or Headache**, please complete the following table, grouping by like events.

Unique Subject ID	Age/ Gender /Race	Previous History of Cardio-vascular Disease (Y/N)	Dictionary Derived Term (Day-Onset-Day End)	Grade	Causality	Criterion 1 Flag Systolic (Y/N)	Criterion 1 Flag Diastolic (Y/N)	Criterion 2 Flag Systolic (Y/N)	Criterion 2 Flag Diastolic (Y/N)	Max Change from Baseline Systolic Blood Pressure mmHg (Day)	Max Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events (Day Onset-Day End)	Past Medical History	Concomitant Medications

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 301-796-3953.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
04/14/2017

From: Moruf, Alicia
To: ["Gandhi, Virajkumar B"](#)
Subject: RE: NDA-209394 Information Request
Date: Wednesday, April 12, 2017 7:34:00 AM
Attachments: [image001.png](#)
Importance: High

Viraj- Please see responses below in red to your clarification questions.

Kind Regards,
Alicia Moruf

From: Gandhi, Virajkumar B [mailto:viraj.b.gandhi@abbvie.com]
Sent: Monday, April 10, 2017 6:09 PM
To: Moruf, Alicia
Subject: RE: NDA-209394 Information Request

Dear Dr. Moruf,

We had the following clarification questions regarding the information request and would appreciate a response at your earliest convenience.

- The Phase 3 studies did not have chemistry and hematology measurements at Post-Treatment Week 12. AbbVie could provide a summary of the values at Post-Treatment Week 4. However, in order to do this, the Treatment Period would need to be defined as specified in the SAPs (i.e., through Post-Treatment Day 2 instead of Post-Treatment Day 30 as proposed in the information request). Does FDA want the Post-Treatment Week 4 time point summarized with the corresponding change in the definition of the Treatment Period?
For this exercise, Post-treatment Week 4 data with the changed definition of Treatment Period is acceptable.
- The proposed table layout has summaries by grade for hemoglobin and GFR, but not for total bilirubin or uric acid. Please confirm that no summary by grade is needed for total bilirubin or uric acid.
If grades are available, they would be an appreciated addition.
- The information request includes a request for subject identification numbers for subjects included in each cell. However, most of the requested data summaries are continuous data summaries (i.e., mean, SD, median, min and max) and all of the requested summaries will include over 2,000 subjects. AbbVie proposes to provide subject identification numbers for a subset of the categorical summaries; more specifically, AbbVie proposes to provide subject identification numbers only for subjects with Grade 3 or 4 hemoglobin or GFR values on treatment. Does FDA agree?
Please only provide identification for subject with a decline in one or more stages of kidney function.
- AbbVie intends to provide Analysis Ready Programs that will produce the output going into the tables, but will not include code to format the table. Is this acceptable?
This is acceptable.

Also, since the request includes datasets and programs AbbVie requests an extension to submit a response by **April 21, 2017**. Please let me know if you are in agreement with this proposal.

Please submit by close of business April 20, 2017.

Kind regards,

Viraj

VIRAJ GANDHI, MS MBA, RAC (US)

Senior Manager
Global Regulatory Strategy



One North Waukegan Rd
Dept. PA72/Bldg. AP30-1
North Chicago, Illinois 60064

OFFICE: +1 847-938-1967

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FAX: +1 847-935-5344

EMAIL: viraj.b.gandhi@abbvie.com

OTHER

abbvie.com

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From: Moruf, Alicia [<mailto:Alicia.Moruf@fda.hhs.gov>]

Sent: Monday, April 10, 2017 11:26 AM

To: Gandhi, Virajkumar B

Subject: NDA-209394 Information Request

Dear Vraj-

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

Enclosed, please find requests for information. Please respond by COB 04/18/2017

Kind Regards,

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Email: alicia.moruf@fda.hhs.gov
Phone: 301-796-3953

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/s/

ALICIA MORUF
04/12/2017



NDA 209394

INFORMATION REQUEST

AbbVie Inc.
Attention: Viraj Gandhi, MS MBA, RAC
Senior Manager, Regulatory Affairs
One North Waukegan Road, Dept. PA72/Bldg. AP30
North Chicago, IL 60064-6194

Dear Mr. Gandhi:

Please refer to your New Drug Application (NDA) dated December 14, 2016, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- Glecaprevir/Pibrentasvir, 100 mg/40 mg, fixed dose combination film-coated tablets

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a written response by **Friday April 21, 2017**, in order to continue our evaluation of your NDA. A partial response at that time, with clarification of the timeline for the remaining questions, would also be satisfactory.

1.



2. Indicate which process (b) (4) was used to produce the following batches of Glecaprevir drug substance, which were used to produce drug product which was used for both stability and clinical studies: 1000124304, 1000124308, 1000117606.

3. Please provide representative XRPD diffractograms [REDACTED] (b) (4)
[REDACTED]. Also, provide examples (u) (4)
[REDACTED]
for glecaprevir and [REDACTED] (b) (4) for glecaprevir).

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Luz
Rivera

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Date: 4/11/2017 08:12:22PM
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: April 10, 2017

To: Viraj Gandhi, MS MBA, RAC, Senior Manager, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Information Request

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We have the following requests for information.

Clinical

Please complete the attached tables for analyses of hemoglobin, bilirubin, eGFR and uric acid. In addition, please provide subject identification number for each subject who contributes data to each cell. Please use the maximum and nadir (minimum) on-treatment values for each subject, as indicated, in the tables. Please also provide the SAS programming files and data sets used for this analysis.

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 301-796-3953.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Table 1: Hemoglobin

	ENDURANCE-2		ENDURANCE -3			Pooled studies, excluding subjects with renal impairment	
	M15-464 (Placebo Controlled)		Study M13-594 (Active Controlled)				
	Placebo 12 weeks (N=100)	GLE/PIB 12 weeks (N=202)	SOF/DCV 12 weeks (N=115)	GLE/PIB 12 weeks (N=233)	GLE/PIB 8 weeks (N=157)	GLE/PIB All Durations No Cirrhosis (n=1,977)	GLE/PIB All Durations Cirrhosis (n=288)
Baseline Hgb (g/dl) N Mean (SD) Median Min, Max							
Maximum change from baseline to Hgb nadir during treatment (within 30 days after last dose) N Mean (SD) Median Min, Max AE Grade Normal: >= lower normal limit Grade 1: < lower normal limit to 10.0 g/dL Grade 2: 8.0 to < 10.0 g/dL Grade 3: 6.5 to < 8.0 g/dL Grade 4: < 6.5 g/dL Missing							
Time to hgb nadir (days) N Mean (SD) Median Min, Max							

Table 5: GFR in conventional units (ml/min/1.73m²)

	ENDURANCE-2		ENDURANCE -3			Pooled studies, excluding subjects with renal impairment	
	M15-464 (Placebo Controlled)		Study M13-594 (Active Controlled)				
	Placebo 12 weeks (N=100)	GLE/PIB 12 weeks (N=202)	SOF/DCV 12 weeks (N=115)	GLE/PIB 12 weeks (N=233)	GLE/PIB 8 weeks (N=157)	GLE/PIB All Durations No Cirrhosis (n=1,977)	GLE/PIB All Durations Cirrhosis (n=288)
Baseline GFR n Mean (SD) Median Min, Max Baseline GFR on Treatment GFR 90+ GFR 60-89 GFR 45-59 GFR 30-44 GFR 15-29 GFR<15							
Maximum change from baseline GFR on treatment (within 30 days before last dose day) n Mean (SD) Median Min, Max Nadir GFR on Treatment GFR 90+ GFR 60-89 GFR 45-59 GFR 30-44 GFR 15-29 GFR<15							
GFR Post treatment Week 12 n Mean (SD) Median Min, Max Post Treatment Week 12 GFR on Treatment GFR 90+ GFR 60-89 GFR 45-59 GFR 30-44 GFR 15-29 GFR<15							

Time to nadir GFR (days)							
N							
Mean (SD)							
Median							
Min, Max							

Table 2-4: Complete for total bilirubin, direct bilirubin and indirect bilirubin

	ENDURANCE-2		ENDURANCE -3			Pooled studies, excluding subjects with renal impairment	
	M15-464 (Placebo Controlled)		Study M13-594 (Active Controlled)				
	Placebo 12 weeks (N=100)	GLE/PIB 12 weeks (N=202)	SOF/DCV 12 weeks (N=115)	GLE/PIB 12 weeks (N=233)	GLE/PIB 8 weeks (N=157)	GLE/PIB All Durations No Cirrhosis (n=19,77)	GLE/PIB All Durations Cirrhosis (n=288)
Baseline bilirubin (mg/dl) n Mean (SD) Median Min, Max							
Max bilirubin on treatment (within 30 days before last dose day) (mg/dl) n Mean (SD) Median Min, Max							
Post treatment Week 12 (mg/dl) n Mean (SD) Median Min, Max							
Time to max bilirubin (days) N Mean (SD) Median Min, Max							

Table 6: Uric Acid in (mg/dL)

	ENDURANCE-2		ENDURANCE -3			Pooled studies, excluding subjects with renal impairment	
	M15-464 (Placebo Controlled)		Study M13-594 (Active Controlled)				
	Placebo 12 weeks (N=100)	GLE/PIB 12 weeks (N=202)	SOF/DCV 12 weeks (N=115)	GLE/PIB 12 weeks (N=233)	GLE/PIB 8 weeks (N=157)	GLE/PIB All Durations No Cirrhosis (n=1,977)	GLE/PIB All Durations Cirrhosis (n=288)
Baseline Uric Acid n Mean (SD) Median Min, Max							
Maximum change from baseline Uric Acid on treatment (within 30 days before last dose day) n Mean (SD) Median Min, Max							
Uric Acid Post treatment Week 12 n Mean (SD) Median Min, Max							
Time to maximum Uric Acid Levels (days) N Mean (SD) Median Min, Max							

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/s/

ALICIA MORUF
04/10/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: April 7, 2017

To: Viraj Gandhi, MS MBA, RAC, Senior Manager, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Comments to Significant Issues reviewed at Midcycle Communication

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We also refer to the Midcycle Agenda provided to you on March 9, 2017 wherein the Division provided an outline of the significant issues to be reviewed at the Midcycle Communication on March 15, 2017. Further reference is made to your submission dated March 22, 2017 wherein you provided written responses to the review issues identified.

We have the following comments and requests for information. **Please provide revised labeling as described below by COB April 17, 2017.**

Clinical

The review team appreciates AbbVie's responses and additional analyses included in the Midcycle response document. We have carefully considered your responses and positions on the issues identified in the Midcycle communication, have conducted additional independent analyses, and have held multiple internal meetings to discuss these issues. Based on our review of your responses, and in concurrence with DAVP leadership, we agree with some but not all of your positions, as outlined below.

1. GLE/PIB for 16 weeks in HCV GT1-infected, NS5A inhibitor-experienced patients who are protease inhibitor (PI) naïve (MAGELLAN-1).

We agree the totality of data indicate that GLE/PIB for 16 weeks is a reasonably effective regimen for HCV GT1 infected patients who have previously failed a regimen that includes an NS5A inhibitor, but are naïve to NS3/4A PIs. The proposed label should describe the prior NS5A inhibitor-containing treatment experience represented in the MAGELLAN-1 trial for this population. Please also be aware that we will likely request a PMR or PMC for additional clinical evaluation of GLE/PIB efficacy and drug resistance in NS5A inhibitor-experienced, NS3/4A PI-naïve patients.

Consistent with our previous position, we do not agree to include patients who are NS5A inhibitor and NS3/4A PI treatment-experienced (either in combination or in sequential treatment regimens) in the indicated population and treatment recommendations. Also note that the recommended treatment duration for GT1-infected, prior NS3/4A PI-experienced/NS5A-naïve patients should be as studied in MAGELLAN-1 (i.e., GLE/PIB for 12 weeks), (b) (4)



2. GLE/PIB for 8 weeks in HCV GT3-infected, treatment-naïve, non-cirrhotic patients.

While we scientifically disagree with your claim of statistical non-inferiority of GLE/PIB 8W vs. 12W based on the nonrandomized comparison of these regimens, we nevertheless agree that GLE/PIB for 8W in this population is supported by the high SVR12 rate and low relapse rate observed in ENDURANCE-3, as well as supporting data from SURVEYOR-2 and preliminary data from the HCV/HIV co-infected population in EXPEDITION-2.

3. GLE/PIB for 8 versus 12 weeks in HCV GT5- or GT6-infected, non-cirrhotic patients.

We have concluded, with concurrence from DAVP leadership, that the currently available efficacy data and other supportive data described in your response document are not sufficient to recommend the shorter, 8-week duration for non-cirrhotic patients with HCV GT5 or GT6 infection. However, based on the available data, we can accept a 12-week GLE/PIB regimen for these genotypes.

We agree that the lower prevalence of GT5 and GT6 necessitates some flexibility in the data required to support an indication and treatment recommendations for these genotypes. Even with the 12-week duration, however, some extrapolation/extension of available data needs to be conducted to support including GT5- or GT6-infected patients with compensated cirrhosis or prior sofosbuvir- or interferon-based treatment experience in the indicated population.

In addition, as noted previously, for GT5 we remain concerned that SVR12 data with the 8-week duration are available for only 2 subjects, neither of whom appear to be representative of the overall GT5 population (i.e., very low baseline HCV RNA and no reported NS3

D168E polymorphism that appears to be common in GT5). Although GLE/PIB for 12 weeks was effective in GT5 infected subjects with or without the D168E polymorphism, it remains unknown if the shorter, 8-week duration is effective in this population. Similarly, for GT6 we remain concerned about the limited SVR12 data for subjects who received the 8-week treatment duration (n=9, excluding 1 non-virologic failure subject; plus a few additional subjects described in the Midcycle response document), particularly considering the diversity of HCV GT6 subtypes and expected amino acid sequence variability at NS5A inhibitor resistance-associated positions.

We generally do not accept comparable early on-treatment virologic responses across different genotypes as proof of comparable treatment efficacy. Early rapid declines in HCV RNA levels are typically observed with combination DAA regimens, but an early virologic response does not always necessarily result in a durable response (i.e., SVR). As an example, in the MAGELLAN-1 trial most of the subjects who experienced virologic failure (with the exception of cases of early virologic breakthrough) had impressive HCV RNA declines during the initial weeks of treatment.

Finally, for both GT5 and GT6, available efficacy (SVR12) results with the GLE/PIB 12-week duration, but not the 8-week duration, are comparable to current approved standard-of-care regimens for these genotypes, both in terms of efficacy findings and subject sample sizes.

While we acknowledge your position that a simple, 8-week duration for treatment-naïve, noncirrhotic patients that applies to any HCV genotype would be clinically desirable, standard-of-care HCV treatment recommendations continue to be based largely according to HCV genotype. Furthermore, we do not believe it is overly burdensome for a small subset of the treatment-naïve, non-cirrhotic indicated population to receive a 12-week duration rather than an 8-week duration.

We are open to reconsidering this position when additional SVR12 results are submitted from HCV GT5 or GT6 infected patients treated with GLE/PIB for 8 weeks.

Request for Revised Labeling

To ensure an efficient label review, we are requesting that you provide updated labeling for Sections 2, 6, and 14 based on the above comments for Sections 2 and 14 and the following comments for Sections 6 and 14, by April 17, 2017. Additionally, please include the FDA Class Labeling language for HBV Reactivation in this update.

Section 2 Labeling Requests

The following tables summarize DAVP's position on the GLE/PIB indicated populations and treatment duration recommendations to include in labeling, as detailed above. Note that we are open to your proposals for organization and formatting for presentation in labeling.

Table 1. Recommended Treatment Duration of TRADENAME by HCV Genotype for Treatment-Naïve or PRS* Treatment-Experienced Patients

HCV Genotype	Patient Population	Recommended Treatment Duration of TRADENAME	
		Without cirrhosis	Compensated Cirrhosis (Child-Pugh A)
Genotype 1, 2, or 4	Treatment-naïve and PRS* treatment-experienced	8 weeks	12 weeks
Genotype 3	Treatment-naïve	8 weeks	12 weeks
	PRS*treatment-experienced	16 weeks	16 weeks
Genotype 5 or 6	Treatment-naïve and PRS* treatment-experienced	12 weeks	12 weeks

*PRS Treatment-Experience is defined as prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A protease inhibitor or NS5A inhibitor.

Table 2. Recommended Treatment Duration of TRADENAME for HCV Genotype 1 Infected Patients Without Cirrhosis or With Compensated Cirrhosis (Child-Pugh A), with prior NS5A Inhibitor or NS3/4A Protease Inhibitor Treatment-Experience.

Patient Population	Recommended Treatment Duration of TRADENAME
Genotype 1 NS5A inhibitor treatment-experienced ¹ and NS3/4A inhibitor treatment-naïve	16 weeks
Genotype 1 NS3/4A protease inhibitor treatment-experienced ² and NS5A inhibitor treatment-naïve	12 weeks

1. Regimens containing ledipasvir or daclatasvir in combination with sofosbuvir (with or without ribavirin) or pegylated interferon and ribavirin
2. Regimens containing simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with pegylated interferon and ribavirin

Section 6 Labeling Requests

We are providing some preliminary requests for labeling in Section 6, acknowledging that further edits will be forthcoming. For guidance, please see the Epclusa labeling. In Section 6 please include the following:

- 1) For ENDURANCE- 2 (M15-464): According to the Guidance for Industry on Adverse Reaction Section of Labeling, the data in the listing of common ADVERSE REACTIONS should be derived from the best available data. In general, if placebo-controlled data are sufficiently large to be informative, this information should be used in development of the adverse reaction table. Please include a table that displays an analysis of all treatment-emergent adverse events (by Preferred Terms), all grades and regardless of causality, occurring at $\geq 2\%$ incidence and at a rate greater than placebo. The percentages should be displayed rounded to the nearest whole number.
- 2) For ENDURANCE-3 (M15-594): Please include a table that displays an analysis of all treatment-emergent adverse reactions (at least possibly related AE), all grades and occurring at $\geq 5\%$ incidence. All three arms of the trial, GLE/PIB 8 and 12 weeks and DCV/SOF, should be displayed in the table. The percentages should be displayed rounded to the nearest whole number.
- 3) For the pooled phase 2/3 trials, please provide text that describes any different adverse reactions not otherwise observed in ENDURANCE 2 and 3. You should highlight any differences by duration or cirrhosis status. Please provide the number of subjects who had drug-related SAEs and those who discontinued due to a drug-related Adverse Event in this summary.
- 4) The current display of safety information in Section 6.1 from EXPEDITION-4 appears reasonable; however, additional edits may be forthcoming after future internal meetings are held.

Section 14 Labeling Requests

We are providing some preliminary comments for labeling for Section 14 based on the indications and treatment durations discussed above. To guide this section, we have modified Table 10 and are providing section headings and descriptions for trial inclusions in each subsection. Again, we are open to your suggestions to improve organization or presentation of the data, but, in general, we believe the trials we have identified should be displayed in table and text format, as specified.

Table 10. Clinical Studies Conducted with TRADENAME (b) (4) in Subjects with HCV Genotype 1, 2, 3, 4, 5 or 6 Infection

Genotype (GT)	Clinical Study	(b) (4)
TN and PRS-TE Subjects without Cirrhosis		
GT1	ENDURANCE-1	Tradename for 8 (n=351) or 12 weeks (n=352)
GT2	SURVEYOR-2	Tradename for 8 weeks (n=(b) (4))
GT3	ENDURANCE-3	Tradename for 8 (n=157) or 12 weeks (n=233) Sofosbuvir + daclatasvir for 12 weeks (n=115)
	SURVEYOR-2	16 (PRS-TE only) weeks (n=22)
GT4, 5, 6	ENDURANCE-4	Tradename for 12 weeks (n=26, GT5; n=19, GT6)
	SURVEYOR-1	Tradename for 12 weeks (n=1, GT5; n=11, GT6)
	SURVEYOR-2	Tradename for 8 weeks (n=46; GT4)
TN and PRS-TE Subjects with Compensated Cirrhosis		

- Table to display MAGELLAN-1

Genotype 1, 2, 3, 4, 5, or 6 Subjects with CKD Stage 4 and 5 without Cirrhosis or with Compensated Cirrhosis

- EXPEDITION-4 described in text

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
04/07/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: April 3, 2017

To: Viraj Gandhi, MS MBA, RAC, Senior Manager, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Information Request- Clinical Pharmacology

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We have the following requests for information. **Please provide a response by COB April 16, 2017.**

Clinical Pharmacology

1. Please submit subject level SLCO1B1 genotype data for all subjects genotyped and included in the analyses presented in the study report entitled "*Pharmacogenetic Analysis of Genes Encoding Drug Metabolizing Enzymes and Transporter (R&D/16/0712)*".

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 301-796-1182 or 301-796-1500.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
04/03/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: March 24, 2017

To: Viraj Gandhi, MS MBA, RAC, Senior Manager, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Information Request

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We have the following requests for information. **Please provide a response by COB March 31, 2017.**

Pharmacology/Toxicology

1. Please clarify the lot numbers and respective % purity values for A-1282576 and A-1325912 (Free Form) in study #TA16-040 (RD160097).
2. Please clarify % purity for A-1325912.0 (Lot Number 2288349) and A-1325912 (Lot Number 2288348) in study #TD16-109 (RD 160640).

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 301-796-1182 or 301-796-1500.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
03/24/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209394

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

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

ATTENTION: Viraj Gandhi, MS, MBA, RAC (US)
Senior Manager, Regulatory Affairs

Dear Mr. Gandhi:

Please refer to your New Drug Application (NDA) dated and received December 14, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glecaprevir/Pibrentasvir Tablets, 100 mg/40 mg.

We acknowledge receipt of your correspondence dated and received March 17, 2017, requesting a review of your proposed proprietary name, Mavyret.

The target date is June 15, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact Alicia Moruf, Regulatory Project Manager, in the Office of New Drugs at (301) 796-3953.

Sincerely,

{See appended electronic signature page}

Danyal Chaudhry, M.P.H.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
03/21/2017



NDA 209394

MID-CYCLE COMMUNICATION

AbbVie Inc.
Attention: Viraj Gandhi, MS MBA, RAC
Senior Manager, Regulatory Affairs
One North Waukegan Road
Department PA72/ Building AP30
North Chicago, IL 60064-6194

Dear Mr. Ghandi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We also refer to the teleconference between representatives of your firm and the FDA on March 15, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-3953.

Sincerely,

{See appended electronic signature page}

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial 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: March 15, 2017

Application Number: NDA 209394

Product Name: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Indication: HCV

Applicant Name: AbbVie Inc.

Meeting Recorder: Alicia Moruf, PharmD, MPH

FDA ATTENDEES

Office of Antimicrobial Products

Ed Cox, MD, MPH, Director

Division of Antiviral Products

Jeff Murray, MD, MPH, Deputy Director

Wendy Carter, DO, Clinical Team Leader

Larissa Stabinski, MD, Clinical Reviewer

Aimee Hodowanec, MD, Clinical Reviewer

Kim Struble, PharmD, Clinical Team Leader

Poonam Mishra, MD, MPH, Deputy Director of Safety

Patrick Harrington, PhD, Clinical Virology Reviewer

Eric Donaldson, PhD, Clinical Virology Reviewer

Julian O'Rear, PhD, Clinical Virology Team Leader

Alicia Moruf, PharmD, MPH, Regulatory Project Manager

Elizabeth Thompson, MS, Chief Project Management Staff

Office of Biostatistics

Thamban Valappil, PhD, Biometrics Team Leader

Therri Usher, PhD, Biometrics Reviewer

LaRee Tracy, MA, PhD, Biometrics Reviewer

Office of Clinical Pharmacology

Amal Ayyoub, Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality

Stephen Miller, PhD, Product Quality Team Leader

APPLICANT ATTENDEES

Andrew L Campbell, MD, Senior Project Leader, Next Generation HCV, Pharmaceutical Development

Federico J Mensa, MD, Group Medical Director, HCV Clinical Development

Janet M Hammond, MD, PhD, Vice President, Infectious Diseases

Nancy S Shulman, MD, Executive Medical Director, HCV Development

Andrew Storey, BSc, Vice President, Regulatory Affairs, Global Regulatory Strategy

Christine A Collins, PhD, Director, HCV Clinical Virology

Tami J Pilot-Matias, PhD, Associate Director II, HCV Clinical Virology

Lois M Larsen, PhD, Director, Statistics, Data and Statistical Sciences

Sandra S Lovell, PhD, Associate Director, Statistics, Data and Statistical Sciences

Ariel R Porcalla, MD, MPH, Medical Director, Global Pharmacovigilance

Meenal Patwardhan, MD, MHSA, Therapeutic Area Head, Infectious Diseases, Neurosciences, General Medicine

Wei Liu, PhD, Senior Director, Clinical Pharmacology and Pharmacometrics

Sherry Morgan, DVM, PhD, ACVP, ABVT, ABT Senior Research Fellow, Preclinical Safety

Debra Webb, MS, Director, Regulatory Affairs CMC

Nancy E Sever, PhD, CMC Scientific Director, Global Program Management

Molly Blake-Michaels, MS, PMP Program Lead II, HCV Clinical Program Development

Maryam A Voth, BS, Director, Strategic Labeling, Regulatory Affairs

Nella Barshteyn, PhD, Manager, Strategic Labeling, Regulatory Affairs

Thomas J Podsadecki, MD, Vice President, Regulatory Affairs

Toni A Glinsey, MS, RQC, Senior Director, Regulatory Affairs, Global Regulatory Strategy

Sejal Emerson, PharmD, Director, Regulatory Affairs, Global Regulatory Strategy

Grant S Griffin, MS, RAC, Manager, Regulatory Affairs, Global Regulatory Strategy

Viraj B Gandhi, MS MBA, RAC, Senior Manager, Regulatory Affairs, Global Regulatory Strategy

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

Please refer to our prior communication dated March 9, 2017 that provided the significant review issues identified to date related to the available GLE/PIB efficacy results for certain patient populations.

AbbVie briefly stated their positions on the key discussion issues, and noted they would provide more detailed written justification to support their positions. FDA requested a response within one week.

Post-meeting note: AbbVie submitted their written response on March 22, 2017.

3.0 INFORMATION REQUESTS

Currently, there is an outstanding Pharmacology/Toxicology information request dated March 24, 2017.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

The safety review remains ongoing; however, at this time no major safety concerns have been identified and no REMS is expected.

5.0 ADVISORY COMMITTEE MEETING

Currently, there are no plans for an advisory committee meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late-Cycle Meeting is scheduled for June 22, 2017 from 10:30AM to 11:30AM EST. The Agency Background Package will be provided by June 9, 2017.

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/s/

ALICIA MORUF
03/30/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: March 14, 2017

To: Viraj Gandhi, MS MBA, RAC, Senior Manager, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Information Request-MAGELLAN-1 Trial

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We have the following requests for information. Please provide a response by COB 3/22/2017.

Clinical Virology

Please submit the following:

From the MAGELLAN-1 trial, please provide a simple .xpt table (see example below) that lists each specific prior DAA-containing regimen(s) for each subject (including all subjects in the trial). Please include the treatment duration in weeks, if known. Please also include the names of any investigational DAAs.

USUBJID	Prior DAA Regimen 1	Prior DAA Regimen 2	Prior DAA Regimen 3
001	Ledipasvir/Sofosbuvir for 12 weeks	Peg-IFN/RBV + Boceprevir	
002	Ombitasvir/Paritaprevir/Ritonavir plus Dasabuvir for 12 weeks		

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 301-796-1182 or 301-796-1500.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
03/14/2017



NDA 209394

INFORMATION REQUEST

AbbVie Inc
Attention: Viraj Gandhi, MS MBA, RAC
Senior Manager, Regulatory Affairs
1 N. Waukegan Road, Dept. PA72/Bldg. AP30
North Chicago, IL 60064

Dear Mr. Gandhi:

Please refer to your New Drug Application (NDA) dated December 14, 2016, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- Glecaprevir/Pibrentasvir, 100 mg/40 mg, fixed dose combination film-coated tablets

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a written response by **Tuesday, March 28, 2017**, in order to continue our evaluation of your NDA. A partial response at that time, with clarification of the timeline for the remaining questions, would also be satisfactory.

1. Clarify whether or not any compounds have been identified as degradation products of Glecaprevir. If there have been, explain how these compounds are controlled. If none have been, describe the specific degradation studies that were performed to determine this.
2. Provide specific control strategies for the (b) (4) compounds in the manufacturing processes for both Glecaprevir and Pibrentasvir. Most of these compounds are listed as organic impurities (b) (4) during the manufacturing process (in sec. 3.2.S.3.2 of the NDA in Table 4 (Glecaprevir) and Table 5 (Pibrentasvir)).
3. Explain how the acceptance criteria for the following (b) (4) used in the Glecaprevir manufacturing process are determined and justified: (b) (4)
(b) (4) These acceptance criteria are part of the specifications

(b) (4) throughout the process ((b) (4) is also used in the Pibrentasvir process).

3. Explain how PDE values were determined for the following (b) (4) which are used in the Pibrentasvir manufacturing process (and are controlled in the Pibrentasvir release specification): (b) (4)
4. Indicate whether or not potential sources such as reagents and manufacturing equipment were evaluated when establishing the control strategy for elemental impurities. If they were not, or if their influence was not considered significant, explain.
5. Indicate whether or not reprocessing or reworking would be considered for either Glecaprevir or Pibrentasvir drug substance. If yes, describe the specific circumstances under which reprocessing or reworking would be performed for either drug substance, what specific actions would be taken, and the specific standards the reprocessed / reworked materials would be expected to meet.
6. Demonstrate the suitability of the XRPD method used in development and on stability for testing crystallinity of the drug substances in the drug product.

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Luz
Rivera

Digitally signed by Luz Rivera
Date: 3/14/2017 12:42:32PM
GUID: 502abbba000025b89fdb52a977a3d336



NDA 209394

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

AbbVie, Inc.
1 N. Waukegan Road
Dept. PA72/Bldg. AP30
North Chicago, IL 60064

ATTENTION: Viraj Gandhi, MS, MBA, RAC
Senior Manager, Regulatory Affairs

Dear Mr. Gandhi:

Please refer to your New Drug Application (NDA) dated and received December, 14, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glecaprevir/Pibrentasvir Tablets, 100 mg/40 mg.

We also refer to your correspondence dated and received December 14, 2016, requesting review of your proposed proprietary name, (b) (4).

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

The proposed name, (b) (4), contains the United States Adopted Name (USAN) stem (b) (4).^[1]

However, the use of a USAN stem within the proprietary names, even when used consistently with the USAN meaning, can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the chance of confusion among those drugs, which may compromise patient safety.^[2] To reduce the potential for confusion, USAN stems should not be incorporated into proprietary names.

^[1] USAN stem search conducted on January 5, 2017.

^[2] Draft Guidance for Industry: Best Practices in Developing Proprietary Names for Drugs. 2014. Available from <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm398997.pdf>.

We note that the external name review performed by (b) (4) acknowledges that (b) (4) contains a USAN stem and identifies several approved U.S. brand names that include the (b) (4) letter string as a prefix, infix, and suffix. However, these brand names were approved prior to the publication of the PDUFA Pilot Project Proprietary Name Review Concept Paper in September 2008^[3].

We note that you have proposed an alternate proprietary name in your submission dated December 14, 2016. In order to initiate the review of the alternate proprietary name, (b) (4), submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- 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 Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-3813. For any other information regarding this application, contact Alicia Moruf, Regulatory Project Manager in the Office of New Drugs, at 301-796-3953.

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

^[3] PDUFA Pilot Project: Proprietary Name Review Concept Paper. 2008. Available from <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072229.pdf>

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/s/

AZEEM D CHAUDHRY
03/09/2017

DANIELLE M HARRIS on behalf of TODD D BRIDGES
03/09/2017

From: Moruf, Alicia
To: ["Emerson, Sejal"](#); [Gandhi, Virajkumar B](#)
Subject: NDA 209394 GLE/PIB Information Request-ENDURANCE-1 Trial
Date: Thursday, March 09, 2017 1:39:00 PM

Dr.Emerson and Mr. Gandhi-

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg. Please provide a response by COB 03/10/2017.

We have the following request for information:

-
-

Clinical Virology

1. Two subjects in the ENDURANCE-1 trial had inconsistent HIV coinfection status results reported. Please clarify.

COINFECT	HIVSTAT	HIVHIST	N
	POSITIVE		<u>2</u>
HIV	POSITIVE	ART-TREATED	33

USUBJIDs

M13590-47040-251105

M13590-50890-106106

Kind Regards,

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Email: alicia.moruf@fda.hhs.gov
Phone: 301-796-3953

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/s/

ALICIA MORUF
03/09/2017



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE AGENDA/TOPICS FOR DISCUSSION

Meeting Date and Time: March 15, 2017 at 1:00PM EST to 2:00PM EST
Application Number: NDA 209394
Product Name: GLE/PIB
Indication: HCV
Applicant Name: AbbVie Inc.

1.0 INTRODUCTION

In advance of the mid-cycle communication planned for 3/15/17, we would like to make you aware that the review team has identified significant review issues related to available GLE/PIB efficacy results and proposed labeling for certain patient populations. These issues are outlined below.

2.0 SIGNIFICANT ISSUES

Clinical/Virology/Biometrics

In advance of the midcycle communication planned for 3/15/17, we would like to make you aware that the review team has identified significant review issues related to available GLE/PIB efficacy results and proposed labeling for certain patient populations. These issues are outlined below.

1. NS3/4A PI and/or NS5A Inhibitor Treatment-Experienced Population: Multiple issues and data limitations have been identified for NS3/4A PI and/or NS5A inhibitor treatment-experienced patients (specific to data supplied from the MAGELLAN-1 trial):
 - a) There are insufficient data to support labeling for treating NS5A inhibitor-experienced patients (with any HCV genotype). The sample size for this subpopulation is relatively small overall, and even smaller for the (b) (4) NS5A inhibitor experienced $\pm$ NS3/4A PI experience). Furthermore, across all arms several cases of virologic failure (n=11) were observed and were associated with additional treatment-emergent drug resistance selection in both drug targets. The fact that 6 of the 11 cases of virologic failure were on-treatment virologic failures strongly suggests that GLE/PIB alone, for any treatment duration, is not an optimal drug regimen to treat this subpopulation.
 - b) The data supporting GLE/PIB for the treatment of NS3/4A PI-experienced, NS5A inhibitor-naïve patients are limited. While the findings in this subset are favorable

showing an SVR12 rate of 23/25 (GT1, GLE/PIB 12 weeks) with no cases of virologic failure, the sample size is comparatively less than what has been reviewed supporting multiple approved DAA regimens with thoroughly proven efficacy in this subpopulation. However, we will likely support inclusion of the NS3/4A PI-experienced HCV genotype 1 population labeling for a 12 week duration.

- c) Given that all but 4 subjects in MAGELLAN-1 were infected with HCV GT1, for this population, the Division is considering data or labeling for HCV genotype 1 only, which is consistent with our position communicated during the pre-NDA meeting.
2. Proposed 8-week GLE/PIB Regimen for Treating Treatment-Naïve HCV GT3: The Division is concerned there was a higher rate of relapse (~3% versus 1%) observed in the ENDURANCE-3 trial, when GLE/PIB was administered for 8 weeks versus 12 weeks. While this is a relatively small difference in relapse rates, treatment failure with GLE/PIB of any duration was associated with the emergence of resistance-associated substitutions in both drug targets in GT3-infected patients. In addition, the totality of evidence provided indicates that HCV GT3 is likely the most difficult-to-treat HCV genotype, often requiring longer treatment durations, similar to observations with other approved DAA. Therefore, the Division recommends a more-conservative approach for treating HCV GT3 consisting of GLE/PIB for 12 weeks (as was studied). Furthermore, this same duration can be used for patients with or without compensated cirrhosis, which also minimizes concerns about administering an 8-week duration to GT3 patients with borderline or misclassified cirrhosis status.
 3. Proposed 8-week GLE/PIB Regimen for Treating Non-Cirrhotic HCV GT5 or GT6: Consistent with our concerns communicated during the pre-NDA meeting, the limited number of patients who received the 8 week GLE/PIB duration (n=2 for GT5, n=10 for GT6; all but 2 tx-naïve) does not support shortening the GLE/PIB duration from 12 weeks to 8 weeks. The two subjects with GT5 infection who received the 8 week duration had low baseline HCV RNA levels <200,000 IU/mL, and neither subject had a reported NS3 D168E polymorphism (data available for 1 subject) that appears to be relatively common in GT5 and theoretically may impact GLE activity or durability. Also, the diversity of GT6 subtypes is not adequately represented with a sample size of only 10 subjects. Furthermore, the lack of information on treatment-emergent resistance and how to potentially re-treat GT5 or GT6 patients who fail GLE/PIB is concerning. In both GT5 and GT6 infected patients, GLE/PIB for 12 weeks was highly effective and is supported by larger sample sizes for both genotypes providing greater confidence that this represents a more reasonable regimen for these genotypes.

Please be aware that we plan to discuss other aspects of your application at an internal meeting prior to our 3/15/17 midcycle meeting, and therefore additional review issues may be presented at the midcycle meeting. A written midcycle communication letter and meeting minutes will be

provided to you after the 3/15/17 meeting. Subsequently, we will be requesting updated labeling based on the above labeling issues. The label update should also include the current HBV reactivation box warning language.

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 301-796-3953.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
03/09/2017

From: Moruf, Alicia
To: ["Emerson, Sejal"](#)
Cc: [Gandhi, Virajkumar B](#)
Subject: RE: Informal TCON with DAVP-NDA 209394 - AbbVie Proposal for Datasets
Date: Tuesday, March 07, 2017 9:02:00 AM

Sejal and Viraj-

We would prefer a March 21 submission of MELD scores with no delay of the other databases (Option 1). We would like MELD submitted for all subjects as many subjects' cirrhosis status was measured with noninvasive measures and there could be some degree of misclassification. We also note that there are some cases of liver related events, for example, one case of HCC that occurred in a subject without previously documented cirrhosis and resulted in a patient death. This measure will help us better evaluate these types of cases, the cases of elevated bilirubin and others with laboratory abnormalities both amongst cirrhotic and non-cirrhotic subjects.

Kind Regards,
Alicia

From: Emerson, Sejal [mailto:sejal.emerson@abbvie.com]
Sent: Monday, March 06, 2017 1:18 PM
To: Moruf, Alicia
Cc: Gandhi, Virajkumar B
Subject: RE: Informal TCON with DAVP-NDA 209394 - AbbVie Proposal for Datasets
Importance: High

Dear Alicia,

We have evaluated this request and had a couple points for clarification as follows:

1. AbbVie proposes to provide Model for End-Stage Liver Disease (MELD) scores at all pre-treatment, on-treatment, and post-treatment visits for cirrhotic subjects only.

AbbVie's rationale for this proposal is that the MELD scoring system is primarily used in patients with end-stage liver disease (i.e., decompensated cirrhotics) to predict 3-month mortality and subsequently prioritize patients awaiting liver transplantation. Moreover, both the AASLD and the EASL HCV guidance documents refer to the MELD's scores usefulness only in patients with decompensated liver disease. Given that MELD scores are unlikely to yield meaningful information in non-cirrhotics, AbbVie therefore proposes to provide MELD scores in all subjects with compensated cirrhotics.

Does the Division agree with this plan?

2. As outlined above, we will be able to send the MELD scores to the Agency. However, unfortunately we would not be able to include the MELD scores in the dataset submission planned for March 7th without jeopardizing the timelines for those datasets. As such, we would like to understand the Division's preference regarding the timelines for all the requested datasets (MELD score dataset, ADLBHY, ADLBPCS, and ADLBMN):
 - *Option 1:* Would receiving the MELD score dataset on March 21st with ADLBMN be acceptable?

- *Option 2:* If you prefer to receive the MELD score dataset sooner, we could submit a dataset with the MELD scores by March 14th, and the remaining datasets (ADLBHY, ADLBPCS, and ADLBMN) by March 21st. Would that be acceptable?

Thanks!

Sejal

Global Regulatory Strategy

OFFICE +1 847-935-6703

CELL (b) (6)

From: Moruf, Alicia [<mailto:Alicia.Moruf@fda.hhs.gov>]

Sent: Thursday, March 02, 2017 8:56 AM

To: Emerson, Sejal

Subject: RE: Informal TCON with DAVP-NDA 209394 - AbbVie Proposal for Datasets

Importance: High

Sejal-

The Division has an additional request to be submitted at the same time as the datasets.

Please include a calculated MELD score at Baseline, Weeks 4, 8, 12 and 16 and at Post-treatment Week 12 in a database for submission. This data can be added to a dataset that you are planning to submit or can be submitted subsequently as a separate dataset submission. The total n should again be 2584 subjects in the pooled dataset. If this can be added to the laboratory dataset without delaying the submission of the dataset, please do so. If not, please submit the dataset subsequently to the 3/7 dataset submission.

Kind Regards,

Alicia Moruf, PharmD, MPH

Regulatory Project Manager

Division of Antiviral Products

Email: alicia.moruf@fda.hhs.gov

Phone: 301-796-3953

From: Moruf, Alicia

Sent: Tuesday, February 28, 2017 12:39 PM

To: 'Emerson, Sejal'

Subject: RE: Informal TCON with DAVP-NDA 209394 - AbbVie Proposal for Datasets

Sejal-

The review team has agreed to your proposal outlined below. Thank you.

Kind Regards,
Alicia

From: Emerson, Sejal [<mailto:sejal.emerson@abbvie.com>]
Sent: Tuesday, February 28, 2017 11:34 AM
To: Moruf, Alicia
Subject: RE: Informal TCON with DAVP-NDA 209394 - AbbVie Proposal for Datasets

Dear Alicia,

Based on our discussion yesterday afternoon, please see below a summary of our submission plan, along with our proposed timelines. **Please confirm that this plan reflects our discussions since we would like to ensure that we are meeting the reviewers' and system needs.**

As mentioned during the call, we will do our best to expedite the submissions. However we also want to ensure that while we expedite the submissions we allot enough time for validation.

Submission #1:	The following 3 datasets will be submitted by March 7, 2017: 1. ADAE 2. ADSL 3. ADLBGRD	• Each dataset will include patients administered the GLE/PIB 300/120 mg dose (and no RBV) from M14-867, M14-868, M14-172, M15-410, M15-464, M13-583, M13-590, M13-594, and M15-462 plus the M15-464 Placebo Arm (Treatment period 1, 12 weeks) and the M13-594 SOF/DCV 12 weeks, • Each dataset will include 18 flags: 1) M15-462 GLE/PIB 12 weeks (renal impairment) 2) M15-464 Placebo Arm (Treatment period 1, 12 weeks) 3) M15-464 GLE/PIB 12 weeks (Treatment period 1) 4) M13-594 SOF/DCV 12 weeks 5) M13-594 GLE/PIB 12 weeks 6) M13-594 GLE/PIB 8 weeks 7) GLE/PIB 8 weeks pooled arm excluding M15-462 8) GLE/PIB 12 weeks pooled arm excluding M15-462 9) GLE/PIB 16 weeks pooled arm excluding M15-462 10) GLE/PIB 8, 12, and 16 weeks excluding M15-462 - all durations pooled into a single arm 11) GLE/PIB 12 weeks pooled arm
----------------	--	--

		excluding M15-462 - no cirrhosis- 12) GLE/PIB 12 weeks pooled arm excluding M15-462 - with cirrhosis 13) GLE/PIB 16 weeks pooled arm excluding M15-462 - no cirrhosis 14) GLE/PIB 16 weeks pooled arm excluding M15-462 - with cirrhosis 15) GLE/PIB 8, 12, and 16 weeks excluding M15-462 - all durations pooled arm - no cirrhosis 16) GLE/PIB 8, 12, and 16 weeks excluding M15-462 – all durations pooled arm – cirrhosis 17) GLE/PIB 12 weeks pooled arm 18) GLE/PIB 8, 12, and 16 weeks - all durations pooled arm
Submission #2:	The following 2 datasets will be submitted by March 14, 2017: 1. ADLBHY 2. ADLBPCS	• Same as above
Submission #3:	The following dataset will be submitted by March 21, 2017: 1. ADLBMN	• Same as above

Thanks!
Sejal

Global Regulatory Strategy
 OFFICE +1 847-935-6703
 CELL (b) (6)

From: Moruf, Alicia [<mailto:Alicia.Moruf@fda.hhs.gov>]
Sent: Monday, February 27, 2017 8:12 AM
To: Emerson, Sejal
Subject: RE: Informal TCON with DAVP-NDA 209394

Sejal-

Thank you, I am confirming 315pm to 330pm. Please provide a call in number.

-
FDA Attendees-

-
Larissa Stabinski- Clinical Reviewer
Wendy Carter- Clinical Team Leader
Alicia Moruf- Regulatory Project Manager
Elizabeth Thompson- Chief Regulatory Project Management Staff

From: Emerson, Sejal [<mailto:sejal.emerson@abbvie.com>]
Sent: Monday, February 27, 2017 9:00 AM
To: Moruf, Alicia
Subject: RE: Informal TCON with DAVP-NDA 209394

Hi Alicia,

Many thanks for your prompt response. That will be much better on our end. Can we plan for 3:15 pm (Eastern) for a telecom instead?

Thanks!
Sejal

Global Regulatory Strategy
OFFICE +1 847-935-6703
CELL (b) (6)

From: Moruf, Alicia [<mailto:Alicia.Moruf@fda.hhs.gov>]
Sent: Monday, February 27, 2017 7:56 AM
To: Emerson, Sejal
Subject: RE: Informal TCON with DAVP-NDA 209394

Sejal-

Thank you.

We have availability at 315 to 330 pm. Thank you

Alicia

From: Emerson, Sejal [<mailto:sejal.emerson@abbvie.com>]
Sent: Monday, February 27, 2017 8:52 AM
To: Moruf, Alicia
Subject: RE: Informal TCON with DAVP-NDA 209394

Dear Alicia,

I will see if I can gather the key team members up for 10 am Eastern (9 am central), but if not, do you have availability any time this afternoon?

Thanks!

Sejal

Global Regulatory Strategy

OFFICE +1 847-935-6703

CELL (b) (6)

From: Moruf, Alicia [<mailto:Alicia.Moruf@fda.hhs.gov>]

Sent: Monday, February 27, 2017 7:30 AM

To: Emerson, Sejal

Subject: Informal TCON with DAVP-NDA 209394

Importance: High

Sejal-

The Clinical reviewer for GLE/PIB, NDA 209394, would like to have a very brief TCON with your team to discuss the Division's Information Request dated Feb.17 (see attached) and AbbVie's Response to this request dated and submitted on February 23, 2017.

Do you have time today for a 15 minute call at 10AM EST to 10:15AM EST?

Thank you

Alicia Moruf, PharmD, MPH

Regulatory Project Manager

Division of Antiviral Products

Email: alicia.moruf@fda.hhs.gov

Phone: 301-796-3953

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/s/

ALICIA MORUF
03/07/2017

From: Moruf, Alicia
To: ["Emerson, Sejal"](#)
Subject: RE: Informal TCON with DAVP-NDA 209394 - AbbVie Proposal for Datasets
Date: Thursday, March 02, 2017 9:55:00 AM
Importance: High

Sejal-

The Division has an additional request to be submitted at the same time as the datasets.

Please include a calculated MELD score at Baseline, Weeks 4, 8, 12 and 16 and at Post-treatment Week 12 in a database for submission. This data can be added to a dataset that you are planning to submit or can be submitted subsequently as a separate dataset submission. The total n should again be 2584 subjects in the pooled dataset. If this can be added to the laboratory dataset without delaying the submission of the dataset, please do so. If not, please submit the dataset subsequently to the 3/7 dataset submission.

Kind Regards,

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Email: alicia.moruf@fda.hhs.gov
Phone: 301-796-3953

From: Moruf, Alicia
Sent: Tuesday, February 28, 2017 12:39 PM
To: 'Emerson, Sejal'
Subject: RE: Informal TCON with DAVP-NDA 209394 - AbbVie Proposal for Datasets

Sejal-

The review team has agreed to your proposal outlined below. Thank you.

Kind Regards,
Alicia

From: Emerson, Sejal [<mailto:sejal.emerson@abbvie.com>]
Sent: Tuesday, February 28, 2017 11:34 AM
To: Moruf, Alicia
Subject: RE: Informal TCON with DAVP-NDA 209394 - AbbVie Proposal for Datasets

Dear Alicia,

Based on our discussion yesterday afternoon, please see below a summary of our submission plan,

along with our proposed timelines. **Please confirm that this plan reflects our discussions since we would like to ensure that we are meeting the reviewers' and system needs.**

As mentioned during the call, we will do our best to expedite the submissions. However we also want to ensure that while we expedite the submissions we allot enough time for validation.

Submission #1:	The following 3 datasets will be submitted by March 7, 2017: 1. ADAE 2. ADSL 3. ADLBGRD	• Each dataset will include patients administered the GLE/PIB 300/120 mg dose (and no RBV) from M14-867, M14-868, M14-172, M15-410, M15-464, M13-583, M13-590, M13-594, and M15-462 plus the M15-464 Placebo Arm (Treatment period 1, 12 weeks) and the M13-594 SOF/DCV 12 weeks, • Each dataset will include 18 flags: 1) M15-462 GLE/PIB 12 weeks (renal impairment) 2) M15-464 Placebo Arm (Treatment period 1, 12 weeks) 3) M15-464 GLE/PIB 12 weeks (Treatment period 1) 4) M13-594 SOF/DCV 12 weeks 5) M13-594 GLE/PIB 12 weeks 6) M13-594 GLE/PIB 8 weeks 7) GLE/PIB 8 weeks pooled arm excluding M15-462 8) GLE/PIB 12 weeks pooled arm excluding M15-462 9) GLE/PIB 16 weeks pooled arm excluding M15-462 10) GLE/PIB 8, 12, and 16 weeks excluding M15-462 - all durations pooled into a single arm 11) GLE/PIB 12 weeks pooled arm excluding M15-462 - no cirrhosis- 12) GLE/PIB 12 weeks pooled arm excluding M15-462 - with cirrhosis 13) GLE/PIB 16 weeks pooled arm excluding M15-462 - no cirrhosis 14) GLE/PIB 16 weeks pooled arm excluding M15-462 - with cirrhosis 15) GLE/PIB 8, 12, and 16 weeks excluding M15-462 - all durations pooled arm - no cirrhosis 16) GLE/PIB 8, 12, and 16 weeks
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		excluding M15-462 – all durations pooled arm – cirrhosis 17) GLE/PIB 12 weeks pooled arm 18) GLE/PIB 8, 12, and 16 weeks - all durations pooled arm
Submission #2:	The following 2 datasets will be submitted by March 14, 2017: 1. ADLBHY 2. ADLBPCS	• Same as above
Submission #3:	The following dataset will be submitted by March 21, 2017: 1. ADLBMN	• Same as above

Thanks!
Sejal

Global Regulatory Strategy
 OFFICE +1 847-935-6703
 CELL (b) (6)

From: Moruf, Alicia [<mailto:Alicia.Moruf@fda.hhs.gov>]
Sent: Monday, February 27, 2017 8:12 AM
To: Emerson, Sejal
Subject: RE: Informal TCON with DAVP-NDA 209394

Sejal-

Thank you, I am confirming 315pm to 330pm. Please provide a call in number.

-
FDA Attendees-

-
 Larissa Stabinski- Clinical Reviewer
 Wendy Carter- Clinical Team Leader
 Alicia Moruf- Regulatory Project Manager
 Elizabeth Thompson- Chief Regulatory Project Management Staff

From: Emerson, Sejal [<mailto:sejal.emerson@abbvie.com>]
Sent: Monday, February 27, 2017 9:00 AM
To: Moruf, Alicia
Subject: RE: Informal TCON with DAVP-NDA 209394

Hi Alicia,

Many thanks for your prompt response. That will be much better on our end. Can we plan for 3:15 pm (Eastern) for a telecom instead?

Thanks!
Sejal

Global Regulatory Strategy
OFFICE +1 847-935-6703
CELL (b) (6)

From: Moruf, Alicia [<mailto:Alicia.Moruf@fda.hhs.gov>]
Sent: Monday, February 27, 2017 7:56 AM
To: Emerson, Sejal
Subject: RE: Informal TCON with DAVP-NDA 209394

Sejal-

Thank you.

We have availability at 315 to 330 pm. Thank you

Alicia

From: Emerson, Sejal [<mailto:sejal.emerson@abbvie.com>]
Sent: Monday, February 27, 2017 8:52 AM
To: Moruf, Alicia
Subject: RE: Informal TCON with DAVP-NDA 209394

Dear Alicia,

I will see if I can gather the key team members up for 10 am Eastern (9 am central), but if not, do you have availability any time this afternoon?

Thanks!
Sejal

Global Regulatory Strategy
OFFICE +1 847-935-6703
CELL (b) (6)

From: Moruf, Alicia [<mailto:Alicia.Moruf@fda.hhs.gov>]
Sent: Monday, February 27, 2017 7:30 AM
To: Emerson, Sejal
Subject: Informal TCON with DAVP-NDA 209394
Importance: High

Sejal-

The Clinical reviewer for GLE/PIB, NDA 209394, would like to have a very brief TCON with your team to discuss the Division's Information Request dated Feb.17 (see attached) and AbbVie's Response to this request dated and submitted on February 23, 2017.

Do you have time today for a 15 minute call at 10AM EST to 10:15AM EST?

Thank you

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Email: alicia.moruf@fda.hhs.gov
Phone: 301-796-3953

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

/s/

ALICIA MORUF
03/02/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209394

INFORMATION REQUEST

AbbVie Inc.
Attention: Sejal P. Emerson, PharmD
Director, Regulatory Affairs
1 N. Waukegan Road, Dept. PA77/Bldg. AP30
North Chicago, IL 60064

Dear Dr. Emerson:

Please refer to your New Drug Application (NDA) dated December 14, 2016, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- Glecaprevir/Pibrentasvir, 100 mg/40 mg, fixed dose combination film-coated tablets

We are reviewing the Biopharmaceutics section of your submission and have the following comments and information requests. We request a written response by **Tuesday, March 7, 2017**, in order to continue our evaluation of your NDA. A partial response at that time, with clarification of the timeline for the remaining questions, would also be satisfactory.

1. The proposed QC dissolution method and acceptance criteria are deemed acceptable for the routine testing of glecaprevir/pibrentasvir 100mg /40 mg film-coated bilayer tablets at batch release and during shelf-life. To clarify that the dissolution testing results will be interpreted consistent with USP Acceptance Table #1 for Immediate-Release Dosage Forms, we recommend that you include "Q" in the dissolution acceptance criteria in the Finished Drug Product Specification and other pertinent NDA documents, as shown below.

Glecaprevir: Q = (b) (4) % at 45 min; Q = (b) (4) % at 120 min
Pibrentasvir: Q = (b) (4) % at 45 min; Q = (b) (4) % at 120 min

2. It appears that the three Production Batches were or are being used in clinical trials. For information purposes only, provide the clinical trial numbers, or direct us to the location of the information in the NDA.

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Luz
Rivera

Digitally signed by Luz Rivera
Date: 2/23/2017 03:45:43PM
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: February 17, 2017

To: Sejal Emerson, PharmD, Director, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Information Request for re-pooled data

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We have the following requests for information. Please respond as soon as possible but no later than by **COB 02/23/2017**.

Clinical

The large amount of data pooling required for safety analysis of NDA 209394 is causing technical difficulties in the systems that FDA reviewers use to analyze safety data. For this reason, and to expedite and ensure a consistent and accurate review, the review team requests the following.

- 1) Please submit new ISS datasets containing the following arms and pooled arms. Please only include registrational and supportive trial arms containing GLE/PIB at the intended marketed dose of 300/120 mg and durations of 8, 12 or 16 weeks (as relevant). Do not include RBV containing arms. Please include the placebo arm of M15-464 and the SOF/DCV comparator arm from trial M15-594 as indicated below.

Trial arms that should be included without pooling:

M15-462 GLE/PIB (renal impairment)

M15-464 Placebo Arm (Treatment period 1, 12 weeks)

M15-464 (Treatment period 1, 12 weeks)

M15-594 SOF/DCV 12 weeks

M15-594 GLE/PIB 12 weeks

M15-594 GLE/PIB 8 weeks

Pooled trial arms by durations (Including trials: (M13-590), (M14-867), (M15-464), (M14-868), (M15-594), (M14-172), (M15-410), (M13-583), using arms with to-be-marketed doses and without RBV and excluding subjects with renal severe impairment (M15-462))

GLE/PIB 8 weeks pooled arm

GLE/PIB 12 weeks pooled arm

GLE/PIB 16 weeks pooled arm

GLE/PIB 8, 12, and 16 weeks - all durations pooled into a single arm

Pooled trial arms by duration and cirrhosis status: (Including trials: (M13-590), (M14-867), (M15-464), (M14-868), (M15-594), (M14-172), (M15-410), (M13-583), using arms with to-be-marketed doses and without RBV and excluding subjects with renal severe impairment (M15-462))

GLE/PIB 12 weeks pooled arm - no cirrhosis

GLE/PIB 12 weeks pooled arm with cirrhosis

GLE/PIB 16 weeks pooled arm - no cirrhosis

GLE/PIB 16 weeks pooled arm with cirrhosis

GLE/PIB 8, 12, and 16 weeks- all durations pooled arm - no cirrhosis

GLE/PIB 8, 12, and 16 weeks – all durations pooled arm - cirrhosis

Pooled trial arms by duration including the renal impairment trial: (Including trials: (M13-590), (M14-867), (M15-464), (M14-868), (M15-594), (M14-172), (M15-410), (M13-583), (M15-462), using arms with to-be-marketed doses and without RBV, and including subjects with renal severe impairment)

GLE/PIB 12 weeks pooled arm

GLE/PIB 8, 12, and 16 weeks - all durations pooled arm

- 2) Please replicate the following tables listing (1) Preferred terms in descending order and (2) System Organ Class and Preferred Terms for each population in the table (total of 4 tables). For each table population also please replicate Table 12 (page 25) and 16 (page 29) in the Summary of Clinical Safety (total of 4 tables).

ENDURANCE-2 M15-464, GT2 (Placebo controlled)		ENDURANCE-3 M15-594,GT3 (Active controlled)			EXPEDITION -4 M15-462, (Severe Renal Impairment)				Pooled Studies ENDURANCE-1 (M13-590),SURVEYOR-1 (M14-867), EDURANCE-2 (M15-464), SURVEYOR-2 (M14-868), ENDURANCE-3 (M15-594), ENDURANCE-4 (M13-583), EXPEDITION-1(M14-172), MAGELLAN-1 (M15-410) (Study drug arm registration studies, excludes subjects with renal impairment)		
<u>Placebo</u> <u>12 weeks</u> n=x	<u>GLE/PI</u> <u>B</u> <u>12 weeks</u> n=x	<u>SOF/DC</u> <u>V</u> <u>12 weeks</u> n=x	<u>GLE/PI</u> <u>B</u> <u>12 weeks</u> n=x	<u>GLE/PI</u> <u>B</u> <u>8 weeks</u> n=x	<u>GLE/PIB</u> <u>12 weeks</u> n=x	<u>GLE/PI</u> <u>B</u> <u>8 weeks</u> n=x	<u>GLE/PI</u> <u>B</u> <u>12 weeks</u> n=x	<u>GLE/PI</u> <u>B</u> <u>16 weeks</u> N=x			

EXPEDITION-4 M15-462, (Severe Renal Impairment)		Pooled Studies ENDURANCE-1 (M13-590),SURVEYOR-1 (M14-867), EDURANCE-2 (M15-464), SURVEYOR-2 (M14-868), ENDURANCE-3 (M15-594), ENDURANCE-4 (M13-583), EXPEDITION-1(M14-172), MAGELLAN-1 (M15-410) (Study drug arm registration studies, excludes subjects with renal impairment)				
<u>GLE/PIB</u> <u>12 weeks</u> No cirrhosis n=x	<u>GLE/PIB</u> <u>12 weeks</u> Cirrhosis n=x	<u>GLE/PIB</u> <u>8 weeks</u> No Cirrhosis n=x	<u>GLE/PIB</u> <u>12 weeks</u> No Cirrhosis n=x	<u>GLE/PIB</u> <u>12 weeks</u> Cirrhosis n=x	<u>GLE/PIB</u> <u>16 weeks</u> No Cirrhosis n=x	<u>GLE/PIB</u> <u>16 weeks</u> Cirrhosis n=x

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 301-796-3953.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
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/

ALICIA MORUF
02/17/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: February 13, 2017

To: Sejal Emerson, PharmD, Director, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Information Request-clinical virology data review

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We have the following requests for information. Please provide a response by COB 02/20/2017.

Clinical Virology

The Division's analysis of baseline resistance data from HCV GT3 infected subjects could not completely reproduce the results presented in study report R&D/16/0492, Tables 10 and 11. Table 1 below summarizes our analyses of SVR12 rates according to the presence or absence of the NS5A A30K and Y93H polymorphisms using the 15% NGS sensitivity cutoff, for the populations and regimens proposed for inclusion in labeling. The attached spreadsheet provides the USUBJIDs and associated data to reproduce this table. Additional summary Tables 2 and 3 show our preliminary analyses of other polymorphisms and populations/regimens. All of these analyses censored subjects who did not achieve SVR for reasons unrelated to virologic failure, including Subject M13594-37739-161301 with hypothesized reinfection, which explains one minor inconsistency. Another inconsistency between our analyses and yours is the n=1 treatment-experienced subject with cirrhosis and the Y93H polymorphisms who received GLE/PIB for 16 weeks and achieved SVR12 (M14868-49354-5914). Please confirm the results in Tables 10 and 11 in R&D/16/0492 are accurate, and if not, please submit revised tables.

Please provide a response by 2/20/2017. If more time is needed to reproduce all of the results in Tables 2 and 3, at minimum please confirm the analyses shown in Table 1 by 2/20/2017. If our results remain inconsistent, please explain where you believe the inconsistencies may exist.

Table 1. SVR12 rates for subjects with NS5A A30K (GT3a only) or Y93H polymorphisms (any GT3 subtype), considering sponsor's label-recommended regimens (15% NGS cutoff, non-VF-censored). ND, no data.

	Tx-Naïve, No Cirrhosis GLE/PIB 8W	Tx-Naïve, w/Cirrhosis GLE/PIB 12W	Tx-Exp, No Cirrhosis GLE/PIB 16W	Tx-Exp, w/Cirrhosis GLE/PIB 16W	Pooled Sponsor's Proposed Recom. Regimens
NS5A A30K (GT3a only)					
Without Polymorphism	159/161 (99%)	62/62 (100%)	19/19 (100%)	47/50 (94%)	287/292 (98%)
With Polymorphism	14/18 (78%)	1/1 (100%)	0/1	ND	15/20 (75%)
NS5A Y93H					
Without Polymorphism	165/171 (96%)	58/58 (100%)	20/21 (95%)	47/50 (94%)	290/300 (97%)
With Polymorphism	10/10 (100%)	5/5 (100%)	ND	1/1	16/16 (100%)
NS5A A30K or Y93H					
Without Polymorphism	151/153 (99%)	57/57 (100%)	20/20 (100%)	47/50 (94%)	275/280 (98%)
With Polymorphism	24/28 (86%)	6/6 (100%)	0/1	1/1	31/36 (86%)

Table 2. SVR12 rates for treatment-naïve subjects with certain baseline resistance-associated polymorphisms (15% NGS cutoff, non-VF-censored). *sponsor-proposed recommended GLE/PIB regimen; ^Subject M13594-45400-139305 had NS5A A30K and Y93H polymorphisms detected. ND, no data; PM, polymorphism.

Polymorphism	Tx-Naïve, No Cirrhosis				Tx-Naïve, w/Cirrhosis	
	GLE/PIB 8W*		GLE/PIB 12W		GLE/PIB 12W*	
	With PM	Without PM	With PM	Without PM	With PM	Without PM
NS3 T54A/S	1/2 (50%)	174/179 (97%)	1/1	251/254 (99%)	ND	63/63 (100%)
NS3 A166S/T	22/25 (88%)	153/156 (98%)	33/33 (100%)	219/222 (99%)	9/9 (100%)	54/54 (100%)
NS3 A166S	14/17 (82%)	161/164 (98%)	21/21 (100%)	231/234 (99%)	6/6 (100%)	57/57 (100%)
NS3 Q168K/R	1/2 (50%)	174/179 (97%)	4/5 (80%)	248/250 (99%)	2/2 (100%)	61/61 (100%)
NS3 Q168R	0/1	175/180 (97%)	1/2 (50%)	251/253 (99%)	ND	63/63 (100%)
NS3-any (54,166,168)	23/27 (85%)	152/154 (99%)	37/38 (97%)	215/217 (99%)	10/10 (100%)	53/53 (100%)
NS5A A/K30-any	26/30 (87%)	149/151 (99%)	25/26 (96%)	229/231 (99%)	5/5 (100%)	58/58 (100%)
NS5A A30K (3a)	14/18 (78%)	159/161 (99%)	13/14^ (93%)	239/240 (100%)	1/1	62/62 (100%)
NS5A Y93H	10/10 (100%)	165/171 (96%)	10/11^ (91%)	244/246 (99%)	5/5 (100%)	58/58 (100%)
NS5A Any	51/55 (93%)	124/126 (98%)	47/49 (96%)	207/208 (100%)	12/12 (100%)	51/51 (100%)
NS5A-any (30,93)	33/37 (89%)	142/144 (99%)	33/34 (97%)	221/223 (99%)	9/9 (100%)	54/54 (100%)

Table 3. SVR12 rates for treatment-experienced subjects with certain baseline resistance-associated polymorphisms (15% NGS cutoff, non-VF-censored). *sponsor-proposed recommended GLE/PIB regimen. ND, no data; PM, polymorphism.

Polymorphism	Tx-Exp., No Cirrhosis				Tx-Exp., w/Cirrhosis	
	GLE/PIB 12W		GLE/PIB 16W*		GLE/PIB 16W*	
	With PM	Without PM	With PM	Without PM	With PM	Without PM
NS3 T54A/S	ND	44/49 (90%)	ND	20/21 (95%)	ND	48/51 (94%)
NS3 A166S/T	7/8 (88%)	37/41 (90%)	2/2 (100%)	18/19 (95%)	7/9 (78%)	41/42 (98%)
NS3 A166S	4/5 (80%)	40/44 (91%)	2/2 (100%)	18/19 (95%)	4/6 (67%)	44/45 (98%)
NS3 Q168K/R	ND	44/49 (90%)	ND	20/21 (95%)	1/1	47/50 (94%)
NS3 Q168R	ND	44/49 (90%)	ND	20/21 (95%)	1/1	47/50 (94%)
NS3 Any (54,166,168)	7/8 (88%)	37/41 (90%)	2/2 (100%)	18/19 (95%)	8/10 (80%)	40/41 (98%)
NS5A A/K30-Any	2/5 (40%)	42/44 (95%)	1/2 (50%)	19/19 (100%)	5/5 (100%)	43/46 (93%)

NS5A A30K (3a)	1/4 (25%)	42/44 (95%)	0/1	19/19 (100%)	ND	47/50 (94%)
NS5A Y93H	2/4 (50%)	42/45 (93%)	ND	20/21 (95%)	1/1	47/50 (94%)
NS5A Any	6/11 (55%)	38/38 (100%)	2/3 (67%)	18/18 (100%)	7/7 (100%)	41/44 (93%)
NS5A Any (30,93)	3/8 (38%)	41/41 (100%)	1/2 (50%)	19/19 (100%)	5/5 (100%)	43/46 (93%)

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/s/

ALICIA MORUF
02/13/2017



NDA 209394

INFORMATION REQUEST

AbbVie Inc
Attention: Sejal P. Emerson, PharmD
Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, IL 60064

Dear Dr. Emerson:

Please refer to your New Drug Application (NDA) dated December 14, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- Glecaprevir/Pibrentasvir, 100 mg/40 mg, fixed dose combination film-coated tablets

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a written response by Feb 16, 2017, in order to continue our evaluation of your NDA.

1. The Summary in 3.2.P.5.4 indicates that the color and debossment are different between the clinical and the commercial drug products. Provide comparative in vitro dissolution profile data to demonstrate that these changes do not impact dissolution of the two APIs.
2. For our clarification, provide details regarding the appearance of the active and the placebo tablets in double-blinded Study M15-464, and the relationship between the Bulk Lot numbers listed in Table 2 of the clinical study report and the "Dosage Strength" Column entries in Table 1 of 3.2.P.5.4.
3. Provide the estimated production in kg/year and the expected introduction concentration (EIC) for each active ingredient, as described in Section III of the FDA EA guidance, <http://www.fda.gov/downloads/Drugs/Guidances/ucm070561.pdf>.

If you have any questions, please call Luz Rivera at (301) 796- 4013 and Thao Vu at (240) 402-2690 or email luz.e.rivera@fda.hhs.gov and thao.vu@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

On Behalf of
LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Thao
Vu

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NDA 209394

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

AbbVie Inc.
Attention: Sejal P. Emerson, PharmD
Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, Illinois 60064

Dear Dr. Emerson:

Please refer to your New Drug Application (NDA) dated and received December 14, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is August 14, 2017. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to:

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

In addition, the planned date for our internal mid-cycle review meeting is March 14, 2017. 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. 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.

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.

We acknowledge your request for a waiver of the requirement that the Highlights of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions.

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) 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) and patient PI (as applicable), 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.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Alicia Moruf, PharmD, MPH, Regulatory Project Manager, at (301) 796-3953.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

DEBRA B BIRNKRANT
01/30/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: January 24, 2017

To: Sejal Emerson, PharmD, Director, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Information Request

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We have the following requests for information regarding financial disclosure information.

Clinical

Please submit the following:

1. Total number of investigators identified in the registrational trials (number principal investigators and sub-investigators)
2. Number of investigators who are sponsor employees (including both full-time and part-time employees)
3. Number of investigators with disclosable financial interests/arrangements (Form FDA 3455)
4. If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):
 - a. Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:

- b. Significant payments of other sorts
 - c. Proprietary interest in the product tested held by investigator
 - d. Significant equity interest held by investigator in sponsor of covered study
5. Number of investigators with certification of due diligence (Form FDA 3454, box 3)
6. Please also provide details regarding any disclosable financial interests/arrangements, a description of the steps taken to minimize potential bias, and an explanation for any investigators with a certification of due diligence.

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 301-796-3953.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
01/24/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: January 12, 2017

To: Sejal Emerson, PharmD, Director, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: **Follow up** Information Request for Study M13-594

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg. Also refer to our information request dated January 10, 2017 and your emailed response dated January 11, 2017. We have the following additional comment and request for information.

Clinical Virology Comment 1/10/2017

For the active control arm in clinical trial M13-594 (ENDURANCE-3), baseline NS5A sequence analyses were conducted but these data are not in the integrated resistance analysis dataset. Were these data submitted elsewhere in the eCTD?

AbbVie's Emailed Response 1/11/2017

Analysis of prevalence of baseline polymorphisms in NS5A and impact of these on SVR12 rate for subjects in Arm B of the study is provided in the M13-594 CSR, Section 11.1.2. As previously outlined in the integrated resistance analysis plan and agreed to by DAVP in the May 26, 2016 Response to Type C Meeting Questions (Reference ID 3936991), the Arm B NS5A sequence analysis was not included in the Integrated Resistance Report or the resistance dataset.

Clinical Virology Follow-up Response and Information Request 1/12/2017

We understood and agreed that the Arm B resistance data would not be presented in the integrated resistance analysis report for GLE/PIB, given that they were to be presented in the M13-594 CSR, but we misunderstood that these subjects would not be included in a resistance dataset. Please submit NS5A resistance analysis data from M13-594 Arm B subjects to the NDA. This will not impact the filing decision or review timeline, but we would like to verify

your results presented in the M13-594 CSR. If not already available in the full dataset format, the data can be provided in a simplified format showing only the polymorphisms/substitutions detected at the $\geq 15\%$ threshold, with the following minimal information provided: USUBJID, Visit, NS5A position, and the specific changes from reference detected at the $\geq 15\%$ threshold. Alternatively the NGS fastq files could be submitted for Arm B subjects if available. Please submit these data by 2/6/2017.

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 301-796-1182 or 301-796-1500.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
01/12/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 209394

Drug: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date: January 10, 2017

To: Sejal Emerson, PharmD, Director, Regulatory Affairs

Applicant: AbbVie Inc.

From: Alicia Moruf, PharmD, MPH, Regulatory Project Manager, DAVP

Subject: Information Request for Study M13-594

Please refer to your submission dated December 14, 2016, wherein a New Drug Application was submitted for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We have the following requests for information. Please respond by COB 01/11/2017.

Clinical Virology

For the active control arm in clinical trial M13-594 (ENDURANCE-3), baseline NS5A sequence analyses were conducted but these data are not in the integrated resistance analysis dataset. Were these data submitted elsewhere in the eCTD?

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at 301-796-1182 or 301-796-1500.

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ALICIA MORUF
01/10/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209394

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

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

ATTENTION: Sejal P. Emerson, PharmD
Director, Regulatory Affairs

Dear Dr. Emerson:

Please refer to your New Drug Application (NDA) dated and received December 14, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glecaprevir/Pibrentasvir Tablets, 100 mg/40 mg.

We acknowledge receipt of your correspondence dated and received December 14, 2016, requesting a review of your proposed proprietary name, (b) (4).

The target date is March 14, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact Alicia Moruf, Regulatory Project Manager, in the Office of New Drugs at (301) 796-3953.

Sincerely,

{See appended electronic signature page}

Danyal Chaudhry, M.P.H.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
01/04/2017



NDA 209394

NDA ACKNOWLEDGMENT

AbbVie Inc.
Attention: Sejal P. Emerson, PharmD
Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, Illinois 60064

Dear Dr. Emerson:

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 Products: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Date of Application: December 14, 2016

Date of Receipt: December 14, 2016

Our Reference Number: NDA 209394

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 12, 2017, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (301) 796-3953.

Sincerely,

{See appended electronic signature page}

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUZANNE K STRAYHORN
12/21/2016



IND 127416
IND 116169
IND 116170

**MEETING REQUEST-
WRITTEN RESPONSES**

AbbVie Inc.
Attention: Sejal Emerson, PharmD
Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30-1
North Chicago, IL 60064

Dear Dr. Emerson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABT-493/ABT-530 co-formulated film-coated bilayer tablets.

We also refer to your submission dated March 16, 2016, containing a Type C meeting request. The purpose of the requested meeting was to discuss and obtain Agency agreement on the overall format and some content of the planned New Drug Application (NDA), the adequacy of the nonclinical package for the planned NDA, the Statistical Analysis Plan (SAP) for the Integrated Summaries of Efficacy and Safety (ISE and ISS), and the Integrated Resistance Analysis Plan (IRAP).

Further reference is made to our Meeting Granted letter dated March 23, 2016, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your April 29, 2016 background package.

IND127416
IND 116169
IND116170
Page 2

If you have any questions, call me at (301) 796-3953.

Sincerely,

{See appended electronic signature page}

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type C

Meeting Category: Other

Application Number: IND 127416
IND 116169
IND 116170

Product Name: ABT-493/ABT-530
ABT-493
ABT-530

Indication: Treatment of HCV (hepatitis C virus) infection

Sponsor/Applicant Name: AbbVie Inc.

Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

AbbVie has been developing 2 “next generation” direct-acting antiviral (DAA) drugs for use in combination with each other (ABT-493/ABT-530). ABT-493 and ABT-530 have been evaluated as individual agents in single and multiple dose ascending studies, and as monotherapy in treatment-naïve, HCV GT1 infected subjects with and without cirrhosis. Safety and efficacy of the ABT-493/ABT-530 combination are being evaluated in ongoing Phase 2 and 3 studies in HCV-infected subjects with or without cirrhosis, HCV/HIV co-infected, and DAA treatment failures with or without renal impairment.

The purpose of the requested meeting was to discuss and obtain Agency agreement on the overall format and some content of the planned New Drug Application (NDA), the adequacy of the nonclinical package for the planned NDA, the Statistical Analysis Plan (SAP) for the Integrated Summaries of Efficacy and Safety (ISE and ISS), and the Integrated Resistance Analysis Plan (IRAP).

2.0 QUESTIONS AND RESPONSES

2.1. NONCLINICAL

Question 1: Does the Agency agree that the nonclinical data package is adequate for the planned NDA submission?

FDA Response to Question 1: Yes, we agree.

Question 2: Does the Agency agree with AbbVie's proposal to submit the nonclinical (i.e., toxicology, pharmacology, and nonclinical pharmacokinetics) information in an integrated format where each compound will be discussed sequentially within each of the major Electronic Common Technical Document (eCTD) subheadings?

FDA Response to Question 2: Yes, we agree.

Question 3: Does the Agency agree with the placement of in vitro reports generated using human source biomaterials in Module 4.2.2 (protein binding, in vitro cytochrome P450 [CYP], and transporter interaction studies, etc.)?

FDA Response to Question 3: Yes, we agree.

Question 4: Does the Agency agree with AbbVie's plan to conduct a repeat-dose toxicology study with only the (b) (4) and not the (b) (4) degradation product?

FDA Response to Question 4: Yes, we agree.

2.2. CLINICAL

Note: In addition to the responses below we refer you to our April 6, 2016 communication.

Question 5: Is it acceptable for Module 2.7 to exceed the suggested size limitations if necessary?

FDA Response to Question 5: No, you should be able to summarize the efficacy of the ABT-493/ABT-530 combination in substantially less than 400 pages. We believe that judicious use of tables to summarize the efficacy data would allow you to meet the 400 page requirement.

2.2.1 Phase 2 and Phase 3 Studies CSRs

Question 6: Does the Agency agree with the proposed content and format of the Phase 2 and Phase 3 CSRs?

FDA Response to Question 6: Safety and efficacy data should be provided for all treatment arms of the key Phase 2 studies. (including M15-410, M14-867 and M14-868) and Phase 3 studies with patients that have received at least one dose of ABT 493 /ABT 530 (with or without ribavirin).

Question 7: Does the Agency agree with the inclusion of narratives for treatment-emergent serious adverse events (SAEs) that are considered related to ABT-493/ABT-530, rather than for all treatment-emergent SAEs, in CSRs for all Phase 2 and Phase 3 studies?

FDA Response to Question 7: No. Narratives for all subjects with SAEs and discontinuations due to adverse events for all Phase 2 and 3 trials should be included in the application.

2.2.2 Clinical Summary of Efficacy and Integrated Summary of Efficacy

Question 8: Does the Agency agree with information to be included from the clinical studies in the Clinical Summary of Efficacy (CSE)/Integrated Summary of Efficacy (ISE) of the upcoming HCV ABT-493/ABT-530 NDA and that these data will be adequate to support filing and review of the planned NDA?

FDA Response to Question 8: In general we agree that the information to be included in the CSE/ISE would likely be sufficient to support submission of an NDA, as long as all treatment arms are accounted for (see response to question 6).

Question 9: Does the Agency agree with the proposed format for the CSE and ISE for the upcoming HCV ABT-493/ABT-530 NDA and that this format will be adequate to support filing and review of the planned NDA?

FDA Response to Question 9: The format appears reasonable. A decision on the adequacy of the application for review will be made at the filing meeting (see also responses to questions 6 and 8).

Question 10: FDA specified in the ISE SAP and that these analyses will be adequate to support filing and review of the NDA?

FDA Response to Question 10: See responses to above questions. In addition, please consider the following statistical comments:

1. For summaries involving individual studies in the ISE SAP see previous statistics comments.
2. For the meta-analysis we recommend that you use the same patient population for each analysis instead of switching from the ITT population to the Per Protocol population for study M13-590 for the comparison of the 8-week to 12-week duration regimens in the GT1 population. Analysis based on the ITT population is interpretable and protected by randomization and is recommended. The analysis with the Per Protocol population could be a supportive analysis.
3. You might also want to consider using an exact test of heterogeneity (e.g. Zelen's test) in addition to the Breslow-Day test when there are small strata.
4. The SAP states that 2-sided 95% confidence intervals will be calculated using the normal approximation to the binomial distribution, unless the SVR12 rate or the difference in SVR12 rates is 0% or 100% then the Wilson's confidence intervals will be used instead. **Wilson's** confidence intervals should also be computed for very high SVR12 rates less than 100% or very low SVR12 rates greater than 0%.

Question 11: Are the proposed efficacy analyses adequate to support filing and review of the planned NDA?

FDA Response to Question 11: The proposed efficacy analysis appears reasonable to support submission of the application with the above caveats.

Question 12: Does the Agency agree with the proposed approach for conducting and submitting population pharmacokinetics and exposure-response analyses to support filing and review of the NDA?

FDA Response to Question 12: We agree that separate population PK and ER analyses and reports are not needed for each Phase 2 and registrational study. Also, it is acceptable to combine datasets from Phase 2 and registrational studies in your planned analyses. However, if there are any genotypes with lower response rates, we recommend that you also conduct separate analyses using only subjects with that genotype rather than a pooled patient analysis with genotype included as a covariate.

For submission of your Population PK and Exposure-Response analyses, please refer to the following guidelines:

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.

2.2.3 Clinical Summary of Safety and Integrated Summary of Safety

Question 13: Does the Agency agree with information to be included from the clinical studies in the Clinical Summary of Safety (CSS)/Integrated Summary of Safety (ISS) of the upcoming HCV ABT-493/ABT-530 NDA and that these data will be adequate to support filing and review of the planned NDA?

FDA Response to Question 13: Please see responses to the above questions.

Question 14: Does the Agency agree with the proposed format for the CSS and ISS for the upcoming NDA and that this format will be adequate to support filing and review of the planned NDA?

FDA Response to Question 14: Please see responses to the above questions.

Question 15: Does the Agency agree with the proposed safety analysis sets and the proposed analyses specified in the ISS SAP and that these analyses will be adequate to support filing and review of the NDA?

FDA Response to Question 15: Please see responses to the above questions as well as the April 6 2016 communication.

Question 16: Are the proposed safety analyses adequate to support filing and review of the planned NDA?

FDA Response to Question 16: The proposed safety analysis appears reasonable to support submission of the application with the above caveats.

2.2.4 Study Data

Question 17: Does the Agency agree with the Study Data Standardization Plan for the ABT-493/ABT-530 NDA?

FDA Response to Question 17: As communicated in our April 6, 2016 response, the current guidance “For CDER and CBER: Guidance for Industry - Providing Regulatory Submissions in Electronic Format — Standardized Study Data” describes how FDA plans to implement the requirements for the electronic submission of standardized study data. After the publication of this guidance, all studies with a start date 24 months after the publication date [December 2014] must use the appropriate FDA-supported standards, formats, and terminologies specified in the Catalog (see section II.C) for NDA, ANDA, and certain BLA submissions. Study data contained in certain IND submissions must use the specified formats for electronic submission in studies with a start date 36 months after the publication of this guidance.

Technical specifications associated with this guidance are provided as separate, stand-alone documents and are updated periodically. These are:

- Data Standards Catalog
- Study Data Technical Conformance Guide
- FDA Specific SEND Validation Rules
- FDA Specific SDTM Validation Rules

To make sure you have the most recent versions, please check:

<http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>

Question 18: Does the Agency agree with submission of the Office of Scientific Investigations [OSI] requested information within 30 calendar days of the initial NDA submission?

FDA Response to Question 18: No. To facilitate selection and assignment of clinical inspections, this information must be included at the time the NDA is submitted. Please see language below related to OSI.

2.3 CLINICAL VIROLOGY

Question 19: Does the Agency agree with the placement of *in vitro* and clinical "virology reports" in Module 5.3.5.4 (Other Study Reports and Related Information)?

FDA Response to Question 19: We agree.

Question 20: Does the Agency agree with the Integrated Resistance Analysis Plan (IRAP)?

FDA Response to Question 20: In general, we agree with your resistance analysis plans. Please be aware that we will analyze the resistance data independently and may explore other criteria for identifying and defining resistance-associated polymorphisms and substitutions. Also, we have the following recommendations related to your virologic response/non-response definitions, if not already addressed in your statistical analysis plans:

- Regarding your definitions of relapse, any single result of HCV RNA $\geq$ LLOQ for the last available follow-up sample should not require a confirmatory result for the definition of relapse to be met.
- Similarly, for your SVR definitions, any single result of HCV RNA $\geq$ LLOQ without subsequent samples or analyses available for confirmation should be reported as an SVR failure, even if an earlier sample in the same SVR analysis window had HCV RNA $<$ LLOQ.
- For your analyses of HCV reinfection, viral subpopulations detected at baseline by NGS analysis should also be considered to help rule out the possibility that the post-treatment viral strain was a pre-existing minority viral population (i.e., in a situation where the subject had been infected prior to treatment with multiple distinct HCV clades/subtypes).

Also, in the integrated resistance report please provide a comprehensive table for each DAA showing all available phenotype data for amino acid substitutions evaluated in site-directed mutant HCV replicons. Include the HCV subtype, EC₅₀ and EC₉₀ values, and replication capacity data if available.

For your baseline resistance analyses, it is our understanding that baseline or other pre-treatment samples from 100% of subjects in all Phase 2/3 trials of ABT-493 plus ABT-530 (integrated report focusing on ABT-493 300 mg QD and ABT-530 120 mg QD), and across all HCV genotypes, will be analyzed to assess the impact of baseline resistance-associated polymorphisms on treatment outcome, and the only baseline data that may be missing would be due to technical problems with the processing or analyses. If this is not correct, please clarify your plans for analyses of baseline samples.

2.4 MISCELLANEOUS/REGULATORY

Question 21: Does the Agency agree with the overall table of contents (TOC) of the NDA?

FDA Response to Question 21: We agree.

Question 22: Does the Agency agree that the requirements under the Combination Rule (21 CFR §300.50) are fulfilled for the ABT-493 and ABT-530 combination regimen?

FDA Response to Question 22: We agree.

Question 23: Does the Agency agree with the plan for submission in the NDA of ongoing results from Study (b) (4), the long-term extension study?

FDA Response to Question 23: We agree.

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.

Please provide your Agreed PSP, along with waiver and deferral requests, with the submission of your sNDA.

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.

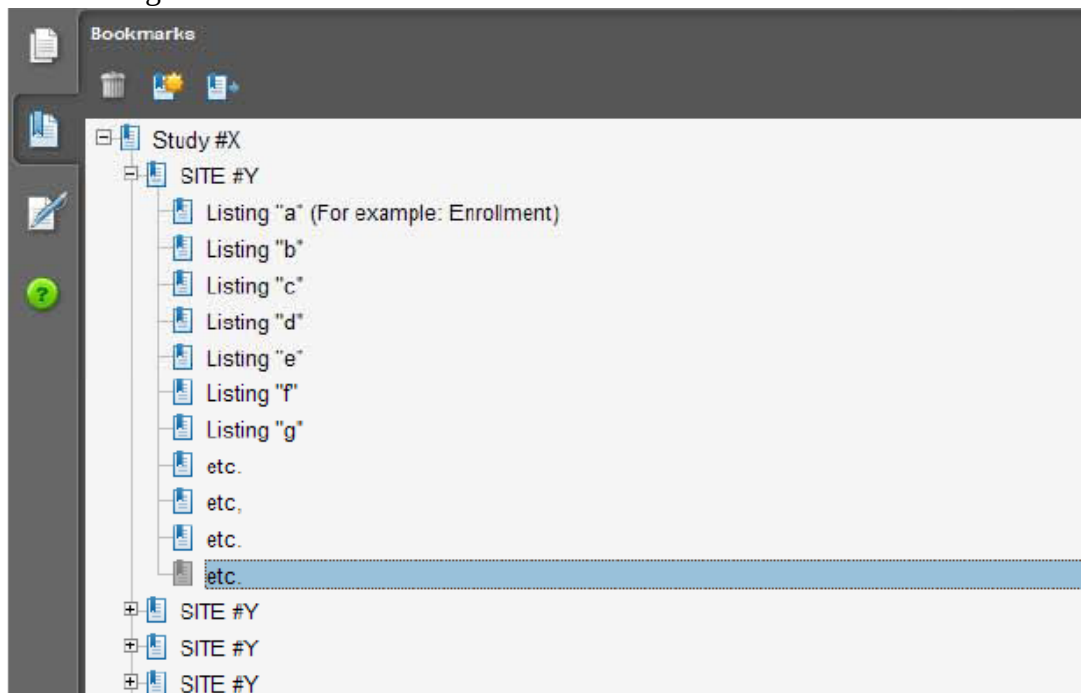
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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 Item¹	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.

IND 127416
IND 116169
IND 116170
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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

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/s/

ALICIA MORUF
05/26/2016



IND 127416

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

AbbVie Inc.
Attention: Sejal Emerson, PharmD
Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30-1
North Chicago, IL 60064

Dear Dr. Emerson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABT-493/ABT-530 co-formulated film-coated bilayer tablets.

We also refer to your February 29, 2016 request for Breakthrough Therapy designation. We have reviewed your request and have determined that ABT-493/ABT-530 for the treatment of DAA-experienced chronic hepatitis C virus (HCV) genotype 1 (GT1) subjects 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 ABT-493/ABT-530 for the treatment of DAA-experienced HCV GT1 subjects 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 meeting². 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 ABT-493/ABT-530 for the treatment of DAA-experienced HCV GT1 subjects 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 Alicia Moruf, Pharm.D, MPH Regulatory Project Manager, at (301) 796-3953.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Division Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/

DEBRA B BIRNKRANT
04/21/2016

Benton, Sandra J

From: Benton, Sandra J
Sent: Monday, April 11, 2016 1:00 PM
To: Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Moscicki, Richard; Marcus, Kendall; Kehoe, Theresa
Cc: Jarow, Jonathan; Hinton, Denise; Sacks, Leonard V; Raggio, Miranda; Wedlake, Lauren; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Throckmorton, Douglas C; Thompson, Elizabeth; Birnkrant, Debra B; Moruf, Alicia; Stabinski, Larissa; Fleischer, Russell D; Murray, Jeffrey S
Subject: RE: April 27, 2016 Medical Policy Council – Breakthrough Therapy Designation - IND 127416

As the Council agrees with DAVP'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 27, 2016 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: Friday, April 08, 2016 2:07 PM
To: Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Moscicki, Richard; Marcus, Kendall; Kehoe, Theresa
Cc: Jarow, Jonathan; Hinton, Denise; Sacks, Leonard V; Raggio, Miranda; Wedlake, Lauren; Benton, Sandra J; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Throckmorton, Douglas C; Thompson, Elizabeth; Birnkrant, Debra B; Moruf, Alicia; Stabinski, Larissa; Fleischer, Russell D; Murray, Jeffrey S
Subject: April 27, 2016 Medical Policy Council – Breakthrough Therapy Designation - IND 127416

Hi! OMP has scheduled a Medical Policy Council discussion on April 27, 2016 regarding the breakthrough therapy designation request from AbbVie Inc for its IND 127416, ABT-493/ABT-530 FDC for treatment of chronic HCV in adults.

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

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

Would you please review DAVP's recommendation and let me know by COB Friday, April 15 if –

- You agree with DAVP's recommendation regarding this breakthrough therapy request and you do not believe a Council discussion is needed.
- You agree with DAVP's recommendation regarding this breakthrough therapy request. However, you would like a Council discussion regarding any questions you have.
- You agree with DAVP's recommendation regarding this breakthrough therapy request. However, you would like to have a discussion of the development plan and what FDA will recommend, if appropriate.
- You disagree with DAVP'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: CDER-MPC Breakthrough Therapy Designation127416DRAFT3finalchangesaccepte....doc >> << File: IND
127416.pdf >>

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	127416
Request Receipt Date	February 29, 2016
Product	ABT-493/ABT-530 co-formulated film-coated bilayer tablets
Indication	Treatment of chronic HCV in adults
Drug Class/Mechanism of Action	ABT-493 is a HCV NS3/4A protease inhibitor (PI) and ABT-530 is a NS5A inhibitor.
Sponsor	AbbVie Inc
ODE/Division	OND/DAVP
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	April 29, 2016

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

The indication for the ABT-493/ABT-530 FDC is for treatment of chronic HCV in adults. However, the BTDR is specifically for the treatment of DAA experienced HCV GT1 subjects, given that all the data to date are based on this population.

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

☐ YES ☒ NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. Consideration of Breakthrough Therapy Criteria:

a. Is the condition serious/life-threatening¹?

☒ YES ☐ NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review

☐ Undetermined

☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence

☐

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Chronic hepatitis C (HCV) is a serious, progressive and potentially life-threatening disease and is a major public health concern in the US and globally. HCV is responsible for a large proportion of worldwide chronic liver disease and accounts for 70% of chronic hepatitis in developed countries. The global prevalence of HCV is estimated at 3%. Of those with chronic HCV infection, as many as 20% may develop significant complications including cirrhosis, end-stage liver disease, and hepatocellular carcinoma. HCV is the leading cause of liver transplantation. transplant and overall mortality. Successful treatment of HCV reduces the incidence of HCC, the need for liver transplant and overall mortality.

Currently there are no FDA approved treatment options indicated specifically for those who have failed prior HCV treatment with an NS5A inhibitor containing direct acting antiviral (DAA) regimen.

Combining two pangenotypic, potent DAAs ABT-493 and ABT-530 into a fixed dose table, allows two unique mechanisms of action to be combined as a complete antiviral treatment regimen.

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

AbbVie's next generation DAAs include ABT-493, a HCV nonstructural (NS) 3/4A protease inhibitor (PI) and ABT-530, an NS5A inhibitor. Each compound has potent antiviral activity against major HCV genotypes (GTs) in vitro with no or little loss of potency against known common single resistant mutants. ABT-493 and ABT-530 have each been evaluated as individual agents in single- and multiple-ascending dose studies in healthy volunteer subjects. In addition, each has been evaluated as monotherapy in treatment-naïve, HCV GT1-infected subjects with and without cirrhosis. Studies demonstrating the safety profile and pharmacokinetics of the combination of ABT-493 and ABT-530 as well as ABT-493 and ABT-530 co-administered with various other drugs have also been conducted in healthy volunteer subjects. Safety and efficacy of the DAA combination is being evaluated in ongoing Phase 2 and Phase 3 studies in HCV infected subjects with or without cirrhosis.

7. Information related to endpoints used in the available clinical data:

The primary objective of anti-HCV treatment is the achievement of a sustained virologic response (SVR), typically defined as unquantifiable HCV RNA 12 weeks following the cessation of treatment (i.e., “SVR12”). SVR12 is generally considered a “virologic cure”.

The Sponsor is relying on sustained virologic response or SVR12 (described above) as the efficacy endpoint to support their request for Breakthrough Therapy Designation and this endpoint is also used in the Sponsor’s clinical trials. SVR12 is accepted by the Division as a clinically significant endpoint for chronic HCV treatment trials. This is a surrogate endpoint known to predict clinical benefit, as achievement of SVR has been associated with reduced all-cause mortality, and liver-related morbidity and mortality.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

There are no available therapies for patients who have previously failed treatment of HCV with a prior NS5A-containing DAA treatment regimen.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

Gilead has applied and been granted Breakthrough Designation for a fixed-dose combination of sofosbuvir (a NS5B polymerase inhibitor), velpatasvir (a NS5A inhibitor) and GS-9857 (a NS3/4A protease inhibitor) for genotype 1.

GS-US-367-1168 (trial 1168) and GS-US-367-1169 (trial 1169) are ongoing, phase 2 multicenter, open-label trials evaluating the safety and efficacy of daily treatment with SOF/VEL+GS-9857 for 6, 8, or 12 weeks in treatment-naïve and treatment-experienced subjects with and without cirrhosis. All subjects received SOF/VEL FDC (400/100 mg) + GS-9857 (100 mg) once daily with food. Study GS-US-367-1168 enrolled subjects with genotype 1 HCV infection and prior DAA experience including those previously treated with either a NS5A inhibitor, or 2 or more DAAs. Study GS-US-367-1169 enrolled subjects with HCV genotype 2, 3, 4 and 6 (ie, non-genotype 1) and any prior treatment history.

SVR12 data are available from 35 subjects who had previously failed an NS5A-containing regimen. Twenty-nine of these subjects had genotype 1 HCV infection (trial 1168) while 6 subjects were NS5A-experienced subjects from trial 1169 who were non-genotype 1 (3 subjects with HCV genotype 3, 2 subjects with HCV genotype 2 and 1 subject with HCV genotype 6). Of the HCV genotype 1 subjects, 41% (12/29) had baseline cirrhosis; only 1 non-genotype 1 subject had cirrhosis in this cohort. Regardless, all 35 subjects with prior NS5A-experience achieved SVR12. The following table displays the SVR12 results from trials 1168 and 1169.

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

The safety profile did not show any safety signals based on the limited available data (n=266 from trials 1168 and 1169); there were no differences in the preliminary safety data from the 35 NS5A inhibitor-experienced subjects from the other subjects enrolled. Overall, most subjects (n=177, 66.5%) had at least 1 AE, and the proportion of subjects reporting AEs was similar across treatment groups. The most frequently reported AEs were headache (n=60, 22.6%), fatigue (n=43, 16.2%), diarrhea (n=43, 16.2%) and nausea (n=40, 15.0%). There were low rates of discontinuations due to AEs (n=3, 1.1%), SAEs (n=3, 1.1%), and Grade 3 or 4 laboratory abnormalities (n=18, 6.8%). Additionally, no deaths were reported.

10. Information related to the preliminary clinical evidence:

Phase 2 studies (Studies M14-867, M14-868, and M15-410) with ABT-493 300 mg + ABT-530 120 mg have resulted in high SVR 12 rates in the populations evaluated, including subjects with HCV GT1 – GT6 infection and GT1-infected subjects who previously failed NS5A and/or PI-containing regimens.

In the breakthrough designation request, Abbvie submitted summarized data from Part 1 of Study M15-410 which was designed to evaluate the efficacy and safety of ABT-493 in combination with ABT-530 for the treatment of HCV GT1-infected subjects previously treated with DAAs. Subjects were randomized to receive once-daily ABT-493 and ABT-530 at doses of 200 mg + 80 mg (Arm A), 300 mg + 120 mg + 800 mg RBV (Arm B), or 300 mg + 120 mg (Arm C), respectively, for 12 weeks. The impact of baseline RAVs and inclusion of RBV were also assessed. Part 1 of the study enrolled 50 DAA-experienced GT1-infected subjects, most of whom received regimens containing more than 1 DAA and 4 subjects that failed two or more DAA-containing regimens (25 had been previously treated with an NS5A inhibitor, 44 with an NS3/4A PI, and 21 with an NS5B polymerase inhibitor). Complete SVR12 data from Study M15-410 Part 1 are summarized below.

SVR₁₂ Results in DAA-Experienced Subjects (Study M15-410 Part 1)

	Arm A ABT-493 200 mg + ABT-530 80 mg ^a (N = 6)	Arm B ABT-493 300 mg + ABT-530 120 mg + RBV 800 mg (N = 22)	Arm C ABT-493 300 mg + ABT-530 120 mg (N = 22)
SVR ₁₂ , n (%) [ITT]	6/6 (100)	20/22 (90.9)	19/22 (86.4)
Breakthrough	0	0	1 ^b
Relapse	0	1 ^c	0
Other	0	1 ^d	2 ^e
SVR ₁₂ , n (%) [non-virologic failures excluded]	6/6 (100)	20/21 (95.2)	19/20 (95.0)

- Enrollment in Arm A was stopped with Amendment 3 in order to prioritize enrollment of subjects in Arms B and C (where dose levels of ABT-493 and ABT-530 represented doses selected for Phase 3).
- Subject with Crohn's disease and history of ileocolectomy experienced virologic breakthrough at Week 8.
- Subject relapsed at PT Week 4.
- Subject is lost to follow-up; last available HCV RNA value at Week 6 was undetectable.
- One subject died due to hepatocellular carcinoma and one subject missed the PT Week 12 visit; each had undetectable HCV RNA at PT Week 8.

Currently, there are no available treatment options for patients who have previously failed an NS5A-inhibitor containing regimen. Patients who fail DAA therapy, can develop resistance-associated substitutions in the NS5A, NS3 or NS5B genes. These resistance-associated substitutions can confer high-level resistance to specific DAA drugs or classes.

At baseline, deep sequencing (1% cutoff) from DAA-experienced subjects treated with ABT 493/530 in all 3 arms identified resistance-associated variants (RAVs) in 41/50 (82%) subjects, and 39/41 (95%) achieved SVR12. Of the 2 GT1a-infected subjects who experienced virologic failure, the subject in Arm C (without RBV) had baseline NS3 (Y56H and D168A/T) and NS5A (M28V and Q30L/R) RAVs, and the one in Arm B (RBV-containing) had baseline NS5A RAVs L31M and H58D. It is unclear whether any specific baseline RAVs led to virologic failures in this study, since the 2 subjects who experienced virologic failure had different baseline RAVs.

All dose combinations of ABT-493 and ABT-530 tested in HCV-infected subjects have demonstrated favorable safety profiles with mostly mild adverse events, and the most common events being headache, fatigue, and nausea. Among the 581 subjects treated in Phase 2 Studies M14-867, M14-868, and M15-410, there were 3 (< 1%) subjects who prematurely discontinued treatment due to AEs. Treatment-emergent serious adverse events were reported in 14 (2.4%) subjects, only 1 was considered related to study drugs. No subjects experienced post-nadir ALT elevations > 3 × ULN during treatment.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

Abbvie should be granted Breakthrough Therapy for ABT-493/ABT-530 for treatment of HCV genotype 1 in patients who have previously failed prior treatment with an NS5A inhibitor- containing DAA regimen for the following reasons:

- HCV is a serious, life-threatening disease
- There are currently no available approved therapies specifically indicated for patients who have previously failed treatment with an NS5A-containing DAA treatment regimen
- Substantial improvement is demonstrated by the overall SVR12 rate of 90% in 50 HCV genotype 1 DAA experienced subjects from the phase 2 trial (M-15 410) when treated for 12 weeks , with or without ribavirin
- ABT-493/ABT-530 are well-tolerated with manageable toxicity profiles

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

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

The ABT-493/ABT-530 regimen is currently in Phase 3 trials and all other development issues have been previously addressed. As such, the Division has no further development advice to discuss with AbbVie.

13. List references, if any:

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: { See appended electronic signature page}
Team Leader Signature: { See appended electronic signature page}
Division Director Signature: { See appended electronic signature page}

Revised 1/15/16/M. Raggio

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/s/

SANDRA J BENTON
04/11/2016

DEBRA B BIRNKRANT
04/11/2016



IND 127416
IND 116169
IND 116170

**MEETING REQUEST-
WRITTEN RESPONSES**

AbbVie Inc.
Attention: Sejal Emerson, PharmD
Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30-1
North Chicago, IL 60064

Dear Dr. Emerson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABT-493/ABT-530 co-formulated film-coated bilayer tablets.

We also refer to your submission dated January 25, 2016, containing a Type C meeting request. The purpose of the requested meeting was to discuss the proposed ABT-493/ABT-530 bilayer tablet packaging design and the content and format of the raw datasets, analysis ready datasets, and SAS programs to be submitted for efficacy, safety, PK and resistance.

Further reference is made to our Meeting Granted letter dated February 4, 2016, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your February 29, 2016 background package.

If you have any questions, call Alicia Moruf, Regulatory Project Manager at (301) 796-3953.

Sincerely,

{See appended electronic signature page}

Alicia Moruf, Pharm.D., MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

IND 127416
IND 116169
IND 116170
Page 2

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type C

Meeting Category: Other

Application Numbers: IND 127416
IND 116169
IND 116170

Product Names: ABT-493/ABT-530
ABT-493
ABT-530

Indication: Treatment of HCV (hepatitis C virus) infection

Sponsor/Applicant Name: AbbVie Inc.

Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

AbbVie has been developing two “next generation” direct-acting antiviral (DAA) drugs for use in combination with each other (ABT-493/ABT-530). ABT-493 and ABT-530 have been evaluated as individual agents in single and multiple ascending dose studies, and as monotherapy in treatment-naïve, HCV GT1 infected subjects with and without cirrhosis. Safety and efficacy of the ABT-493/ABT-530 combination are being evaluated in ongoing Phase 2 and 3 studies in HCV-infected subjects with or without cirrhosis, HCV/HIV co-infected subjects, DAA treatment failure subjects, and HCV-infected subjects with renal impairment.

The purpose of the requested meeting was to seek advice on the human factors strategy proposed for the packaging of the ABT-493/ABT-530 tablets. In addition, AbbVie requested agreement on the datasets and SAS programs to be submitted in the New Drug Application (NDA) for ABT-493/ABT-530.

AbbVie requested a Type C meeting on January 25, 2016. The Division granted the meeting as Type C Written Responses Only (WRO) on February 4, 2016. Background packages were received on February 29, 2016.

2.0 QUESTIONS AND RESPONSES

2.1 HUMAN FACTORS

Question 1:

Does the Agency agree with AbbVie's planned packaging/labeling design?

FDA Response to Question 1:

Your proposed packaging plan appears reasonable and the acceptability of the packaging/labeling design is a review issue.

Question 2:

Does the Agency agree with AbbVie's proposal to not perform patient simulated-use testing or label comprehension testing to support a future NDA?

FDA Response to Question 2:

We agree that you do not need to perform a simulated-use testing or label comprehension study for the ABT-493/ABT-530 proposed packaging and labeling. The information from the labeling comprehension study for 3QD (Viekira XR) can be leveraged to this application; however, the acceptability of the packaging/labeling design is a review issue.

Question 3:

Does the Agency agree that a Pharmacy Differentiation Study is not required for the proposed packaging configuration?

FDA Response to Question 3:

Yes, the Agency agrees that a Pharmacy Differentiation Study is not required.

2.2 CLINICAL AND CLINICAL PHARMACOLOGY STATISTICAL DATASETS

FDA Response to Questions 4-14: The current guidance “For CDER and CBER: Guidance for Industry - Providing Regulatory Submissions in Electronic Format — Standardized Study Data” describes how FDA plans to implement the requirements for the electronic submission of standardized study data. After the publication of this guidance, all studies with a start date 24 months after the publication date [December 2014] must use the appropriate FDA-supported standards, formats, and terminologies specified in the Catalog (see section II.C) for NDA, ANDA, and certain BLA submissions. Study data contained in certain IND submissions must use the specified formats for electronic submission in studies with a start date 36 months after the publication of this guidance.

Technical specifications associated with this guidance are provided as separate, stand-alone documents and are updated periodically. These are:

- Data Standards Catalog
- Study Data Technical Conformance Guide
- FDA Specific SEND Validation Rules
- FDA Specific SDTM Validation Rules

To make sure you have the most recent versions, please check:

<http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>.

Also please note, complete safety, efficacy and resistance datasets should be provided for all treatment arms of key Phase 2 studies (including all treatment arms of M15-410, M14-867 and M14-868) and Phase 3 studies in which subjects received ABT-493/ABT-530 with or without RBV. Raw data with full traceability for all of these studies should be submitted even if data collection predated SDTM guidance and they are in legacy format. The agency will still accept the legacy data. However, data in SDTM format could facilitate a more efficient review, and this is the preferred format. SDTM datasets for resistance data are not required.

Additional response details are provided below for the following questions.

Question 4:

Analysis ready efficacy and safety datasets (ARDs) from all Phase 3 studies and expanded Phase 2 studies intended for inclusion in the NDA (Studies M13-590, M15-464, M13-594, M13-583, M14-172, M15-462, M14-868, and M15-410) will be provided in the "Efficacy Data Submission in ADaM Conversion for HCV Drugs" template format (DAVP template format).

Does the Agency agree?

FDA Response to Question 4:

No. Please see the response above.

Question 5:

Raw data will be provided in SDTM version 1.4, SDTMIG version 3.2 format for the Phase 3 studies included in the NDA (Studies M13-590, M15-464, M13-594, M13-583, M14-172 and M15-462).

Does the Agency agree?

FDA Response to Question 5:

Yes, Please see the response above.

Question 6:

No raw datasets will be submitted for the expanded Phase 2 Studies M14-868 and M15-410, as these studies were initiated before the SDTM format was implemented within AbbVie databases. No data sets will be submitted for the completed Phase 2 Studies M14-213, M13-595, M14-867.

Does the Agency agree?

FDA Response to Question 6:

No. Please see response above. Raw data should be submitted even if they are in legacy format. Datasets are not required for studies M14-213 and M13-595.

Question 7:

No raw data sets will be provided for Phase 1 studies. Pharmacokinetic ARDs for Phase 1 studies will be provided in a CDISC compliant format. For the Phase 2/3 population Pharmacokinetics, exposure-efficacy and exposure-safety analyses, ARDs in the AbbVie format will be submitted.

Does the Agency agree?

FDA Response to Question 7:

Your proposed plan for submitting the ARDs for Phase 1 studies is reasonable.

Regarding the data sets for population pharmacokinetic analysis and exposure-response analysis, it is acceptable to provide population pharmacokinetic and exposure-response efficacy and safety datasets in a format similar to that provided in the Viekira Pak NDA. We remind you that define files and all relevant analysis programs should also be provided with the datasets. If available, programs documenting assembly of these datasets from other datasets included in the submission should be provided to ensure traceability to source information. For additional details regarding submission of population PK and exposure-response datasets and analyses, please refer to the following link:

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>

Question 8:

Other ARDs that are not in DAVP templated format will be provided in ADaM format for all Phase 3 studies and expanded Phase 2 studies intended for inclusion in the NDA (Studies M13-590, M15-464, M13-594, M13-583, M14-172, M15-462, M14-868, and M15 410).

Does the Agency agree?

FDA Response to Question 8:

Please see response above.

Question 9:

Full traceability (SDTM to ARDs SAS programs and SAS programs from ARDs to key final output) will be provided for all Phase 3 studies. Traceability of ARDs to key final output will be provided for the expanded Phase 2 studies (Studies M14-868 and M15-410).

Does the Agency agree?

FDA Response to Question 9:

The approach for the Phase 3 studies is acceptable. As stated above, for key Phase 2 studies we also request that you submit SAS programs used to create ARDs from the raw data, even if the raw data are not in SDTM format.

Question 10:

Integrated Summary of Efficacy (ISE) datasets will be provided that include data for the ISE analysis set(s) in the DAVP template format for ADEFFOUT, along with the program(s) to derive these ADEFFOUT from the individual study datasets. Note that data included in the ISE from Study M14-867 will be included without traceability from SDTM datasets as AbbVie is proposing not to provide SDTM or ARDs datasets for Study M14 867. Analysis ready programs that produce the key primary and secondary outputs for the ISE from ADEFFOUT will be provided.

Does the Agency agree?

FDA Response to Question 10:

Please see response above. In order to maintain traceability, you should submit the raw data even if the raw datasets are not in SDTM format.

Question 11:

Integrated Summary of Safety (ISS) datasets in the DAVP template format will be provided for the ISS analysis set(s) for lab data (lipids, liver, hematology, renal, and electrolytes) and adverse event data. Other safety ARDs will be provided in ADaM format for data in the ISS tables that are not included in the DAVP template format (e.g., assessment of hepatotoxicity). ARD programs that create the ISS ARDs will be provided based on study level ARDs or raw data (i.e., ARDs for Phase 3 and expanded Phase 2 Studies M14-868 and M15-410, and from raw data for

Phase 2 Study M14-867) as needed, along with analysis ready programs to produce key output from the ARDs.

Does the Agency agree?

FDA Response to Question 11:

Please see response above. In order to maintain traceability, you should submit the raw data even if the raw datasets are not in SDTM format.

Question 12:

Does the DAVP require a separate dataset which includes the characteristics of the subjects who failed screening?

FDA Response to Question 12:

DAVP would appreciate a dataset containing the characteristics of subjects who failed screening, however, such a file would not be required.

2.3 RESISTANCE DATA

Question 13:

AbbVie proposes to submit integrated resistance datasets with the Integrated Resistance Report (IRR) that will be separated by genotype (1 to 6).

Does the Agency agree?

FDA Response to Question 13:

The new vertical structure template should be capable of accommodating drug resistance data from all HCV genotypes. Based on the pilot dataset submitted from clinical trial M14-224, merging data from all ~2,000 subjects from Phase 2/3 trials of ABT-493/ABT-530, regardless of HCV genotype, would result in a database size of ~300 MB (or possibly less given only two drug targets analyzed), which is acceptable for submission. Therefore, we prefer that you merge data from all HCV genotypes into a single integrated resistance dataset. If the variables used for study M15-410 differ from those used for other Phase 2/3 trials, it would be acceptable if data from this trial were reported separately; however, again data for all genotypes should be combined.

As noted above, in addition to the Phase 3 and Phase 2 expanded arms, please submit complete resistance data from all arms from key Phase 2 trials that evaluated ABT-493/ABT-530 with or without RBV (M14-867, M14-868 and M15-410). The integrated resistance report can focus only on regimens proposed for labeling, but all available

resistance data from these trials should be included in the dataset(s) submitted with the NDA.

Also, please comment if any data (b) (4) from long-term follow-up study (b) (4) will be available for submission in the planned NDA.

Question 14:

AbbVie proposes to submit NGS sequencing data using the new pilot template from August 2015 and that no raw (SDTM) data sets relating to resistance data will be submitted with the IRR.

Does the Agency agree?

FDA Response to Question 14:

We agree with your plan to use the new vertical structure resistance dataset format. Please see the recommendations communicated to you on 03/21/2016 in reference to the clinical trial M14-224 pilot dataset submitted to IND (b) (4). In this communication we requested that you incorporate a few minor modifications to the dataset format, which are described in an updated template (March 2016). Also, please submit raw NGS data in .fastq format; as communicated to you on 3/21/2016, the Division was able to open the raw NGS .fastq files submitted to IND (b) (4). This format for submission of raw NGS data is acceptable for the ABT-493/ABT-530 NDA, although submission on a portable hard drive will likely be necessary for the NDA due to the expected size of the files. As noted above, SDTM resistance datasets are not required.

3.0 ADDITIONAL COMMENTS

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.

Please provide your Agreed PSP, along with waiver and deferral requests, with the submission of your sNDA.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

OFFICE of SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

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

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is

maintained. As above, this is the actual physical site where documents would be available for inspection.

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

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

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

Attachment 1

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

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

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

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



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

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

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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

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

/s/

ALICIA MORUF
04/08/2016



IND 116169
IND 116170
IND 127416

MEETING PRELIMINARY COMMENTS

AbbVie, Inc.
Attention: Debra Webb, Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg., AP50
North Chicago, IL 60064

Dear Ms. Webb:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABT-493/ABT-530.

We also refer to your February 2, 2016 information package for a Type C CMC End-of-Phase 2 meeting to gain the Agency's feedback concerning specific CMC proposals for ABT-493 genotoxic impurities, crystalline control in drug product, and drug product dissolution methodology for inclusion in the NDA for ABT-493/ABT-530 Film-Coated Bilayer Tablets.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (240) 402-2691.

Sincerely,

{See appended electronic signature page}

Florence Aisida, Pharm.D, BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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Page 2

ENCLOSURE:
Preliminary Meeting Comments



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

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: CMC EOP2 meeting

Meeting Date and Time: March 2, 2016, 10:00 a.m.-11:00 a.m.
Phone Arrangements: Please provide a CALL-IN NUMBER and PASSCODE to the FDA

Application Number: IND 127416
Product Name: ABT-493/ABT-530
Indication: The treatment of chronic hepatitis C genotype 1 to 6 infection.
Sponsor/Applicant Name: AbbVie, Inc.

FDA ATTENDEES (tentative)

Balajee Shanmugam, Ph.D., Acting Branch Chief, New Drug Products
Stephen Miller, Ph.D., Quality Assessment Lead, New Drug Products
Elsbeth Chikhale, Ph.D., Quality Assessment Lead, Biopharmaceutics
George Lunn, Ph.D., CMC Reviewer
Charles Jewel, Ph.D., CMC Reviewer
Gerlie Gieser, Ph.D., Biopharmaceutics Reviewer
Florence Aisida, Pharm D., BCPS, RBPM

SPONSOR ATTENDEES

Sou-Jen Chang, Associate Director, RA CMC
Russell Cink, Sr. Principal Scientist, Process Chemistry
Patrick Marroum, Director, Clinical Pharmacology and Pharmacometrics
Maureen McLaughlin, Sr. Scientist III, Scientific Affairs
Karin Rosenblatt Sr., Scientist III, NCE Analytical
Nancy Sever, CMC Scientific Director
Benedikt Steitz, Principal Scientist, NCE Analytical
Debra Webb, Director, RA CMC

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference meeting scheduled for March 2, 2016, 10:00 a.m.-11:00 a.m., between Abbvie, Inc. and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the

meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

The purpose of the meeting is to seek agreement on Chemistry, Manufacturing and Controls (CMC) development topics for the ABT-493/ABT-530 Film-Coated Tablets program.

2.0 DISCUSSION

Question 1: The two genotoxic impurities (GTIs), (b) (4) are currently tested in the ABT-493 drug substance. Going forward, AbbVie is proposing to change the control strategy for these two GTIs to (b) (4), as defined in ICH M7 guideline, Section 8.1 Control of Process Related Impurities. Does the FDA agree with this proposed control strategy?

FDA Response to Question 1: Based on the data and justification presented in your meeting package we find this proposal acceptable. This data and justification should be included in the marketing application. If there are any changes in the manufacturing process that potentially impact the level of these genotoxic impurities then further studies should be reported to justify continued use of this strategy, or a more pertinent approach should be applied to control these impurities.

Question 2: Does the FDA agree that a test for crystalline ABT-493 in the ABT-493 (b) (4) is not necessary? Does the FDA agree the proposed XRPD test and acceptance criteria for absence of crystalline ABT-530 drug substance material in the ABT-530 (b) (4) is the appropriate control for crystallinity in the drug product?

FDA response to Question 2: We understand that the proposed control strategy for generating and maintaining ABT-493 and ABT-530 (b) (4) includes the following:

(b) (4)

(b) (4)

Based on the information provided, we agree that this proposal is acceptable pending satisfactory results for the study described in Figure 16. We recommend that the following information be included in the NDA:

- a. Confirm that the proposed crystallinity test for the ABT-530 (b) (4)
- b. Address how the FDA recommendations of Oct 21, 2015 to IND 116169 regarding (b) (4)
- c. Commit to test the registration stability batches of tablets for crystalline material using the powder XRD method on at least an annual basis through the intended expiration dating period.
- d. Confirm that the Practical Detection Limits for the powder XRD methods are (b) (4)

Question 3: Does the FDA agree that the dissolution method for immediate release ABT-493/ABT- 530 Film-Coated Tablets is appropriate and is suitably discriminating?

FDA Response to Question 3: We acknowledge your efforts to develop a dissolution method that is not only discriminating but also is clinically or bio-relevant. However, it is premature for FDA to conclude that the current dissolution method is adequate for routine QC testing of the proposed fixed-dose combination bilayer tablets. Based on the comparative *in vivo* PK profiles and parameters provided for the various co-formulations or fixed dose combination tablet designs, it is evident that the manner of incorporating the two active ingredients into a tablet dosage form influences the *in vivo* human exposures to ABT-493 and ABT-530. Therefore, submit to the IND or NDA the dissolution method development report including evidence that the dissolution method is discriminating using the proposed bilayer tablet (as opposed to monolayer tablets). In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant manufacturing variables (e.g.

(b) (4) tablet hardness, (b) (4) etc.). For ease of comparing the dissolution profiles, provide the corresponding profile similarity factor (f_2). Additionally, in the NDA, provide the validation parameters (e.g., robustness) supporting the dissolution method development, in addition to those for the HPLC method used for quantifying drugs in the dissolution samples.

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

/s/

BAMIDELE F AISIDA
02/24/2016



IND 116169
IND 116170

MEETING PRELIMINARY COMMENTS

AbbVie, Inc.
Attention: Sejal Emerson, Pharm.D.
Director, Regulatory Affairs
1 North Waukegan Road
Dept. PA 77/Bldg. AP30
North Chicago, IL 60064

Dear Dr. Sejal:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABT-493 and ABT-530.

We also refer to your correspondence dated and received September 25, 2015, requesting a meeting to discuss and seek agreement on the proposed Phase 3 development plan for AbbVie's direct-acting antiviral (DAA) combination drug regimen of ABT-493 and ABT-530.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me, at (301) 796-3953.

Sincerely,

{See appended electronic signature page}

Alicia Moruf, Pharm.D., M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Drug Antimicrobial Products
Center for Drug Evaluation and Research

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ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: End of Phase 2
Meeting Date and Time: November 19, 2015, 11:00a.m. to 12:30p.m.
Meeting Location: Building 22, Room 1309

Application Numbers: IND 116169
IND 116170

Product Names: ABT-493
ABT-530

Indication: Treatment of adults infected with genotypes (GTs) 1-6 chronic hepatitis C (CHC) infection

Sponsor Name: AbbVie Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 19, 2015, 11:00am-12:30pm in Building 22 Room 1309 between AbbVie, Inc. and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

On October 15, 2012, AbbVie Inc. submitted IND 116169 and IND 116170, ABT-493 and ABT-530 respectively. ABT-493, an oral NS3/4 protease inhibitor is being developed for use in combination with other Direct Acting-Antivirals (DAAs). ABT-530, a hepatitis C nonstructural protein 5A inhibitor with broad genotypic activity is also being developed for use in combination with other DAAs with or without Ribavirin.

AbbVie Inc. initially requested a type B, End of Phase 2 meeting on July 14, 2015, which was canceled due to inadequacies in the meeting package; specifically the lack of preliminary efficacy data (e.g., SVR4 or SVR12) in a number of important subgroups studied in Phase 2 trials. Although the meeting was cancelled, the Division provided written responses to a few of the questions from the August 25, 2015 meeting package. The written responses were dated September 18, 2015. Subsequently, AbbVie Inc., submitted a new EOP2 meeting request dated September 25, 2015 to discuss the proposed Phase 3 development plan for ABT-493 and ABT-530 with the inclusion of more complete Phase 2 efficacy data in the meeting package. An End of Phase 2 meeting was granted on October 7, 2015.

The proposed indication for the fixed-dose combination coated bilayer tablet containing 100mg of ABT-493 and 40mg of ABT-530 is for the treatment of chronic hepatitis C genotypes 1 to 6 infection with a proposed dosing regimen of 300mg ABT-493 and 120mg ABT-530 given as three tablets once daily with food for the proposed treatment duration of 8 to 12 weeks. AbbVie Inc. plans to support this indication by their proposed Phase 3 programs Studies, M13-590, M15-464, M13-594, M13-583, M14-172, M15-462, and (b) (4) which is the ongoing long-term follow-up study (b) (4).

The objectives of the meeting include coming to alignment on the following:

1. Clinical development plan; specifically, the study designs for the following proposed Phase 3 studies:
 - Study M14-172: safety and efficacy in patients with GT1, GT2, GT4, GT5 and GT6 chronic HCV infection and compensated liver cirrhosis
 - Study M13-583: safety and efficacy in patients with GT4, GT5 and GT6 chronic HCV infection without liver cirrhosis
 - Study M15-462: safety and efficacy in patients with GT1, GT2, GT3, GT4, GT5 and GT6 chronic HCV infection and severe renal impairment
2. Overall strategy
 - Adequacy of data package to support a positive risk benefit for the proposed indication

2.0 DISCUSSION

2.1. Multidisciplinary Questions on Clinical Development

Question 1:

AbbVie plans to conduct a single-arm non-comparative Phase 3 study (Study M13-583) in HCV GT4 – 6-infected non-cirrhotic subjects. The Study M13-583 synopsis, including the proposed sample size, will be provided in the meeting information package.

Does FDA agree with the:

- a. proposed study design?
- b. overall sample size for this study as well as that for GT4, specifically?
- c. proposed minimum number of GT5 and GT6 subjects would, in principle, be adequate for inclusion in the labeling?

FDA response to Question 1:

In general the Division agrees with design, dose and duration. A final decision on the adequacy of the number of GT5 and GT6 patients will be a review issue. We again recommend that GT4 and GT6 subjects be enrolled at diverse geographic locations to maximize the diversity of viral subtypes represented in the trial.

Additional Statistics Comments:

1. Sensitivity analyses could be used to treat different reasons for discontinuations (e.g., LTFU, withdrawal of consent) as successes. Every effort should be made to follow up patients even if they discontinue treatment early due to adverse events or other reasons while virologically suppressed.

2. In addition to computing a 95% confidence interval around the SVR₁₂ rate for the 12-week treatment arm, you should also be able to compare the 12-week treatment arm's SVR rate to the standard of care regimens for GT4 and 5 with a 95% confidence interval for the difference in SVR rates.

2.2. Studies in Special Populations with HCV HCV Genotypes 1, 2, 4 to 6 Subjects with Compensated Cirrhosis (Study M14-172)

Question 2:

For subjects with compensated cirrhosis, AbbVie proposes a multicenter, open-label,

single-arm Phase 3 study (Study M14-172) in treatment-naïve and treatment-experienced, HCV GT1, GT2, and GT4 through GT6 infected subjects. The synopsis for Study M14-172 will be provided in the meeting information package.

Does FDA agree with the proposed study design and the sample size per genotype (GT) proposed for Study M14-172?

FDA response to Question 2:

In general, the Division agrees with the proposed doses and duration. There are limited data in subjects with GT1 and cirrhosis, and no data in other GTs with cirrhosis. SVR rates approaching 100% have been observed in clinical trials of other DAAs; as such an SVR of <95% may no longer be acceptable. Therefore, the Division suggests you consider the addition of an arm that would provide a more intensive regimen for comparison, for example ABT-493/530 + RBV x 12 weeks or ABT-493/530 x 16 weeks. This could maximize the likelihood that an optimally effective regimen is identified in this trial, especially if there are genotype-specific decreases in response rates identified. Again, please ensure that you enroll GT4 and GT6 at diverse geographic locations to maximize viral subtype diversity. If you do add a second arm to this trial, we strongly recommend adding more subjects to the trial and designing it in such a way that some of the smaller subgroups of subjects (e.g., GT5 or GT6) are not split across multiple arms, which could make it difficult to draw conclusions about efficacy.

Additional Statistics Comments:

- 1. In addition to computing a single 95% confidence interval around the SVR rate, you should also be able to make between-study comparisons to the standard of care regimens with 95% confidence intervals for the difference in SVR rates.**
- 2. The primary efficacy analysis should be conducted using the ITT population.**
- 3. Sensitivity analyses could be used to treat different reasons for discontinuations (e.g., LTFU, withdrawal of consent) as successes. Every effort should be made to follow up patients even if they discontinue treatment early due to adverse events or other reasons while virologically suppressed.**

2.3 HCV Genotypes 1 to 6 Subjects with Stage 4 to 5 Renal Impairment (Study M15-462)

Question 3:

AbbVie proposes a Phase 3, multicenter, single-arm, open-label study in subjects with chronic kidney disease (CKD) Stage 4 and 5 renal impairment (including hemodialysis) infected with HCV GT1-6 (excluding treatment-experienced GT3-infected subjects and

GT3-infected subjects with cirrhosis). The synopsis for Study M15-462 will be provided in the meeting information package.

- a. Does FDA agree with the proposed study design and the sample size for Study M15-462?
- b. Does the FDA agree with the proposed population for Study M15-462?

FDA response to Question 3:

In general, the Division agrees with the proposed design, doses, and duration.

Additional Statistics Comments:

- 1. The primary efficacy analysis should be conducted using the ITT population.**
- 2. Sensitivity analyses could be used to treat different reasons for discontinuations (e.g., LTFU, withdrawal of consent) as successes. Every effort should be made to follow up patients even if they discontinue treatment early due to adverse events or other reasons while virologically suppressed.**

2.4 Adequacy of the Phase 3 Data Package

Question 4:

Does FDA agree that the proposed Phase 3 clinical development program will adequately evaluate the safety and efficacy of the proposed ABT-493/ABT-530 combination regimen for the treatment of CHC in the following adult subject population?

- *GT1 subjects without cirrhosis: 8 weeks*
- *GT1 subjects with cirrhosis: 12 weeks*
- *GT2 and GT4 – GT6 subjects with and without cirrhosis: 12 weeks*
- *Treatment-naïve GT3 subjects without cirrhosis: 12 weeks*

FDA response to Question 4:

The final indication will be a review issue depending on the populations in which safety and efficacy have been established at the time the NDA is submitted.

The Division does not agree with the exclusion of HIV co-infected subjects from these trials, as there is no clinical rationale for this exclusion.

Please update the Division on your plans for amending/expanding the DAA experienced trial.

3.0 ADDITIONAL COMMENTS

3.1 Clinical Virology

We refer you to our communication dated August 13, 2015, which included a new draft HCV resistance data template and a request to use this template for one of your Phase 3 trials of ABT-493/ABT-530 (or alternatively, a post-approval trial of the Viekira Pak™ regimen). Please summarize your plans for submission of resistance data for the initial NDA for ABT-493/ABT-530.

3.2 Clinical Pharmacology

We have reviewed your response to our comment regarding administering ABT-493/ABT-530 without regard to food in the Phase 3 trials. Based on the available SVR data for the various genotypes, non-linear increase of ABT-493 exposures between the 200 mg and 300 mg doses, and the dose (exposure)-response relationships, we don't believe that restricting the administration of ABT-493/ABT-530 with food is warranted. It is important to note that trials M14-867 and M14-868 (which form the basis of dose selection for Phase 3 trials) were also conducted without regard to food. We strongly recommend that you consider administering ABT-493/ABT-530 without regards to food in the Phase 3 trials to simplify the dosing instructions for patients.

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and*

Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) 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.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards 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. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the

Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.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 the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

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.

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

/s/

ALICIA MORUF
11/16/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 116169
IND 116170
IND 127416

MEETING MINUTES

AbbVie, Inc.
Attention: Sejal Emerson, Pharm.D.
Director, Regulatory Affairs
1 North Waukegan Road
Dept. PA 77/Bldg. AP30
North Chicago, IL 60064

Dear Dr. Emerson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for glecaprevir (ABT-493)/pibrentasvir (ABT-530).

We also refer to the meeting between representatives of your firm and the FDA on November 3, 2016. The purpose of the meeting was to discuss the adequacy of the clinical data for glecaprevir (ABT-493)/pibrentasvir (ABT-530) to support a New Drug Application (NDA) expected in December 2016.

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 me, Regulatory Project Manager at (301) 796-3953.

Sincerely,

{See appended electronic signature page}

Alicia Moruf, PharmD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial 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: November 3, 2016 1:00PM to 2:30PM EST
Meeting Location: Building 22, Room 1311

Application Number: IND 116169
IND 116170
IND 127416

Product Name: Glecaprevir
Pibrentasvir
Glecaprevir/ Pibrentasvir

Indication: Treatment of adults infected with genotypes (GTs) 1-6 chronic hepatitis C (CHC) infection

Sponsor/Applicant Name: AbbVie Inc.

FDA ATTENDEES

John Farley, MD, Deputy Director, Office of Antimicrobial Products (OAP)
Jeff Murray, MD, MPH, Deputy Director, Division of Antiviral Products (DAVP)
Larissa Stabinski, MD, Clinical Reviewer, DAVP
Russell Fleischer, PA-C, MPH, Acting Clinical Team Leader, DAVP
Patrick Harrington, PhD, Clinical Virology Reviewer, DAVP
Julian O'Rear, PhD, Clinical Virology Team Leader, DAVP
Ilona Bebenek, PhD, Pharmacology/Toxicology Reviewer, DAVP
Suzanne Strayhorn, MsC, RPM, DAVP
Elizabeth Thompson, MS, CPMS, DAVP
Fraser Smith, PhD, Biometrics Reviewer, Office of Biostatistics (OB)
Thamban Valappil, PhD, Biometrics Acting Team Leader, OB
Vikram Arya, PhD, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
Islam Younis, PhD, Clinical Pharmacology Team Leader, OCP
Antoine El Hage, PhD, Office of Scientific Investigations (OSI)

SPONSOR ATTENDEES

Thomas J. Podsadecki, MD, Group Project Leader, HCV Development, Pharmaceutical Development

Andrew J. Campbell, MD, Senior Project Leader, Next Generation HCV, Pharmaceutical Development
Federico J. Mensa, MD, Group Medical Director, HCV Clinical Development
Nancy Shulman, MD, Executive Medical Director, HCV Development
Neddie Zadeikis, MD, MBA, Senior Medical Director, HCV Development
Ariel R. Porcalla, MD, MPH, Medical Director, Global Pharmacovigilance
Lois Larsen, PhD, Director, Statistics, Data and Statistical Sciences
Martin King, PhD, Senior Director, Statistics, Data and Statistical Sciences
Tami Pilot-Matias, PhD, Associate Director II, HCV Clinical Virology
Wei Liu, PhD, Director, Clinical Pharmacology and Pharmacometrics
Chih-Wei (Charlie) Lin, PhD, Associate Principal Pharmacokineticist, Clinical Pharmacology and Pharmacometrics
Sejal Emerson, PharmD, Director, Regulatory Affairs, Global Regulatory Strategy
Toni A. Glinsey, MS, RQC, Senior Director, Regulatory Affairs, Global Regulatory Strategy
Grant Griffin, MS, RAC, Manager, Regulatory Affairs, Global Regulatory Strategy
Imran Shah, PhD, Vice President, Global Regulatory Strategy

(b) (4)

1.0 BACKGROUND

On October 15, 2012, AbbVie Inc. submitted IND 116169 and IND 116170, ABT-493 and ABT-530 respectively and on October 16, 2015 IND 127416 was submitted for the fixed dose combination tablet of ABT-493 and ABT-530. Glecaprevir (ABT-493, GLE), is a hepatitis C virus (HCV) nonstructural (NS) 3/4A protease inhibitor (PI), and pibrentasvir (ABT-530, PIB) is an NS5A inhibitor. This direct-acting antiviral agent (DAA) combination regimen is currently being evaluated in eight registrational studies for the treatment of chronic HCV genotypes (GTs) 1 to 6 infection. Studies M13-590, M15-464, M13-594, M13-583, M14-172, M15-462, M15-410 Part 2, M14-868 Part 3, and M14-868 Part 4 will be used in support of a once daily (QD), ribavirin (RBV)-free oral dose across all genotypes in subjects with compensated liver disease with and without cirrhosis including HCV/human immunodeficiency virus (HIV) co-infected, subjects treatment-experienced to previous PI and/or NS5A inhibitors (TE-PI/NS5A), and subjects with chronic kidney disease (CKD) Stages 4 and 5, using treatment durations for 8 to 12 weeks, with an option for 16 weeks for more difficult to treat populations.

Reference is made to the May 26, 2016 Type C Written Responses Only communication in which agreement was reached between the Agency and AbbVie Inc. on the adequacy of the nonclinical data package, the Statistical Analysis Plan (SAP) for the Integrated Summaries efficacy and Safety (ISE and ISS), and the Integrated Resistance Analysis Plan (IRAP) for the planned NDA submission in December 2016.

AbbVie Inc. requested a Type B, pre-NDA meeting on August 4, 2016 to obtain Agency agreement on the adequacy of the clinical package for the planned NDA submission in December 2016. A face to face meeting was granted for November 3, 2016. AbbVie provided a meeting package on October 7, 2016.

The Division sent Preliminary Comments to AbbVie Inc. on October 27, 2016. During the meeting, question 3 from the meeting package was discussed. Additionally, AbbVie provided an overview of their preliminary clinical data and addressed the information request from the Agency dated October 28, 2016.

2. DISCUSSION

During the presentation of the preliminary clinical data, AbbVie presented the study design, efficacy results, and the relationship between baseline HCV amino acid polymorphisms/substitutions and treatment outcome for the MAGELLAN-1 (Study M15-410) Part 2 study reflected in slides 8, 9, and 10. The Division noted that most of the data from the Magellan-1 trial are from patients with HCV GT1 infection. AbbVie confirmed that while all HCV GTs were eligible, only 4 GT4 infected patients enrolled, and the rest had GT1 infection. With respect to GLE/PIB efficacy results in HCV GT3 infected patients, the Division asked AbbVie if they have SVR data for patients with HCV GT3 infection with the NS5A Y93H polymorphism. AbbVie responded that there were some patients with this polymorphism and the results will be provided in the NDA. The Division asked about treatment-emergent substitutions in patients who experienced virologic failure, and AbbVie responded that most patients who experienced virologic failure had virus with multiple resistance-associated amino acid changes at the time of virologic failure.

The Division raised a question referencing slide 4 of the presentation as to whether the sample sizes shown matched those provided in Table 2 of the pre-NDA meeting briefing package to which we requested AbbVie provide reconciliation study tables. AbbVie agreed to submit these data tables shortly after the meeting.

The Division requested AbbVie to take into account exposure-response information from all ABT-493/ABT-530 doses evaluated in the clinical development program (and not restrict the analysis to exposure-safety data from Phase 3 trials where only the 300/120 mg dose was evaluated). The exposures of ABT-493 are higher in cirrhotic subjects than non-cirrhotic subjects, hence, a comprehensive review of all available data will help to address safety related implications of ABT-493 exposures higher than the ABT-493 exposures observed in Phase 3 trials. For example, the anticipated ABT-493 exposures in a cirrhotic subject who may be administered ABT-493/ABT-530 and a concomitant drug which may increase ABT-493 exposures by several-fold may be higher than the ABT-493 exposures observed in the Phase 3 trials. Overall, taking into account all exposure-response information will help to determine clinical recommendations derived either based on results of dedicated drug-drug interaction trials or theoretical predictions for cirrhotic and non-cirrhotic subjects.

In reference to slide 16 of the presentation, the Division noted and requested pharmacokinetic final exposure response analyses and a comprehensive narrative and table outlining the 30 patients with total bilirubin increases above baseline of $\geq 2X$ ULN and the 7 patients with total bilirubin increases above baseline of $\geq 2X$ ULN and Direct/TB ratio > 0.4 . In addition, the Division requested that AbbVie collaborate with the hepatic expert panel to review all patients in

a timely manner, prioritizing the nine patients with direct/TB ratio > 0.4 or total bilirubin increases above baseline of $\geq 2X$ ULN and ALT $\geq 3X$ ULN. Included in this assessment should be narratives and tables including all laboratory abnormalities, all adverse events, MELD and Child' Pugh scores, concomitant medications past medical history and an assessment of progression of liver disease or any exacerbation of chronic illness. All procedures (for example endoscopy), findings during procedures and outcomes of procedures should be included in the analysis. The assessment should at minimum cover the time on study drug through SVR 12.

2.1. Clinical Pharmacology

Question 1:

Does the Agency agree that the clinical pharmacology package is adequate for the proposed NDA?

FDA response to Question 1:

We agree that the completed and ongoing trials can support registration of GLE/PIB, however a final determination is a review issue. Please note that at this point, we have not identified the need for additional studies.

Meeting Discussion:

No further discussion occurred.

2.2. Clinical Development Questions

Question 2:

Does the Agency agree that the safety and efficacy data from the clinical program are sufficient to support the review and filing of the planned NDA for the proposed pan-genotypic indication?

FDA response to Question 2:

The data are sufficient to support submission of the NDA pending SVR12 results. Determination of indications across genotypes requires a full assessment of SVR12 data for each subgroup for which an indication is being requested, and will be a review issue.

Meeting Discussion:

No further discussion occurred.

Question 3:

Does the Agency agree that the safety and efficacy data from the clinical program are sufficient to support the proposed dosing recommendations, including treatment durations, for studied subpopulations?

FDA response to Question 3:

The data are sufficient to support submission of the NDA. The regimens proposed for patients with HCV GT1, GT2 or GT4 infection appear to be well supported based on currently available data. However, you may not have sufficient evidence to support an 8-week treatment duration for noncirrhotic patients with HCV GT5 or GT6 (n=2 and n=10, respectively). Minimal data from clinical trial M15-410 were provided for patients with non-GT1 infection who are treatment-experienced with an NS3/4A protease inhibitor or NS5A inhibitor, and thus it is likely that any treatment recommendations for this DAA-experienced population will be restricted to patients with GT1 infection. Determining the optimal treatment regimens for patients with GT3 infection or GT1-infected patients with prior NS3/4A protease inhibitor or NS5A inhibitor treatment experience will likely be a major focus of the NDA review.

Meeting Discussion:

AbbVie presented their rationale for an 8 week treatment duration in patients with Genotype 5 and 6 without cirrhosis (slides 21-22). During the discussion, AbbVie asked the Division if there was any additional information requested to support this duration recommendation. The Division responded that the duration to be recommended in labeling will be a review issue. The Division noted that the sponsor has supporting information to hypothesize that an 8-week duration will be just as effective as a 12-week duration for these genotypes, but is concerned that this has not been directly confirmed because of the small number of GT5 or GT6 infected subjects who received the 8-week duration in trials. The Division also noted that it would be helpful to know the GT6 subtype distribution among the small number of GT6 infected patients who received the 8-week treatment duration, given the extensive diversity of GT6 subtypes.

2.3 Regulatory Questions

Question 4:

Does the Agency agree that the planned content of the NDA, as displayed in The table of contents (TOC), is adequate to be considered a complete application?

FDA response to Question 4:

The planned content of the NDA appears adequate for submission of the NDA.

Clinical Virology: Please inform the Division of any substantive changes to your resistance analysis and data submission plans documented previously in eCTD SNs 34, 45 and 47.

Meeting Discussion:

No further discussion occurred.

Question 5:

Does the Agency agree that a Risk Evaluation and Mitigation Strategy (REMS) is not needed for glecaprevir/pibrentasvir?

FDA response to Question 5:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Meeting Discussion:

No further discussion occurred.

Question 6:

Does the Agency agree with the proposed plan for the 4-month safety update?

FDA response to Question 6:

The Division agrees.

Meeting Discussion:

No further discussion occurred.

Question 7:

Does the Agency agree that the Agreed Initial Pediatric Study Plan (iPSP) would fulfill the Pediatric Research Equity Act (PREA) requirements for this NDA?

FDA response to Question 7:

The Agency agrees. Please provide your Agreed PSP, along with waiver and deferral requests, with the submission of your NDA.

Meeting Discussion:

No further discussion occurred.

Question 8:

Does the Agency agree that the data provided in support of this regimen for the treatment of DAA-experienced HCV GT1 subjects are sufficient to support designation of a priority review for the NDA?

FDA response to Question 8:

A final designation regarding the type of review will be made before or at the filing meeting pending an assessment of the completeness and quality of the submitted data.

Meeting Discussion:

No further discussion occurred.

Question 9:

Does the Agency agree that an advisory committee meeting will not be required during the NDA review?

FDA response to Question 9:

At this time, the Division agrees that an advisory meeting does not appear necessary. However, this could change if there are significant review issues identified.

Meeting Discussion:

No further discussion occurred.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. AbbVie Inc. will provide the hepatic panel review of the lab abnormality cases as soon as they are available. They were not able to commit to the 30 day timeframe post initial submission as the submission is heavily dependent on the availability and timing of the hepatic expert panel.

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.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted as soon as possible after the submission of the original application:

Hepatic Expert Panel review of lab abnormality cases

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA NUMBER: LATE COMPONENT - CLINICAL

4.0 ADDITIONAL INFORMATION

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.

We reference your agreed iPSP dated June 16, 2016. Please include your agreed iPSP, along with any requests for waivers and deferrals, with your original marketing application submission.

Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

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).

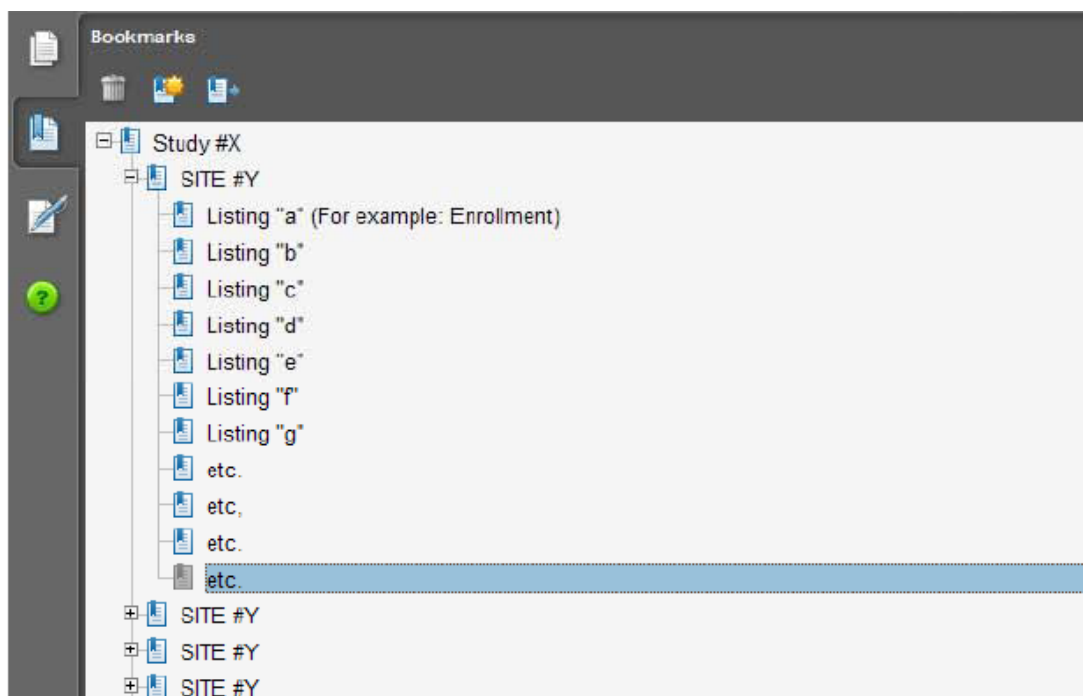
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - 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 Item¹	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

IND 116169
IND 116170
IND 127416
Page 14

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

Action Item/Description	Owner	Due Date
AbbVie will evaluate timing and follow up with FDA after the meeting to reach agreement on submission timing of the expert hepatic panel's assessment.	AbbVie Inc.	Prior to December 16, 2016
AbbVie will provide a written reconciliation of the subject numbers presented in the slides vs Table 2 of the briefing package.	AbbVie Inc.	11/17/2016 Note: sponsor submitted on 11/14/2016

6.0 ATTACHMENTS AND HANDOUTS

Attached are the sponsor's slides that were presented at the meeting.

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/s/

ALICIA MORUF
11/29/2016

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 209394

LATE-CYCLE MEETING MINUTES

AbbVie Inc.
Attention: Sejal P. Emerson, PharmD
Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, Illinois 60064

Dear Dr. Emerson:

Please refer to your New Drug Application (NDA) dated December 14, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for MAVYRET™ (glecaprevir and pibrentasvir) tablets, 100 mg/40 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 22, 2017.

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

If you have any questions, call Alicia Moruf, PharmD, MPH, Regulatory Project Manager at (301) 796-3953.

Sincerely,

{See appended electronic signature page}

Wendy Carter, DO
Clinical Team Leader
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: June 22, 2017
Meeting Location: Teleconference

Application Number: NDA 209394
Product Name: MAVYRET™ (glecaprevir/pibrentasvir)
Applicant Name: AbbVie Inc.

Meeting Chair: Wendy Carter, DO
Meeting Recorder: Alicia Moruf, PharmD, MPH

FDA ATTENDEES

Division of Antiviral Products

Debra Birnkrant, MD, Director
Jeff Murray, MD, MPH, Deputy Director
Wendy Carter, DO, Clinical Team Leader
Larissa Stabinski, MD, Clinical Reviewer
Aimee Hodowanec, MD, Clinical Reviewer
Poonam Mishra, MD, MPH, Deputy Director of Safety
Patrick Harrington, PhD, Clinical Virology Reviewer
Julian O'Rear, PhD, Clinical Virology Team Leader
Alicia Moruf, PharmD, MPH, Regulatory Project Manager
Elizabeth Thompson, MS, Chief Project Management Staff

Office of Biostatistics

Therri Usher, PhD, Biometrics Reviewer
LaRee Tracy, MA, PhD, Biometrics Reviewer

Office of Clinical Pharmacology

Amal Ayyoub, PhD, Clinical Pharmacology Reviewer
Kellie Reynolds, PharmD, Deputy Director

APPLICANT ATTENDEES

Andrew L Campbell, MD, Senior Project Leader, Next Generation HCV, Pharmaceutical Development
Federico J Mensa, MD, Group Medical Director, HCV Clinical Development
Janet M Hammond, MD, PhD, Vice President, Infectious Diseases
Nancy S Shulman, MD, Executive Medical Director, HCV Development
Neddie S Zadeikis, MD, MBA, Senior Medical Director, HCV Development
Stanley Wang, MD, PhD, Associate Medical Director, HCV Development
Christine A Collins, PhD, Director, HCV Clinical Virology

Lois M Larsen, PhD, Director, Statistics, Data and Statistical Sciences
Sandra S Lovell, PhD, Associate Director, Statistics, Data and Statistical Sciences
Yiran Bonnie Hu, PhD, Manager, Statistics, Data and Statistical Sciences
Ariel R Porcalla, MD, MPH, Medical Director, Global Pharmacovigilance
Wei Liu, PhD, Senior Director, Clinical Pharmacology and Pharmacometrics
Chih-Wei Lin, PhD, Assistant Director, Clinical Pharmacology and Pharmacometrics
Debra Webb, MS, Director, Regulatory Affairs CMC
Maryam A Voth, BS, Director, Strategic Labeling, Regulatory Affairs
Nella Barshteyn, PharmD, PhD, Manager, Strategic Labeling, Regulatory Affairs
Toni A Glinsey, MS, RQC, Senior Director, Global Regulatory Strategy
Sejal Emerson, PharmD, Director, Global Regulatory Strategy
Grant S Griffin, MS, RAC, Manager, Global Regulatory Strategy
Viraj B Gandhi, MS, MBA, RAC, Senior Manager, Global Regulatory Strategy

1.0 BACKGROUND

NDA 209394 was submitted on December 14, 2016 for MAVYRET™ (glecaprevir/pibrentasvir) tablets, 100 mg/40 mg.

Proposed indication(s): Treatment of HCV

PDUFA goal date: August 14, 2017

FDA issued a Background Package in preparation for this meeting on June 21, 2017.

2.0 DISCUSSION

1. Introductory Comments

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

Discussion: None

2. Discussion of Substantive Review Issues

- a. **Indication statement:** DAVP has had extensive internal discussions regarding the language for the indication. We believe it is important to both allow for the broad indication, and to clearly state that treatment is also indicated specifically for HCV GT1 in patients with prior NS5A or NS3/4A treatment-experience, but not both. In addition, consistent with recent HCV labeling practices, DAVP believes that it is important to retain language pertaining to compensated cirrhosis status in the indication statement.

Discussion: *None. AbbVie Inc. agreed to the Agency's recommended changes.*

- b. **GT5/GT6 Treatment Duration:** DAVP is agreeable to an 8 week duration for both GT5 and GT6 treatment-naïve and PRS-treatment-experienced patients without cirrhosis. Additionally, the data for both the 8 and 12 week duration in GT5 and GT6 should be displayed in Section 14 of the labeling, because these data are supportive to the overall decision to allow the 8 week duration. AbbVie to provide an update on emerging data available at the time of the Late Cycle Meeting (SVR4 through SVR24 for all GT5 or GT6 data).

Discussion: *AbbVie Inc., provided updated GT5/6 data on June 20th, 2017. However, at this time, DAVP has provided agreement for the 8 week duration based on the totality of data available in the NDA. Given the limited time left in the review cycle, the Agency explained that the additional data will not be under consideration for labeling under this current review cycle.*

- c. **Contraindications of carbamazepine, efavirenz, and St. John's Wort:** DAVP believes that the co-administration of carbamazepine, efavirenz, and St. John's Wort should be contraindicated due to > 50% reduction in GLE and PIB AUC which will lead to significant loss of efficacy in harder to treat patients, such as patients with GT3.

Discussion:

The Agency acknowledged the analyses pertaining to the observed SVR12 calculations in GT3 patients with decreased glecaprevir and pibrentasvir exposures. In addition, it was noted that comparisons of labeling recommendations between different drugs are complicated because the risk-benefit assessments vary across drugs.

After further consideration of the risk:benefit of the coadministration of MAVYRET with carbamazepine, efavirenz, and St. John's Wort, the Agency agreed to change the USPI language from "contraindicated" to "not recommended". The specific warning language will be communicated to AbbVie in upcoming labeling discussions.

- d. AbbVie submitted a slide deck (attached) to discuss additional clinical pharmacology comments as it relates to USPI Section 12.3.

Discussion:

The Agency informed AbbVie that the information contained in the slide deck was reviewed and acknowledged that inclusion of all clinical drug interaction studies with PK parameters outside of the 0.8 to 1.25 range would lengthen the tables in Section 12.3. Nonetheless, it was conveyed that this approach has been utilized consistently for all antiviral drug labels. Section 7 of the USPI includes a more concise and clinically relevant description of drug interaction information. Changes to language in 12.3 will require further internal discussion across clinical pharmacology teams and, therefore, a final recommendation was not discussed at the LCM.

3. Postmarketing Requirements/Postmarketing Commitments

- Pediatric PREA requirements
- Other PMCs/PMRs are under discussion which may include, but are not limited to:
 - Submission of clinical study report and data from M16-126 regarding genotype 5 and 6 treated with GLE/PIB for 8 weeks duration;
 - Submission of clinical study report and data from M14-730 in HCV/HIV co-infected subjects.
 - Submission of a clinical study report summarizing efficacy and drug resistance analyses of GLE/PIB in HCV GT1 infected, NS5A inhibitor + sofosbuvir-experienced subjects.
 - Submission of a study report characterizing the phenotypic effect of the following NS3/4A substitutions on glecaprevir anti-HCV activity: NS3_I18V, NS3_N77S, NS3_V116A, NS3_I354V and NS4A_V23A in genotype 1a replicons, and NS3_I366V in a genotype 3a replicon.
 - Submission of a study report characterizing the phenotypic effect of an NS5A_A61T substitution on pibrentasvir anti-HCV activity in an HCV genotype 1a replicon.

○

(b) (4)

Discussion: None

4. Review Plans

Discussion: The Agency informed the applicant that the review is ongoing and will await the completion of CMC and facility inspections and address any issues that may arise.

5. Wrap-up and Action Items

Discussion: None

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/

WENDY W CARTER
07/13/2017



NDA 209394

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

AbbVie Inc.
Attention: Viraj Gandhi, MS MBA, RAC
Senior Manager, Regulatory Affairs
One North Waukegan Road
Department PA72/ Building AP30-1
North Chicago, IL 60064-6194

Dear Mr. Ghandi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for June 22, 2017. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees at alicia.moruf@fda.hhs.gov, at least one week prior to the meeting.

If you have any questions, call Alicia Moruf, PharmD, MPH, Regulatory Project Manager, at (301) 796-3953.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: June 22, 2017 10:30 AM EST- 11:30 AM EST

Meeting Location: Teleconference

Application Number: 209394

Product Name: glecaprevir/pibrentasvir film-coated tablets, 100 mg/40 mg

Indication: HCV

Applicant Name: AbbVie Inc.

FDA ATTENDEES (tentative)

Office of Antimicrobial Products
Edward Cox, MD, MPH, Director

Division of Antiviral Products
Jeff Murray, MD, MPH, Deputy Director
Wendy Carter, DO, Clinical Team Leader
Larissa Stabinski, MD, Clinical Reviewer
Aimee Hodowanec, MD, Clinical Reviewer
Kim Struble, PharmD, Clinical Team Leader
Poonam Mishra, MD, MPH, Deputy Director of Safety
Patrick Harrington, PhD, Clinical Virology Reviewer
Eric Donaldson, PhD, Clinical Virology Reviewer
Julian O'Rear, PhD, Clinical Virology Team Leader
Alicia Moruf, PharmD, MPH, Regulatory Project Manager
Elizabeth Thompson, MS, Chief Project Management Staff

Office of Biostatistics
Thamban Valappil, PhD, Biometrics Team Leader
Therri Usher, PhD, Biometrics Reviewer
LaRee Tracy, MA, PhD, Biometrics Reviewer

Office of Clinical Pharmacology
Amal Ayyoub, Clinical Pharmacology Reviewer
Islam R. Younis, PhD, Clinical Pharmacology Team Leader

Office of Pharmaceutical Quality
Stephen Miller, PhD, Product Quality Team Leader,
Danuta Gromek-Woods, Ph.D., Application Team Lead (acting)

APPLICANT ATTENDEES

Andrew L Campbell, MD, Senior Project Leader, Next Generation HCV, Pharmaceutical Development

Federico J Mensa, MD, Group Medical Director, HCV Clinical Development

Janet M Hammond, MD, PhD, Vice President, Infectious Diseases

Nancy S Shulman, MD, Executive Medical Director, HCV Development

Andrew Storey, BSc, Vice President, Regulatory Affairs, Global Regulatory Strategy

Christine A Collins, PhD, Director, HCV Clinical Virology

Tami J Pilot-Matias, PhD, Associate Director II, HCV Clinical Virology

Lois M Larsen, PhD, Director, Statistics, Data and Statistical Sciences

Sandra S Lovell, PhD, Associate Director, Statistics, Data and Statistical Sciences

Ariel R Porcalla, MD, MPH, Medical Director, Global Pharmacovigilance

Meenal Patwardhan, MD, MHSA, Therapeutic Area Head, Infectious Diseases, Neurosciences, General Medicine

Wei Liu, PhD, Senior Director, Clinical Pharmacology and Pharmacometrics

Sherry Morgan, DVM, PhD, ACVP, ABVT, ABT Senior Research Fellow, Preclinical Safety

Debra Webb, MS, Director, Regulatory Affairs CMC

Nancy E Sever, PhD, CMC Scientific Director, Global Program Management

Molly Blake-Michaels, MS, PMP Program Lead II, HCV Clinical Program Development

Maryam A Voth, BS, Director, Strategic Labeling, Regulatory Affairs

Nella Barshteyn, PhD, Manager, Strategic Labeling, Regulatory Affairs

Thomas J Podsadecki, MD, Vice President, Regulatory Affairs

Toni A Glinsey, MS, RQC, Senior Director, Regulatory Affairs, Global Regulatory Strategy

Sejal Emerson, PharmD, Director, Regulatory Affairs, Global Regulatory Strategy

Grant S Griffin, MS, RAC, Manager, Regulatory Affairs, Global Regulatory Strategy

Viraj B Gandhi, MS MBA, RAC, Senior Manager, Regulatory Affairs, Global Regulatory Strategy

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

- Indication statement: language highlighting both the broad indication and prior NS5A inhibitor- or NS3/4A PI-experienced indication
- Treatment duration for HCV GT5 or GT6 infected patients without cirrhosis
- Contraindicating the co-administration of carbamazepine, efavirenz, and St. John's Wort.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (Alicia Moruf/Wendy Carter)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 40 minutes

Each issue will be introduced by FDA and followed by a discussion.

Clinical

- **Indication statement:** DAVP has had extensive internal discussions regarding the language for the indication. We believe it is important to both allow for the broad indication, and to clearly state that treatment is also indicated specifically for HCV GT1 in patients with prior NS5A or NS3/4A treatment-experience, but not both. In addition, consistent with recent HCV labeling practices, DAVP believes that it is important to retain language pertaining to compensated cirrhosis status in the indication statement.
- **GT5/GT6 Treatment Duration:** DAVP is agreeable to an 8 week duration for both GT5 and GT6 treatment-naïve and PRS-treatment-experienced patients without cirrhosis. Additionally, the data for both the 8 and 12 week duration in GT 5 and GT6 should be displayed in Section 14 of the labeling, because these data are supportive to the overall decision to allow the 8 week duration.
 - AbbVie to provide an update on emerging data available at the time of the Late Cycle Meeting (SVR4 through SVR24 for all GT5 or GT6 data).

Clinical Pharmacology

- **Contraindications of carbamazepine, efavirenz, and St. John's Wort:** DAVP believes that the co-administration of carbamazepine, efavirenz, and St. John's Wort should be contraindicated due to > 50% reduction in GLE and PIB AUC which will lead to significant loss of efficacy in harder to treat patients, such as patients with GT3.

Product Quality Update

- The evaluation of the manufacturing facilities is on-going

3. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

- Pediatric PREA requirements
- Other PMCs/PMRs are under discussion which may include, but are not limited to:

- o Submission of clinical study report and data from M16-126 regarding genotype 5 and 6 treated with GLE/PIB for 8 weeks duration;
- o Submission of clinical study report and data from M14-730 in HCV/HIV co-infected subjects.
- o Submission of a clinical study report summarizing efficacy and drug resistance analyses of GLE/PIB in HCV GT1 infected, NS5A inhibitor + sofosbuvir-experienced subjects.
- o Submission of a study report characterizing the phenotypic effect of the following NS3/4A substitutions on glecaprevir anti-HCV activity: NS3_I18V, NS3_N77S, NS3_V116A, NS3_I354V and NS4A_V23A in genotype 1a replicons, and NS3_I366V in a genotype 3a replicon.
- o Submission of a study report characterizing the phenotypic effect of an NS5A_A61T substitution on pibrentasvir anti-HCV activity in an HCV genotype 1a replicon.
- o  (b) (4)

4. Review Plans –5 minutes

- Continue application review including finalizing labeling and PMR/PMCs
- Await completion of CMC and facility inspections and address any issues that may arise

5. Wrap-up and Action Items –5 minutes

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/s/

JEFFREY S MURRAY
06/13/2017