CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206619Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 206619 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: VIEKIRA PAK Established/Proper Name: ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets Dosage Form: tablets, co-packaged		Applicant: AbbVie Inc. Agent for Applicant (if applicable): N/A
RPM: Katherine Schumann		Division: Division of Antiviral Products

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

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

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

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

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

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

❖ Actions	
• Proposed action • User Fee Goal Date is December 21, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

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

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): 1, 4
(confirm chemical classification at time of approval)

☒ Fast Track
☒ Rolling Review
☐ Orphan drug designation
☒ Breakthrough Therapy designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

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

CONTENTS OF ACTION PACKAGE

Officer/Employee List

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

Version: 5/14/2014

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval, 12/19/14
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included 12/17/14
• Original applicant-proposed labeling	☒ Included 4/21/14
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)* **Note: Submitted as Patient Package Insert and converted to Medication Guide during review cycle at the Agency's request.*	☒ Medication Guide* ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included 12/17/14
• Original applicant-proposed labeling	☒ Included (originally proposed as PPI) 4/21/14
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included 10/22/14
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Proprietary Name Conditionally Acceptable Letters: 8/22/14 and 5/7/2014 Review Addendum: 11/12/14 Review Memorandum: 8/20/14 Review: 5/5/14
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 6/16/14, PLR Format Review DMEPA: ☐ None 11/6/14, 9/19/14 & 9/10/14 DMPP/PLT (DRISK): ☐ None 12/5/14 OPDP: ☐ None 12/5/14 SEALD: ☒ None CSS: ☒ None Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	6/16/14 ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included

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

❖ 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 o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 10/15/14 If PeRC review not necessary, explain: _____	
❖ 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, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	Included
❖ 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)	PeRC Meeting Minutes, 10/29/14, 10/28/13, 8/29/13 Medical Policy Council Breakthrough Therapy Designation Internal Minutes, 4/15/13
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 1/29/14
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 10/1/12
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A 7/14/14
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A 10/20/14
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	Type B CMC Meeting, 9/17/13 Type B Initial Breakthrough Therapy Meeting, 7/22/13 CMC EOP2 Meeting, 4/3/13 EOP1 Meeting, 9/14/11
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 12/19/14
Division Director Summary Review *(indicate date for each review)*	☐ None 12/11/14
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 11/24/14
PMR/PMC Development Templates *(indicate total number)*	☐ None 17 PMR/PMC templates
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	11/17/14, review addendum 9/18/14, primary review

	5/29/14, filing review
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Included in 9/18/14 primary review, appendix 9.4
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None 10/6/14, DAVP hepatology review 9/18/14, Maternal Health review
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None 10/15/14, REMS review (no REMS required)
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested Review Summary: 9/9/14 Letters to Investigators: 11/13/14 11/03/14 10/31/14 10/29/14 10/28/14 8/01/14 7/31/14 7/29/14
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None 11/18/14, review addendum 9/18/14, primary review 5/22/14, filing review
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)*	☐ None 10/31/14, review addendum 9/19/14, primary review 6/12/14, filing review

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)*	☐ None 12/18/14, review addendum 9/19/14, primary review 6/19/14, filing review Consult Reviews: 11/04/14, DGIEP & DCP III consult review of drug interaction recommendation (omeprazole) 7/23/14, QT IRT review
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review 9/11/14, ADP/T review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 9/16/14, primary review 5/23/14, filing review
❖ 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 9/4/14, carc stats review
❖ ECAC/CAC report/memo of meeting	☐ None 7/24/14, ECAC meeting minutes
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 12/18/14, product quality review addendum #2 11/14/14, product quality review addendum 9/21/2014, biopharmaceutics review 9/19/14, product quality primary review 6/17/14, filing review
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 5/6/14, quality microbiology review
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	9/19/14 review, page 288-9
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: 12/18/2014 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable *Refer to Product Quality Review Addendum #2 dated 12/18/2014*
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☒ Requested ☐ Not yet requested ☐ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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

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

/s/

KATHERINE SCHUMANN
12/19/2014

EXCLUSIVITY SUMMARY

NDA # 206619 SUPPL # HFD # 530

Trade Name VIEKIRA PAK

Generic Name ombitasvir, paritaprevir, ritonavir tablets; dasabuvir tablets, co-packaged for oral use

Applicant Name AbbVie Inc.

Approval Date, If Known December 19, 2014

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)

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

YES ☒ NO ☐

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

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

d) 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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☒ NO ☐

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

NDA# 20659, 20680, 20945, 22417 NORVIR (ritonavir) capsules, tablets, oral solution

NDA# 21226, 21251, 21906 KALETRA (lopinavir/ritonavir) capsules, oral solution, tablets

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.

NDA 206619 contains ombitasvir, paritaprevir and dasabuvir, three new chemical entities, in combination with ritonavir, a previously approved active moiety. Ombitasvir, paritaprevir and ritonavir are co-formulated in a fixed-dose combination tablet and co-packaged with dasabuvir, which is provided as a separate tablet. Under the Agency's new interpretation described in the Agency's Guidance for Industry, New Chemical Entity Exclusivity for Certain Fixed-Combination Drug Products, a drug substance is eligible for 5-year exclusivity, provided it meets the regulatory definition of new chemical entity, regardless of whether that drug substance is approved in a single-ingredient drug product or in a fixed-combination with another drug substance that contains no previously approved active moiety, or in a fixed-combination with

another drug substance that contains a previously approved active moiety. This NDA is thus eligible for 5-year new chemical entity exclusivity pursuant to the new interpretation.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

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

! Explain:

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

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

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

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

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Katherine Schumann
Title: Regulatory Project Manager
Date: November 20, 2014

Name of Office/Division Director signing form: Jeffrey Murray
Title: Deputy Director

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/

KATHERINE SCHUMANN
12/18/2014

JEFFREY S MURRAY
12/19/2014

From: Schumann, Katherine
To: "ZumBrunnen, Troy L"
Cc: "Rogers, Sarah R"
Subject: RE: NDA 206619 - Labeling Request
Date: Wednesday, December 17, 2014 12:53:00 PM
Attachments: 2014_12_17 Med Guide Comments.docx
2014_12_17 Med Guide Comments.pdf

Troy,

Please find attached additional comments from the Patient Labeling team and DAVP regarding the Viekira Pak Medication Guide.

Let me know if your team has any questions.

Please submit the final PI and Medication Guide to NDA 206619 by COB tomorrow (Thursday, December 18, 2014).

Warm Regards,
Katie

47 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

KATHERINE SCHUMANN
12/17/2014

From:	Schumann, Katherine
To:	"ZumBrunnen, Troy L"
Cc:	"Rogers, Sarah R"
Subject:	NDA 206619 labeling
Date:	Wednesday, December 03, 2014 4:36:00 PM
Attachments:	2014_12_03 NDA 206619 draft labeling.docx

Troy,

Please find attached the draft Viekira Pak labeling with comments from the review team embedded.

We would appreciate a response by COB on Friday, December 5. Let me know if that is not feasible.

Please let me know if you have any questions.

Warm Regards,
Katie

Katherine Schumann, M.S.
Senior Regulatory Project Manager
FDA/OMPT/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
12/05/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: December 5, 2014

NDA: 206619

PRODUCT: ombitasvir/paritaprevir/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: NDA 206619 - Request for Additional PMR

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets co-packaged with dasabuvir tablets).

> During further upper level review of your application, we have identified the need for an additional PMR. Your application contains insufficient numbers of Blacks/African Americans to conduct meaningful subgroup analyses for efficacy or safety. This application contains a substantially lower proportion of Blacks than some other applications recently reviewed. Your application's safety data base for Blacks/African Americans was insufficient to identify potential unexpected toxicities in this subgroup of the population which may be more vulnerable to drug toxicity based on increased frequencies of certain comorbidities. Please propose a trial or observational study (e.g., HCV Target data) that will evaluate safety and efficacy in at least 250-300 Black/African Americans and conduct comparative analyses with White enrollees in the same trial or observational study.

Please provide a response by Monday, December 8, 2014.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
12/05/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: November 14, 2014, 9:45 – 10:15 AM

Application Number: NDA 206619
Product Name: Viekira Pak (ombitasvir, paritaprevir, ritonavir tablets; dasabuvir tablets)
Sponsor/Applicant Name: AbbVie, Inc.

Subject: Labeling Discussion

FDA Participants:
John Farley, Deputy Office Director, OAP
Jeffrey Murray, Deputy Director, DAVP
Debra Birnkrant, Director, DAVP
Russell Fleischer, Clinical Reviewer, DAVP
Katherine Schumann, Regulatory Project Manager, DAVP

Sponsor/Applicant Participants:
Michael Severino, Executive Vice President, Research and Development
Ron Robison, Vice President, Regulatory Affairs
Andrew Storey, Vice President, Regulatory Affairs, US and Canada
Barry Bernstein, Divisional Vice President, Infectious Disease Development
Scot Brun, Vice President, Clinical Development
Barbara McGovern, Medical Affairs

1.0 BACKGROUND:

On November 11, 2014, AbbVie Inc. requested a teleconference with OAP and DAVP management to discuss the issue of the duration of Viekira Pak treatment for patients with HCV genotype 1a and cirrhosis.

2.0 DISCUSSION:

AbbVie explained there is continued disagreement with the Agency regarding the appropriate duration of therapy for patients with HCV genotype 1a (GT1a) and cirrhosis. AbbVie argued (b) (4) [redacted] AbbVie suggested that prescribers should be able to evaluate the available data on both durations for GT1a cirrhotics and make a decision for each individual patient. To facilitate this in labeling, AbbVie proposed a footnote to Table 1 in Dosage and Administration that states that "(b) (4)" and references the data from M13-099 in GT1a cirrhotic subjects displayed in Table 10, Section 14. The Agency asked AbbVie to clarify if the proposed footnote is meant to communicate that prior response to

PegIFN therapy (treatment naïve, relapser, partial responder, null responder) would be the criteria used to determine duration of therapy for these patients, and AbbVie confirmed that this was the intention.

The Agency noted that prescribers at the annual AASLD meeting expressed the desire for individualized treatment options. However, the Agency cautioned that SVR12 rates are likely to decrease in a real world setting and the lack of available re-treatment options is still a significant concern.

The Agency noted that AbbVie's labeling proposal may be reasonable and it is likely that the review team will be able to come to an agreement with the company. The Agency agreed to review AbbVie's labeling proposal expected later in the afternoon and provide feedback by the middle of the next week.

3.0 ACTION ITEMS:

AbbVie Inc. will provide revised labeling on the date of the teleconference, including a proposal for considering 12 weeks of treatment in certain patients with GT1a HCV and cirrhosis. The Agency will provide a response by the middle of the week of November 17, 2014.

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/s/

KATHERINE SCHUMANN
11/25/2014

From: Schumann, Katherine
To: "ZumBrunnen, Troy L"
Cc: "Rogers, Sarah R"
Subject: NDA 206619 Additional Labeling Comment
Date: Thursday, November 20, 2014 3:29:00 PM

Troy,

Please note that the review team has identified one error in Section 14.1 of the PI. In the first bullet under Table 9, [redacted] (b) (4) [redacted] However, because the number of subjects in each arm is already listed in the table, DAVP prefers [redacted] (b) (4) [redacted], as shown below:

- In SAPPHIRE I and II, subjects without cirrhosis were randomized; [redacted] (b) (4) to VIEKIRA PAK in combination with ribavirin (RBV) for 12 weeks or to placebo. Subjects in the placebo arm received placebo for 12 weeks, after which they received open-label VIEKIRA PAK in combination with RBV for 12 weeks *[see Clinical Studies (14.2)]*.
- In PEARL II, III and IV, subjects without cirrhosis, were randomized [redacted] (b) (4) to receive VIEKIRA PAK with or without RBV for 12 weeks of treatment *[see Clinical Studies (14.2)]*.
- In the open-label TURQUOISE-II trial, subjects with compensated cirrhosis (Child-Pugh A) who were either treatment-naïve or pegylated interferon/RBV (pegIFN/RBV) treatment-experienced were randomized to receive VIEKIRA PAK in combination with RBV for either 12 or 24 weeks of treatment. Subjects who previously failed therapy with a treatment regimen that included VIEKIRA PAK or other direct-acting antiviral agents were excluded *[see Clinical Studies (14.3)]*.

Could you please communicate this request to your team as you review the labeling?

Please let me know if you have any questions.

Warm Regards,
Katie

From: Schumann, Katherine
Sent: Wednesday, November 19, 2014 6:04 PM
To: 'ZumBrunnen, Troy L'
Cc: Rogers, Sarah R
Subject: NDA 206619 Labeling Comments

Troy,

Please find attached the Division's response to your proposed labeling emailed on Friday 11/14 and submitted on 11/17.

We are asking for a response by 12/1/14. As we discussed, comments on the Medication Guide will follow at a later date, probably during the week of 12/1.

Warm Regards,
Katie

Katherine Schumann, M.S.
Senior Regulatory Project Manager
FDA/OMPT/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
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/s/

KATHERINE SCHUMANN
11/20/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: November 19, 2014

NDA: 206619

PRODUCT: ombitasvir/ABT-450/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Labeling Comments

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir.

Please find comments on the Viekira Pak prescribing information (PI) submitted on November 17, 2014 in the attached document. Note that comments on the draft Medication Guide will be provided at a later date.

Please submit revised labeling to the NDA by December 1, 2014.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
11/19/2014

From: Rogers, Sarah R
To: Schumann, Katherine
Cc: ZumBrunnen, Troy L; Sansone, Andrew J
Subject: (b) (4) Paritaprevir
Date: Tuesday, November 11, 2014 12:00:29 PM
Attachments: (b) (4) pdf

Hi Katie,

(b) (4)

Please let us know if you or your team have any questions.

Kindly,
Sarah

SARAH ROGERS, PHARMD, RPH
Manager, Regulatory Affairs
Area and Affiliate Strategy, US/Canada

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abbvie.com

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KATHERINE SCHUMANN
11/13/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: November 7, 2014

NDA: 206619

PRODUCT: ombitasvir/ABT-450/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Labeling Comments

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir.

Please find comments on the Viekira Pak prescribing information (PI) submitted on October 17, 2014 in the attached document.

Please submit revised labeling to the NDA by November 14, 2014.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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KATHERINE SCHUMANN
11/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Office of Clinical Pharmacology** **Division of Clinical Pharmacology 3** **Tracking/Action Sheet for Formal/Informal Consults**

From: Sandhya Apparaju			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 10/31/2014	IND No.: Doc No.:	NDA No. **206619**	DATE OF DOCUMENT **September 9, 2014 (consult)** **October 17, 2014 (Assigned)**	
NAME OF DRUG **VIEKIRA PAK and Omeprazole**	PRIORITY CONSIDERATION		Date of informal/Formal Consult:	

NAME OF THE SPONSOR: AbbVie, Inc.; Consult from the Division of Antiviral Products Regarding new NDA review issue

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☒ OTHER *(SPECIFY BELOW):* [Consult Review]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☒ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☒ See comments below
☐Medical ☐Chemist ☐Pharm-Tox	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ See submission cover letter
☐Micro ☐Pharmacometrics ☐Others		☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)		[ ]

REVIEW COMMENT(S)

☐ **NAI** ☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

Consult Questions and Responses:

The applicant's proposed labeling recommendation does not seem to be consistent with the relevant information in the approved omeprazole prescribing information. Hence, please comment on:

1) Is the applicant's proposed recommendation reasonable based on the observed decrease in omeprazole exposures?
   Clinical Pharmacology Response: We are partly in agreement. Please see our alternative labeling suggestion below for your consideration to avoid inconsistency with existing Prilosec labeling.

2) If the applicant's proposed recommendation is not reasonable, please suggest alternate clinical recommendation.

   Clinical Pharmacology Response: Avoid concomitant use with omeprazole. If use is unavoidable, omeprazole 40 mg once daily can be used for GERD.

Background: A consult to DGIEP originated from the Division of Antiviral Products on September 9, 2014 which states the following:

"The applicant [*Abbvie Inc., NDA 206619; VIEKIRA PAK*] assessed the effect of ombitasvir, paritaprevir, and ritonavir co-administered with dasabuvir on the pharmacokinetics of omeprazole (M12-199). The results of the trial showed that the mean Cmax and AUC of omeprazole decreased by approximately 40 %. The applicant has proposed the following clinical recommendation:

"[redacted (b) (4)]".

The current Omeprazole label provides the following information regarding drug-drug interactions in which the magnitude of decrease in omeprazole concentrations was similar to the magnitude of decrease in omeprazole concentrations observed in trial M12-199":

Drugs known to induce CYP2C19 or CYP3A4 (such as rifampin) may lead to decreased omeprazole serum levels. In a cross-over study in 12 healthy male subjects, St. John's wort (300 mg three times daily for 14 days), an inducer of CYP3A4, decreased the systemic exposure of omeprazole in CYP2C19 poor metabolisers (C_{max} and AUC decreased by 37.5% and 37.9%, respectively) and extensive metabolisers (C_{max} and AUC decreased by 49.6% and 43.9%, respectively). Avoid concomitant use of St. John's Wort or rifampin with omeprazole.

Discussion: Omeprazole is primarily a substrate of CYP2C19, with CYP3A4 also contributing to its metabolism. Based on *in vitro* drug-drug interaction potential information presented in the Clinical Pharmacology review of NDA 206619 (Induction of metabolic enzymes by ABT-267, ABT450, ritonavir, and ABT-333 on page 49), it appears that two of the drugs in the proposed product, namely ABT-450 and ritonavir are weak *in vitro* inducers of CYP3A4 (final review in DARRTs signed September 19, 2014). Information in the Clinical Pharmacology review doesn't suggest potential for CYP2C19 induction by these drugs.

Based on personal/email communication by Dr. Sue Chih Lee with Dr. Vikram Arya, the Clinical Pharmacology reviewer for this NDA, it appears that the sponsor has proposed CYP2C19 induction by ritonavir to be the potential rationale for this observed interaction with omeprazole. Sponsor appears to base this rationale on a publication by Foisy et al (2008), titled "Induction effects of ritonavir: implications for drug interactions". In this publication, the authors note that "Numerous pharmacokinetic studies suggested that ritonavir induces cytochrome P450 enzymes 3A, 1A2, 2B6, 2C9, and 2C19, as well as glucuronyl transferase. Additionally, several case reports described clinically significant subtherapeutic effects of drugs metabolized by these isoenzymes when coadministered with ritonavir. Both therapeutic and boosting doses of ritonavir appear to induce these enzymes; *however, most of the studies of low-dose ritonavir involved a second protease inhibitor such as lopinavir, darunavir, or tipranavir. It is, therefore, difficult to distinguish the relative effects of additional medications unless well-designed, 3-way studies are conducted*".

Conclusion: Based on available evidence, the mechanism of action for the observed *in vivo* drug-drug interaction (decreased concentrations of omeprazole) by the drug combination in VIEKIRA PAK cannot be conclusively established and therefore potential for a class-effect labeling for all proton-pump inhibitors cannot be ascertained. However, based on the observed decrease in omeprazole concentrations following co-administration in study M12-199, it appears reasonable to address this interaction in the labeling for the new drug (VIEKIRA PAK) at this time. An alternative to sponsor's proposed language is suggested in order to be consistent with existing label for omeprazole.

COMMENTS/SPECIAL INSTRUCTIONS: Please see the responses to your consult questions at the beginning of this review.	
SIGNATURE OF REVIEWER: Sandhya Apparaju, Ph.D. **SIGNATURE OF TEAM LEADER: Sue-Chih Lee, Ph.D.**	Date _____ Date _____
CC.: TL: Lee; DD: Bashaw	**Project Manager:_____ Date _____**

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/s/

SANDHYA K APPARAJU
11/04/2014

SUE CHIH H LEE
11/04/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: October 30, 2014

NDA: 206619

PRODUCT: ombitasvir/ABT-450/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Proposed CMC Post-Marketing Commitment

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir, paritaprevir, ritonavir co-packaged with dasabuvir.

ONDQA is proposing the following post-marketing commitment (PMC) for Viekira Pak. Please review the proposed PMC and provide a response to the NDA.

> Develop a test for [redacted] (b) (4) with a sensitivity of [redacted] (b) (4) % in the ombitasvir, paritaprevir, ritonavir drug product tablet for the release and stability specification.
>
> Proposed final report submission: December 31, 2016

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
10/30/2014

PeRC PREA Subcommittee Meeting Minutes
October 15, 2014

PeRC Members Attending:
Lynne Yao
Rosemary Addy
Jane Inglese
Tom Smith
Melissa Tassinari (for Karen Davis-Bruno)
Gregory Reaman
Freda Cooner
Lily Mulugeta
Olivia Ziolkowski
Barbara Buch
Rachel Witten

Agenda

NDA	206619	Viekira Pak (ombitasvir, paritaprevir, ritonavir, dasabuvir) Partial Waiver/Deferral/Plan	Treatment of genotype 1 chronic hepatitis C virus infection, including patients with cirrhosis

(b) (4)

[redacted]

Viekira Pak (ombitasvir, paritaprevir, ritonavir, dasabuvir) Partial Waiver/Deferral/Plan

- NDA 206619 was approved for Viekira Pak (ombitasvir, paritaprevir, ritonavir, dasabuvir) for treatment of genotype 1 chronic hepatitis C virus infection, including patients with cirrhosis.
- The application triggers PREA as directed to a new active ingredient.
- The application has a PDUFA a goal date of December 21, 2014.
- The pediatric plan is based in an Agreed iPSP and this plan is consistent with the Agreed iPSP.
- *PeRC Recommendations:*
    - The PeRC agreed with a partial waiver for pediatric patients aged birth to less than 3 years of age because the product fails to represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of pediatric patients of this age.
    - The PeRC agreed with a deferral for pediatric patients 3 to less than 18 years of age because adult studies have been completed and the product is ready for approval.

(b) (4)

[redacted]

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/s/

JANE E INGLESE
10/29/2014

From:	Schumann, Katherine
To:	"ZumBrunnen, Troy L"
Cc:	Rogers, Sarah R
Subject:	RE: NDA 206619 - Comment regarding carton and container labels
Date:	Friday, October 17, 2014 3:38:00 PM

Troy,

Please find responses from the review team below in bolt font regarding your carton/container label proposals.

Let me know if you have any questions.

Warm Regards,
Katie

From: ZumBrunnen, Troy L [mailto:troy.zumbrunnen@abbvie.com]
Sent: Thursday, October 09, 2014 3:22 PM
To: Schumann, Katherine
Cc: Rogers, Sarah R
Subject: RE: NDA 206619 - Comment regarding carton and container labels

Katie,

Please find below two counter proposals regarding the salt statement and storage conditions.

1. AbbVie would prefer to specify that the product contains the monohydrate salt. The proposal to include 'mono' prior to hydrate is below.

   Each tablet contains 270.3 mg dasabuvir sodium **mono**hydrate equivalent to 250 mg dasabuvir

   Is the addition of modifier 'mono' prior to hydrate acceptable?

   FDA Response: Addition of the modifier 'mono' prior to hydrate is acceptable.

2. Regarding removal of the '"at or" statement in the storage conditions, AbbVie is concerned that the instructional statement "Store below 30°C (86°F)" would increase patient confusion should the product be stored at 30°C (86°F), or exposed to that temperature for a period of time. The inclusion of the "*at or*" in the statement would assure a patient and/or customer that storage at 30°C (86°F)is acceptable and avoid potential interruption in therapy due to their uncertainty of the quality of the product. While the frequency of this occurring (a patient storing the product at exactly 30°C) may be low, we believe it is worth retaining the clarity in the label.

   Is it acceptable to retain the statement on storage conditions as " Store at or below 30°C

(86°F)"?

FDA Response: It is acceptable to retain the statement on storage conditions as "Store at or below 30°C (86°F)"

Regards, Troy

TROY ZUMBRUNNEN, PHARM.D.
Director, Regulatory Affairs
Area and Affiliate Strategy, US/Canada

abbvie

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EMAIL troy.zumbrunnen@abbvie.com

abbvie.com

From: Schumann, Katherine [mailto:Katherine.Schumann@fda.hhs.gov]
Sent: Wednesday, October 08, 2014 12:26
To: ZumBrunnen, Troy L
Cc: Rogers, Sarah R
Subject: RE: NDA 206619 - Comment regarding carton and container labels

Troy,

In response to your requests for clarification regarding the carton and container labels, ONDQA has the following responses:

1. For the container labels, our recommended wording is:
   Each tablet contains 270.3 mg dasabuvir sodium hydrate equivalent to 250 mg dasabuvir
   and should be consistent throughout its placement in the PI and on the Carton/Container labels

2. Regarding the storage temperature statement on the container labels, where the tablet is shown to be stable at the long-term condition of 30degC/75%RH, we have generally been recommending "Store below 30degC (86degF)." Our thinking is that

this is simpler language than “Store at or below 30degC (86degF)” and does not impose any meaningful difference in storage conditions. However, we are very open to additional considerations about this, and if you have a preference for the “at or below” language, please explain the reason(s).

3. Regarding placement of the trademark symbol, neither ONDQA nor DMEPA review this, provided that the symbol does not impact readability.

Please let me know if you have any additional questions.

Warm Regards,
Katie

From: ZumBrunnen, Troy L [mailto:troy.zumbrunnen@abbvie.com]
Sent: Tuesday, October 07, 2014 12:10 PM
To: Schumann, Katherine
Cc: Rogers, Sarah R
Subject: RE: NDA 206619 - Comment regarding carton and container labels

Katie,

Thanks for the quick response. We did note the statement provided below *“Each tablet contains 270.3 dasabuvir sodium, hydrate equivalent to 250 mg dasabuvir”* differs slightly from the language requested in the USPI *“Each tablet contains 270.3* ***mg*** *dasabuvir sodium hydrat****e,*** *equivalent to 250 mg dasabuvir.”* .

Could you confirm that the second statement from the USPI containing the ‘mg’ strength and the comma after the word ‘hydrate’ is the correct statement to include on the carton/container pieces?

Regards, Troy

TROY ZUMBRUNNEN, PHARM.D.
Director, Regulatory Affairs
Area and Affiliate Strategy, US/Canada

abbvie

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EMAIL troy.zumbrunnen@abbvie.com

abbvie.com

From: Schumann, Katherine [mailto:Katherine.Schumann@fda.hhs.gov]
Sent: Tuesday, October 07, 2014 10:36
To: ZumBrunnen, Troy L
Cc: Rogers, Sarah R
Subject: RE: NDA 206619 - Comment regarding carton and container labels

Hi Troy,

I do not expect additional comments on the carton/container labels.

I am waiting to hear back from the CMC team regarding the storage statement in the PI, but I will let them know you have the same question regarding the carton/container labels. It is acceptable to wait to resubmit until the issue has been resolved.

I don't think the Agency generally comments on the location of trademark information, at least not for the PI. I will confirm with ONDQA that this change would not be an issue for the carton/container labels.

Regards,
Katie

From: ZumBrunnen, Troy L [mailto:troy.zumbrunnen@abbvie.com]
Sent: Tuesday, October 07, 2014 11:32 AM
To: Schumann, Katherine
Cc: Rogers, Sarah R
Subject: RE: NDA 206619 - Comment regarding carton and container labels

Katie,

Thanks for providing the comment for the carton and container labels. Should we expect any additional comments?

In the last USPI proposal we noted the request to change the storage conditions in Section 16 from 'Store at or below 30^{O}C' to 'Store at ~~or below~~ 30^{O}C'. In our last submission we requested to retain the 'Store at or below 30^{O}C' language and provided justification. Similar wording is provided on all of the carton/container labeling and we expect to need to apply the final language to carton/container. Based on this we plan to wait for agreement on this language before altering the artwork. Is this acceptable?

Also, internally we noted the Trademark symbo (b) (4)

Regards, Troy

TROY ZUMBRUNNEN, PHARM.D.
Director, Regulatory Affairs
Area and Affiliate Strategy, US/Canada

abbvie

AbbVie Inc
Regulatory Affairs
Dept. PA77, Bldg AP30
1 North Waukegan Road
North Chicago, IL 60064-6194
OFFICE +1 847-938-9445
CELL +1 (b) (6)
EMAIL troy.zumbrunnen@abbvie.com

abbvie.com

From: Schumann, Katherine [mailto:Katherine.Schumann@fda.hhs.gov]
Sent: Monday, October 06, 2014 20:05
To: ZumBrunnen, Troy L
Cc: Rogers, Sarah R
Subject: NDA 206619 - Comment regarding carton and container labels

Troy,

Please refer to your NDA submitted on April 21, 2014 for Viekira Pak. The review team has the following comment regarding the proposed carton and container labels:

> The following statement should replace the current description for (b) (4) on the carton and container labels:
>
> Each tablet contains 270.3 dasabuvir sodium, hydrate equivalent to 250 mg dasabuvir

Please let me know if you have any questions.

Warm Regards,
Katie

Katherine Schumann, M.S.
Senior Regulatory Project Manager
FDA/OMPT/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
10/22/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: October 17, 2014

NDA: 206619

PRODUCT: ombitasvir/ABT-450/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Request to Revise 3.2.P.3.1

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir.

> Please revise Table 1 of section 3.2.P.3.1 Manufacturers of the NDA to remove stability testing as a function of (b) (4), as the recent inspection of this facility established that no stability studies were performed at this site.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
10/17/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: October 10, 2014

NDA: 206619

PRODUCT: ombitasvir/ABT-450/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Labeling Comments

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir.

Please find comments on the Viekira Pak prescribing information (PI) submitted on October 1, 2014 in the attached document.

Please submit revised labeling to the NDA by October 17, 2014.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
10/10/2014

From: Schumann, Katherine
To: "ZumBrunnen, Troy L"
Cc: Rogers, Sarah R
Subject: RE: NDA 206619 - Comment regarding carton and container labels
Date: Wednesday, October 08, 2014 1:25:00 PM

Troy,

In response to your requests for clarification regarding the carton and container labels, ONDQA has the following responses:

1. For the container labels, our recommended wording is:
   Each tablet contains 270.3 mg dasabuvir sodium hydrate equivalent to 250 mg dasabuvir
   and should be consistent throughout its placement in the PI and on the Carton/Container labels

2. Regarding the storage temperature statement on the container labels, where the tablet is shown to be stable at the long-term condition of 30degC/75%RH, we have generally been recommending "Store below 30degC (86degF)." Our thinking is that this is simpler language than "Store at or below 30degC (86degF)" and does not impose any meaningful difference in storage conditions. However, we are very open to additional considerations about this, and if you have a preference for the "at or below" language, please explain the reason(s).

3. Regarding placement of the trademark symbol, neither ONDQA nor DMEPA review this, provided that the symbol does not impact readability.

Please let me know if you have any additional questions.

Warm Regards,
Katie

From: ZumBrunnen, Troy L [mailto:troy.zumbrunnen@abbvie.com]
Sent: Tuesday, October 07, 2014 12:10 PM
To: Schumann, Katherine
Cc: Rogers, Sarah R
Subject: RE: NDA 206619 - Comment regarding carton and container labels

Katie,

Thanks for the quick response. We did note the statement provided below *"Each tablet contains 270.3 dasabuvir sodium, hydrate equivalent to 250 mg dasabuvir"* differs slightly from the language requested in the USPI *"Each tablet contains 270.3* ***mg*** *dasabuvir sodium hydrat****e,*** *equivalent to 250 mg dasabuvir."* .

Could you confirm that the second statement from the USPI containing the 'mg' strength and the

comma after the word 'hydrate' is the correct statement to include on the carton/container pieces?

Regards, Troy

TROY ZUMBRUNNEN, PHARM.D.
Director, Regulatory Affairs
Area and Affiliate Strategy, US/Canada

abbvie

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North Chicago, IL 60064-6194
OFFICE +1 847-938-9445
CELL +1 (b) (6)
EMAIL troy.zumbrunnen@abbvie.com

abbvie.com

From: Schumann, Katherine [mailto:Katherine.Schumann@fda.hhs.gov]
Sent: Tuesday, October 07, 2014 10:36
To: ZumBrunnen, Troy L
Cc: Rogers, Sarah R
Subject: RE: NDA 206619 - Comment regarding carton and container labels

Hi Troy,

I do not expect additional comments on the carton/container labels.

I am waiting to hear back from the CMC team regarding the storage statement in the PI, but I will let them know you have the same question regarding the carton/container labels. It is acceptable to wait to resubmit until the issue has been resolved.

I don't think the Agency generally comments on the location of trademark information, at least not for the PI. I will confirm with ONDQA that this change would not be an issue for the carton/container labels.

Regards,
Katie

From: ZumBrunnen, Troy L [mailto:troy.zumbrunnen@abbvie.com]

Sent: Tuesday, October 07, 2014 11:32 AM
To: Schumann, Katherine
Cc: Rogers, Sarah R
Subject: RE: NDA 206619 - Comment regarding carton and container labels

Katie,

Thanks for providing the comment for the carton and container labels. Should we expect any additional comments?

In the last USPI proposal we noted the request to change the storage conditions in Section 16 from 'Store at or below 30^{O}C' to 'Store at ~~or below~~ 30^{O}C'. In our last submission we requested to retain the 'Store at or below 30^{O}C' language and provided justification. Similar wording is provided on all of the carton/container labeling and we expect to need to apply the final language to carton/container. Based on this we plan to wait for agreement on this language before altering the artwork. Is this acceptable?

Also, internally we noted the Trademark symbol [redacted] (b) (4)

Regards, Troy

TROY ZUMBRUNNEN, PHARM.D.
Director, Regulatory Affairs
Area and Affiliate Strategy, US/Canada

abbvie

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OFFICE +1 847-938-9445
CELL +1 [redacted] (b) (6)
EMAIL troy.zumbrunnen@abbvie.com

abbvie.com

From: Schumann, Katherine [mailto:Katherine.Schumann@fda.hhs.gov]
Sent: Monday, October 06, 2014 20:05
To: ZumBrunnen, Troy L
Cc: Rogers, Sarah R
Subject: NDA 206619 - Comment regarding carton and container labels

Troy,

Please refer to your NDA submitted on April 21, 2014 for Viekira Pak. The review team has the following comment regarding the proposed carton and container labels:

> The following statement should replace the current description for "(b) (4)" on the carton and container labels:
>
> Each tablet contains 270.3 dasabuvir sodium, hydrate equivalent to 250 mg dasabuvir

Please let me know if you have any questions.

Warm Regards,
Katie

Katherine Schumann, M.S.
Senior Regulatory Project Manager
FDA/OMPT/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
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Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
10/08/2014

From: Schumann, Katherine
To: "Rogers, Sarah R"
Cc: ZumBrunnen, Troy L
Subject: RE: NDA 206619 - information request - LBBB narrative
Date: Monday, October 06, 2014 10:17:00 PM

Sarah,

The review team has a follow-up request regarding subject 101308:

Please provide this subject's hemoglobin levels over the course of the study and if he underwent a RBV dose reduction at any time.

Please let me know if you have any questions.

Warm Regards,
Katie

From: Rogers, Sarah R [mailto:sarah.rogers@abbvie.com]
Sent: Thursday, October 02, 2014 4:06 PM
To: Schumann, Katherine
Cc: ZumBrunnen, Troy L
Subject: RE: NDA 206619 - information request - LBBB narrative

Hi Katie,

Please find attached AbbVie's response to the Agency's information request below. The response includes a narrative and cardiology consultation reports for subject 101308.

We plan to formally submit this to the NDA tomorrow.

Please let me know if you or your team have any questions.

Kindly,
Sarah

SARAH ROGERS, PHARMD, RPH
Manager, Regulatory Affairs
Area and Affiliate Strategy, US/Canada

abbvie

1 North Waukegan Road
Builiding AP30-1
Department PA77
OFFICE +1 847-938-7199
CELL +1 (b) (6)

EMAIL sarah.rogers@abbvie.com

abbvie.com

From: Schumann, Katherine [mailto:Katherine.Schumann@fda.hhs.gov]
Sent: Wednesday, October 01, 2014 3:36 PM
To: ZumBrunnen, Troy L
Cc: Rogers, Sarah R
Subject: NDA 206619 - information request - LBBB narrative

Troy,

Please refer to your NDA 206619 submitted on April 21, 2014 for Viekira Pak.

Please find below an information request from the review team.

> Please provide a narrative for Subject 101308 in study M13-098 who experienced an AE of LBBB on day 170, including any associated symptoms, as well as the outcome of the cardiology consultation.

Please provide a response by close of business on Friday, October 3, 2014. The response may be provided via email and submitted to the NDA subsequently.

Warm Regards,
Katie

Katherine Schumann, M.S.
Senior Regulatory Project Manager
FDA/OMPT/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
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Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
10/06/2014

From:	Schumann, Katherine
To:	ZumBrunnen, Troy L
Cc:	"Rogers, Sarah R"
Subject:	NDA 206619 - Comment regarding carton and container labels
Date:	Monday, October 06, 2014 9:04:00 PM

Troy,

Please refer to your NDA submitted on April 21, 2014 for Viekira Pak. The review team has the following comment regarding the proposed carton and container labels:

> The following statement should replace the current description for "(b) (4) on the carton and container labels:
>
> Each tablet contains 270.3 dasabuvir sodium, hydrate equivalent to 250 mg dasabuvir

Please let me know if you have any questions.

Warm Regards,
Katie

Katherine Schumann, M.S.
Senior Regulatory Project Manager
FDA/OMPT/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
10/06/2014

From: Schumann, Katherine
To: "ZumBrunnen, Troy L"
Cc: "Rogers, Sarah R"
Subject: NDA 206619 - information request - LBBB narrative
Date: Wednesday, October 01, 2014 4:35:00 PM

Troy,

Please refer to your NDA 206619 submitted on April 21, 2014 for Viekira Pak.

Please find below an information request from the review team.

> Please provide a narrative for Subject 101308 in study M13-098 who experienced an AE of LBBB on day 170, including any associated symptoms, as well as the outcome of the cardiology consultation.

Please provide a response by close of business on Friday, October 3, 2014. The response may be provided via email and submitted to the NDA subsequently.
Warm Regards,
Katie

Katherine Schumann, M.S.
Senior Regulatory Project Manager
FDA/OMPT/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
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Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
10/02/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: September 29, 2014

NDA: 206619

PRODUCT: ombitasvir, paritaprevir, and ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: M14-004 Information Request

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir, paritaprevir, and ritonavir co-packaged with dasabuvir and to your submission of September 19, 2014.

The review team has the following request for information regarding M14-004:

> Please submit additional information regarding the two subjects that met the PCS criteria for inorganic phosphate, as well as the subject with PCS increase in creatinine.

Please provide the information by Monday, October 6, 2014.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
09/29/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: September 26, 2014

NDA: 206619

PRODUCT: ombitasvir/ABT-450/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Labeling Comments

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir.

Please find comments on the Viekira Pak prescribing information (PI) submitted on August 29, 2014 in the attached document. Additional sections of the PI are currently under review and comments on those sections will be provided at a later date.

Please submit revised labeling to the NDA by COB October 1, 2014.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
09/26/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: September 24, 2014

NDA: 206619

PRODUCT: ombitasvir, paritaprevir, and ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: M14-004 Information Request

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir, paritaprevir, and ritonavir co-packaged with dasabuvir and to your submission of September 19, 2014.

DAVP acknowledges receipt of the interim study report and datasets from M14-004 Part 1a and agrees to review the information during the current review cycle. The extent of information that may be included in labeling will be a review issue, however, (b) (4) .

Additionally, the review team has the following request for information regarding M14-004:

1. Please provide an analysis dataset (.xpt) that includes all of the available data on $CD4^+$ T cell counts, $CD4^+$ T cell percentage, and total lymphocyte counts from the subjects included in the interim report. Include columns that report both the analysis result as well as the change from baseline for each parameter for each visit.

2. Please provide additional descriptive information about the two subjects (101907 and 101908) who were possibly re-infected with HCV relatively early during the follow-up period. For example, were there any reports of behaviors that could possibly explain re-infection?

3. Also referring to Subjects 101907 and 101908, although we agree that your nucleotide sequencing and phylogenetic analyses indicate possible reinfection for these two subjects, we recommend analyzing additional samples (e.g. either a screening or duplicate baseline isolate plus a later follow-up isolate) from each subject to confirm the sequence analyses were not mistakenly conducted on samples from the wrong subjects. These data can be submitted at a later date and would not be reviewed in this current review cycle.

4. Please provide an update on the status of Part 1a of the protocol. Further comments regarding Part 2 of the trial will be forwarded separately.

Please provide the information in requests #1, #2 and #4 by Thursday, October 2, 2014.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
09/24/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: September 24, 2014

NDA: 206619

PRODUCT: ombitasvir, paritaprevir, and ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Clinical Pharmacology Information Request

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir, paritaprevir, and ritonavir co-packaged with dasabuvir.

The review team has the following request for information:

The results of trial M13-103 and M13-491 showed that the magnitude of increase in trough concentrations of Cyclosporine (CsA) and Tacrolimus (Tac) when co-administered with the 3-DAA regimen were quantitatively different from the magnitude of increase in AUCs of CsA and Tac. The results indicate that when CsA or Tac are co-administered with the 3-DAA regimen, maintaining trough concentrations of CsA and Tac similar to the trough concentrations of CsA and Tac when given alone, may result in substantially different AUCs. It should be noted that the efficacy and safety of CsA and Tac are related to the total exposure (i.e. AUC). Because trough concentrations are clinically used to adjust the dose of CsA and Tac, we are concerned whether the target concentration ranges routinely used for therapeutic drug monitoring of CsA and Tac can be applied in cases where CsA or Tac is co-administered with the 3-DAA regimen.

In order to further characterize the pharmacokinetic interaction between the 3-DAA regimen with CsA and Tac, please provide the following information from trial M12-199:

1) Description of the criteria (concentration ranges) used to adjust the dose of CsA and Tac.
2) How often was the dose of CsA and Tac adjusted for each patient during the trial.
3) Individual CsA and Tac pharmacokinetic data from all subjects enrolled in the trial.
4) Any modeling/simulation conducted to determine the adjusted dose of CsA and Tac prior to initiating trial M12-199.

Please provide the requested information by Wednesday, October 1, 2014.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
09/24/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206619

INFORMATION REQUEST

AbbVie
Attention: Troy ZumBrunnen, PharmD
AbbVie Inc.
1 N Waukegan Road
Dept. PA77/Bldg, AP30
North Chicago, IL 60064

Dear Mr. ZumBrunnen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ombitasvir/ABT-450/Ritonavir and Dasabuvir 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 prompt written response in order to continue our evaluation of your NDA.

1. The NDA states that the Ombitasvir/Paritaprevir/Ritonavir tablets "(b) (4) Establish a test and acceptance criterion for the detection of (b) (4) in the Ombitasvir/Paritaprevir/Ritonavir Drug Product Release and Stability Specification. The method should be sensitive enough to detect (b) (4)% (b) (4) for each of the drug substances.

2. Clarify how the desired (b) (4) is maintained throughout manufacture and stability of the Dasabuvir Drug Product.

3. Clarify the following inconsistency regarding control parameter for paritaprevir (b) (4) :

   - Manufacturing Description states: (b) (4)
   - Justification of Specification states: (b) (4) (b) (4)

(b) (4)

4. You state in the NDA (b) (4) . Please clarify and correct as appropriate.

5. (b) (4) Please also submit the updated specification sheet reflecting the USAN approved name, paritaprevir.

6. Until sufficient experience from routine commercial manufacture is obtained, please update the specification tables to include the following tests:

   - Include tests with appropriate acceptance criteria for water content and particle size distribution in the dasabuvir sodium drug substance specification.
   - Include a USP<231> test for heavy metals in each drug substance specification, as requested at the Sept 17, 2013 meeting.

7. Please provide available updates on stability data.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURAWE
09/17/2014

From:	Schumann, Katherine
To:	"ZumBrunnen, Troy L"
Cc:	Rogers, Sarah R
Subject:	NDA 206619 Clinical Information Request - M13-099 Narratives
Date:	Monday, September 15, 2014 9:28:00 AM

Troy,

Please refer to your NDA 206619 submitted on April 21, 2014 for Viekira Pak.

Please find below an information request from the clinical team.

> Please identify the 4 subjects in M13-099 who experienced hepatic decompensation. Submit narratives for each subject or describe where previously-submitted narratives are located within the NDA.

Please provide a response by close of business on Tuesday, September 16, 2014. If the requested information cannot be provided tomorrow, please send a proposed timeline for response.

Warm Regards,
Katie

Katherine Schumann, M.S.
Senior Regulatory Project Manager
FDA/OMPT/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
09/15/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: September 11, 2014

NDA: 206619

PRODUCT: ombitasvir, paritaprevir, and ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Clinical Virology Information Request

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir, paritaprevir, and ritonavir co-packaged with dasabuvir and your submission of August 20, 2014 containing the 120-day safety update for this application.

The 4-Month Safety Update Report included a summary of post-SVR12 relapse rates, with relapse defined as confirmed HCV RNA ≥LLOQ. Please comment if there were any additional subjects in this analysis who were not counted as relapsers but had HCV RNA ≥LLOQ during follow-up that had not yet been confirmed (e.g., lost to follow-up or pending confirmation). Please provide USUBJIDs for these subjects.

Please provide a response by COB September 17, 2014.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
09/11/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: August 27, 2014

NDA: 206619

PRODUCT: ombitasvir/paritaprevir/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Information Request

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir/paritaprevir/ritonavir co-packaged with dasabuvir.

Please confirm (b) (4)

Also, please indicate (b) (4)

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
08/27/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: August 26, 2014

NDA: 206619

PRODUCT: ombitasvir/paritaprevir/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Response to Clinical Virology Labeling Questions

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir/paritaprevir/ritonavir co-packaged with dasabuvir. Also refer to your August 22, 2014 email correspondence containing questions regarding the Agency's proposed revisions to the Clinical Pharmacology, Microbiology section of the draft labeling sent on August 20, 2014.

Please find the Division's response to your questions appended.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

AbbVie Question 1:

(A) Could the agency provide further clarification on the amino acid positions within NS5A that were included in the analyses in section "*Effect of baseline HCV polymorphisms on treatment response*"?

(B) Could the agency provide their numerical analysis, if different from the above table, leading to the statement below in the USPI?

"*Ombitasvir resistance-associated polymorphisms in NS5A (pooling data from all resistance-associated amino acid positions) were detected in approximately* (b) (4) *% of subjects in this analysis and similarly enriched approximately 2-fold in virologic failure subjects.*"

DAVP RESPONSE TO QUESTION 1

We believe the discrepancies are based on the specific NS5A polymorphisms considered in these analyses. The specific polymorphisms considered by DAVP were based on the substitutions that emerged in Phase 2/3 trials of the 3-DAA +/- RBV regimens: K24R, M28A/T/V, Q30E/K/R, H54Y, H58D/P, E62D, Y93C/H/N. This list is based on all available treatment-emergent resistance data from all subjects who did not achieve SVR, including genotype 1a and 1b subjects. From this list, the following NS5A polymorphisms were detected in the 141 subjects included in the analysis (censoring subjects who failed for non-virologic reasons): K24R (n=3), M28T/V (n=11), Q30E/R (n=3), H54Y (n=3), H58D/P (n=11), E62D (n=9), Y93C/H/N (n=6). A total of 38/141 (27%) subjects in the Phase 3 analysis population had one or more of these baseline polymorphisms; we apologize that the "approximately (b) (4) %" quoted in the label was a rounding error.

This "FDA List" of NS5A resistance-associated polymorphisms/substitutions does not include NS5A position L31. Although L31 is a key resistance-associated position for other NS5A inhibitors, there was no evidence from our treatment-emergent resistance analyses that this position plays a role in ombitasvir resistance, as no L31 substitutions appeared to emerge in any subjects. Three HCV genotype 1a subjects with Baseline L31M achieved SVR.

The H54Y polymorphism was included in our list as this position has been described as being associated with NS5A inhibitor resistance, and H54Y emerged in a single HCV genotype 1b subject who experienced virologic failure. Nevertheless, DAVP acknowledges that H54Y is unlikely to play a major role in ombitasvir resistance, particularly in HCV genotype 1a, and all 3 subjects with Baseline H54Y achieved SVR in this analysis.

The E62D polymorphism was included in our list as this position has also been described as being associated with NS5A inhibitor resistance, and E62D emerged in a single HCV genotype 1a subject who experienced virologic failure; this subject failed treatment with the 8-week regimen in M11-652. (b) (4)

Table 1 below summarizes our re-analysis considering the "FDA List," "AbbVie List," and the "FDA List without H54Y/E62D." As shown in the table, we were able to reproduce your analysis. Furthermore, even if excluding H54Y and E62D there is still a 1.6-fold enrichment of NS5A polymorphisms in the virologic failure population.

Table 1. FDA re-analysis of baseline polymorphism prevalence in subjects who experienced virologic failure versus those who achieved SVR in Phase 3 trials of 3-DAA +/- RBV regimen.

	Any NS5A PM (FDA List)		Any NS5A PM (AbbVie List)		Any NS5A PM (FDA List w/o 54/62)	
EFFICFL	**#**	**%**	**#**	**%**	**#**	**%**
N	18	38.3%	(b) (4)		14	29.8%
Y	20	21.3%			17	18.1%
Fold-enrichment in VFs		1.8				1.6

Despite the small number of subjects with any single specific NS5A polymorphism, DAVP believes that the overall trend observed across each position further strengthens the observation that NS5A resistance-associated polymorphisms were enriched in virologic failures. Figure 1 illustrates the prevalence of specific NS5A polymorphisms in the SVR and virologic failure groups. Polymorphisms at NS5A positions 28, 30 and 93 were clearly enriched in the virologic failure group, which is consistent with their strong association with ombitasvir resistance based on treatment-emergent resistance patterns and site-directed mutant phenotype analyses. It is our understanding that the impact of E62D on ombitasvir anti-HCV activity (alone or in combination with other NS5A substitutions) has not been evaluated in a phenotype assay.

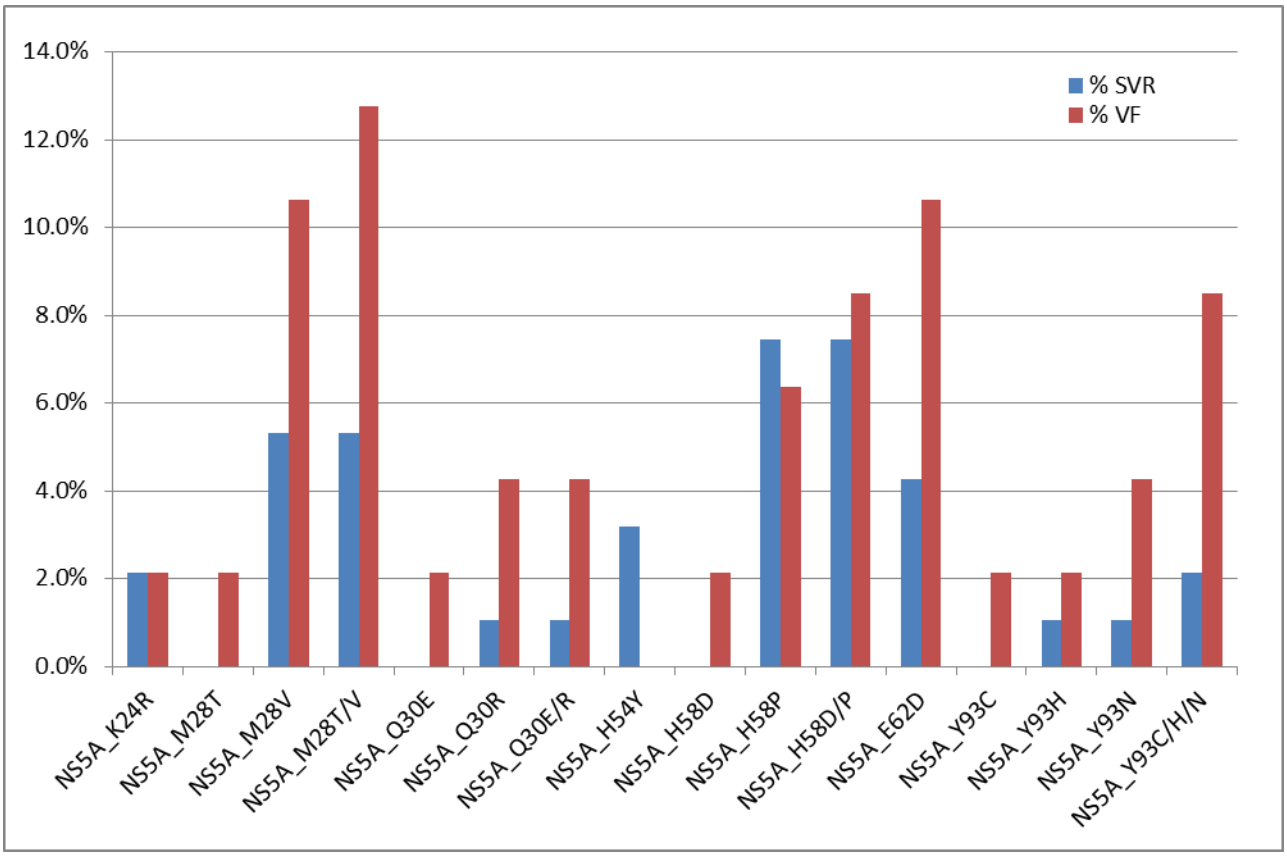

Figure 1. Proportion of SVR and virologic failure (VF) subjects with specific NS5A polymorphisms.

The statement about the lack of an association in the Phase 2b trial comes from an analysis of SVR rates for subjects in M11-652 with or without any NS5A polymorphisms of interest (Table 2). In this analysis L31 polymorphisms are also included for completeness, although only 2 subjects had L31 polymorphisms, both from the 8-week duration arm in M11-652.

Table 2. SVR rates (non-VF-censored) for HCV genotype 1a subjects with or without Baseline NS5A polymorphisms in M11-652.

NS5A Polymorphism	Overall SVR 3-DAA ± RBV 8-24 Weeks	Overall SVR 3-DAA ± RBV 12-24 Weeks
K24R	4/4 (100.0%)	2/2 (100.0%)
M28T	1/1 (100.0%)	1/1 (100.0%)
M28V	11/13 (84.6%)	9/10 (90.0%)
M28T/V	12/14 (85.7%)	10/11 (90.9%)
Q30R	3/3 (100.0%)	3/3 (100.0%)
L31M	0/1 (0.0%)	n/a
L31V	1/1 (100.0%)	n/a
L31M/V	1/2 (50.0%)	n/a
H54Y	9/9 (100.0%)	7/7 (100.0%)
H58P	3/3 (100.0%)	2/2 (100.0%)
H58R	3/3 (100.0%)	3/3 (100.0%)
H58P/R	6/6 (100.0%)	5/5 (100.0%)

E62D	5/5 (100.0%)	4/4 (100.0%)
Y93C	1/1 (100.0%)	1/1 (100.0%)
Y93H	3/3 (100.0%)	n/a
Y93N	0/1 (0.0%)	0/1 (0.0%)
Y93C/H/N	4/5 (80.0%)	1/2 (50.0%)
NS5A any (from above)	39/43 (90.7%)	28/30 (93.3%)
No NS5A Polymorphism	165/181 (91.2%)	140/149 (94.0%)

For clarity in labeling, DAVP proposes that the specific polymorphisms considered in the Phase 3 analyses be listed: "Ombitasvir resistance-associated polymorphisms in NS5A (~~pooling data from all resistance-associated amino acid positions~~ (b) (4) were detected in approximately (b) (4) %…"

AbbVie Question 2:
We are in general agreement with the agency's edits to the section "*Persistence of resistance-associated substitutions*", but request additional clarification on how the analysis time windows and the total number of subjects at the follow-up time points were calculated to aid in our validation process.

(b) (4)

DAVP RESPONSE TO QUESTION 2

Analyses of Phase 2 trials of 2- or 3-DAA +/- RBV combination regimens were conducted to evaluate the persistence of resistance-associated substitutions in NS3, NS5A and NS5B, as limited long-term follow-up data are available from Phase 3 trials. Analyses were conducted only for subjects with available data through Post-Treatment Week 24 or later. Because of the low virologic failure rate in HCV genotype 1b subjects these analyses were conducted only for HCV genotype 1a subjects. All treatment-emergent resistance-associated positions/substitutions identified in the analyses of the 3-DAA +/- RBV regimens were monitored for persistence after treatment, specifically:

- **NS3** V36A/M/T, F43L, V55I, Y56H, Q80L, I132V, R155K, A156G, D168x, P334S, S342P, E357K, V406A/I, T449I and P470S (note that V55A was also considered as it emerged in 2 subjects in this analysis population)
- **NS5A** K24R, M28A/T/V, Q30E/K/R, H58D/P/R, E62D and Y93C/N
- **NS5B** G307R, C316Y, M414T, E446K/Q, A450V, A553T, G554S, S556G/R, G558R, D559G/I/N/V, Y561H and L588F (note that A450T was also considered as it emerged in 1 subject in this analysis population)

Both population and clonal nucleotide sequencing data were considered for the NS3 and NS5B persistence analyses. For analyses of NS5A, only population nucleotide sequencing data were analyzed because limited clonal data were provided and persistence of resistance-associated substitutions was clearly observed based on the population nucleotide sequencing assay. The timepoints analyzed were based on the visits indicated in the resistance datasets; visit windows

were not adjusted except that the visits after Post-Treatment Week 48 were considered in the analyses of persistence through Post-Treatment Week ≥48.

Tables 3-5 below include the data for all subjects considered in these analyses. Each subject was analyzed individually, and in some cases the clonal sequence data were not considered subjectively based on the timing and frequency of detection (see 'Additional Notes' in tables).

For the descriptive summaries associated with the tables (which were included in the recommended label edits), when a subject had no sequence data at Post-Treatment Week 24, substitutions that were detected at Post-Treatment Week ≥48 were considered detectable at Post-Treatment Week 24 and imputed accordingly. Conversely, when a subject had no data at Post-Treatment Week ≥48, if no treatment-emergent substitutions were detected through Post-Treatment Week 24 it was assumed that no substitutions would have been detected at Post-Treatment Week ≥48. Also, if no data were available for Post-Treatment Week 24 and the subject had no emergent substitutions detected at Post-Treatment Week ≥48, the subject was considered "missing" from the Post-Treatment Week 24 analysis and therefore not included in the denominator.

Persistence of NS3 resistance-associated substitutions

Table 3 summarizes the persistence of ABT-450 treatment-emergent substitutions for 32 subjects with ≥1 treatment-emergent substitution in NS3 (from list indicated above) and at least 24 weeks of post-treatment follow-up. The following conclusions can be drawn from these data:

- 17/29 (59%) subjects still had at least 1 treatment-emergent NS3 substitution detected through at least Post-Treatment Week 24, and 5/22 (23%) through at least Post-Treatment Week 48.
- Treatment-emergent R155K remained detected in 5/8 (63%) subjects through Post-Treatment Week 24, and in 1/5 (20%) subjects through Post-Treatment Week 48.
- Treatment-emergent D168 substitutions, which are most commonly observed in ABT-450-based treatment failure subjects, remained detected in 6/22 (27%) subjects through Post-Treatment Week 24, and in 0/22 (0%) subjects through Post-Treatment Week 48.

Table 3. Persistence of treatment-emergent substitutions in NS3. Note that both population and clonal nucleotide sequence analysis data were considered for these analyses, although clonal analyses only covered NS3 amino acids 1-181. ND, no data; PTW, Post-Treatment Week. Red cells indicate "positive" detection of substitutions and yellow cells indicate "negative" detection of substitutions (imputed or observed).

USUBJID	Last Visit w/Data	Tx-emergent Substitutions (Pop. Seq., except where noted*)	Detected @PTW24	Detected @PTW48+	Additional Notes about Analyses
M11652-12538-5377	PTW 24	R155K, D168V	none	ND	R155G detected only by clonal seq. (6% of clones) at PTW24 but not earlier, not considered in analyses
M11652-12649-5316	PTW 24	R155K, P334S	R155K	ND	
M11652-22271-5181	PTW 24	V36A, Y56H, D168A/V, P334S	Y56H, D168A	ND	
M11652-36975-5308	PTW 48	D168V, S342P	D168V, S342P	none	
M11652-37388-5593	PTW 48	V406A	ND	V406A	
M11652-37868-5413	PTW 48	D168V	D168V	none	D168V at PTW24 by clonal seq.
M11652-37868-8028	PTW 48	Y56H, D168V, E357K	ND	none	
M11652-37869-8071	PTW 24	D168V	none	ND	
M11652-38624-5256	PTW 24	D168V	none	ND	
M11652-38624-8108	PTW 24	D168F/V/Y, S342P, T449I	S342P	ND	
M11652-38627-5687	PTW 59	D168V	ND	none	
M11652-38646-5751	PTW 24	D168A	none	ND	
M11652-38853-5309	PTW 24	D168V	none	ND	
M11652-40076-5424	PTW 24	Y56H, D168V, E357K	E357K	ND	
M11652-40526-5297	PTW 48	R155K, A156G	R155K	R155K	
M11652-40784-8118	PTW 24	A156V, D168V	none	ND	
M11652-42362-5144	PTW 24	Y56H, D168Y	none	ND	
M11652-42364-8215	PTW 24	V36M, I132V, R155K	I132V, R155K	ND	
M11652-42368-5174	PTW 24	D168V, T449I	T449I	ND	
M11652-42371-5525	PTW 24	D168V	none	ND	
M11652-42420-8192	PTW 24	I132V, D168Y, P334S, P470S	I132V, P334S, P470S	ND	
M11652-42808-5435	PTW 48	D168V	ND	none	V36A detected only by clonal seq. (3% of clones) at PTW48 and not earlier, not considered in analyses.
M11652-42808-8035	PTW 24	V36A/M/T, R155K	R155K	ND	
M11652-44319-8246	PTW 48	V55A, D168V	V55A, D168V	V55A	V55A considered tx-emergent
M11652-44367-8224	PTW 24	D168V, E357K	none	ND	
M11652-44372-5610	PTW 24	D168V*	D168V	ND	D168V detected only by clonal seq. (2% of clones) only at PTW24
M12746-22854-2146	PTW 48	V36M, Y56H, R155K*, D168V	V36M, R155K	V36M	R155K detected only by clonal seq. (3% of clones) at PTW24, V36M detected at PTW48 only by clonal seq.
M12746-37869-2095	PTW 48	Q80L	Q80L	Q80L	Q80L detected at Baseline only by clonal analyses in 7% of clones, considered treatment-emergent (enriched to 100% of clones)
M12746-37869-2096	PTW 48	V55A, I132V, D168V	none	none	V55A considered tx-emergent
M12746-38934-2187	PTW 48	R155K*	none	none	R155K detected only by clonal seq. (2% of clones) at two different timepoints
M12746-40537-2507	PTW 48	V36M, Y56H, R155K, A156G, D168A	none	none	
M12998-37869-3094	PTW 24	Y56H, D168A	Y56H, D168A	ND	R155S detected only by clonal seq. (4% of clones) at PTW24 and was not considered in this analysis

Persistence of NS5A resistance-associated substitutions

Table 4 summarizes the persistence of ombitasvir treatment-emergent substitutions for 24 subjects with ≥1 treatment-emergent substitution in NS5A (from list indicated above) and at least 24 weeks of post-treatment follow-up. All 24 subjects (100%) had treatment-emergent NS5A substitutions detected through at least Post-Treatment Week 24, and 18/18 (100%) subjects with available data had treatment-emergent substitutions detected through at least Post-Treatment Week 48, clearly indicating the long-term persistence of resistance-associated substitutions in NS5A.

Table 4. Persistence of treatment-emergent substitutions in NS5A. Only population sequence analysis data were considered for these analyses. ND, no data; PTW, Post-Treatment Week. Red cells indicate "positive" detection of substitutions (imputed or observed).

USUBJID	Last Visit w/Data	Tx-emergent Substitutions	Detected @PTW24	Detected @PTW48+
M11652-02965-5213	PTW 48	M28T, H58P, E62D	M28T, H58P, E62D	M28T, H58P, E62D
M11652-12649-5316	PTW 24	M28A/T, Q30R	M28A/T, Q30R	ND
M11652-36975-5308	PTW 48	K24R, Q30R	Q30R	K24R, Q30R
M11652-37868-5413	PTW 48	Q30R	Q30R	Q30R
M11652-37869-8071	PTW 48	Q30R	Q30R	Q30R
M11652-38624-8108	PTW 48	M28A/T/V, Q30R	Q30R	M28A/T/V, Q30R
M11652-38627-5687	PTW 48	Q30R	ND	Q30R
M11652-38646-5751	PTW 48	M28T, Q30R	M28T	M28T
M11652-38853-5309	PTW 24	Q30R	Q30R	ND
M11652-40784-8118	PTW 24	Q24R, M28T	Q24R, M28T	ND
M11652-42361-5765	PTW 48	M28V	ND	M28V
M11652-42362-5144	PTW 48	M28V, Q30K	M28V, Q30K	M28V, Q30K
M11652-42364-8215	PTW 24	M28T	M28T	ND
M11652-42368-5174	PTW 48	Y93N	Y93N	Y93N
M11652-42371-5525	PTW 48	M28V	M28V	M28V
M11652-42420-8192	PTW 48	Q30R	Q30R	Q30R
M11652-42808-5435	PTW 48	M28T	ND	M28T
M11652-42808-8035	PTW 24	Q30R	Q30R	ND
M11652-43114-5554	PTW 48	H58D	H58D	H58D
M11652-44319-8246	PTW 48	Q30R	Q30R	Q30R
M11652-44367-8224	PTW 59	Q30R	Q30R	Q30R
M11652-44372-5610	PTW 48	Q30R	Q30R	Q30R
M12998-31542-3049	PTW 48	Q30R	ND	Q30R
M12998-37869-3094	PTW 24	Q30R	Q30R	ND

Persistence of NS5B resistance-associated substitutions

Table 5 summarizes the persistence of dasabuvir (or possibly RBV) treatment-emergent substitutions for 16 subjects with ≥1 treatment-emergent substitution in NS5B (from list indicated above) and at least 24 weeks of post-treatment follow-up. The following conclusions can be drawn from these data:

- 11/16 (69%) subjects still had at least 1 treatment-emergent NS5B substitution detected through at least Post-Treatment Week 24, and 8/15 (53%) [Note: in our label edits we stated (b) (4) in error, please correct when you resubmit the updated label] through at least Post-Treatment Week 48.
- S556G, which was the most commonly observed dasabuvir resistance-associated substitution, remained detected in 8/9 (89%) subjects through at least Post-Treatment Week 24, 6/9 (67%) through at least Post-Treatment Week 48.

Table 5. Persistence of treatment-emergent substitutions in NS5B. Note that both population and clonal nucleotide sequence analysis data were considered for these analyses. ND, no data; PTW, Post-Treatment Week. Red cells indicate "positive" detection of substitutions and yellow cells indicate "negative" detection of substitutions (imputed or observed).

USUBJID	Last Visit w/Data	Tx-emergent Substitutions (Pop. Seq.,except where noted*)	Detected @PTW24	Detected @PTW48+	Additional Notes about Analyses
M11652-12649-5316	PTW 24	G554S, S556G	none	ND	
M11652-36975-5308	PTW 48	S556G	S556G	none	S556G detected in 5% of clones at BL, considered tx-emergent (enriched to 100% of clones)
M11652-38624-5256	PTW 48	M414T	M414T	M414T	
M11652-38627-5687	PTW 59	S556G	ND	S556G	
M11652-40526-5297	PTW 24	G307R*, D559N	G307R	ND	G307R detected only by clonal seq. (5% of clones) only at PTW24
M11652-42362-5144	PTW 48	S556G	S556G	S556G	
M11652-42364-8215	PTW 24	D559G	none	ND	
M11652-42368-5174	PTW 48	M414T, S556G	S556G	S556G	L588F/H/Y detected only at PTW48 and not at earlier follow-up timepoints, and was not considered in this analysis
M11652-42420-8192	PTW 48	G307R, S556G	G307R, S556G	G307R, S556G	
M11652-42808-8035	PTW 24	G307R*, G558R	none	ND	G307R detected only by clonal seq. (2% of clones) during treatment
M11652-44367-8224	PTW 24	G307R*, A553T	none	ND	G307R detected only by clonal seq. (5% of clones in 2 samples)
M11652-44372-5610	PTW 48	S556G	S556G	S556G	
M12746-22854-2146	PTW 48	S556G	S556G	S556G	
M12746-37869-2095	PTW 48	A450T	A450T	A450T	A450T was not a treatment-emergent substitution in pooled analyses of the 3-DAA +/- RBV regimens, but A450V was; A450T considered tx-emergent.
M12746-37869-2096	PTW 48	C316Y, A553D, G554S*, S556G, G558R, D559G/N*	S556G	none	A553D was not a treatment-emergent substitution in pooled analyses of the 3-DAA +/- RBV regimens, but A553T was; A553D considered tx-emergent. G554S and D559G/N detected only by clonal sequencing on-treatment (2-7% of clones)
M12746-40537-2507	PTW 48	M414T*, G554S, G558R*	none	none	M414T and G558R detected only by clonal seq. on-treatment (3% of clones)

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/s/

KATHERINE SCHUMANN
08/26/2014

From: Schumann, Katherine
To: "ZumBrunnen, Troy L"
Cc: Rogers, Sarah R
Subject: NDA 206619 - Clinical Information Request
Date: Tuesday, August 26, 2014 9:55:00 AM

Troy,

Please refer to your NDA 206619 submitted on April 21, 2014 for Viekira Pak.

DAVP has the following request for information:

> Please create a table and populate Grades 1, 2, 3, and 4 values by treatment arm for each of the hematology and chemistry parameters evaluated in the Phase 3 trials.
>
> Please provide this information no later than close of business on Tuesday, September 2, 2014.

Let me know if you have any questions.

Warm Regards,
Katie

Katherine Schumann, M.S.
Senior Regulatory Project Manager
FDA/OMPT/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
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/s/

KATHERINE SCHUMANN
08/26/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 206619

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Troy ZumBrunnen, Pharm.D.
Director, Regulatory Affairs

Dear Dr. ZumBrunnen:

Please refer to your New Drug Application (NDA) dated and received April 21, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ombitasvir, Paritaprevir, Ritonavir copackaged with Dasabuvir Tablets, 12.5 mg/75 mg/50 mg and 250 mg.

We also refer to your correspondence dated and received August 4, 2014, requesting review of your proposed proprietary name, Viekira Pak. We have completed our review of the proposed proprietary name Viekira Pak, and have concluded that this name is acceptable.

If **any** of the proposed product characteristics as stated in your August 4, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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 the Office of New Drugs (OND) Regulatory Project Manager Katherine Schumann, at (301) 796-1182.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
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
08/22/2014

TODD D BRIDGES on behalf of KELLIE A TAYLOR
08/22/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: August 20, 2014

NDA: 206619

PRODUCT: ombitasvir, paritaprevir, ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Initial Labeling Comments

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir, paritaprevir, ritonavir co-packaged with dasabuvir. Also refer to your August 8, 2014 submission of revised draft prescribing information.

The Division has begun review of the draft prescribing information (PI) for NDA 206619. Please find comments on Sections 1, 2, 4, 12.1 and 12.4 in the attached document. The remaining sections of the PI are currently under review and comments on those sections will be provided later in the review cycle.

Please submit revised labeling to the NDA by August 29, 2014.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

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/s/

KATHERINE SCHUMANN
08/20/2014

From: Schumann, Katherine
To: "ZumBrunnen, Troy L"
Cc: "sarah.rogers@abbvie.com"
Subject: NDA 206619 Clinical Information Request
Date: Thursday, August 07, 2014 3:16:00 PM

Troy,

Please refer to your NDA 206619 submitted on April 21, 2014 for ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets.

The review team has the following request for information:

1. Please submit all relevant liver pathology reports for patient 382123.

2. Please provide the mean and median baseline ALT levels by treatment arm for each of the Phase 3 trials.

Please provide a response by close of business on Monday, August 11, 2014.

Warm Regards,
Katie

Katherine Schumann, M.S.
Senior Regulatory Project Manager
FDA/OMPT/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
08/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206619

MID-CYCLE COMMUNICATION

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

Dear Dr. ZumBrunnen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ombitasvir, ABT-450, ritonavir (12.5 mg/75 mg/50 mg) tablets copackaged with dasabuvir (250 mg) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on July 14, 2014. 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 Katherine Schumann, Regulatory Project Manager at (301) 796-1182.

Sincerely,

{See appended electronic signature page}

Linda L. Lewis, MD
Medical Team Leader
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: July 14, 2014 2:30 – 4:00 PM

Application Number: NDA 206619
Product Name: ombitasvir, ABT-450, ritonavir tablets copackaged with dasabuvir tablets
Indication: Treatment of genotype 1 chronic hepatitis C virus infection
Applicant Name: AbbVie Inc.

Meeting Chair: Linda Lewis, MD
Meeting Recorder: Katherine Schumann, MS

FDA ATTENDEES

Office of Antimicrobial Products
- Edward Cox, Director
- David Roeder, Associate Director for Regulatory Affairs

Division of Antiviral Products
- Debra Birnkrant, Division Director
- Jeffrey Murray, Deputy Director,
- William Tauber, Acting Deputy Director for Safety
- Linda Lewis, Medical Team Leader
- Russell Fleischer, Medical Reviewer
- Mark Seaton, Pharmacology/Toxicology Reviewer
- Jules O'Rear, Clinical Virology Team Leader
- Patrick Harrington, Clinical Virology Reviewer
- Elizabeth Thompson, Chief, Project Management Staff
- Katherine Schumann, Regulatory Project Manager

Office of Biostatistics
- Joy Mele, Biostatistician, DB IV
- Lisa Rodriguez, Acting Biostatistics Team Leader, DB IV

Office of Clinical Pharmacology
- Islam Younis, Clinical Pharmacology Team Leader, DCP IV
- Vikram Arya, Clinical Pharmacology Reviewer, DCP IV

Office of New Drug Quality Assessment
- Stephen Miller, CMC Lead, DNDQA II

Office of Surveillance and Epidemiology
Felicia Duffy, Risk Management Analyst, DRISK
Jamie Wilkins Parker, Team Leader, DRISK
Monica Calderon, Reviewer, DMEPA

Office of Medical Policy
Sharon Mills, Senior Patient Labeling Reviewer, DMPP

APPLICANT ATTENDEES

Nihar Baxi, Associate Director, Regulatory Strategic Planning
Barry M. Bernstein, Vice President, Infectious Disease Development
Mondira Bhattacharya, Senior Medical Director, Therapeutic Area Head, Infectious Disease
Christine Collins, Director, HCV Clinical Virology
Barbara Da Silva-Tillmann, Senior Medical Director, HCV Product Safety Lead
Melanie Gloria, Associate Director, Clinical Program Development
Patty Hintzman, Director, Clinical Program Development
Olga Kavetskaia, Associate Director, Drug Analysis
Martin King, Director, Statistics
Lois Larsen, Director, Statistics
Jinrong Liu, Senior Scientist Pharmacology (Visiting Scientist Regulatory Affairs)
Sherie Masse, Associate Director, Regulatory Affairs, CMC
Rajeev M. Menon, Director, Clinical Pharmacology and Pharmacometrics
Sherry Morgan, Director, PCS Scientific Projects
John Morris, Director, CMC Project Management
Cheryl Pape, Director, Regulatory Affairs, CMC
Nancy Peterson, Associate Director, Global Project Management
Thomas J. Podsadecki, Project Director, Antiviral Clinical Project Team
Sarah Rogers, Manager, Regulatory Affairs, US and Canada
Anutosh R. Saha, Director, Regulatory Affairs, GPS
Drew Sansone, Senior Director, Regulatory Affairs, US and Canada
Imran Shah, Director, Regulatory Affairs, GPS
Nancy Shulman, Senior Medical Director, Antiviral Clinical Project Team
Andrew Storey, Vice President, Regulatory Affairs, US and Canada
Bruce Trela, Director, Preclinical Safety
Troy ZumBrunnen, Director, Regulatory Affairs, US and Canada

EASTERN RESEARCH GROUP ATTENDEES

(b) (6) Independent Assessor

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

The Division explained that there would be a pause after each discussion item to allow for clarifying questions.

The Division commented that the review is ongoing and the team has generally been able to confirm the high rates of efficacy of the regimen. The issues to be discussed during the meeting are being shared in the interest of transparency and enhanced communication.

The following issues were discussed:

Clinical

1. Based on our review of the Phase 2 and 3 clinical trials, we are considering recommending that all GT1a, non-cirrhotic patients receive 12 weeks of 3-DAA + RBV as we are unable to identify specific subgroups of patients for whom co-administration of RBV is not beneficial in reducing the virologic failure rate. Specifically, the data in non-cirrhotic GT 1a treatment naïve subjects suggests that RBV is an important component necessary to reduce virologic failure (and presumably treatment-emergent resistance), especially in subjects with non-CC IL28b genotypes. An argument could be made that GT1a subjects with the CC genotype could be treated with the 3-DAA alone regimen as there was a small difference in response rates between regimens. However, this would require pre-treatment IL28B genotype testing, which may not be universally available and would likely require use of unapproved assays. Although the risk of virologic failure is relatively low when RBV is not co-administered, for those subjects who fail with resistance substitutions in multiple DAA targets there are currently no ideal retreatment choices, and any retreatment regimen would likely involve use of a pegIFN/RBV-based regimen, or the patient may have to delay re-treatment until newer agents become available. We acknowledge there were more RBV-associated adverse events such as anemia, pruritus and skin rash, and bilirubin elevations; however, these events were generally tolerable and manageable.

2. We are considering recommending that all GT1a cirrhotic subjects be treated with 24 weeks of 3-DAA + RBV, again to reduce the relapse rate. Extending the duration of 3-DAA + RBV treatment by 12 weeks appeared to decrease the virologic failure rate by nearly 50% in all subgroups of GT1a-infected subjects. Extending treatment was associated with an increase in the frequency of certain adverse events, but they were generally mild to moderate, manageable, and there were no clinically relevant differences in SAEs or discontinuations due to adverse events.

AbbVie asked the Division to clarify whether this comment applies only to GT1a cirrhotic subjects or all GT1 cirrhotic subjects. The Division responded that it applies only to GT1a cirrhotic subjects.

3. We are considering including in the labeling monitoring and management recommendations for LFT abnormalities to be carried out in all patients receiving the 3-DAA regimen. We are concerned that there were significant events of transaminitis among subjects not receiving estrogen-containing products. It may be more concerning to a clinician to check LFTs and find significantly increased ALT levels without any precautionary language about how to manage such patients, and without guidance, clinicians may inappropriately discontinue DAA treatment. Thus, with precise guidance and recommendations for liver function monitoring , the risk to patients being prematurely discontinued from treatment should be mitigated.

4. We have also noted some events of cholecystitis and cholelithiasis among subjects enrolled in the clinical trials that may reproduce a potential safety signal identified in the non-clinical studies.

Clinical Pharmacology

1. We are considering contraindicating the co-administration of estrogen-containing products with the 3-DAA regimen in the labeling. Your proposed labeling recommendation (b) (4) is not acceptable based on the higher rate of Grade 3or higher ALT elevations and treatment discontinuations observed in the healthy volunteer drug-drug interaction trial with estrogen containing oral contraceptives (M12-205) and the safety data from Phase 2 and Phase 3 trials. Further, increases in Grade 3 or higher ALT elevations were observed in cases where only ethinyl estradiol was used as hormone replacement therapy, therefore, the clinical recommendation in the labeling should refer to "estrogen containing therapies" (b) (4)

   We agree with your proposal to allow the concomitant use of "progestin only" contraceptives with the 3-DAA regimen and allowing patients to resume using estrogen containing products 2 weeks after stopping 3-DAA therapy.

Clinical Virology

1. We believe that Baseline HCV resistance-associated polymorphisms may have impacted treatment efficacy in genotype 1a subjects in the Phase 3 trials. Our Baseline analyses were conducted in two ways, one considering the Phase 3 trials and the other specifically analyzing the Phase 2b trial M11-652. In the analysis of Phase 3 trials, since only a subset of SVR-achieving subjects were analyzed for the detection of Baseline polymorphisms, we compared the proportions of virologic failure and SVR subjects with Baseline polymorphisms in each drug target. In this analysis, both NS3 Q80K and NS5A polymorphisms were clearly enriched in virologic failure subjects relative to SVR subjects. Your analyses similarly identified Q80K as enriched in virologic failures.

Although no single NS5A polymorphism is detected in a large number of subjects, by pooling all polymorphisms at key resistance-associated positions in NS5A it can be shown that these polymorphisms were also enriched in virologic failures. We are considering requesting additional language to the Microbiology section of the label to report that these Baseline polymorphisms can impact the efficacy of these regimens, but by recommending an optimally effective treatment regimen their impact on treatment efficacy is reduced.

2. In our treatment-emergent resistance analyses, we observed that several substitutions across all 3 drug targets emerged in virologic failures (b) (4) so we will likely request that additional treatment-emergent substitutions are reported in that table. Furthermore, several substitutions in the NS3 helicase domain emerged in virologic failure subjects, in addition to E357K which you previously identified, and we will likely request that you conduct phenotype analyses to evaluate the impact of these substitutions on ABT-450 anti-HCV activity.

3.0 INFORMATION REQUESTS

The Division notes the following pending information requests:

Product Quality/Biopharmaceutics:

- Information request regarding dasabuvir drug substance dated July 3, 2014 (response requested by July 18, 2014).

- CMC and biopharmaceutics information request dated July 11, 2014 (response requested by July 25, 2014).

  AbbVie noted that a teleconference would likely be requested to discuss biopharmaceutics comment #3, as offered by the Agency in the July 11, 2014 information request. The Division replied that AbbVie should contact Althea Cuff, ONDQA Regulatory Project Manager, to arrange this teleconference.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There is currently no anticipated need for a Risk Evaluation and Mitigation Strategy (REMS). However, at the present time, there are two major safety concerns with the3-DAA combination product regimen:

1. The known risk of teratogenicity related to a ribavirin-containing regimen and the need for effective contraception, and

2. Hepatotoxicity with or without concomitant administration of estrogen-containing therapies with the 3-DAA combination.

These safety concerns will require the addition of information to labeling that addresses hepatotoxicity and the use of estrogen-containing therapies. Additionally, the conversion of the proposed Patient Package Insert to a Medication Guide is warranted to help mitigate the potential risk to patients.

AbbVie asked if they should submit the requested draft Medication Guide immediately. The Division responded that submission should be delayed until labeling discussions begin, to prevent the need for substantial modifications to the document. The Division agreed to coordinate the timing of this submission with AbbVie later in the review cycle.

5.0 ADVISORY COMMITTEE MEETING

There are no plans for an Advisory Committee meeting at this time.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The Late-Cycle Meeting (LCM) is scheduled for October 20, 2014. The background package will be sent to the applicant by October 9, 2014. The purpose of the LCM is to share information and discuss any substantive review issues identified to date, as well as our objectives for the remainder of the review cycle.

The projected date that the Division will have initial proposed Post Marketing Requirements (PMRs), Post Marketing Commitments (PMCs), and labeling to the applicant will be September 23, 2014.

The Division informed AbbVie that meeting minutes will be issued within 30 days.

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/s/

LINDA L LEWIS
07/30/2014

From:	Schumann, Katherine
To:	ZumBrunnen, Troy L (troy.zumbrunnen@abbvie.com)
Cc:	Rogers, Sarah R (sarah.rogers@abbvie.com)
Subject:	NDA 206619 - human factors information request
Date:	Wednesday, July 30, 2014 7:12:00 AM

Dear Troy,

Please refer to your NDA 206619 submitted on April 21, 2014 for ombitasvir, ABT-450, ritonavir tablets copackaged with dasabuvir tablets.

The Division of Medication Error Prevention and Analysis (DMEPA) has the following request for information regarding your human use factors study:

1. What additional measures were considered or implemented to minimize the risk for AM dosing failures to an acceptable level?
2. If no additional measures were considered to further minimize the risk for AM dosing failures, please provide your rationale.
3. Please provide a list of all changes that were made to the labels and labeling after the validation study was completed and the rationale for the changes.
4. For the formative 2 study, were nurses included in the Healthcare Provider Population?
5. In the Validation Study, what were the education levels, ethnicities, and income level of the 35 participants that were unspecified?
6. We note that incorrect dosing occurred during your clinical trials. Was the same packaging used in clinical trials as was tested in the validation usability study? If no, please clarify how the packages differ.

Please provide your response as soon as possible. A response via email followed by formal submission to the NDA would be preferred.

Please let me know if you have any questions.

Warm Regards,
Katie

Katherine Schumann, M.S.
Senior Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
07/30/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: July 24, 2014

NDA: 206619

PRODUCT: ombitasvir/ABT-450/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Clinical information request regarding M12-999

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir.

We also refer to your submission of May 21, 2014, containing preliminary data from study M12-999 in liver transplant recipients. The Division has the following request for information regarding M12-999.

1. In Table 8 of the interim report it shows that 9 subjects had an adverse event leading to a RBV dose modification. (b) (4) 19 subjects underwent a RBV dose modification. Please provide an explanation for this difference and provide the reasons and timing for each subject that underwent any type of RBV dose modification.

2. For the subject that interrupted RBV, please provide the reason, timing and duration of interruption.

3. (b) (4) the frequency of many adverse events (such as, but not limited to, abdominal pain, dyspnea, fatigue, headache, insomnia) were much higher in the transplant trial and this information will need to be accurately conveyed.

4. Please provide an update when the SVR12 data from all 34 subjects will be available.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
07/24/2014

Executive CAC
Date of Meeting: July 22, 2014

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Haleh Saber, Ph.D., DHOT, Alternate Member
Hanan Ghantous, Ph.D., DABT, DAVP Team Leader
Mark Seaton, Ph.D., DABT, DAVP Presenting Reviewer

Author of Minutes: Seaton

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #206-619
Drug Name: Viekira Pak
Sponsor: AbbVie, Inc.

Background:

The applicant is seeking marketing approval for Viekira Pak, consisting of:
A non-nucleoside inhibitor of nonstructural protein 5B (NS5B) RNA polymerase (Dasabuvir), a nonstructural protein 3 (NS3) protease inhibitor (ABT-450) combined with Ritonavir to enhance systemic exposures, and a nonstructural protein 5A (NS5A) inhibitor (Ombitasvir). Viekira Pak would be marketed as a treatment of chronic HCV genotype 1 infection in adults, including those with compensated cirrhosis, who are either treatment-naïve or previously treated with pegylated interferon (pegIFN) and ribavirin. The proposed daily dosages for the components of Viekira Pak are Dasabuvir (500 mg), ABT-450 (150 mg)/ Ritonavir (100 mg), and Ombitasvir (25 mg). The applicant has submitted a complete nonclinical package consisting of studies in mice, rats, rabbits, monkeys and dogs. The applicant has completed six-month carcinogenicity studies in transgenic mice. Two-year studies in rats are completed (ABT-450) or are ongoing (ombitasvir and dasabuvir). Completed studies are presented below.

Mouse Carcinogenicity Studies

ABT-450/Ritonavir carcinogenicity in CByB6F1-Tg(HRAS)2Jic mice was assessed at doses of 0 (water), 0 (vehicle: Cremophor EL®:PEG 400:Oleic acid (10:10:80, w/w/w)), 6/30, 60/30 and 300/30 mg/kg/day by oral gavage. Dose selection was based on saturation of absorption. Dose spacing was based on AUC. No treatment-related effects on survival were noted. No drug-related tumors were observed in mice. The doses used for this study were appropriately selected based on saturation of absorption. The steady state (day 87) $AUC_{0\text{-}24h}$ values for ABT-450 in the high dose groups were 143 and 395 µg.h/mL for males and females, respectively, which were 20-fold and 56-fold the estimated mean steady-state human $AUC_{0\text{-}24h}$ of 7 µg.h/mL (150/50 mg/day to adults).

Ombitasvir carcinogenicity in CByB6F1-Tg(HRAS)2Jic mice was assessed at doses of 0 (water), 0 (vehicle: 40% Phosal 53 MCT: 20% Polyethylene Glycol 400: 20% Poloxamer 124: 20% Cremophor RH40, by weight), 2.5, 10 and 150 mg/kg/day in males and 0 (water), 0 (vehicle-insert details), 5, 20, and 150 mg/kg/day in females, by oral gavage. Dose selection was based on saturation of absorption. Dose spacing was based on AUC. No treatment-related effects on survival were noted. No drug-related tumors were observed in mice. The doses used for this study were appropriately selected based on saturation of absorption. The steady state (day 87) AUC_{0-24h} values for the high dose groups were 37 µg.h/mL for males and females, which was 26-fold the estimated mean steady-state human AUC_{0-24h} of 1.4 µg.h/mL (25 mg/day to adults).

Dasabuvir carcinogenicity in CByB6F1-Tg(HRAS)2Jic mice was assessed at doses of 0 (water), 0 (vehicle: 0.2% hydroxypropyl methylcellulose (HPMC) prepared in distilled water), 200, 600, and 2000 mg/kg/day, by oral gavage. Dose selection was based on the maximum tolerated dose in a previous study (toxicity and death at higher doses). Dose spacing was based on AUC. No treatment-related effects on survival were noted. No drug-related tumors were observed in mice. The steady state (day 91) AUC_{0-24h} values for the high dose groups were 265 µg.h/mL for males and females combined, which was 39 -fold the estimated mean steady-state human AUC_{0-24h} of 6.8 µg.h/mL (250 mg/day to adults).

Rat Carcinogenicity Study

ABT-450/ritonavir carcinogenicity in Sprague Dawley rats was assessed at doses of 0 (water), 0 (vehicle: Cremophor EL®:PEG 400:Oleic acid (10:10:80, w/w/w)), 6/30, 60/30 and 300/30 mg/kg/day, by oral gavage. Dose selection was based on saturation of absorption. Dose spacing was based on AUC. No treatment-related effects on survival were noted. No drug-related tumors were observed in rats. The doses used for this study were appropriately selected based on saturation of absorption. The highest steady state (Day 182) AUC_{0-24h} values for ABT-450 were seen in the middle dose group, and were 49 and 81 (combined 65) µg.h/mL for males and females. Exposures in rats were 9-fold (combined) the mean estimated steady-state human AUC_{0-24h} of 7 µg.h/mL (150/50 mg qd to adults).

Executive CAC Recommendations and Conclusions:

Tg.rasH2 Mouse:

- The Committee concurred that the studies were acceptable, noting prior Exec CAC concurrence with the protocols.

- The Committee concluded that there were no drug-related neoplasms in the studies.

Rat:

- The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.

- The Committee concluded that there were no drug-related neoplasms in the study.

Abby Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\
/Division File, DAVP
/HGhantous, DAVP
/Seaton, DAVP
/Schumann, DAVP

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/s/

ADELE S SEIFRIED
07/24/2014

ABIGAIL C JACOBS
07/24/2014

From:	Schumann, Katherine
To:	ZumBrunnen, Troy L (troy.zumbrunnen@abbvie.com)
Cc:	Rogers, Sarah R (sarah.rogers@abbvie.com)
Subject:	NDA 206619 Clinical Virology Information Request
Date:	Thursday, July 17, 2014 7:41:00 AM

Troy,

Please refer your NDA 206619 submitted on April 21, 2014 for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir. The clinical virology team has the following request for information.

1. Please provide additional information about the clonal sequencing methods for the Phase 2 trials that were used for analyses of persistence of resistance-associated substitutions. What were the median and range for the numbers of clones analyzed per sample for each drug target for subjects with available follow-up data? Also, your analyses of clonal sequencing data considered only substitutions that were detected in at least 2 clones from a given sample. For the clonal sequencing datasets, were substitution results from single clones reported, or was detection in at least 2 clones required to report a substitution for a given sample?

2. Please confirm that the FDA-approved Roche COBAS® TaqMan® HCV v2.0 test was used for HCV RNA assessments in Phase 3 trials.

Please submit a response by close of business on July 31, 2014.

Let me know if you have any questions.

Warm Regards,
Katie

Katherine Schumann, M.S.
Senior Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
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/s/

KATHERINE SCHUMANN
07/17/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206619

INFORMATION REQUEST

AbbVie
Attention: Troy ZumBrunnen, PharmD
AbbVir Inc.
1 N Waukegan Road
Dept. PA77/Bldg, AP30
North Chicago, IL 60064

Dear Troy ZumBrunnen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ombitasvir/ABT-450/Ritonavir and Dasabuvir Film-Coated Tablets.

We are reviewing the Chemistry, Manufacturing and Control and Biopharmaceutics sections of your submission and have the following comments and information requests. We request a prompt written response by July 25, 2014, in order to continue our evaluation of your NDA.

CMC

1. Provide information regarding the sensitivity of the [(b) (4)] methods used during development to monitor [(b) (4)] of all the drug substances in the "combined drug substance tablet". If spiking studies were performed, provide the limit of detection for all three drug substances using [(b) (4)].

Biopharmaceutics

2. Provide an assessment of the percentage of batches of ABT-333 drug product that would require stage 2 and stage 3 testing at lot release if the dissolution acceptance criterion would be set at Q=[(b) (4)]% at 15 minutes. Please perform this assessment with and without lot #12-007842.

3. Although we acknowledge that your proposed product is an immediate release dosage form, [(b) (4)] ombitasvir, ABT-450, and ritonavir (12.5/75/50 mg) tablets, the dissolution acceptance criteria for these drugs requires more than one sampling time point. Therefore, based on the dissolution profile data of these three drug substances [(b) (4)] we recommend the inclusion of additional dissolution testing time points at 30 minutes and 60 minutes, [(b) (4)] Specifically, we recommend that the following dissolution acceptance criteria be implemented for these three actives:

FDA's Recommended Dissolution Acceptance Criteria for Ombitasvir, ABT-450, and Ritonavir	
Sampling Time	**% Drug Dissolved**
30 minutes	(b) (4)
60 minutes	
180 minutes	

Either revise your specifications table for the ombitasvir, ABT-450, and ritonavir FDC tablet accordingly and provide an updated drug product specification sheet for the ombitasvir, ABT-450, and ritonavir FDC tablet or request a telephone conference to discuss our recommendation.

4. Provide the location of the Bio-analytical methods (description and validation) used for the analysis of ombitasvir, ABT-450 and ritonavir in studies 13-391 and 12-683, and the location of the Bio-analytical methods (description and validation) used for the analysis of ABT-333 and it's metabolite in studies 13-331 and 14-196.

   For each method, provide a summary table with the following information:

Matrix		
Sample Volume Required Storage Conditions Extraction Procedure		
Concentration Range		
HPLC Procedure		
Detection		
Regression Type		
Coefficient of Determination		
Between-Batch Accuracy	standards QCs	
Between-Batch CV	standards QCs	
Within-Batch	Accuracy CV	
Recovery	Drug Reference	
Stability in human plasma	Room temp Freeze/thaw Long term	
Solution Stability	at room temp at 4°C	
Reference Solution Stability	at room temp at 4°C	
LLOQ (Accuracy / CV)		
Processed Stability	at 4°C	
Dilution Integrity (v:v sample-blank)		

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

STEPHEN MILLER
07/11/2014
For R.Madurawe

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206619

INFORMATION REQUEST

AbbVie
Attention: Troy ZumBrunnen, PharmD
AbbVir Inc.
1 N Waukegan Road
Dept. PA77/Bldg, AP30
North Chicago, IL 60064

Dear Troy ZumBrunnen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ombitasvir/ABT-450/Ritonavir and Dasabuvir 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 prompt written response by July 18, 2014, in order to continue our evaluation of your NDA.

1. We found the manufacturing process description for dasabuvir sodium drug substance in Section 3.2.S.2.2 [Dasabuvir Sodium] is not in sufficient detail to allow for a knowledgeable assessment of the application. Please provide a complete description of the drug substance manufacturing process that includes ranges or set points for process parameters. You can either revise the manufacturing process description in section 3.2.S.2.2 or submit a master batch record.

2. In reference to Section 3.2.S.2.3 [Dasabuvir], we recommend that the acceptance criteria for the following specified impurities be tightened in the (b) (4) specification based on the available spiking data and batch history data.

Impurity	Structure	Highest level in batch data	Spike level	Proposed Limit	FDA recommends
(b) (4)					

3. In reference to Section 3.2.S.2.6 [Dasabuvir], please provide your rationale to change the dasabuvir drug substance manufacturing process [redacted] and has been used in the manufacturing of the clinical batches.

4. In reference to Section 3.2.S.4.1 [Dasabuvir] on dasabuvir sodium drug substance specification, please propose an acceptance criterion for sodium content in the dasabuvir sodium drug substance specification.

5. In reference to Section 3.2.S.4.1 [Dasabuvir] on dasabuvir sodium drug substance specification, please tighten the following impurity acceptance criteria based on the available batch analysis and stability data.
   1) [redacted] from [redacted]% to [redacted]%
   2) [redacted]: from [redacted]% to [redacted]%
   3) Total Impurities: from [redacted]% to [redacted]%

6. In reference to Section 3.2.S.4.3 Validation of Assay and Identification Procedure [Dasabuvir Sodium], you have used the terms "X-intercept" ([redacted] and "X-intercept as Percentage of nominal concentration of sample/standard" [redacted] to justify validation results for linearity. Please clarify how these are calculated and justify why they were used instead of the respective "Y-intercept" and "Y-intercept as Percentage".

7. In reference to Section 3.2.S.4.3 Validation of Residual Solvent Procedure by [redacted] [Dasabuvir Sodium], you have used the terms "X-intercept" (-[redacted] and "X-intercept as percentage of nominal concentration of sample/standard" [redacted]) to justify validation results for linearity. Please clarify how these were calculated and justify why they were used instead of the respective Y-intercept and Y-intercept as percentage.

8. [redacted].

9. In reference to Section 3.2.S.2.6 [Dasabuvir Sodium], we note that the following two process parameters, [redacted] Please reconcile.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

STEPHEN MILLER
07/03/2014
For R.Madurawe

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206619

METHODS VALIDATION
MATERIALS RECEIVED

AbbVie
Attention: Troy ZumBrunnen, PharmD
AbbVir Inc.
1 N Waukegan Road
Dept. PA77/Bldg, AP30
North Chicago, IL 60064

Dear Troy ZumBrunnen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ombitasvir/ABT-450/Ritonavir and Dasabuvir Film-Coated Tablets and to our June 17, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on July 1, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
07/01/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: June 25, 2014

NDA: 206619

PRODUCT: ombitasvir/ABT-450/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Response to Request for Clarification

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir.

We also refer to your email correspondence of June 20, 2014, requesting clarification of our June 19, 2014 request for information. The Division has the following response to your questions:

1. **Can the Agency please confirm the HCV RNA analysis datasets expected for these studies is ADVL?**

   At this time we are asking that the analysis datasets named ADEFFOUT be updated to include the new information. Our expectation is that you will also submit the ADVL datasets and any other datasets that would need updating with the new information later in the review cycle.

2. **Regarding CRFs for the 5 subjects, can the Agency please clarify if they expect full CRFs for these subjects? The additional SVR information will be captured in the laboratory data and not in the CRFs for the individual subjects.**

   We are looking for supportive data for this new information so please provide what you have that supports the derived data updated in ADEFFOUT. If complete, updated ADVL datasets for these trials cannot be submitted in a timely manner, a partial ADVL dataset including just the follow-up HCV RNA results from these 5 subjects can be submitted in the meantime (by first week of July), with complete ADVL datasets provided later in the review cycle.

3. **Finally, Table 16 of the draft labeling contains** (b) (4) **. AbbVie proposes to provide an updated**

(b) (4)

Is this acceptable?

You may submit proposed updates to the draft labeling but at this time we will not comment on which data will be acceptable to include in the final labeling.

Additional Comment:
Please be aware that no further updates to pivotal efficacy data will be accepted for this review cycle.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
06/25/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: June 19, 2014

NDA: 206619

PRODUCT: ombitasvir/ABT-450/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Clinical Information Request

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir.

We also refer to your email correspondence of June 12, 2014, notifying us that SVR12 data is available for four subjects reported as "missing" in the initial NDA submission.

> The Division would like to consider the additional SVR12 data for these four subjects during the current review cycle. Please update the ADEFFOUT datasets for M11-646, M13-099 and M13-961 with this information and submit them to the NDA as soon as possible. Please respond to this correspondence with an estimated timeframe for providing the three updated datasets.
>
> Please also submit CRFs for the four subjects to support the updated datasets.
>
> Finally, please update and submit complete HCV RNA analysis datasets for these three trials. These datasets can be submitted when available and do not need to be included with the updated ADEFFOUT datasets.
>
> Please note that should data from additional missing subjects become available prior to the goal date, the Division does not anticipate accepting it for review during the current review cycle.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
06/19/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206619

REQUEST FOR METHODS VALIDATION MATERIALS

AbbVie
Attention: Troy ZumBrunnen, PharmD
AbbVir Inc.
1 N Waukegan Road
Dept. PA77/Bldg, AP30
North Chicago, IL 60064
FAX: (847) 775-4956

Dear Troy ZumBrunnen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ombitasvir/ABT-450/Ritonavir and Dasabuvir Film-Coated Tablets.

We will be performing methods validation studies on Ombitasvir/ABT-450/Ritonavir and Dasabuvir Film-Coated Tablets, as described in NDA 206619.

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

Method, current version

Determination of degradation products in dasabuvir film-coated tablets by HPLC
Determination of degradation products in ombitasvir/veruprevir (ABT-450)/ritonavir film-coated tablets by HPLC
Determination of (b) (4) in Ombitasvir/ABT-450/Ritonavir film-coated tablets by HPLC
Determination of impurities in Veruprevir (ABT 450) by HPLC
Determination of impurities in Ombitasvir by HPLC
Determination of impurities in dasabuvir by HPLC
Dissolution test method for Dasabuvir Film-Coated Tablets by HPLC
Dissolution of Ombitasvir/ABT-450/Ritonavir film-coated tablets

Samples and Reference Standards

2 x 200 mg veruprevir reference standard
2 vials of Multi ID reference standard for Impurities in veruprevir
300 mg veruprevir drug substance
2 x 200 mg Dasabuvir sodium reference standard
300 mg Dasabuvir drug substance
80 mg (b) (4) reference standard
80 mg (b) (4) reference standard
60 Dasabuvir Film-Coated Tablets
2 x 200 mg Ombitasvir reference standard
3 vials of Multi ID reference standard for Impurities in Ombitasvir
300 mg Ombitasvir drug substance
2 x 200 mg ABT-450 reference standard
2 x 200 mg Ritonavir reference standard
60 Ombitasvir/ABT-450/Ritonavir film-coated tablets
500 g (b) (4)

Equipment

(b) (4)

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

Forward these materials via express or overnight mail to:

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

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
06/17/2014

From:	Schumann, Katherine
To:	ZumBrunnen, Troy L (troy.zumbrunnen@abbvie.com)
Cc:	Rogers, Sarah R (sarah.rogers@abbvie.com)
Subject:	NDA 206619 - Clinical Information Request (Narratives)
Date:	Thursday, June 12, 2014 3:19:00 PM

Dear Troy,

Please refer to your NDA 206619 submitted on April 21, 2014 for ombitasvir/ABT-450/ritonavir copackaged with dasabuvir. The review team has the following request for information.

Please submit narratives for the following subjects: 112104, 114504, 125406, 132101, 135110, 404303, 440305, 560302, 600101, and 760206

Please let me know if you have any questions.

Warm Regards,
Katie

Katherine Schumann, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
06/12/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206619

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

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

Dear Dr. ZumBrunnen:

Please refer to your New Drug Application (NDA) dated April 21, 2014, received April 21, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for ombitasvir/ABT-450/ritonavir (12.5 mg/75 mg/50 mg) tablets copackaged with dasabuvir (250 mg) tablets.

We also refer to your amendments dated May 5, 2014, May 8, 2014, May 14, 2014, May 19, 2014, May 21, 2014, May 22, 2014, May 27, 2014, June 2, 2014 and June 3, 2014.

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**. 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 . Therefore, the user fee goal date is December 21, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 23, 2014. In addition, the planned date for our internal mid-cycle review meeting is July 8, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Product Quality

1. We note that you have cross-referenced all CMC information on ritonavir drug substance to NDA 20-659. However, a cross-reference is not generally appropriate for the following information, which we recommend you directly include in the application:

    - Physical or chemical attributes of the drug substance which are important for dosage form performance
    - The specification that is used for acceptance of the drug substance
    - The analytical methods that will be used for acceptance of the drug substance
    - Complete information on the manufacturing, release and stability testing, packaging, and labeling facilities for the drug substance, as applicable.

2. As discussed during the Type C teleconference on May 14, 2014, please update NDA sections 2.3.S.1, 3.2.S1, and all proposed labeling with appropriate USAN nomenclature for the ABT-450 drug substance once a non-proprietary name is adopted.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. We note that in your request for deferral of pediatric studies, you have not included certification of the grounds for deferral as required by FDCA Section 505B(a)(3). Please submit a revised request including the certification.

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. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. In the HIGHLIGHTS section, please extend the horizontal line surrounding each heading over the entire width of the column.

2. In the HIGHLIGHTS section, please remove the white space between the initial heading and the limitation statement. Please add a space between the limitation statement and the product title.

3. In the HIGHLIGHTS section, please add white space before the following major headings: INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, and DRUG INTERACTIONS. Please refer to the SRPI, Appendix A for a sample tool illustrating white space.

4. In the HIGHLIGHTS section, please add a comma after the parentheses and before "for oral use."

5. Please update the following cross-reference in the INDICATIONS AND USAGE section to remove the reference to Table 1: *[see Dosage and Administration, Table 1 (2.1) and Clinical Studies (14)]*.

6. Subheadings and headings should be presented in either underlining or italics, and used consistently throughout the labeling (as opposed to numbered subsections, which should be bolded). Please reformat the bolded subheadings in Section 13 NONCLINICAL TOXICOLOGY and Section 17 PATIENT COUNSELING INFORMATION.

7. It is unclear whether the Patient Information is intended to be a stand-alone document. If the FDA-approved patient labeling is a separate document or is to be detached and distributed to patients, the manufacturer information should be located both after the PATIENT COUNSELING INFORMATION section and after the Patient Information. If it is not a separate

document, the manufacter information should be located at the end of the Patient Information. Please revise this information if applicable.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by July 18, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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 (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

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 Katherine Schumann, M.S., Regulatory Project Manager, at (301) 796-1182.

Sincerely,

{See appended electronic signature page}

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

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/s/

JEFFREY S MURRAY
06/12/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: June 4, 2014

NDA: 206619

PRODUCT: ombitasvir/ABT-450/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Clinical Information Request

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir.

The following table shows an analysis of rash-related adverse events evaluated using the pre-specified MedDRA CMQ query.

1. It appears that inclusion of RBV may be responsible for the increased frequency of rash and pruritus events in non-cirrhotic subjects. The mere inclusion of RBV in the regimen does not appear to explain the increased frequency of events observed among cirrhotic subjects compared to non-cirrhotic subjects. Also, much like the analysis of bilirubin elevations, cirrhotic subjects received the same treatment for the first 12 weeks, so the duration of treatment is unlikely to explain the differences between the 12 and 24-week treatment groups. Please provide your analysis of these findings.

	3-DAA + RBV X 12 weeks Non-cirrhotic n=1171	**3-DAA + RBV X 12 weeks Cirrhotic N=208**	**3-DAA + RBV X 24 weeks Cirrhotic N=172**	**3-DAA X 12 weeks Non-cirrhotic N=509**	**PBO* N=255**
Subjects with any CMQ event	309 (26)	77 (37)	75 (44)	70 (14)	39 (15)
Pruritus events[1]	135 (11.5)	37 (18)	34 (20)	30 (6)	11 (4)
Rash events[2]	298 (14)	38 (18)	44 (26)	34 (7)	22 (9)
Other events	Stomatitis 8, scalp tenderness 1, conjunctivitis 1	Stomatitis 3, conjunctivitis 1	Conjunctivitis 1, stomatitis 1, capillaritis 1	Stomatitis 4, impetigo 1, conjunctivitis 1	Stomatitis 4, conjunctivitis 2

*During DB treatment period

1. Grouped term 'pruritus' included the preferred terms pruritus and pruritus generalized
2. Grouped term 'rash' included the following preferred terms: rash, erythema, eczema, rash maculo-papular, rash macular, dermatitis, rash papular, skin exfoliation, rash pruritic, rash erythematous, urticaria, rash generalized, dermatitis allergic, dermatitis contact, exfoliative rash, erythema, dermatitis, photosensitivity reaction, psoriasis, skin reaction, ulcer, urticaria

2. Please populate the following table for each subject in the Phase 3 trials who had a CM prescribed.

Subject ID #	Preferred term	CM prescribed (prescription and OTC)
Study #		

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
06/04/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: May 30, 2014

NDA: 206619

PRODUCT: ombitasvir/ABT-450/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Information Request Proposed Packaging Configurations

---

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir.

The review team has the following requests for information regarding your proposed packaging:

1. Please submit a rationale supporting the need for two co-packaging configurations (wallets and blister cards) for the regimen of ombitasvir/ABT-450/ritonavir and dasabuvir.

2. Please clarify whether the (b) (4) described in Module 3.2.P.7 Container Closure System and 3.2.P.8 Stability are intended for marketing, as there are no proposed container labels for the (b) (4) nor are they described in the proposed prescribing information.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
05/30/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: May 27, 2014

NDA: 206619

PRODUCT: ombitasvir/ABT-450/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Clinical Information Request

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir.

The review team has the following request for information:

> The following table shows the mean change from baseline and the frequency of Grade 2, 3 and 4 elevations in bilirubin levels in the Phase 3 trials. We note similar changes from baseline in bilirubin levels and maximum bilirubin elevations (≥Grade 3) between the 12 week non-cirrhotic and 24 week cirrhotic groups of subjects treated with the 3-DAA + RBV. It is not clear why the 12 week cirrhotic group experienced substantially higher mean change from baseline and maximum grade increases in bilirubin levels compared to the other two groups. Please provide possible explanations for these differences.

	3-DAA + RBV Non-cirrhotic X 12 weeks N=1546	3-DAA + RBV Cirrhotic X 12 weeks N=208	3-DAA + RBV Cirrhotic X 24 weeks N=172
Mean change from baseline	+3.0	+6.0	+1.8
Grade 2	18%	28%	38%
Grade 3	4%	13.5%	5%
Grade 4	<1	0	0

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or

Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
05/27/2014

From:	Schumann, Katherine
To:	Sansone, Andrew J (andrew.sansone@abbvie.com)
Cc:	Rogers, Sarah R (sarah.rogers@abbvie.com); ZumBrunnen, Troy L (troy.zumbrunnen@abbvie.com); Gandhi, Virajkumar B (viraj.b.gandhi@abbvie.com)
Subject:	NDA 206619 - M12-680 information request
Date:	Friday, May 23, 2014 2:39:00 PM

Drew,

The QT Interdisciplinary Review Team has the following request regarding the information submitted for M12-680:

> Please submit a demographic dataset for study M12-680. Please make sure the dataset has basic information such as subject id, sequence randomized, ethnicity, race, age, sex, weight, height, bmi, etc.

Please let me know if you have any questions.

Warm Regards,
Katie

Katherine Schumann, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
05/23/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: May 13, 2014

NDA: 206619

PRODUCT: ombitasvir/ABT-450/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Clinical Information Request Regarding M13-099

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir.

The review team has the following request for information:

> Subject 382123 in Study M13-099 died due to liver failure following a liver transplant. The narrative notes that her metformin dose (which she was taking for ~15 years) was increased from 1000 mg QD to 1000 mg TID at her screening visit. According to the metformin labeling, patients with liver disease (including liver failure and cirrhosis) can experience an increase the risk of lactic acidosis and should not be taking metformin if their liver is not functioning normally. Please provide a clinically plausible rationale for why her metformin dose was increased, and why you believe metformin use alone explained this subject's rapid deterioration, need for a liver transplant and subsequent death.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
05/13/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: May 12, 2014

NDA: 206619

PRODUCT: ombitasvir/ABT-450/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Clinical Virology Information Request Integrated Resistance Analysis

---

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir.

The review team has the following request for information:

For the integrated resistance analysis and summary in the prescribing information, it is unclear to DAVP how you calculated a total of (b) (4) HCV genotype 1 infected subjects in Phase 2b/3 trials who were treated with the 3-DAA +/- RBV regimen for 8, 12 or 24 weeks. Our calculations are illustrated below. Please provide a similar table that shows the breakdown of trials and regimens that make up your total of (b) (4) subjects.

Trial	Phase of trial	N (3-DAA +/- RBV)	N (3-DAA)	N (3-DAA + RBV)	N placebo
M11-646	Phase 3	473	0	473	158
M13-098	Phase 3	297	0	297	97
M13-099	Phase 3	380	0	380	
M13-961	Phase 3	419	209	210	
M13-389	Phase 3	186	95	91	
M14-002	Phase 3	305	205	100	
M11-652	Phase 2b	406	79	327	
M14-103	Phase 2b	38	0	38	
Total		**2504**	**588**	**1916**	
Total according to AbbVie		(b) (4)			

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
05/12/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

IND 103526
IND 101636
IND 108434
NDA 206619

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Troy ZumBrunnen, Pharm.D.
Director, Regulatory Affairs

Dear Dr. ZumBrunnen:

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act, and to your New Drug Application (NDA) dated and received April 21, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dasabuvir, Veruprivir, Ritonavir and Ombitasvir Tablets, 250 mg/75 mg/50 mg/12.5 mg.

We also refer to:

- Your correspondence to your INDs, dated January 10, 2014, received January 13, 2014, requesting review of your proposed proprietary name, Viekira Pak

- Your correspondence to your NDA, dated and received April 21, 2014, requesting review of your proposed proprietary name, Viekira Pak

We have completed our review of the proposed proprietary name Viekira Pak, and have concluded that this name is acceptable.

If **any** of the proposed product characteristics as stated in your April 21, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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 the Office of New Drugs (OND) Regulatory Project Manager Katherine Schumann, at (301) 796-1182.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
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
05/07/2014

TODD D BRIDGES on behalf of KELLIE A TAYLOR
05/07/2014

From:	ZumBrunnen, Troy L
To:	Schumann, Katherine
Cc:	Rogers, Sarah R
Subject:	RE: NDA 206619 - Clinical Information Request regarding M13-389
Date:	Monday, May 05, 2014 4:03:20 PM

Hi Katie,
See the responses to the follow-up questions directly below. Please let us know if you need additional clarification.

Did these 6 subjects roll into one of the co-formulated arms, did they continue treatment with the individual agents or did they stop treatment?

These 6 subjects continued treatment with the individual agents as these subjects completed dosing before enrollment with coformulated drug in Amendment 5 began.

If they were rolled into Arm 3 or 4, are their data included in the overall safety data?

Not applicable. As noted above, these 6 six subjects continued treatment with the individual agents and did not roll into one of the coformulated arms. Therefore subjects treated with the individual agents were included in ARMCD 01and 02 and not in ARMCD 03 and 04.

If they were not rolled into Arm 3 or 4, and continued treatment with the individual agents, where are their safety data?

Subjects treated with the individual agents were included in the ITT population on which safety analyses were performed. All randomized subjects who received at least one dose of study drug regardless of
subgenotype or formulation were included in the safety population. This is described in the SAP on pages 9 to 10.

Regards, Troy

TROY ZUMBRUNNEN, PHARM.D.
Director, Regulatory Affairs
Area and Affiliate Strategy, US/Canada

abbvie

AbbVie Inc
Regulatory Affairs
Dept. PA77, Bldg AP30
1 North Waukegan Road
North Chicago, IL 60064-6194
OFFICE +1 847-938-9445
CELL +1 (b) (6)
EMAIL troy.zumbrunnen@abbvie.com

From: Schumann, Katherine [mailto:Katherine.Schumann@fda.hhs.gov]
Sent: Monday, May 05, 2014 14:14
To: ZumBrunnen, Troy L
Cc: Rogers, Sarah R
Subject: RE: NDA 206619 - Clinical Information Request regarding M13-389

Thank you for the prompt response, Troy.

Our question relates specifically to how subjects and subject data were managed:

> Did these 6 subjects roll into one of the co-formulated arms, did they continue treatment with the individual agents or did they stop treatment?
> If they were rolled into Arm 3 or 4, are their data included in the overall safety data?
> If they were not rolled into Arm 3 or 4, and continued treatment with the individual agents, where are their safety data?

Please let me know if you have any questions.

Warm Regards,
Katie

From: ZumBrunnen, Troy L [mailto:troy.zumbrunnen@abbvie.com]
Sent: Monday, May 05, 2014 2:25 PM
To: Schumann, Katherine
Cc: Rogers, Sarah R
Subject: RE: NDA 206619 - Clinical Information Request regarding M13-389

Katie,

This is described in the attached define data file for study M13-389 on page 5 for ARMCD (Planned Arm Code). The subjects are listed in different treatment arms due different formulations used in study M13-389. Prior to Protocol Amendment 5, subjects received separate tablets of ABT-450 at 150mg QD, ritonavir capsules at 100mg QD, ABT-267 at 25mg QD, and ABT-333 at 400 mg BID. After protocol amendment 5, all subjects received coformulated tablets of ABT-450/r/ABT267 at 150mg/100mg/25mg QD and ABT-333 BID with or without ribavirin. Additional information is located in section '9.4.1 Treatment Administered' of the Clinical Study Report.

A copy of the ARMCD section is provided below. Please let us know if you have any further questions.

ARMCD	PLANNED ARM CODE	CHARACTER	'01', '02', '03', '04'	Derived from RN.RANDCD. Decode of ARMCD:

				'01'='ABT-450/R 150/100 MG QD + ABT-267 25 MG QD + ABT-333 400 MG BID + RBV FOR 12 WEEKS' (This group includes ARM 1 subjects administered separate ABT-450, ritonavir, and ABT-267 who are not included in the GT1B efficacy subset in M13-389 CSR.), '02'='ABT-450/R 150/100 MG QD + ABT-267 25 MG QD + ABT-333 400 MG BID FOR 12 WEEKS', ((This group includes ARM 2 subjects administered separate ABT-450, ritonavir, and ABT-267 who are not included in the GT1B efficacy subset in M13-389 CSR.), '03'='ABT-450/R/ABT-267 150/100/25 MG QD + ABT-333 250 MG BID + RBV FOR 12 WEEKS' (This group includes ARM 1 subjects administered coformulated ABT-450/r/ABT-267 who are included in the GT1B efficacy subset in M13-389 CSR.), '04'='ABT-450/R/ABT-267 150/100/25 MG QD + ABT-333 250 MG BID FOR 12 WEEKS'. (This group includes ARM 2 subjects administered coformulated ABT-450/r/ABT-267 who are included in the GT1B efficacy subset in M13-389 CSR.).

Regards, Troy

TROY ZUMBRUNNEN, PHARM.D.
Director, Regulatory Affairs
Area and Affiliate Strategy, US/Canada

abbvie

AbbVie Inc

Regulatory Affairs
Dept. PA77, Bldg AP30
1 North Waukegan Road
North Chicago, IL 60064-6194
OFFICE +1 847-938-9445
CELL +1 (b) (6)
EMAIL troy.zumbrunnen@abbvie.com

abbvie.com

From: Schumann, Katherine [mailto:Katherine.Schumann@fda.hhs.gov]
Sent: Monday, May 05, 2014 11:58
To: ZumBrunnen, Troy L
Cc: Rogers, Sarah R
Subject: NDA 206619 - Clinical Information Request regarding M13-389

Troy,

Please refer your NDA 206619 submitted on April 21, 2014 for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir. The clinical review team has the following request for information.

> The datasets for Study M13-389 identify 4 arms:
>
> 1. 450/r + 267 + 333 + RBV
> 2. 450/r + 267 + 333
> 3. 450/r/267 + 333 + RBV
> 4. 450/r/267 + 333
>
> There are 6 subjects listed in arms 1 and 2 (3 in each). In arms 3 and 4 there are 92 and 88 subjects, respectively. Which is the correct number for this study? Please provide an immediate discussion of these findings.

Please let me know if you have any questions.

Warm Regards,
Katie

Katherine Schumann, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
Silver Spring, MD 20993-0002
Phone: (301) 796-1182

Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
05/07/2014

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: May 7, 2014

NDA: 206619

PRODUCT: ombitasvir/ABT-450/ritonavir copackaged with dasabuvir

TO: Troy ZumBrunnen, PharmD, Director, Regulatory Affairs

FROM: Katherine Schumann, MS, Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: Clinical Virology Information Request Regarding M13-098

Please refer to your New Drug Application (NDA) dated April 21, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir.

The clinical virology team has the following request for information:

> For the primary analysis of efficacy for clinical trial M13-098, it appears that Subject M13098-47651-361303 was considered an SVR12 responder based on a local laboratory HCV RNA result at Post-Treatment Week ~19. This result was not included in the HCV RNA analysis dataset (ADVL) but was included in the individual efficacy response data file, reported as "UNQUANTIFIABLE" with a "REAL TIME PCR" assay. Is there any other information available for this local laboratory result? Specifically, are the local assay name and performance characteristics (e.g., LLOQ) available?

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
05/07/2014

From:	Schumann, Katherine
To:	ZumBrunnen, Troy L (troy.zumbrunnen@abbvie.com)
Cc:	Rogers, Sarah R (sarah.rogers@abbvie.com)
Subject:	NDA 206619 - Clinical Information Request regarding M13-389
Date:	Monday, May 05, 2014 12:58:00 PM

Troy,

Please refer your NDA 206619 submitted on April 21, 2014 for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir. The clinical review team has the following request for information.

> The datasets for Study M13-389 identify 4 arms:
>
> 1. 450/r + 267 + 333 + RBV
> 2. 450/r + 267 + 333
> 3. 450/r/267 + 333 + RBV
> 4. 450/r/267 + 333
>
> There are 6 subjects listed in arms 1 and 2 (3 in each). In arms 3 and 4 there are 92 and 88 subjects, respectively. Which is the correct number for this study? Please provide an immediate discussion of these findings.

Please let me know if you have any questions.

Warm Regards,
Katie

Katherine Schumann, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
05/05/2014

From:	Schumann, Katherine
To:	ZumBrunnen, Troy L (troy.zumbrunnen@abbvie.com)
Cc:	Rogers, Sarah R (sarah.rogers@abbvie.com)
Subject:	NDA 206619 Clinical Information Request
Date:	Thursday, May 01, 2014 10:48:00 AM

Troy,

Please refer your NDA 206619 submitted on April 21, 2014 for ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir. The clinical review team has the following request for information.

> Please submit narratives for **ALL** deaths, SAEs, and discontinuations due to adverse events. For those that have already been submitted for events considered related to DAA treatment, you do not have to resubmit narratives.

Please submit a response to the NDA by May 19, 2014. Let me know if you have any questions.

Warm Regards,
Katie

Katherine Schumann, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
05/01/2014

From:	Schumann, Katherine
To:	ZumBrunnen, Troy L (troy.zumbrunnen@abbvie.com)
Cc:	Rogers, Sarah R (sarah.rogers@abbvie.com)
Subject:	NDA 206619 - Information Request
Date:	Wednesday, April 30, 2014 2:39:00 PM

Troy,

I have the following request for you from the review team.

Please identify where in the NDA the following information is located, or submit it if it has not been provided:

- A benefit-risk assessment analysis
- A rationale for assuming the applicability of foreign data to the U.S. population
- A statement of Good Clinical Practice that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures

Please provide a response as soon as possible, no later than Monday, May 5, 2014.

Warm Regards,
Katie

Katherine Schumann, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
04/30/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206619

NDA ACKNOWLEDGMENT

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

Dear Dr. ZumBrunnen:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product:	ombitasvir/ABT-450/ritonavir (12.5 mg/75 mg/50 mg) tablets copackaged with dasabuvir (250 mg) tablets
Date of Application:	April 21, 2014
Date of Receipt:	April 21, 2014
Our Reference Number:	NDA 206619

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 June 20, 2014, 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

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

If you have any questions, call me at (301) 796-1182 or the Division's main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Katherine Schumann, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
04/29/2014

From:	Thompson, Elizabeth
To:	ZumBrunnen, Troy L
Cc:	Rogers, Sarah R; Sansone, Andrew J; Schumann, Katherine; Thompson, Elizabeth
Subject:	RE: NDA 206619: carcinogenicity data
Date:	Tuesday, April 01, 2014 10:43:47 AM
Attachments:	datafmt.pdf

Troy-

For the statistical analysis, the review team still prefers the carcinogenicity data in the OB requested format (please see attached). SEND data (Standard for the Exchange of Nonclinical Data) is acceptable provided all domains are included (actually only the DM, DS, EX, MI, TF, and TX domains would suffice for our current needs).

Please let me know if you have any questions.

Regards,

Beth
Chief, Project Management Staff
FDA/CDER/OAP/DAVP
301-796-0824

-----Original Message-----
From: ZumBrunnen, Troy L [mailto:troy.zumbrunnen@abbvie.com]
Sent: Tuesday, March 25, 2014 4:32 PM
To: Thompson, Elizabeth
Cc: Rogers, Sarah R; Sansone, Andrew J
Subject: RE: NDA 206619: carcinogenicity data

Beth,

As a follow up to the request below for carcinogenicity data sets, we confirm we intend to provide the carcinogenicity data in the specified format within the NDA. We do not plan to submit associated program files.

Is this acceptable?

Regards, Troy

-----Original Message-----
From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Wednesday, March 12, 2014 11:28
To: ZumBrunnen, Troy L
Cc: Thompson, Elizabeth
Subject: NDA 206619: carcinogenicity data

Troy-

As a reminder, please submit the carcinogenicity data per the attached document. The nonclinical carcinogenicity stats data is reviewed by a separate group, not our nonclinical team, and the attached guidance is how they would like that data.

Can you confirm if the data submitted to date has been presented this way (as in the attached guidance)? If not, could you please update.

Regards,

Beth
Chief, Project Management Staff
FDA/CDER/OAP/DAVP
301-796-0824

FDA Guidance

Data Standard for Electronic Submission

Tumor-Data Format

[Close this window] [Print this page]

Tumor Dataset For Statistical Analysis[1,2] (tumor.xpt)			
Variable	**Label**	**Type**	**Codes**
STUDYNUM	Study number	char	
ANIMLNUM	Animal number	char	
SPECIES	Animal species	char	M=mouse R= rat
SEX	Sex	char	M=male F=female
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4, . . . in ascending order from control. Provide the dosing for each group.
DTHSACTM	Time in days to death or sacrifice	num	
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4 = Accidental death
ANIMLEXM	Animal microscopic examination code	num	0 = No tissues were examined 1 = At least one tissue was examined
TUMORCOD	Tumor type code	char	
TUMORNAM	Tumor name	char	
ORGANCOD	Organ/tissue code	char	
ORGANNAM	Organ/tissue name	char	
DETECTTM	Time in days of detection of tumor	num	
MALIGNST	Malignancy status	num	1 = Malignant 2 = Benign 3 = Undetermined
DEATHCAU	Cause of death	num	1 = Tumor caused death 2 = Tumor did not cause death 3 = Undetermined
ORGANEXM	Organ/Tissue microscopic examination code	num	1 = Organ/Tissue was examined and was usable 2 = Organ/Tissue was examined but was not usable (e.g., autolyzed tissue) 3 = Organ/Tissue was not examined

[1] Each animal in the study should have at least one record even if it does not have a tumor.
[2] Additional variables, as appropriate, can be added to the bottom of this dataset.
[3] ANIMLNUM limit to no more than 12 characters; ORGANCOD and TUMORCOD limited to no more than 8 characters; ORGAN and TUMOR should be as concise as possible.
[4] A missing value should be given for the variable MALIGNST, DEATHCAU, TUMOR and TUMORCO

For more information regarding	Please visit:
Guidance for Industry Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals	http://www.fda.gov/cder/guidance/815dft.pdf
Entire **FDA Guidance Documents**	http://www.fda.gov/cder/guidance/ Appendix 1

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/s/

ELIZABETH G THOMPSON
04/07/2014

From:	Thompson, Elizabeth
To:	troy.zumbrunnen@abbvie.com
Cc:	Thompson, Elizabeth
Subject:	NDA 206619: carcinogenicity data
Date:	Wednesday, March 12, 2014 12:28:01 PM
Attachments:	Carci Data Format and Stat Guidance Info Sheets 07-16-09.DOC

Troy-

As a reminder, please submit the carcinogenicity data per the attached document. The nonclinical carcinogenicity stats data is reviewed by a separate group, not our nonclinical team, and the attached guidance is how they would like that data.

Can you confirm if the data submitted to date has been presented this way (as in the attached guidance)? If not, could you please update.

Regards,

Beth
Chief, Project Management Staff
FDA/CDER/OAP/DAVP
301-796-0824

Office of Biostatistics Information Sheet for Submission of Data and for Methods of Data Analysis of Carcinogenicity Studies

(The electronic data format is for two-year studies as well as transgenic mouse studies using all except the TgAC mouse models)

Revised 07/16/2009

The statistical reviewer responsible for the review of the carcinogenicity studies of this NDA/IND submission requests that the sponsor recreate the tumor data in conformance to the electronic format specified in the Agency's April 2008 guidance document entitled "*Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications*". The guidance document can be found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf. The cover page of the document is attached to this information sheet (Attachment A).

In Section III.D.3 of the above document the Agency gives a general description of the data formats for the pharmacology and toxicology datasets and refers readers to the associated document "*Study Data Specifications*" for more information about the format specifications of the data submission. This associated document can be found at the FDA website http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163561.pdf. At this time, we are only requesting the tumor dataset in the format described on page 7 (APPENDIX 1) of the associated document. The table containing the format for tumor data in the document is attached to this information sheet (Attachment B).

Please contact the Agency to provide a time line regarding providing the tumor data. The sponsor needs to carefully meet the data format specifications in order to comply with the above guidance. Any data without 100% conformity will have to be returned for resubmission.

Note that the draft guidance for the statistical analysis of chronic rodent carcinogenicity studies is available on the FDA web site at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079272.pdf. Sponsors are urged to use the statistical methods recommended in the guidance to analyze the carcinogenicity study data in their IND or NDA submissions. The cover page of the document is also attached to this information sheet (Attachment C).

For questions related to the data format and the methods of statistical analysis, please contact Karl K. Lin, Ph.D., Room 4670, Building 21, Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, 301-796-0943, karl.lin@fda.hhs.gov.

(Attachment A)

Cover page of "*Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications*"

Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2008
Electronic Submissions

Revision 2

(Attachment B)

Data format table on page 7 (APPENDIX 1) of the associated document "*Study Data Specifications*"

Tumor Dataset For Statistical Analysis[1,2] (tumor.xpt)				
Variable	**Label**	**Type**	**Codes**	**Comments**
STUDYNUM	Study number	char		[3]
ANIMLNUM	Animal number	char		[1,3]
SPECIES	Animal species	char	M=mouse R=rat	
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3,4,... in ascending order from control. Provide the dosing for each group.	
DTHSACTM	Time in days to death or sacrifice	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4= Accidental death	
ANIMLEXM	Animal microscopic examination code	num	0= No tissues were examined 1 = At least one tissue was examined	
TUMORCOD	Tumor type code	char		[3,4]
TUMORNAM	Tumor name	char		[3,4]
ORGANCOD	Organ/tissue code	char		[3,5]
ORGANNAM	Organ/tissue name	char		[3,5]
DETECTTM	Time in days of detection of tumor	num		
MALIGNST	Malignancy status	num	1 = Malignant 2= Benign 3 = Undetermined	[4]
DEATHCAU	Cause of death	num	1 = Tumor caused death 2= Tumor did not cause death 3 = Undetermined	[4]
ORGANEXM	Organ/Tissue microscopic examination code	num	1 = Organ/Tissue was examined and was usable 2= Organ/Tissue was examined but was not usable (e.g., autolyzed tissue) 3 = Organ/Tissue was not examined	

[1] Each animal in the study should have at least one record even if it does not have a tumor.

[2] Additional variables, as appropriate, can be added to the bottom of this dataset.

[3] ANIMLNUM is limited to no more than 12 characters; ORGANCOD and TUMORCOD are limited to no more than 8 characters; ORGANNAM and TUMORNAM should be as concise as possible.

[4] A missing value should be given for the variable MALIGNST, DEATHCAU, TUMORNAM and TUMORCOD when the organ is unusable or not examined.

[5] Do not include a record for an organ that was useable and no tumor was found on examination. A record should be included for organs with a tumor, organs found unusable, and organs not examined.

(Attachment C)

Cover page of *"Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals"*

Guidance for Industry

Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability.

For questions regarding this draft document contact (CDER) Karl K. Lin, Ph.D., 301-796-0943, e-mail link.lin@fda.hhs.gov or link@cder.fda.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2001

Pharm/Tox

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11/22/05

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/s/

ELIZABETH G THOMPSON
03/18/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206619

ACKNOWLEDGE NDA PRESUBMISSION

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

Dear Dr. ZumBrunnen:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: ombitasvir (ABT-267; 12.5 mg)/veruprevir (ABT-450; 75 mg)/ritonavir (50 mg) tablets and dasabuvir (ABT-333; 250 mg) tablets

Date of Submission: January 14, 2014

Date of Receipt: January 15, 2014

Our Reference Number: NDA 206619

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the NDA number listed above at the top of the first page of any communications concerning this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions 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 contact Elizabeth Thompson, M.S., Chief, Project Management Staff, at (301) 796-0824 or via email at elizabeth.thompson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Elizabeth Thompson, M.S.
LCDR, U.S. Public Health Service
Chief, Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ELIZABETH G THOMPSON
03/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 103526

MEETING MINUTES

AbbVie Inc.
Attention: Troy ZumBrunnen, Pharm.D.
Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, IL 60064

Dear Dr. ZumBrunnen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABT-450. Please also refer to your INDs for ABT-267 (IND 108,434) and ABT-333 (IND 101,636).

We also refer to the meeting between representatives of your firm and the FDA on January 29, 2014. The purpose of the meeting was to discuss the efficacy and safety results that will be submitted in the initial NDA to support the proposed indication, as well as the content and format of the planned NDA for your HCV DAA combination regimen of ABT-267, ABT-450, ritonavir copackaged with ABT-333, administered with and without ribavirin (RBV).

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, please contact Elizabeth Thompson, M.S., Chief, Project Management Staff, at (301) 796-0824 or via email at elizabeth.thompson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
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:	January 29, 2014, 2:30 PM – 4:00 PM EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 2205 Silver Spring, Maryland 20903
Application Number:	IND 103,526 (references IND 108,434 and IND 101,636)
Product Name:	ABT-267, ABT-450, ritonavir copackaged with ABT-333
Indication:	The treatment of chronic HCV GT1 infection in adults, including those with compensated cirrhosis, who are either treatment-naïve or previously treated with pegylated interferon (pegIFN) and RBV
Sponsor/Applicant Name:	AbbVie Inc.

FDA ATTENDEES

Office of Antimicrobial Products (OAP)
Edward Cox, Director
David Roeder, Associate Director of Regulatory Affairs

Division of Antiviral Products (DAVP)
Debra Birnkrant, Division Director
Linda Lewis, Medical Team Leader
Mary Singer, Medical Team Leader
Kim Struble, Medical Team Leader
Russell Fleischer, Medical Reviewer
Peter Miele, Medical Reviewer
Poonam Mishra, Medical Reviewer
Hanan Ghantous, Pharmacology/Toxicology Team Leader
Mark Seaton, Pharmacology/Toxicology Reviewer
Jules O'Rear, Clinical Virology Team Leader
Patrick Harrington, Clinical Virology Reviewer
Elizabeth Thompson, Chief, Project Management Staff
Nina Mani, Regulatory Project Manager
Suzanne Strayhorn, Regulatory Project Manager
Kathleen Trexler, Pharmacy Student
Irene Kim, Pharmacy Student

Office of Biostatistics
Fraser Smith, Acting Biostatistics Team Leader, DBIV
Joy Mele, Biostatistician, DBIV

Office of Clinical Pharmacology
Islam Younis, Clinical Pharmacology Team Leader
Vikram Arya, Clinical Pharmacology Reviewer
Jeffry Florian, Pharmacometrics Team Leader
Dhananjay Marathe, Pharmacometrics Reviewer

Office of New Drug Quality Assessment
Stephen Miller, CMC Team Lead, DNDQA II

Office of Surveillance and Epidemiology
Carolyn Yancey, DRISK

Office of Scientific Investigations
Antoine El-Hage, DSI

EASTERN RESEARCH GROUP ATTENDEES

1. (b) (6), Independent Assessor

SPONSOR ATTENDEES

1. Scott Brun, Vice President, Pharmaceutical Development
2. Barry M. Bernstein, Vice President, Infectious Disease Development
3. Thomas J. Podsadecki, Project Director, Antiviral Clinical Project Team
4. Melanie Gloria, Associate Director, Clinical Program Development
5. Barbara Da Silva-Tillmann, Senior Medical Director, HCV Product Safety Lead
6. Mondira Bhattacharya, Senior Medical Director, Therapeutic Area Head, Infectious Disease
7. Christine Collins, Director, HCV Clinical Virology
8. Rajeev M. Menon, Director, Clinical Pharmacology and Pharmacometrics
9. Sandeep Dutta, Senior Director, Clinical Pharmacology and Pharmacometrics
10. Lois Larsen, Associate Director, Statistics
11. Martin King, Director, Statistics
12. Sarah Rogers, Manager, Regulatory Affairs
13. Drew Sansone, Senior Director, Regulatory Affairs, US and Canada
14. Andrew Storey, Vice President, Regulatory Affairs, US and Canada
15. Steven Wojtanowski, Vice President, Regulatory Affairs
16. Mish Gerhardt, Senior Director, Global Product Strategy, Regulatory Affairs
17. Troy ZumBrunnen, Director, Regulatory Affairs, US and Canada
18. Anutosh R. Saha, Director, Regulatory Affairs, GPS

19. Jay R. Luly, President and CEO, Enanta Pharmaceuticals

1.0 BACKGROUND

AbbVie Inc. is developing a three component direct-acting antiviral (DAA) regimen for the treatment of genotype 1 chronic hepatitis C virus (HCV) infection. The triple DAA regimen includes the following drugs:

- ABT-450 (veruprevir), an NS3/4A protease inhibitor
- ABT-267 (ombitasvir), an NS5A inhibitor
- ABT-333 (dasabuvir), a non-nucleoside NS5B polymerase inhibitor

The regimen proposed for the planned NDA includes a coformulated tablet of ABT-267, ABT-450, and ritonavir co-packaged with tablets containing ABT-333. The sponsor is proposing this regimen for the treatment of genotype 1 chronic hepatitis C virus infection in adults, including those without cirrhosis or with compensated cirrhosis, who are either treatment-naïve or previously treated with interferon (IFN) and ribavirin (RBV). The sponsor is recommending coadministration with RBV for patients with compensated cirrhosis (b) (4)

The 3-DAA combination regimen was granted Breakthrough Therapy designation on May 1, 2013 and a request for rolling review was granted on December 31, 2013.

This Type B, pre-NDA meeting was requested on December 4, 2013 and the background package was received by DAVP on December 31, 2013. The purpose of the meeting is to discuss the efficacy and safety results that will be submitted in the initial NDA to support the proposed indication, as well as the content and format of the planned NDA. The meeting should result in an agreement between the sponsor and the Division on the content of a complete application.

Preliminary comments were sent by the Division on January 24, 2014.

2.0 DISCUSSION

The sponsor's questions are in **bold** font, FDA preliminary responses in normal font, and meeting discussion in *italicized* font.

2.1. CMC

Module 3 Ritonavir Information

Question 1:
Does the Agency agree that the proposed format and content is sufficient for review purpose?

FDA Response to Question 1:
Yes, the format and content of the review guide for ritonavir drug substance information seem appropriate from the review perspective.

Discussion:
No discussion occurred.

Question 2:
Does the Agency agree to the proposed electronic Common Technical Document (eCTD) location for the review guide?

FDA Response to Question 2:
We recommend that you include a single drug substance element in Module 3, which clarifies that all drug substance information is cross-referenced to the Norvir NDA. This could simply indicate that the review guide table and the cross-reference authorization letter are included in Module 1.4.4. Alternatively, the review guide table could be located in the single drug substance element in Module 3. The document on "Cross Application Hyperlinking" may provide other options (see attachment).

Discussion:
No discussion occurred.

Question 3:
Does the Agency agree with AbbVie's approach to the ritonavir (b) (4) documentation?

FDA Response to Question 3:
AbbVie's proposal is that future changes to the ritonavir (b) (4) process or controls will be filed to the Norvir NDA, and only cross-reference letters will be submitted to the HCV NDA. To make the future record clear in the NDA for ABT-450/r/ABT-267 tablets and ABT-333 tablets, we recommend you begin Sections 3.2.P.3.3 and 3.2.P.3.4 with a statement that any changes to the ritonavir (b) (4) information after 2014 will only be documented in the Norvir NDA.

Discussion:
No discussion occurred.

2.2. Nonclinical

Abuse Liability Potential

Question 4:
Based on the data and rationale presented in Appendix B, does the Agency agree that no further studies are required to assess abuse potential of AbbVie's 3-DAA combination and that the available data provide adequate characterization of abuse liability potential?

FDA Response to Question 4:
Yes, we agree.

Discussion:
No discussion occurred.

2.3. Clinical

Rationale for Selection of the 3-DAA Regimen and Addressing the Combination Rule

Question 5:
Based on the information provided in Section 16.0, does the Agency agree that AbbVie has demonstrated appropriate rationale for the use of the 3-DAA ± RBV regimen in HCV GT1 patients and has satisfied the combination drug rule requirements?

FDA Response to Question 5:
It is likely that you have satisfied the combination drug rule requirements to support the 3- DAA + RBV regimen in GT 1a treatment naïve and experienced subjects without cirrhosis; however, the final decision on the regimen for these subgroups will be a review issue. Please see the response to Question 6 regarding GT 1b subjects.

Discussion:
No discussion occurred.

Treatment with RBV

Question 6:
Does the Agency agree that the study results outlined in Section 15.3.2.1 and Section 15.3.2.2 from Studies M13-389 and M13-961, respectively, support the use of the 3-DAA regimen without RBV in the GT1b naïve and experienced populations without cirrhosis?

FDA Response to Question 6:
For GT 1b treatment experienced subjects, again, it appears likely that the combination rule has been satisfied and that the regimen of the 3-DAAs (without RBV) may be appropriate in this subgroup. (b) (4) The final decision on the most appropriate regimen will be a review issue.

Discussion:

(b) (4)

FDA noted that the data needs to be reviewed, and that a detailed rationale (safety and efficacy) should be provided for (b) (4)

Question 7:

Does the Agency agree that the study results provided from Study M14-002 in Section 15.3.2.3 support the use of the 3-DAA regimen without RBV in GT1a (b) (4) **populations without cirrhosis** (b) (4) **?**

FDA Response to Question 7:

DAVP does not agree with this proposal because:

- (b) (4)
-
-
-

Discussion:

AbbVie noted that they are continuing to analyze the data for possible predictors of response or failure and will describe the outcome of these analyses in the NDA application.

Treatment Duration for Cirrhotic Patients

Question 8:

Does the Agency agree that the study results provided in Section 15.3.2.4 from Study M13-099 support the recommended 12-week treatment duration for all patients except HCV GT1a-infected (b) (4) **where a 24-week duration is recommended?**

FDA Response to Question 8:

In principle we agree; the final decision on the optimal duration of dosing for each subgroup will be a review issue.

Discussion:

No discussion occurred.

ALT Monitoring

Question 9:
Does the Agency agree with the proposed alanine aminotransferase (ALT) monitoring and drug discontinuation recommendations for those receiving systemic estrogen containing therapies as outlined in Section 15.4.4?

FDA Response to Question 9:
See response to Q10.

Discussion:
No discussion occurred.

Question 10:
Based on the information presented in Section 15.4.4, AbbVie believes specific ALT monitoring is only required (b) (4) **Does the Agency agree?**

FDA Response to Question 10:
It is premature for DAVP to agree to the proposed ALT monitoring and management guidelines. The final wording of any safety labeling will be a review issue and will not be decided until after ALT data from all clinical trials and drug-drug interaction data from relevant studies have been reviewed and a benefit/risk assessment has been made.

Discussion:
No discussion occurred.

Pharmacovigilance and Risk Management

Question 11:
Does the Agency agree that the Pharmacovigilance (PV) Plan (Appendix C) is appropriate for the postmarketing setting based on the observed clinical data?

FDA Response to Question 11:
In principle we agree. A final decision on the acceptability of the PV plan will be made following review of the safety data in the NDA. Please submit the proposed PV directed questionnaires in the NDA (Module 5).

Discussion:
No discussion occurred.

Question 12:

(b) (4)

Does the Agency agree that a Risk Evaluation Mitigation Strategy (REMS) is not necessary for the 3-DAA treatment regimen?

FDA Response to Question 12:
At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether or not a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the proposed 3-DAA treatment regimen outweigh the risks, and if it is necessary, what the required elements would be. We will determine the need for a REMS during the review of your application.

Discussion:
No discussion occurred.

Clinical Datasets to be Included in the NDA

Question 13:
Table 2 below summarizes the agreements the AbbVie has made with the Agency regarding all clinical datasets to be included in the NDA. Does the Agency agree with the summarized proposal?

FDA Response to Question 13:
Your plan to provide datasets in the format we have recommended for your six Phase 3 trials and two of your Phase 2 trials is acceptable. You state that you will be using the data from ongoing studies (M13-393, M12-998 and M12-536) to support the 3-DAA regimen but you will not be submitting that data. We would like you to submit data from these trials that support your regimen selection. These datasets can be limited to the patient-level data that supports your presentations of these three trials in your submission. We can provide more details as to the scope of the required data at a later date.

Discussion:
AbbVie outlined the dataset for the Phase 2 studies to be included in the regimen justification section (slide 2). FDA noted that their proposal was acceptable. FDA suggested that the variable ARMCD should be consistently coded across studies such that the character variable ARM values correspond to the same values of ARMCD in each dataset. AbbVie agreed to do this. AbbVie requested the FDA statistician review the details of the define file for the Phase 2

trials that was provided the morning of the meeting day. The FDA statistician agreed to get back to AbbVie quickly.

Question 14:

The resistance data for the Integrated Resistance Report (IRR) will be provided in resistance datasets according to the DAVP template. The Resistance dataset per DAVP template provides variants from prototypic reference sequence (1a-H77 or 1b-Con1), not from postbaseline to baseline sequencing. Therefore, AbbVie will not be providing the associated case report tabulations (CRTs), analysis-ready datasets (ARDs), or programs to derive either the Resistance datasets per template or the results in the tables. Does the Agency agree with this proposal?

FDA Response to Question 14:

In general your plan appears reasonable, although a formal decision regarding the adequacy of submitted resistance data will be made at NDA filing. You are encouraged to submit any additional analysis-ready datasets that you believe could enhance the NDA review. Although per the DAVP resistance template individual subjects' baseline sequences are not used as references for populating the datasets, we expect listings/summaries of all known or potentially novel substitutions that frequently emerged among virologic failure subjects will be included in the Integrated Resistance Report.

Discussion:

AbbVie summarized previous submissions and communications regarding HCV resistance datasets, and requested if there were any additional elements that are needed to ensure the resistance data are adequate for filing (slides 3-4). FDA responded by emphasizing that based on previous communications and the draft datasets AbbVie has provided, at this point there is no reason to believe that there will be any problems, and there are no recommendations for additional elements to add to the datasets.

Regarding the request for any additional analysis-ready datasets, FDA noted that these additional datasets are not critical for filing, although we sometimes receive additional or supplemental analysis resistance datasets that are in a different format from what is in the DAVP guidance, and these can be helpful in NDA reviews. Also, DAVP has been considering different ways to simplify resistance dataset formats, and eventually the goal is to move towards a CDISC-compliant format, so by receiving and reviewing a variety of different dataset formats we may identify new data formatting approaches.

FDA asked AbbVie if they have constructed any datasets following the published CDISC virology standards, and AbbVie replied that they have not.

AbbVie summarized a proposal for generating a listing of treatment-emergent variants in individual subjects. FDA responded that the proposal is generally acceptable, and requested that the listings from Phase 3 trials are pooled into a single table with a column(s) to indicate

the trial and study arm. FDA also requested the listing be provided in a .xpt file, if feasible. AbbVie stated that they will assess if this is possible and will respond to DAVP within ~1 week.

For the summary of emerged variants in ≥2 subjects, FDA asked if the data will be summarized considering pooled data across all Phase 3 trials, and AbbVie confirmed that these summary listings will consider pooled resistance data.

Finally, FDA noted that when it comes to calling a particular amino acid substitution as being associated with treatment failure, DAVP generally makes this determination based on the clinical data, and site-directed mutant phenotype data can help to confirm that a substitution is resistance-associated, but the lack of a phenotype does not necessarily rule it out. If a substitution frequently emerges in subjects who fail treatment but does not confer a clear resistant phenotype, it will still be flagged as being associated with treatment failure.

Plan for Inclusion of Dose, Duration, and Regimen Justification information in the NDA

Question 15:
Does the Agency agree with AbbVie's content and planned presentation of data from the 2-DAA program in the ISE?

FDA Response to Question 15:
Please see our response to Question 13.

Discussion:
No discussion occurred.

120-Day Safety Update

Question 16:
Does the Agency agree with the proposed plan for the 120-day safety update?

FDA Response to Question 16:
Your plan appears reasonable.

Discussion:
AbbVie requested clarification if FDA wanted late relapse data in the 120-day safety update. FDA stated yes, and clarified that a signal of late relapse can be viewed as a safety issue. AbbVie asked if resistance data need to be submitted in the safety update, and FDA responded that resistance data do not need to be included in this update.

ABT-450 Exposures and Drug-Drug Interactions

Question 17:
Does the Agency agree the additional analyses adequately address the Agency's concern regarding extrapolation of DDI information?

FDA Response to Question 17:
The proposed strategy and the additional analyses conducted regarding extrapolation of drug-drug interactions appear reasonable. The final decision regarding whether the analysis supports the proposed recommendations will be based on the review of all available information in the NDA.

Discussion:
No discussion occurred.

2.4. Regulatory

Format and Content of the eCTD

Question 18:
Does the Agency agree that the proposed format and content for the planned NDA, as presented in Appendix E, is adequate and considered a complete application?

FDA Response to Question 18:
The proposed format and content appear reasonable, pending a formal filing review. Please place the Integrated Resistance Report in Module 5.3.5.4.

Discussion:
No discussion occurred.

Priority Review

Question 19:
Does the Agency agree that the data provided in support of this regimen for the treatment of HCV GT1-infected patients are sufficient to support designation of priority review?

FDA Response to Question 19:
Yes, we agree.

Discussion:
No discussion occurred.

Timeline and Advisory Committee Meeting

Question 20:
Can the Agency confirm whether an advisory committee meeting will be required during the NDA review?

FDA Response to Question 20:
At this time, DAVP does not anticipate the need for an advisory committee meeting. This opinion may change should any important issues be identified once the NDA has been submitted and the review initiated.

Discussion:
AbbVie asked when during the review a decision is expected on the need for an advisory committee (AC) meeting. FDA noted that they do not anticipate the need for an AC but the final decision would be made at the time of the 74-day filing letter.

Question 21:
Can the Agency confirm the timelines for a late-cycle review meeting and advisory committee meeting under priority review based on an April 2014 NDA submission?

FDA Response to Question 21:
The NDA will be reviewed under the PDUFA V program timeframes and all meetings will be scheduled as required. We will inform you of the schedule once the NDA has been submitted and filed.

Discussion:
No discussion occurred.

(b) (4)

Question 22:

(b) (4)

FDA Response to Question 22:

(b) (4)

Discussion:

(b) (4)

[redacted]

2.5 Additional Meeting Discussion

Complete Application
FDA noted that since the application that was the subject of the meeting would be reviewed under the PDUFA V NME Program, that discussion of a complete application, any minor components, and REMS would need to be discussed and agreed upon at the conclusion of the meeting.

AbbVie questioned whether FDA wanted the data for the co-infection and transplant studies to be included in the original NDA submission. FDA asked when SVR_{12} data from the co-infection study would be available and on how many subjects. AbbVie noted that data would be available in June for approximately 32 subjects. FDA stated this seems small and that we could possibly approve the wrong regimen (12 versus 24 weeks) if only 12 week data were available. AbbVie stated that they would only move forward if the 12 week data looked promising. Regarding the transplant study, FDA noted this was a population that needed better therapies and would be interested in this for labeling, but would depend on the numbers of subjects/data available. FDA requested that AbbVie submit a detailed timeline for both studies to the IND for review, before a determination could be made that these would be reviewed during the original NDA review. FDA also noted that these trials might be subject to inspections. AbbVie mentioned that the data would not be integrated, if included in the NDA. FDA agreed this was acceptable.

SVR_{12} Update
AbbVie provided a brief update on the SVR_{12} data from studies M14-103, M13-389 and M13-099 (SVR4 data provided in background package; slide 1). AbbVie noted that since submission of the background package, no additional relapses have been observed between the SVR_4 and SVR_{12} analysis timepoints, and there was only one additional SVR_{12} non-responder in Study M13-389 (lost to follow-up). FDA stated that if possible, AbbVie should try to find that patient, as missing SVR_{12} will be classified as treatment failure.

M12-205 (DAAs + oral contraceptives) Discussion
Abbvie presented a summary of the available data from trial M12-205 (DAAs + oral contraceptive trial). Nine of 12 subjects showed ALT elevations and discontinued dosing in Arm 4 (Norethindrone/ethinylestradiol). DAVP asked if there are any plans to evaluate other

combination oral contraceptives. Abbvie indicated that all the data is being analyzed and the next steps are under discussion.

(b) (4)

M14-004 (3 DAAs + RBV in HIV/HCV co-infected) Discussion

AbbVie noted that 21/32 subjects have completed treatment in the 12 week arm and that no subjects in the 24 week arm have completed treatment (slide 9). (b) (4)

(b) (4)

(b) (4)

DAVP reiterated its position that Abbvie's proposal of (b) (4) is unacceptable. (b) (4)

(b) (4)

(b) (4)

Chemistry, Manufacturing, and Controls Discussion
AbbVie noted that a response to CMC amendment is pending and requested a response by February 7, 2014, if possible.

AbbVie also asked about manufacturing site inspections, and noted that the information was included on the 356h. FDA stated that internal discussions regarding the timing of inspections will occur once the drug substance portion of the rolling submission arrives.

3.0 ADDITIONAL COMMENTS

Clinical

1. Please submit as soon as possible a list of all investigators for the Phase 3 trials, including number of subjects enrolled and number discontinued. Please provide full contact information for each investigator including email address and fax number.

   Discussion:
   AbbVie stated that they are working on putting a list together of all investigators for the Phase 3 trials.

2. DAVP notes the recent Quality submission for (b) (4). Please provide an update at the meeting on the to-be-marketed formulation and whether you intend to submit one of these (b) (4) as the to-be marketed formulation.

   Discussion:
   AbbVie noted that they do not plan to submit the proposed (b) (4) as part of the NDA. DAVP asked if there are any differences between the formulations of ABT-450, ABT-267, and ABT-333 used in the Phase III clinical trials and the formulations that are intended for commercialization. Abbvie indicated that there are no differences in ABT-450 and ABT-267 formulations; for ABT-333, the formulation intended for commercialization and the formulation used in Phase 3 trials are identical, however, they are manufactured at different sites. Abbvie further stated that the results of a bioavailability trial indicate that the systemic exposure of ABT-333 after administration of ABT-333 formulations manufactured at either site is similar.

Clinical Pharmacology/Pharmacometrics

3. For submission of your Population PK and Exposure-Response analyses, please refer to the following pharmacometric data and models submission guidelines: (http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm)

Discussion:
AbbVie confirmed that the Population PK and Exposure-Response analyses will follow the referenced guidance.

4.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. FDA stated that the application needed to be complete at the time of submission (no major components to be received after NDA submission). It was noted that further discussions would be needed to determine whether data from the co-infection and transplant trials could be submitted with the original NDA application for review and inclusion in labeling.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that insufficient information is available at this time to determine whether a REMS is needed. Therefore, a REMS determination will be a review issue.

- 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 pending further review, the following minor application components may ***possibly*** be submitted within 30 calendar days after the submission of the original application: co-infection and transplant trials/data.

  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 206619: LATE COMPONENT – CLINICAL

5.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your Agreed PSP dated November 19, 2013.

6.0 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. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements of Prescribing Information* website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents , and the Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

7.0 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.				

8.0 ISSUES REQUIRING FURTHER DISCUSSION

- (b) (4)
- Transplant studies for inclusion in NDA

9.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Review define file for Phase 2 trials to assess acceptability	FDA	Within 30 days; FDA provided comments to AbbVie on 2/1/14
Timeline/data for HCV/HIV co-infection and transplant trials (for consideration during review of original NDA)	AbbVie	Asap; transplant trial timeline submitted to IND 103526 (eCTD sequence number 0496) on 2/10/14
Follow-up on SVR12 non-responder from M13-389	AbbVie	NDA submission
Treatment-emergent substitution line listing (.xpt format)	AbbVie	One week; submitted to IND 103526 (eCTD sequence number 0492) on 2/5/14 Note: format is acceptable to DAVP

10.0 ATTACHMENTS AND HANDOUTS

- Cross Application Hyperlinking (refer to Question 2; sent with preliminary meeting comments)
- Sponsor slide deck presented during meeting

16 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

ELIZABETH G THOMPSON
01/30/2014

From:	Thompson, Elizabeth
To:	troy.zumbrunnen@abbvie.com
Cc:	Thompson, Elizabeth
Subject:	NDA 206619 AbbVie Rolling Review: nonclinical advice/information request
Date:	Wednesday, January 22, 2014 10:29:42 AM
Importance:	High

Troy-

Please refer to the Nonclinical Rolling Review submission dated January 14, 2014. We have the following advice/information request:

In an earlier meeting, DAVP asked that the nonclinical study files be given names that designate the drug studied. Below is an example of a folder/file naming convention used in this submission:

> Folder title: tb07-235
> File title: c-tox-tb07235-rd07962-5d-po-dog

The above designation is difficult for the review team to know which one of the three possible drugs were studied. DAVP prefers to have the files renamed with an ABT-XXX designation included, although we acknowledge that may not be practical. If renaming is not possible, please provide an indexed list of study report files associated with the individual ABT-XXX products. Another option would be to group study report files in unique folders according to ABT-XXX drug studied.

Please let me know if you have any questions regarding this request.

Regards,

Beth

Elizabeth Thompson, M.S.
LCDR, U.S. Public Health Service
Chief, Project Management Staff
FDA/CDER/OND/DAVP
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELIZABETH G THOMPSON
01/22/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 103526

MEETING MINUTES

AbbVie Inc.
Attention: John M. Sall, PharmD., Ph.D.
Senior Director, Regulatory Affairs
1 N Waukegan Road
Dept. PA77/Bldg AP30-1
North Chicago, IL 60064

Dear Dr. Sall:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (ABT-450) Hepatitis C Viral (HCV) NS3 Protease Inhibitor for Treatment of Hepatitis C Infection.

Please also refer to your INDs for ABT-267 (IND 108434) and ABT-333 (IND 101636)

We also refer to the meeting between representatives of your firm and the FDA on September 17, 2013. The purpose of the meeting was to gain FDA advice concerning key CMC topics and to expedite the development timeline for the NDA.

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 Althea Cuff, Regulatory Project Manager at (301) 796- 4061.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
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:	Chemistry
Meeting Date and Time:	September 17, 2013 – 1:30 – 2:30 pm, EST
Meeting Location:	FDA, White Oak
Application Number:	IND 103526 (with reference to IND 108,434 and IND 101,636)
Product Name:	(ABT-450/r/ABT-267 + ABT-333) Hepatitis C Viral
Indication:	Treatment of Hepatitis Infection
Sponsor/Applicant Name:	AbbVie
Meeting Chair:	Rapti Madurawe, Ph.D., Branch Chief, ONDQA
Meeting Recorder:	Althea Cuff, MS, ONDQA RPM

FDA ATTENDEES
Rapti Madurawe, Ph.D., Branch Chief, ONDQA
Stephen Miller, Ph.D., CMC Lead, ONDQA
Li Qi, Ph.D., Chemist, ONDQA
George Lunn, Ph.D., Chemist, ONDQA
Minerva Hughes, Ph.D., Biopharmaceutics, ONDQA
Althea Cuff, MS., RPM, ONDQA
Vipul Dholakia, Ph.D., Chemist, Office of Compliance
Linda Lewis, MD., Lead Medical Officer, DAVP
Katherine Schumann, MS., RPM, DAVP

SPONSOR ATTENDEES
Rajeev M. Menon, PhD Director, CPPM
John Morris, PhD Director, CMC Project Management
Kelly Norton, PhD Associate Director, CMC Coordination
John Donaubauer, PhD Director, CMC Scientific Affairs
Seble Wagaw, PhD Associate Director, Process R&D
Shailendra Bordawekar, PhD Director, Process R&D
Devalina Law, PhD Research Fellow, Manufacturing Science and Technology
Paul D. Curry, Jr., PhD Associate Director, Analytical R&D
John M. Sall, Pharm D, PhD Senior Director, Regulatory Affairs, US and Canada
Cheryl Pape, MS, RAC Director, CMC Regulatory Affairs
Sherie Masse, MS, RAC Associate Director, CMC Regulatory Affairs
Sou-Jen Chang, PhD Associate Director, CMC Regulatory Affairs
Anutosh R. Saha, PhD Director, Regulatory Affairs, GPS

1.0 BACKGROUND

The purpose of this Type B meeting is to request the Agency's feedback concerning key Chemistry, Manufacturing, and Controls (CMC) topics which are considered critical to expedite the development timeline for the planned New Drug Application (NDA). These topics either have not yet been addressed with the agency or are AbbVie responses to agency comments from the July 22nd Type B Multidisciplinary meeting.

AbbVie is currently developing DAAs for administration in combination for the treatment of chronic HCV infection: ABT-450 (nonstructural protein [NS] 3/4A protease inhibitor co-administered with ritonavir as a pharmacokinetic enhancer, ABT-450/r), ABT-267 (NS5A inhibitor), and ABT-333 (NS5B polymerase inhibitor). ABT-450 and ritonavir are co-formulated with ABT-267 into a fixed-dose tablet (ABT-450/r/ABT-267).

On September 16, 2013, AbbVie provided a slide deck with their responses and feedback to the Agency's Preliminary Responses.

Introduction and Opening Remarks	5 minutes
Discussion of Questions	50 minutes
Question 7: Dissolution Methods	
Question 4: (b) (4)	
Question 2: Drug Substance Specifications – Critical Quality Attributes	
Question 6: Drug Product Intermediates and Drug Product Specifications	
Questions 1 and 3: Drug Substance Control Strategy Implementation	
Question 5: (b) (4)	
Meeting Summary and Review of Agreements	5 minutes

2. DISCUSSION

Question 1: Drug Substance Control Strategy Implementation

AbbVie's approach to commercial process development is consistent with and applies the principles of ICH Guidelines Q8, Q9 and Q11. AbbVie used the principles of risk assessment, multivariate analyses, and experimental design to establish significant process understanding as part of developing the commercial process and the associated control strategy.

The majority of the control elements for the various unit operations across the three drug substances and two drug products will be traditional. For AbbVie, this means that thecontrol elements are expressed as a combination of specifications for material attributes and process parameter ranges or limits.

Appendix B describes the development of (b) (4) as an example of AbbVie's non-traditional control elements. This specific control element is based on a fundamental parameter, (b) (4) The process validation approach, data that will be available at the time of commercial site inspection, and the quality system requirements that ensure that the process will continue to be operated within the (b) (4) range are described.

Does FDA agree with this approach for implementation of a non-traditional control element of the control strategy at the commercial site and its management through our quality system?

Agency Response:

Your approach to controlling the [redacted] (b) (4) via the proposed iterative approach as described in page 55 of the background package seems reasonable as long as you have clear instructions in the batch record. You should also provide a copy of the Master Batch Record in the NDA so that we may evaluate the control strategy. We recommend that you clarify in the NDA how any subsequent changes to this control approach will be handled from the regulatory perspective.

We do note that the approach described in the second paragraph in section 1.3 (page 55) appears to lack some details, e.g., [redacted] (b) (4) We recommend establishing an appropriate [redacted] (b) (4) range (upper and lower limits).

Explain line 4 of Table 2 (page 55) [redacted] (b) (4) ".

Indicate if [redacted] (b) (4) would also be expected to be converted to the [redacted] (b) (4) under the proposed [redacted] (b) (4) conditions.

Additional Comments

FDA does not approve validation approaches or protocols used in process validation studies. The actual protocols, acceptance criteria and study outcomes will be evaluated during an inspection. The firm should conduct all studies necessary to assure the commercial manufacturing process for API is capable of consistently providing material meeting the established specifications. It is necessary for firms to justify and confirm earlier process design and development work for their proposed scale up to commercial scale.

For additional information, please refer to "Guidance for Industry, Process Validation: General Principles and Practices" posted at the following link.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf.

In addition, Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf

Meeting Discussion:

AbbVie Response: See AbbVie's response sent on 9/16/2013 slides 17 on Drug Substance Control Strategy Implementation

The Agency states that we do not comment on the appropriateness of the process validation, the Agency does not prescribe how that is to be accomplished as it will depend on multiple factors, some of which are specific to the complexity of the product and process; AbbVie need to define the variations, design, and provide justification. This will be reviewed at inspection.

Question 2: Drug Substance Specifications - Critical Quality Attributes

A control strategy should ensure that each drug substance CQA is within the appropriate range, limit or distribution to assure drug substance quality. The drug substance specification is one part of the overall control strategy and not all CQAs need to be included on the drug substance specification.

AbbVie has followed the recommendations provided in ICH Q11 (section **6.1.2**) during development and will provide a justification of specification for each drug substance with the following attribute categories in the NDA:

1. CQAs included on the specification and confirmed through testing of the drug Substance
2. CQAs included on the specification and confirmed through upstream control (e.g., as in Real Time Release Testing [RTRT])
3. CQAs not included on the specification but ensured through upstream control. Appendix C provides a summary of justification of the attributes that fit in Categories 2 and 3, if applicable. In addition, it discusses any drug substance attributes considered to be non-critical

Does the Agency agree with AbbVie's proposal of the CQAs to be included in the commercial ABT-450, ABT-267, and ABT-333 drug substance specifications?

Agency Response:

In general your approach of using upstream control, testing and specification methods for controlling CQAs is reasonable. However, the acceptability of the "attribute category" assignments, specifications, the various quantitative limits and the adequacy of the various spiking experiments will be NDA review decisions.

Include a USP <231> test for heavy metals in each drug substance specification.

Test each drug substance for each solvent that was used during the manufacturing process, (b) (4)

Explain how the assay value of ABT-333 is corrected for the presence of water if water is not included in the ABT-333 specification.

Meeting Discussion:

AbbVie Response: See AbbVie's response sent on 9/16/2013 slides 11- 13 on Drug Substance Specifications – Critical Quality Attributes

The Agency states that AbbVie should provide a justification for not performing water content testing in the NDA. The Agency stated that this justification could be strengthened by noting how the process controls this attribute, and by describing in general terms whether water content testing might be done on a non-routine basis (e.g., situational or periodic testing). The information can be provided in the summary of the control strategy.

Question 3: Drug Substance Specification - ABT-267 Impurities

The drug substance specification impurity limits have been developed using process knowledge, toxicological qualification levels, analytical and manufacturing variability, and drug substance lot history. The lot history available at the time of NDA submission will be limited and insufficient to use a fully statistical approach for setting acceptance criteria; the proposed impurity acceptance criteria were established based on toxicological qualification. The process ranges chosen for commercial manufacture will ensure that the impurity levels do not exceed qualified levels and reflect a reasonable level of manufacturing variability.

Does the agency agree with AbbVie's approach for setting the impurity acceptance criteria for ABT-267 drug substance and the application of this approach to ABT-333 and ABT-450 drug substances, as appropriate?

Agency Response:

Impurities should be toxicologically qualified and you indicate that the impurities [redacted] in ABT-267 are qualified at [redacted]% and [redacted]%, respectively. Information to support these values should be included in the NDA.

The manufacturing process and process capability for impurity control/clearance should be understood. You have accumulated a large body of information concerning [redacted] the manufacture of ABT-267 which should be of value [redacted] mentioned previously. We request that you provide a copy of the intended master batch record in the NDA so that we can understand how this approach to impurity control will be implemented.

The above principles, i.e., toxicological qualification of impurities as appropriate and a thorough understanding of the manufacturing process so as to set robust operating parameter ranges, also generally apply to the manufacture of ABT-333 and ABT-450.

The control strategy and the acceptance criteria will be evaluated for acceptability at the time of NDA review.

Question 4: [redacted]

[redacted]

Does the agency agree with this control strategy to limit the formation of [redacted] ***during storage?***

Agency Response:

We acknowledge the stability data and study results provided to support the proposed control strategy to limit the formation of [redacted] during manufacturing and storage of the drug product by including a "not less than" limit for [redacted] specification. It is noted that additional [redacted] laboratory experiments and additional retrospective analysis of [redacted] formation rates from additional Phase 3 clinical batches

are anticipated and will further assist the selection of an appropriate limit for (b) (4) . (b) (4) Therefore, a range is recommended as the acceptable criteria for (b) (4). Provide justifications for controls on the (b) (4) degradants in the final tablet before the NDA submission. The acceptability of the proposed acceptance criteria and supporting data will be evaluated during NDA review.

Meeting Discussion:

AbbVie Response: See AbbVie's response sent on 9/16/2013 slides 10 on (b) (4)

Regarding the concern about the (b) (4) *, the Agency stated* (b) (4) *AbbVie should provide information about the potential toxicity of* (b) (4) *at the levels likely to be present in drug product. The information can be provided in the IND.*

AbbVie stated that they will search for and provide information on the (b) (4) *and the potential impact on the drug product.*

AbbVie will specify a range for (b) (4)

Question 5: ABT-450/r/ABT-267 (b) (4)**:**

(b) (4) is proposed for ABT-450/r/ABT-267 Film-Coated Tablets. Development studies have been conducted to show equivalency of the two manufacturing processes on final product quality and are detailed in Appendix F. Process validation will be performed prior to commercialization of the manufacturing process.

Does the agency agree with the inclusion of both (b) (4) ***processes and corresponding batch size ranges in the original NDA submission?***

Agency Response:

The inclusion of both (b) (4) processes and corresponding batch size ranges in the original NDA submission appear reasonable. The adequacy of the comparability of the two processes will be evaluated during NDA review.

We recommend a comprehensive discussion of the alternate process prior to NDA submission. Sufficient details and supporting data on the two manufacturing processes, process control and equivalency demonstration should be submitted in the NDA. Given below are some examples of information/supporting data we recommend including in the NDA for both processes.

- Potential impacts of the process parameters on the physical-chemical properties of the (b) (4) and the quality of the final tablets
- Selections of process parameters and In-Process Controls
- Process equivalence/comparability studies results
- Release data

Meeting Discussion:

AbbVie Response: See AbbVie's response sent on 9/16/2013 slides 19 on (b) (4)

AbbVie proposes to submit the alternate (b) (4) process as a post-approval change via a comparability protocol in the NDA.

The Agency states that comparability protocol can be submitted. However it is recommended that a thorough discussion in the form of a teleconference should occur prior to submitting the comparability protocol in the NDA.

Question 6: Drug Product Intermediates and Drug Product Specifications

AbbVie has developed specifications in compliance with ICH recommendations. The drug product specification is one part of the overall control strategy and not all CQAs are included on the drug product specification. AbbVie will provide a justification of specification for each drug product and intermediate, if applicable, with the following attribute categories in the NDA:

1. CQAs included on the specification and confirmed through testing of the drug product or intermediate
2. CQAs included on the specification and confirmed through upstream control (e.g., as in Real Time Release Testing [RTRT])
3. CQAs not included on the specification but ensured through upstream control Appendix G provides a summary of justification of the attributes that fit in Categories 2 and 3, if applicable, is listed. In addition, there is a discussion any drug product attributes considered to be non-critical.

Does the Agency agree with AbbVie's proposal of the CQAs to be included in the commercial ABT-450/r/ABT-267 FDC tablet, ABT-450 intermediate, ABT-267 intermediate and ABT-333 tablet specifications?

Agency Response:

For ABT-450/r/ABT-267 FDC tablet:

In general your approach of using upstream control, testing and specification methods for controlling CQAs is reasonable. There are insufficient data at the current stage to permit further evaluation. The adequacy of the proposed control strategy will be evaluated during review of the

NDA in its entirety. [redacted]

[redacted]

For ABT-450 intermediate, ABT-267 intermediate:

In general, your approach of using upstream control, testing and specification methods for controlling CQAs is reasonable. The adequacy of the proposed control strategy for the intermediates will be evaluated during NDA review based on the available stability data (plus [redacted] testing results obtained using [redacted]), proposed storage conditions, and proposed expiration dating period. Justification and supporting data are needed for not including the [redacted] test in the specification. Consider developing a quantitative [redacted]

For ABT-333 tablet:

Generally the drug product specification tests are reasonable. You should perform stress testing to show that the [redacted] does not change in [redacted] in the coated tablets and submit the results of this testing in the NDA.

Meeting Discussion:

AbbVie Response: See AbbVie's response sent on 9/16/2013 slides 14 - 16 on Drug Product Intermediates and Drug Product Specifications

AbbVie described and explained their [redacted], and stated that this [redacted] test is a more sensitive and appropriate technique to use.

The Agency stated that achieving and maintaining the [redacted] is an important quality attribute. The total control strategy for this attribute will be evaluated during the NDA review, and the adequacy of this [redacted] test can then be assessed.

The Agency states that AbbVie should continue to work to see how to improve the development plan and look at the potential impact of risk.

Question 7: Dissolution Methods

Details of the ABT-450/r/ABT-267 and ABT-333 dissolution methods and justifications are presented in Appendix H. In both cases, complete drug release is accomplished within the observed Tmax for each compound indicating that drug release is not rate limiting to absorption.

Does FDA agree that the dissolution method for ABT-450/ritonavir/ABT-267 is suitably discriminating? Does FDA agree that ABT-450/ritonavir/ABT-267 is an immediate release product and that the proposed (b) (4) ***is justified?***

Does FDA agree that the dissolution method for ABT-333 is suitably discriminating?

Does FDA agree that ABT-333 is an immediate release product and that a proposed (b) (4) ***are justified??***

Agency Response:

A suitably discriminating dissolution method is one that is capable of detecting and rejecting batches that are not bioequivalent. Demonstrating that a dissolution method is sensitive to extreme changes that are highly unlikely to occur does not necessarily provide adequate assurance that the method can detect meaningful process/product deviations before product performance is impacted. Please include the following method development information in your NDA for review.

- A standalone method development report that includes the description of the optimal in vitro dissolution methodology and the developmental parameters (i.e., solubility data for the drug substance across the pH range, selection of the equipment/apparatus, in vitro dissolution media, selection of type and concentration of surfactant used, agitation/rotation speed, pH, assay, sink conditions, etc.). The testing conditions used for each test should be clearly specified, and the complete dissolution information summarized (i.e., individual values, mean values, RSDs, and profiles).
- A summary of the relevant in vivo bioavailability data supporting the discriminating ability of the proposed method. The chosen method should be discriminating and sensitive enough to reject lots that would have less than acceptable clinical performance.
- A listing of all critical process/formulation attributes likely to impact dissolution and your justification for the proposed ranges based on the capability of the dissolution method. In addition, include a tabular summary of the formulation and dissolution method changes throughout development and the dissolution data for all formulations used in development using the final method, if available.
- A summary of the studies completed to evaluate the robustness of the proposed method (i.e., sensitivity to small changes in test parameters).

- The complete analytical method validation report.

Depending on your NDA submission timelines, you may submit your report under the IND for FDA review and acceptance. All IND submissions requesting FDA feedback should clearly indicate so in the cover letter.

Further, we do not agree that a (b) (4) is appropriate for your FDC tablet. We recommend that you re-analyze your data and propose three-point acceptance criteria in your future NDA for FDA's review, with your justification. We also recommend that you collect and submit the complete dissolution profile data for all pivotal clinical and registration stability lots at release and on stability testing.

(b) (4) . A determination on the immediate release designation for your product will be made during the NDA review when the complete clinical PK data are available for review. Regardless of the designation, however, differences in the drug release rate for (b) (4) tablets are known to affect bioavailability.

In addition, FDA is concerned about the potential for dose-dumping or precipitation issues in the presence of alcohol. Therefore, include in your NDA the results of in-vitro alcohol dose dumping studies for review.

- The following alcohol concentrations for the in vitro dissolution studies (using 12 units each) are recommended: 0%, 5%, 10%, 20%, and 40%.
- Generally a range of alcohol concentrations in 0.1 N HCl and the QC dissolution medium is recommended. If the optimal dissolution medium has not been identified, then dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.
- Report f2 values to assess the similarity (or lack thereof) in the dissolution profiles. Compare the shape of the dissolution profile to see if the modified release characteristics are maintained, especially in the first 2 hours. The report should include the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study.

Meeting Discussion:

AbbVie Response: See AbbVie's response sent on 9/16/2013 slides 3-9 on Dissolution Methods:

For ABT-450/r/ABT-267 and ABT-333 tablets, AbbVie will submit method development and analytical validation reports to the INDs for the Agency's review. The method development reports will contain the following.

- *Summary of developmental parameters*
- *Summary of dissolution method changes throughout development*
- *Summary of robustness studies*
- *Dissolution data for all formulations used in development using the final method*

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AbbVie also intends to provide supportive pharmacokinetic data regarding the immediate release claim, as well as an assessment of the method's discriminating capabilities in the context of rejecting batches that are not bioequivalent in the IND submission.

The Agency agreed that AbbVie's approach was reasonable and requested that the future IND submission clearly specify a request for Agency review and feedback. The Agency further clarified that the in vitro alcohol study comments relate to product in-use risks (e.g., no exposure) (b) (4) *Other approaches evaluating the product in-use risks may be considered, as deemed appropriate.*

Post Meeting Clarification Note: AbbVie may submit the product in-use risk assessment studies at the time of NDA filing.

Additional Comment:

The Agency informed AbbVie of the August 20, 2013 published report on: "EMA-FDA pilot program for parallel assessment of Quality-by-Design applications: lessons learnt and Q&A resulting from the first parallel assessment."

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/s/

RAPTI D MADURAWE
10/09/2013

PeRC BPCA Subcommittee Meeting Minutes
July 10, 2013

PeRC Members Attending:
Peter Starke
Tom Smith
Robert "Skip" Nelson
William J. Rodriguez
Wiley Chambers (did not review saxagliptin/metformin WR)
Lily Mulugeta
Daiva Shetty
Gregory Reaman
Kevin Krudys
Ruthanna Davi
Jane Inglese
George Greeley
Rosemary Addy
Maura O'Leary
Andrew Mosholder
Melissa Tassinari
Shrikant Pagay
Diane Murphy
Susan McCune
Rachel Witten

Guests Attending:
Dionna Green (OCP)
Erica Radden (PMHS)
Courtney Suggs (OCP)
Gilbert Burckart (OCP)
Donna Snyder (PMHS)
Terrie Crescenzi (OPT)
GT Wharton (OPT)
Allyson Karesh (PMHS)
Renan Bonnel (OPT)
Fred Alavi (DMEP)
William Chong (DMEP)
Karen Mahoney (DMEP)
Lokesh Jain (OCP)
Satjit Brar (OCP)
Colette Jackson (DPARP)
Sang Chung (OCP)
Raymond Chiang (DMEP)
Le Ping Pian (DB2)
Frank Pucino (DMEP)
Mark Rothmann (DB2)
Kevin Watt (OPT)
Jeffry Florian (OCP)
Katherine Schumann (OCP)
Linda Lewis (DAVP)
Mary Singer (DAVP)
Sofia Chaudhry (DPARP)
Susan Limb (DPARP)
Ping Ji (OCP)
Jennifer Pippins (DPARP)

Agenda

(b) (4)

INDs 103526, 108434, 101636 ABT-450, ABT-267, ABT-333 iPSP (Partial Waiver/Deferral)

(b) (4)

(b) (4)

ABT-450, ABT-267, ABT-333 Initial PSP (Partial Waiver/Deferral)

- Recommendations:
  - The PeRC reviewed comments provided by the Division to the iPSP and agreed to recommendations offered for the treatment of Hepatitis C Virus Infection.
  - The PeRC also agreed to the plan offered for a partial waiver, deferral and plan offered for this triple combination product.

(b) (4)

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/s/

GEORGE E GREELEY
08/29/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 103,526

MEETING MINUTES

AbbVie Inc.
Attention: John M. Sall, PharmD, Phd
Senior Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77, Bldg. AP30-1
North Chicago, IL 60064

Dear Dr. Sall:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABT-450. Please also refer to your INDs for ABT-267 (IND 108,434) and ABT-333 (IND 101,636).

We also refer to the meeting between representatives of your firm and the FDA on July 22, 2013. The purpose of the meeting was for you to provide a multidisciplinary update on the development program with your HCV DAA combination regimen, ABT-450/ritonavir/ABT-267 + ABT-333 with or without ribavirin (RBV) that was granted Breakthrough Therapy Designation on May 1, 2013.

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 Katherine Schumann, Regulatory Project Manager at (301) 796-1182.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
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:	Breakthrough Therapy
Meeting Date and Time:	July 22, 2013 9:30 am – 11:00 am EDT
Meeting Location:	White Oak, Building 22, Room 1309
Application Number:	IND 103,526 (references IND 108,434 and IND 101,636)
Product Name:	ABT-450/ritonavir/ABT-267 + ABT-333 with or without ribavirin
Indication:	Treatment of genotype-1 chronic hepatitis C virus infection
Sponsor/Applicant Name:	AbbVie Inc.
Meeting Chair:	Russell Fleischer, PAC, MPH
Meeting Recorder:	Katherine Schumann, MS

FDA ATTENDEES

1. Debra Birnkrant, M.D., Division Director, Division of Antiviral Products (DAVP)
2. Jeffrey Murray, M.D., MPH, Deputy Director, DAVP
3. Kendall Marcus, M.D., Deputy Director for Safety, DAVP
4. Linda Lewis, M.D., Medical Team Leader, DAVP
5. Russell Fleischer, PA-C, MPH, Medical Reviewer, DAVP
6. Mark Seaton, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
7. Jules O'Rear, Ph.D., Clinical Virology Team Leader, DAVP
8. Patrick Harrington, Ph.D., Clinical Virology Reviewer, DAVP
9. Lei Nei, Ph.D., Statistician, Division of Biometrics IV
10. John Lazor, Pharm.D., Director, Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology IV (DCP IV) (via telephone)
11. Kellie Reynolds, Pharm.D., Deputy Director, OCP, DCP IV(via telephone)
12. Islam Younis, Ph.D., Clinical Pharmacology Team Leader, OCP, DCP IV
13. Vikram Arya, Ph.D., Clinical Pharmacology Reviewer, OCP, DCP IV
14. Jeffry Florian, Ph.D., Pharmacometrics Reviewer, OCP
15. Stephen Miller, Ph.D., CMC-Lead, Office of New Drug Quality Assessment (ONDQA), Division of New Drug Quality Assessment II (DNDQA II)
16. Minerva Hughes, Ph.D., Biopharmaceutics Reviewer, ONDQA (via telephone)
17. Lin Qi, Ph.D., CMC Reviewer, ONDQA, DNDQA II (via telephone)

18. Scott Dallas, Pharm.D., Associate Director, Division of Medication Error Prevention and Analysis (DMEPA), OSE (via telephone)
19. Morgan Walker, Pharm.D., M.B.A., Safety Evaluator, DMEPA, OSE (via telephone)
20. Alfred Sorbello, D.O., M.P.H., Medical Officer, Division of Pharmacovigilance, OSE (via telephone)
21. Douglas Warfield, eData Team, Office of Business Informatics (via telephone)
22. Elizabeth Thompson, Chief, Project Management Staff, DAVP
23. Katherine Schumann, M.S., Regulatory Project Manager, DAVP
24. Nina Mani, M.S., Ph.D., Regulatory Project Manager, DAVP (via telephone)

SPONSOR ATTENDEES

1. Barry M. Bernstein, M.D., Divisional Vice President, Infectious Diseases Development
2. Thomas J. Podsadecki, M.D., Project Director, Antiviral Clinical Project Team
3. Tami Pilot-Mathias, Ph.D., Senior Principal Research Scientist, HCV Clinical Virology
4. Sandeep Dutta, Ph.D., Director, Clinical Pharmacology and Pharmacometrics
5. Rajeev M. Menon, Ph.D., Director, Clinical Pharmacology and Pharmacometrics
6. Martin King, Ph.D., Director, Statistics
7. Lois Larsen, Ph.D., Associate Director, Statistics
8. Carolyn Setze, MS, Principal Research Statistician
9. John Morris, Ph.D., Director, CMC Project Management
10. Bruce Trela, Ph.D., Director, Preclinical Safety
11. Cheryl Pape, MS, RAC, Associate Director, CMC Regulatory Affairs
12. Khyati Roberts, Senior Director, Regulatory Policy and Intelligence
13. Andrew Storey, Vice President, Regulatory Affairs, US & Canada
14. John M. Sall, Pharm.D., Ph.D., Senior Director, Regulatory Affairs, US & Canada
15. Margarita Aguilera, M.Sc., Senior Director, Regulatory Affairs, Global Product Strategy (GPS)
16. Anutosh R. Saha, Ph.D., Director, Regulatory Affairs, GPS
17. Janette Meyer, RAC, Associate Director, Regulatory Affairs, US & Canada

1.0 BACKGROUND

The Sponsor (AbbVie) requested this Type B meeting to discuss the continued development of their Breakthrough Therapy combination regimen of ABT-450/ritonavir with ABT-267 (coformulated tablet ABT-450/r/ABT-267) and ABT-333 administered with and without ribavirin (RBV). The combination regimen received Breakthrough Therapy Designation on May 1, 2013.

The purpose of this Type B meeting is to provide a multidisciplinary update concerning the HCV development program, including the status of the ongoing and planned Phase 2 and 3 studies with the 3-DAA regimen ± RBV and AbbVie's plans to expedite the manufacturing. Additionally, discussions are to take place regarding outstanding development issues.

DAVP sent preliminary comments to AbbVie on July 17, 2013.

On July 19, 2013, AbbVie provided a preliminary slide deck to DAVP and communicated that they would like to focus the meeting discussion on questions 1, 2, 3a/b, 4a, 7 and the additional comments on oral contraceptive use, bridging drug interaction studies and ABT-267 metabolites. On July 21, 2013, AbbVie provided the final version of their presentation (attached), along with preliminary responses to the CMC comments to be officially submitted prior to the Type B CMC meeting scheduled for September 17, 2013.

2. DISCUSSION

Questions submitted by the Sponsor are in regular font, the Agency's preliminary comments are in **bold** font, and discussions during the July 22, 2013 meeting are in *italic* font.

AbbVie began the meeting by providing an update on the status of enrollment of their Phase 3 clinical trials and their plans for a compassionate use program (slides 2-4 of the sponsor's presentation, attached).

2.1. Clinical

Question 1. Clinical Study Reports

As described, AbbVie's current plan is to include CSRs for all studies including groups administered the 3 DAAs in combination at doses at least as high as those proposed for the indication in the NDA. This includes Phase 2 Studies M11-652 and M14-103 and Phase 3 Studies M11-646, M13-098, M13-099, M13-961, M13-389 and M14-002. The M11-652 CSR will include all data from 48 weeks of post-treatment follow up. The other 7 CSRs will include SVR12 and available SVR24, late relapse, and population sequence resistance data.
A summary of resistance and maintenance of efficacy results from and interim analysis of the long-term follow-up Study M13-102 (no treatment administered) will also be provided in the NDA. The data cut-off for this interim analysis will be December 2013.

Does the Agency agree with the data to be included in the 8 Phase 2 and 3 studies that are the key studies for the HCV GT1 NDA and that these data will be adequate to support filing and review of the planned NDA?

DAVP Response: In general, it appears the Phase 3 studies are sufficiently comprehensive to evaluate the three DAA ± RBV regimen in multiple populations of GT1-infected patients. As noted in our June 10, 2013 advice letter, in the absence of study results it is not possible to determine if these data will be adequate to support filing and review of the planned NDA.

Please summarize the data that you expect to be available from the long-term follow-up study (M13-102), including the number of SVR and non-SVR subjects with at least 48 weeks of follow-up data in this or other on-going trials. Also, please comment if there have been any additional post-SVR24 relapses observed beyond the two subjects reported previously.

Meeting Discussion:
AbbVie explained that 50 subjects are currently enrolled in M13-102 and they expect approximately 200 subjects at the time of NDA submission. AbbVie offered to submit additional information on these subjects with a breakdown by SVR versus non-SVR. DAVP responded that a submission of the data prior to the NDA is not necessary, as the purpose of the question was to get a sense of what long-term follow up data will be included in the NDA.

AbbVie confirmed that there have been no additional post-SVR24 relapses beyond the two subjects reported previously.

Question 2. Clinical Study Report Submission Timing

As described, accelerated enrollment of Phase 3 Studies M11-646 and M13-098 may enable submission of these CSRs (including SVR12 data for all subjects in the active (3-DAA + RBV) arm, but excluding SVR12 data for the placebo arm) by February 2014 (approximately 2 months prior to the final NDA, which will include the remaining CSRs), if agreeable to the Agency.

Final CSRs from the 7 studies (Studies M11-646, M13-098, M13-099, M13-961, M13-389, M14-002, and M14-103) will be submitted to the subject INDs when all subjects have reached Post Treatment Week 48 or discontinued the study, and after the NDA review. Resistance data through Post Treatment Week 48 will be included in the final CSRs.

Does the Agency agree with AbbVie's proposal to provide individual CSRs for Studies M11-652, M11-646 and M13-098 ahead of the upcoming HCV GT1 NDA to facilitate review?

DAVP Response: In general, DAVP's preference is that only fully completed CSRs with their complete data sets be submitted. Submission of incomplete datasets followed by "updated" datasets is not useful. If the complete CSR and accompanying datasets for M11-

652 are available, submission of these data prior to the full NDA submission would be acceptable.

Please note that any preliminary agreements for rolling review, a feature available for products granted Fast Track Designation and/or Breakthrough Therapy Designation, should be followed by a formal request to your INDs as described in Appendix 2 of the draft guidance document "Guidance for Industry: Expedited Programs for Serious Conditions – Drug and Biologics" dated June 2013. This also applies to your proposal for submission of CMC information under Question 12.

Meeting Discussion:
AbbVie acknowledged DAVP's request for fully completed CSRs and confirmed that the M11-652 CSR will be completed with data through Week 48. AbbVie clarified that for M11-646 and M13-098, the completed CSRs and the ISE will include all primary and secondary endpoints, but will not contain SVR12 data for the placebo crossover arms (Arm B), although end-of-treatment (EOT) data would be provided for these subjects. AbbVie also explained that if they submit M11-646 and M13-098 early in February, they would not be updating the datasets, ISS/ISE or CSRs with any new data from those trials when the final pieces of the NDA are submitted in April. AbbVie mentioned that due to the 3:1 randomization scheme of these trials, the subjects in the placebo crossover arms of M11-636 and M13-098 only represent 10% or less of the total number of subjects enrolled in the Phase 2 and 3 trials that are planned for inclusion in the NDA.

DAVP responded that additional internal discussion would be needed before a final response can be provided regarding this proposal. DAVP will hold additional discussion on this issue and respond to AbbVie at a later date.

Question 3. Summary of Efficacy/Integrated Summary of Efficacy

a. Data from the 6 Phase 3 studies (Studies M11-646, M13-098, M13-099, M13-961, M13-389, and M14-002) will be summarized in CSE (Module 2.7.4)/ISE as outlined. The same data included in the CSRs from the 10 arms included in the primary and secondary efficacy endpoints in these 6 studies will be used to compare efficacy results across studies and to perform the integrated analyses across studies as specified by the Draft Guidance for Industry: Integrated Summary of Effectiveness (August 2008). Thus, all data associated with primary and secondary efficacy endpoints for SVR12, ALT normalization, and Hgb decreases will be summarized in the CSE/ISE.

   Data from the Phase 2 Studies M11-652 and M14-103 will not be included in the primary analysis sets in the CSE/ISE as these are uncontrolled studies. In addition, Study M11-652 used a different formulation of the DAAs. However, data from the Phase 2 Study M11-652 groups with 3 DAAs ± RBV at DAA doses and duration at least as high as those proposed for the NDA will be combined with data from the Phase 3 studies and Study M14-103 to assess persistence of efficacy as Study M11-652 will have the longest duration of follow-up at the time of submission of the NDA. Subjects on stable opiate substitution from these groups in

Study M11-652 and the small number of such subjects in other Phase 3 studies will also be combined with subjects in Study M14-103 for an examination of efficacy in this subpopulation.

Does the Agency agree with information to be included from the clinical studies in the CSE/ISE of the upcoming HCV GT1 NDA and that these data will be adequate to support filing and review of the planned NDA?

DAVP Response: As noted in our guidance documents, the ISE should include an integrated analysis of all key clinical trials for which efficacy results can reasonably be pooled or compared. Your approach to the CSE/ISE appears reasonable but we are unable to provide any more specific comments at this time.

The ISE should include a detailed summary of data demonstrating the contribution of each component (each DAA and RBV) in the combination drug regimen(s) proposed for use in key patient populations, particularly those infected with HCV genotype 1a versus 1b.

Meeting Discussion:
AbbVie acknowledged DAVP's request for them to demonstrate the contribution of each component in the regimen. AbbVie explained that the ISE will follow the guidance document and include justification for the dose, duration and regimen.

(b) (4)

The Division acknowledged this limitation, but cautioned that if the results of the 2-DAA trials are public by the time of the Advisory Committee meeting for the 3-DAA NDA, then the appropriateness of the 3-DAA regimen for genotype 1b patients may be raised at the meeting. DAVP also expressed concern that labeling of the 3-DAA regimen for this sub-population may be difficult if preliminary data suggest the 2-DAA regimen is adequate. The company will likely need to justify why ABT-333 and ribavirin are necessary for these patients.

(b) (4)

(b) (4)

The 3-DAA regimen was selected for all sub-populations based on the Phase 2 data in order to avoid as many virologic failures as possible.

DAVP suggested that AbbVie (b) (4) *, and AbbVie responded that this option was already under consideration.*

DAVP mentioned that the End-of-Phase 2 meeting package included some helpful charts demonstrating the SVR impact of adding additional drugs based on data from ongoing Phase 2 trials. DAVP recommended that the same types of charts be included in the ISE using both Phase 3 and updated Phase 2 data. DAVP also asked whether data from the M13-393 trial will be included in the ISE (implying that data from the genotype 1b arms treated with ABT-450/r/ABT-267 could be helpful to demonstrate the benefit of adding ABT-333). AbbVie responded that the data from M13-393 could be included if they are considered relevant, noting that the regimen in M13-393 is different from the regimens currently being studied in Phase 3. The sponsor noted earlier in the discussion that there have been some virologic failures (~10%) in the M13-393 genotype 1b arms, implying that they may have some evidence that ABT-333 provides an efficacy benefit in genotype 1b, although the sponsor also noted that the numbers are small and there are no comparator arms in which subjects received all 3 HCV DAAs. DAVP concluded this discussion topic by stating that the sponsor should summarize the available data at a pre-NDA meeting to determine which data should be included in the ISE.

(b) (4)

b. The format for the CSE/ISE will be similar to that planned for the CSS/ISS (with the ISE in Module 5, Section 5.3.5.3 and the CSE in Module 2, Section 2.7.3) to summarize/discuss the efficacy of the proposed DAA combination.

Does the Agency agree with the proposed format for the CSE and ISE for the upcoming HCV GT1 NDA and that this format will be adequate to support filing and review of the planned NDA?

DAVP Response: In general, your proposal for placement and format of the CSE/ISE is reasonable. You should include data from arms with doses/durations different from the selected regimen(s) to help support regimen selection. As noted above, in the absence of study results it is not possible to determine if these data will be adequate to support filing and review of the planned NDA.

Meeting Discussion:
AbbVie agreed to the inclusion of information to support selection of the chosen regimen, but clarified that most of the supportive data are derived from Phase 2 rather than the Phase 3 program, as the Phase 3 program did not include dose/duration variation with the exception of the duration comparison in M13-099 (12 weeks versus 24 weeks).

c. The proposed efficacy analysis sets and proposed efficacy analyses are described in Section 7.1.3.

Does the Agency agree with the proposed efficacy analysis sets and the proposed analyses for each of the analysis sets and that these analyses will be adequate to support filing and review of the NDA? Are any additional analyses required?

DAVP Response: Your proposed efficacy analyses sets appear reasonable in general. However, we recommend you submit a statistical analysis plan (SAP) for the ISE as the current high-level summary in the information package does not provide enough details. As one example, rather than simply stating "stratum-weighted proportions and variances will be used to calculate the CIs across studies", please further specify how the weight is calculated before the results are known. As another example, rather than simply stating "a test for heterogeneity in rates across strata will be performed using a chi-square test", please further specify the chi-square test.

We recommend that you develop the SAP following the guidance "Integrated Summary of Effectiveness". We remind you that pooling studies/strata with drastic heterogeneity should be avoided. Therefore, your SAP should specify how your heterogeneity assessment impacts your pooling analysis and your conclusion. We will make more specific comments after receiving your SAP.

Meeting Discussion:
AbbVie agreed to submit the ISE Statistical Analysis Plan, with a proposed submission timeline of August 2013.

d. Population pharmacokinetics and exposure-response analyses will be conducted separately for Phase 2 studies and for Phase 3 studies as described in Section 7.1.9.1. Data from Phase 2 studies for the DAAs given as monotherapy and with pegIFN plus RBV (Studies M10-351, M10-380, M11-602, M12-114 and M12-116) and in combination with other DAAs (Studies M12-746, M11-652, M12-998, and M13-386) will be combined for the population pharmacokinetics and exposure-response analyses. Similarly, data from the 6 Phase 3 studies (Studies M11-646, M13-098, M13-099, M13-961, M13-389, and M14-002) will be combined for the population pharmacokinetics and exposure-response analyses. In addition, data from the Phase 2 Study M14-103 (HCV GT1-infected subjects on methadone or buprenorphine) will be combined with data from the Phase 3 studies for exposure-response analyses to compare pharmacokinetics of subjects on methadone or buprenorphine with the other subjects in the Phase 3 studies. Population pharmacokinetics or exposure-response analyses reports will not b generated for the individual studies.

Does the Agency agree with this approach for conducting and submitting population pharmacokinetics and exposure-response analyses for the upcoming HCV GT1 NDA?

DAVP Response: Your proposed approach to conduct population pharmacokinetics and exposure-response analyses separately for the Phase 2 and Phase 3 data is acceptable given the differences in formulations and dosing utilized.

Question 4. Clinical Summary of Safety/Integrated Safety Summary

a. For the 8 Phase 2 and Phase 3 studies described in Question 1, safety analyses willbe provided in the CSS (Module 2.7.4)/ISS as outlined in Section 7.1.4 to Section 7.1.6. The groups administered doses of the 3 DAAs as high as those proposed for the NDA will be included from Study M11-652. Treatment-emergent adverse events and follow-up safety labs obtained up to 30 days after the last dose of study drug will be included in analyses. All available serious adverse events (whether treatment-emergent or not) as of the cut-offs for each study (SVR12 in most cases) will also be provided. The final data cut-off date for the last study to be included in the CSS/ISS is anticipated to be January 2014.

Does the Agency agree with this plan to provide safety information from the clinical studies in the CSS/ISS of the upcoming HCV GT1 NDA and that these data will be adequate to support filing and review of the planned NDA?

DAVP Response: In general, your proposal is reasonable. You should include data from arms with doses/durations different from the selected regimen(s) to help support regimen selection. As noted above, in the absence of study results it is not possible to determine if these data will be adequate to support filing and review of the planned NDA.

Meeting Discussion:
Regarding duration, AbbVie commented that they will only have information on durations other than 12 weeks from the Phase 2 trial M11-652 and the Phase 3 trial M13-099 in cirrhotic subjects, as the other trials did not evaluate multiple durations. The evaluation of different doses of ABT-450 will only be available from M11-652.

DAVP responded that it does not necessarily matter which trial(s) the information is derived from, as long as AbbVie clearly explains in the ISS how the doses were selected, with a particular focus on safety. This information regarding dose and duration should be summarized in the ISS, not just included in the CSRs.

b. The CSS/ISS mentioned above will be provided in the format that is consistent with the Draft Guidance for Industry, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (January 2007), Example 1: Large ISS including the tables and appendices in Module 5, and a smaller text portion summarizing clinical safety in Module 2.7.4.

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

DAVP Response: In general, your proposal is reasonable.

Does the Agency agree with the proposed safety analysis sets and the proposed analyses for each of the analysis sets and that these analyses will be adequate to support filing and review of the NDA? Are there any additional analyses that will be required?

DAVP Response: This appears to be a reasonable approach for format and content. Please follow the instructions in relevant guidances. Final determination about additional safety analyses will be made once data from the clinical studies becomes available, and can be discussed at the pre-NDA meeting.

Question 5. Integrated Resistance Report

As requested by DAVP, the integrated resistance analysis will include data from subjects administered 2 or 3 DAAs ± RBV in Phase 2 or 3 studies. Included are Studies M12-746, M12-998 (GT1), M11-652, M13-386, M14-103, M11-646, M13-098, M13-099, M13-961, M13-389, and M14-002. For all subjects randomized to any treatment arm included in the primary analysis in each Phase 2 and 3 study who experience VF, sequencing data from the failure time point and the corresponding baseline sample will be included. For the subjects initially randomized to placebo in Studies M11-646 and M13-098, resistance data will be included for those who experience on-treatment VF, but data from subjects who experience VF post-treatment will not be included.

Resistance data not included in the CSRs or integrated resistance analysis for the NDA, such as post-treatment VF of subjects initially randomized to placebo in Studies M11-646 and M13-098, VF occurring after Post-Treatment Week 12 through Post-Treatment Week 48 for other Phase 3 subjects, and emergence and persistence of resistance-associated variants through Post-Treatment Week 48, will be included in final CSRs and in an updated integrated resistance report.

The proposed resistance analysis sets and proposed integrated resistance analyses are discussed in Section 7.1.7 and sample datasets from Study M11-652 are attached in Module 5, Section 5.3.5.4.

The integrated resistance analyses will be provided in 5.3.5.3 Reports of Analyses of Data from More than One Study.

Does the Agency agree with the clinical studies to be included for each of the integrated analyses?

Does the Agency agree with the data to be included for the integrated resistance analyses for the upcoming HCV GT1 NDA from those clinical studies and that these data will be adequate to support filing and review of the NDA?

Does the Agency agree with the proposed integrated analyses to be included in the integrated resistance report?

Are there any additional analyses that will be required?

DAVP Response: We generally agree.

Please include NS3 position Q80 in your list of positions to analyze for your Baseline resistance analyses.

Please also plan to include a "Virology Summary", to be provided in Section 2.7.2.4-Special Studies. This document should summarize all of the nonclinical virology data (e.g., mechanism of action, cell culture and biochemical studies, cytotoxicity, resistance selection, etc.). Please include an up-to-date table listing all amino acid substitutions and associated phenotype data that have been evaluated in site-directed mutant phenotype studies. Please also provide cross-links to the individual nonclinical virology study reports as well as the integrated resistance analysis report.

Question 6. Electronic Datasets

AbbVie proposes to submit electronic CRT datasets and ARDs for 2 Phase 2 studies (Studies M11-652 and M14-103) and from the 6 Phase 3 studies (Studies M11-646, M13-098, M13-099, M13-961, M13-389, and M14-002) included in the CSS/ISS and for which CSRs will be submitted. The CRTs will not be provided in SDTM format. The ARD for efficacy will be in the format described in "Efficacy Data Submission in ADaM Conversion for HCV Drugs" [as provided by the Division as an appendix to comments on the Statistical Analysis Plans received on 24 April 2013]. The data sets for raw HCV RNA, safety laboratory data, and adverse event data described in that appendix (parts II, III, and IV) will also be included, as will SAS programs that generate the datasets from the CRT datasets. Analysis-ready SAS programs that produce key efficacy analysis results from the ARDs in the format requested will also be provided.

Additional ARDs will be submitted for safety laboratory data and adverse event data that will not be in ADaM format. Analysis-ready SAS programs that produce key safety analysis results from the ARDs will also be provided, as will SAS programs that create the ARDs from CRT datasets. For safety endpoints, the analysis-ready programs will be based on these ARDs rather than the datasets described under parts III and IV of the "Efficacy Data Submission in ADaM Conversion for HCV Drugs" appendix.

AbbVie expects to submit sample CRTs, ARDs, and SAS programs, as described above, for Study M11-652 in Q32013 as part of a Request for Advice to the subject INDs. The resistance data will be provided in the format specified by the template provided in the Attachment to the Draft Guidance: Guidance on Antiviral Product Development-Conducting and Submitting Virology Studies to the Agency (Guidance for Submitting HCV Resistance Data); February 2013. A sample resistance dataset in the proposed Phase 3 resistance data format using Study

M11-652 data is included in Module 5, Section 5.3.5.4. Note that the complete Study M11-652 resistance data will be submitted with the CSR in January 2014.

For Phase 1b and Phase 2 studies that did not include all 3 DAAs or had monotherapy phases (Studies M10-351, M10-380, M12-114, M11-602, M12-116, M12-746, M12-998, M13-386, and M12-114) but are included in pharmacokinetic or exposure response studies, CRT datasets will be provided. For the ISS/CSS, ISE/CSE, and Integrated Resistance Analysis, ARDs and ARPs will be provided for key analyses. The analyses to be included will be described in a future request for advice.

Does the Agency have comments on the sample resistance dataset provided? Does the Agency agree with the following specific choices for the resistance dataset?

1. *The format used specifically for submission of clonal sequence data*
2. *The split into 6 resistance datasets (based on DAA target and clonal versus population sequencing)*
3. *The exclusion from the resistance data set of subjects for whom no population sequencing was performed (i.e., those subjects achieving SVR12 who were not included in the matched baseline analysis)*

Does the Agency agree with this plan to provide CRTs, ARDs, resistance datasets, and ARPs in the specified format for the 8 indicated Phase 2 and Phase 3 studies?

Does the Agency agree with the plan for submission of data sets for other Phase 2 and Phase 1b studies?

Does the Agency agree with the plan for submission of data sets for Phase 1 studies?

Does the Agency agree with the plan to submit ARDs and ARPs for the ISS, ISE, and Integrated Resistance Analysis, and to establish the list of key analyses to be included as part of a future Request for Advice?

DAVP Response: Submitting data from Study M11-652 as a sample dataset is acceptable, as long as the same data that is being collected in the Phase 3 studies was collected in that study and they use similar dataset structure.

We note that you propose to submit your electronic datasets in non-SDTM format. Additional information regarding construction and submission of non-standard datasets can be found in the following FDA Study Data Specifications guidance: http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

If your datasets are non-standard, it will be critical for them to be "user-friendly" for all FDA review disciplines. Further feedback will be provided following review of your sample datasets.

<u>Regarding the submission of resistance data:</u> DAVP appreciates AbbVie's efforts in constructing the resistance datasets according to the 2013 draft guidance. Based on an initial review of the sample datasets, the datasets generally appear to provide data in the format intended in the draft guidance. We have the following comments and requests:

- **We agree with your plans for submission of clonal sequence data for the initial NDA. However, we may request additional data or analyses for the long-term follow-up study, which can be addressed at a later time when a sequence analysis plan is in place and more subjects have enrolled.**
- **We agree with your approach to assemble and submit separate datasets for each drug target.**
- **We agree with your approach to pool genotype 1a and 1b sequence data for each genome target dataset.**
- **We agree with your plans to include only subjects with available nucleotide sequence analysis data in the resistance datasets, assuming complete HCV RNA data for all other subjects will be reported elsewhere.**
- **If feasible, for the initial NDA submission please pool data from all six Phase 3 trials in your datasets. In other words, for each drug target gene report all population sequencing data across all six trials in a single dataset. We request pooling data from all six Phase 3 trials for the NDA even if individual trial datasets are also submitted earlier for M11-646 and M13-098.**
- **Please provide a listing of all subjects in the six Phase 3 trials who did not achieve SVR and for whom no resistance data were collected (i.e., non-SVR subjects not included in resistance datasets). For each subject, please provide a very brief explanation for why resistance data were not collected (e.g., "Subject lost to follow-up while HCV RNA suppressed" or "Post-Baseline sample with HCV RNA >1,000 IU/mL not available"). Any subjects for whom only partial data are available (e.g., NS3/4A but not NS5A or NS5B, perhaps due to technical reasons or insufficient sample) should also be included in this listing. This listing can be provided either as a separate .xpt dataset or as a summary table in your integrated resistance analysis summary report.**
- **Please populate EFFICFL (achieved primary efficacy endpoint) with Y or N.**
- **Please summarize the source of data used to populate the reference sequence conservation and variants rows.**

Also note that we recommend some minor edits and clarifications to the February 2013 version of the HCV resistance template draft guidance based on comments DAVP received in the public docket, and also based on internal discussions. We recognize that changes may be difficult to incorporate into scripts or datasets that have already been constructed, and therefore you are not required to change your procedures to incorporate these changes if they cause a significant technical burden. Please keep us informed if you incorporate these changes into your resistance datasets:

- **A new column heading (ISOLDY) should be added, and should refer to the *actual* day of the isolate obtained, relative to initiation of treatment.**

- **VISTDY should refer to the *planned*, protocol-defined treatment day.**
- **For HCVGTSC and HCVGTAN, if subtype level data are not available, report only genotype (e.g., 1). If data are ambiguous, report all results and add the word "AMBIGUOUS" (e.g., 2a/2c AMBIGUOUS). Clear mixed infections should be reported as Gt/Gt (e.g., 1a/1b).**
- **The planned inclusion and precise placement of any amino acid insertion columns in datasets should be discussed with DAVP. The insertion columns can be located in datasets in relation to other sequence positions (as in the draft guidance example, placed between amino acid positions 131 and 132). Alternatively, the insertion can be placed at the C-terminal end of the sequence columns. For datasets that include insertion columns, cells for rows/sequences without the insertion(s) should be populated with a dash (-) so it is clear these sequences do not contain the insertion.**
- **To report deletions in subject sequence data relative to the prototypic reference strain used to generate the dataset, a dash (-) should be reported for appropriate positions.**
- **For ambiguous amino acids (i.e., nucleotide information was present but amino acid could not be called due to non-interpretable translation), X should be reported for appropriate positions.**
- **Missing sequence data caused by poor sequence quality or other technical problems should be reported as a question mark (?) for appropriate positions. Efforts should be made not to have stretches of missing sequence information caused by poor sequence quality or other technical problems.**
- **If an amino acid region is included in the dataset columns, but no sequence information was obtained for a particular sample, a question mark (?) should be reported for all amino acid positions where no sequence information was obtained for that sample.**

Meeting Discussion:

DAVP re-iterated that early submission of sample datasets will be helpful in planning for such a complex NDA submission. DAVP acknowledged AbbVie's plans to submit the M11-652 datasets as a sample, and explained that submission of M11-652 datasets should be acceptable, provided that they do not differ greatly from those planned for the Phase 3 trials. AbbVie responded that there will be some minor differences, such as different variables, and offered to include a document outlining the differences with the submission. DAVP replied that such a document would be helpful.

AbbVie asked for DAVP input on how advantageous it would be for them to convert their datasets to a standardized format. DAVP responded that the review process has been developed around standardized data and that the reviewers can perform their pre-analysis work more quickly when standardized datasets are provided. DAVP responded that as applications become larger and more complex, standardized data becomes increasingly helpful. However, it is ultimately up to the sponsor to decide, as it depends upon what conversion would entail on the sponsor's side. AbbVie responded that they will consider converting to a standardized format prior to submission of the NDA, although that would ultimately affect their timeline for

submitting the sample datasets. AbbVie will update the Division at a later date regarding their decision.

2.2. Nonclinical

Question 7: Nonclinical Module Format

AbbVie will be submitting documentation for 3 different DAAs in the NDA. While clinical documentation will typically involve information from all 3 DAAs administered in combination, the documentation for other disciplines (i.e., toxicology, pharmacology, nonclinical pharmacokinetics) will typically be distinct for each compound. For the NDA submission, AbbVie proposes to submit the information in an "integrated format" (within each of the major subheadings, discuss each compound sequentially, then move on to the next subheading) rather than in a "sequential format" in which we would have complete and separate summaries for each of the 3 compounds.

Does the Agency agree with this proposed approach for the nonclinical summary?

DAVP Response: For completeness, our review of nonclinical data submitted as part of the NDA will include not only an integrated summary of the data for all three DAAs, but also full evaluations of the individual DAAs. Therefore, in order to facilitate our review, please submit toxicology, pharmacology, and nonclinical pharmacokinetic data in both an "integrated format" and a "sequential format".

Meeting Discussion:
AbbVie clarified that the content of the "integrated format" and the "sequential format" would be the same and asked DAVP to confirm that both formats should be provided. DAVP responded that both formats would still be preferred and explained that the sequential format is useful for applications containing multiple active ingredients, as the application may be split between multiple nonclinical reviewers. DAVP also requested that drug identifiers be included in the file names, to which AbbVie agreed. AbbVie committed to take the request for both formats back to their submissions team and respond to DAVP at a later date to confirm their ability to submit the nonclinical module as requested.

2.3. CMC

Question 8: Stability Program

AbbVie's combination dosing regimen includes ABT-450/r/ABT-267 FDC film-coated tablets (two 75 mg/50 mg/12.5 mg tablets QD) and ABT-333 film-coated tablets (one 250 mg tablet BID). The dosage forms are formulated as immediate release tablets. The FDC film-coated tablet is comprised of 2 new chemical entities (NCEs), ABT-450 and ABT-267, coformulated with the pharmacokinetic enhancer, ritonavir. ABT-333 film-coated tablets are comprised of a single NCE (ABT-333). The inactive ingredients of both drug products are common pharmaceutical excipients.

AbbVie has provided in Appendix G a complete description of the manufacturing supply chain for the ABT-450/r/ABT-267 and ABT-333 film-coated tablets and details of the drug substance and drug product stability data program.

For ABT-450 drug substance, data from 3 primary stability lots from an R&D manufacturing site and data from at least 1 lot from the commercial site will be available at the time of submission as described in Appendix G.

For ABT-267 drug substance, data from 3 primary stability lots from an R&D manufacturing site and data from at least 1 lot from the commercial site will be available at the time of submission as described in Appendix G.

For ABT-333 drug substance, data from 3 primary stability lots from an R&D manufacturing site and data from at least 1 lot from the commercial site will be available at the time of submission as described in Appendix G.

For ABT-450/r/ABT-267 FDC tablet, data from 3 primary stability lots from the commercial site will be available at the time of submission as described in Appendix G.

For ABT-333 tablet, data from 3 primary stability lots from an R&D manufacturing site and data from 3 lots from the commercial site will be available at the time of submission as described in Appendix G.

Does the Agency agree that AbbVie's NDA stability data package as detailed in Appendix G (i.e., data from 3 primary stability batches for each of the 3 drug substances and the 2 drug products) will be adequate to support filing and review of ABT-450, ABT-267, and ABT-333 drug substances, ABT-450/r/ABT-267 FDC tablets, and ABT-333 film-coated tablets? Does the Agency agree that site-specific stability would only be filed in the postapproval Annual Report?

DAVP Response: For all 3 new drug substances, we agree that the extent of the proposed stability data is sufficient.

For ABT-333 drug product, we understand that at the time of the final NDA submission you will have 12 months of long-term stability data for 3 primary stability drug product batches manufactured by AbbVie Waukegan Road and 6 months for 1 batch manufactured by AbbVie Ireland as well as other supporting data. We agree that this is sufficient.

For ABT-450/r/ABT267 drug product we understand that at the time of the final NDA submission you will have 12 months of long-term stability data for at least 4 primary stability drug product batches manufactured by the proposed commercial sites (b) (4) **. We agree that this is sufficient.**

As indicated in the meeting package, three months stability data will be available on process validation new drug substance batches (ABT-450, ABT-267, and ABT-333) from the proposed commercial sites in April 2014. Please include the data in the NDA submission. It is acceptable to provide future site-specific stability in the post-approval annual report.

Question 9: Start of Shelf Life

(b) (4)

AbbVie has provided additional details to justify this proposed start of shelf life strategy in Appendix H.

Does the Agency agree with AbbVie's proposal to define the beginning of shelf life of the ABT-450/r/ABT-267 FDC film-coated tablets at (b) (4)

DAVP Response: **We agree that the proposal to define the beginning of shelf life of the ABT-450/r/ABT-267 FDC film-coated tablets at** (b) (4) **is science based. The proposed study to provide stability data in the NDA for drug product made from** (b) (4) **is an important part of the justification. Eventually, this stability study should be extended out to cover the full expiration dating periods, with the data provided post-approval. Additionally, data showing** (b) (4) **will also be an important of the NDA submission. We recommend that the**

tests to be included on the specifications for the (b) (4) be discussed in the CMC meeting in September.

Question 10: ABT-333 Drug Substance Intermediate Suppliers

During development, (b) (4) manufactured the (b) (4) for the ABT-333 drug substance. (b) (4) provided the (b) (4) used in the manufacture of the drug substance primary stability batches. Drug substance lots produced using (b) (4) were also used to manufacture the drug product primary stability batches, Phase 3 clinical supplies, and drug product site-specific stability batches. In the NDA submission, (b) (4) will be listed as a manufacturer through (b) (4) in the 3.2.S.2.1 Manufacturer(s) section.

(b) (4)

AbbVie plans to use the process validation materials from (b) (4) to build launch supplies for market distribution. (b) (4) is currently in good GMP standing (as indicated by recent FDA inspection of (b) (4)), and any (b) (4) used for launch supplies will meet the commercial specifications. The process validation documentation from (b) (4) will be available for inspection at either (b) (4) or an AbbVie site.

New drug substance (b) (4) suppliers will be qualified through a demonstration of equivalence as discussed below.

The commercial (b) (4) used to prepare ABT-333 is provided in Appendix F.

Does the Agency agree that material produced by the drug substance (b) (4) supplier ((b) (4) is suitable for commercial use upon approval of the ABT-333 drug product? If (b) (4) (b) (4) at the time of the NDA submission, should AbbVie list this site on the Form 356h?

DAVP Response: We can accept the data obtained on ABT-333 drug substance or drug product produced from (b) (4) to support the NDA. If (b) (4) is to be used as a commercial supplier for (b) (4), facility information should be listed in the NDA. If the (b) (4) are to be used for commercial ABT-333 manufacture, and the (b) (4) facility is not available for inspection, please include in the September 2013 CMC meeting package information about the accessibility of the manufacturing records for those (b) (4)

Question 11: Registration of New ABT-333 Drug Substance Intermediate Suppliers

AbbVie will register 2 new suppliers of ABT-333 drug substance (b) (4) as presented in Appendix G Manufacturing Sites and Stability Data. (b) (4)

(b) (4) will not change from that in place with the current supplier ((b) (4) As per the EOP2 meeting with FDA on 03 April 2013, demonstration of equivalence (b) (4) produced by the new suppliers to those of the current supplier will be presented at time of registration in accordance with the recommendations of FDA's (withdrawn) BACPAC guidance. Three lots from each new (b) (4) supplier will be used to demonstrate equivalence. Consistent with the provisions of BACPAC, stability data for drug substance lots using the (b) (4) produced by the new suppliers will not be included in the NDA.

Does the Agency agree that AbbVie's proposal for a demonstration of equivalence of the drug substance (b) (4) is sufficient to support approval of the new suppliers?

DAVP Response: Your plan is generally acceptable, given that the (b) (4), manufacturing process, and controls will not change. However, please note that critical quality attributes (CQA) of ABT-333 that are not included on the specification for the (b) (4) or the ABT-333 specification should also be included in the demonstration of equivalence. Please place batches of drug substance made from the new (b) (4) in the long-term stability program and report the results as they become available.

Question 12. CMC Module Submission Timing:

The manufacturing process for each drug substance and the formulations and manufacturing process for each drug product are fixed and well understood. The proposed commercial formulation of the 2 drug products are the same as have been used in the Phase 3 studies. The manufacturing processes for the 3 drug substances and the 2 drug products used in the Phase 3 studies are representative of each of the proposed commercial processes. AbbVie has provided proposals for early submission of the CMC package in Appendix I. All CMC documentation will be filed by April 2014 (NDA submission date).

Does the Agency agree to a proposed rolling submission of CMC information in 2 separate datasets as per AbbVie's Option 1 (complete drug substance information for all 3 NCEs submitted in December 2013 with complete information for the 2 drug products submitted in April 2014)?

Does the Agency agree to the proposed CMC dataset 1 including the summative human factors protocol in December 2013 and the summative human factors report in April 2014?

DAVP Response: Your Option I proposal for a staged CMC submission is acceptable. Please submit a request and plan for a rolling submission as noted in our response to Question 2.

Meeting Discussion:
At the end of the meeting, AbbVie asked if FDA anticipates that GMP pre-approval inspections may be scheduled prior to submission of the complete NDA in April 2014, if the CMC information is provided as a rolling submission. DAVP responded that the current approach is to

schedule inspections after the final package is complete. DAVP recommended that the issue be discussed again at a later time, such as the September CMC meeting, as that approach could change.

Note for clarification added after meeting:
All facilities are expected to be ready for inspection when the NDA is submitted. For a rolling submission, the facilities' readiness at the time the CMC module is submitted may facilitate the scheduling of the inspection.

Question 13: Human Factors Testing

AbbVie is currently undertaking a user-centered design and development process for the DAA packaging and labeling. A first formative simulated-use test with representative users was completed in early June 2013. Also, an initial user test of (b) (4) is scheduled for later in June 2013. A second formative simulated-use test and a (b) (4) test are scheduled concurrently for Fall 2013. Each combined round of a formative simulated-use test and a (b) (4) test will be followed by iterative design improvements to the packaging and labeling. Additional rounds of formative simulated-use testing and (b) (4) testing will be conducted if results indicate their necessity or value. Subsequently, a summative simulated-use test is planned to confirm the package and labeling is safe and effective for patients and likewise a summative (b) (4) test is planned for late 2013/early 2014. The protocols for the upcoming formative simulated-use testing and for the summative simulated-use test will be based on the protocols for the first formative simulated-use test. The protocol includes no training for users and direct observation of representative users in a setting consistent with the intended use environment. Measures include, but are not limited to, task performance and subjective feedback from users on the essential tasks of opening the daily (b) (4) cards, identifying the appropriate dosing regimen and evaluating user comprehension of risk information. Usability testing for packaging and labeling comprehension is limited in the degrees of freedom—the potential changes—in how such a study is conducted. The methods used will remain largely unchanged, even as the design of the packaging and labeling is iteratively changed in response to the test results. Further details of the testing are provided in Appendix B. AbbVie requests advice from CDER DMEPA on the planned packaging/labeling design and development activities.

Does the Agency agree with AbbVie's planned packaging/labeling design and development activities, as summarized?

AbbVie requests the opportunity to submit the summative simulated-use test protocol when available to DMEPA for pretest protocol review. What mechanism may be used to submit the summative simulated-use protocol to DMEPA for review?

DAVP Response: After consultation with our colleagues in DMEPA, we will provide this information at a later time.

Meeting Discussion:
Comments from DMEPA in response to this question were provided in a separate document on July 19, 2013, attached. AbbVie decided not to discuss the specific comments during the July 22 meeting. However, prior to the meeting, AbbVie asked for DMEPA to comment on the preferred mechanism for obtaining feedback on the second formative simulated-use test protocol (a teleconference or a written request), and whether a submission date of early September would allow for DMEPA feedback to be provided by late September. DMEPA responded during the meeting by asking for the protocol to be submitted to the INDs as a written request for advice as soon as possible.

Note for clarification added after meeting:
DMEPA provided more specific feedback on the preferred timeline for submission of the second formative simulated-use test protocol to AbbVie, requesting that the protocol be submitted by mid-August at the latest. On July 26, 2013 AbbVie confirmed that the formative 2 protocol and samples could be submitted by mid-August; however, the samples will not have the branding elements included (color/creative elements). Samples including the branding elements will be provided in a subsequent submission in early September. DMEPA confirmed that this proposal for submission is acceptable. DMEPA also advises that the most appropriate location for the human factors data to be submitted in the NDA eCTD is Module 1, Section 1.12 Other Correspondence.

Question 14: Cross References to Other Applications

Ritonavir is used as a pharmacokinetic enhancer in the ABT-450/r/ABT-267 FDC film-coated tablets. (b) (4)

AbbVie plans to cross-reference NDA (20-659) for the ritonavir drug substance information. AbbVie plans to cross-reference the Norvir Tablet NDA (22-417) for all ritonavir (b) (4) information including the formulation and process development and the manufacturing and controls sections. (b) (4)

Does the Agency agree with AbbVie's proposal for referencing existing NDAs for the ritonavir drug substance (b) (4)

DAVP Response: We agree with your proposal for referencing existing NDAs for the ritonavir drug substance (b) (4) **Please provide a review guide (e.g., table) to show the location and date of submission for the current ritonavir processes and controls. Please clarify whether the information on the new drug substances will be provided in the application(s) or through Drug Master Files.**

Question 15: Executed Batch Records

AbbVie proposes to submit the complete executed batch record from the pivotal biobatch (1 of the primary stability lots) of each drug product in this application. For the ABT-450/r/ABT-267 FDC film-coated tablets, this will include the Drug Product Intermediate operations for ABT-450 and ABT-267. Where applicable, an English translation of the executed batch records will also be provided.

Does the Agency agree with this proposal?

DAVP Response: We agree with submitting the complete executed batch record on one batch of each drug product. This should include the manufacturing record for the batch of (b) (4) **that was used to manufacture the ABT-450/r/ABT-267 batch. Please ensure that a complete drug product manufacturing process description is provided in 3.2.P.3.3 of the NDA.**

Meeting Discussion
DAVP informed AbbVie that there is a proposed reorganization of the Quality evaluation functions in CDER. One goal is increasing coordination between review and the evaluation of the manufacturing facilities. It is conceivable that the optimal answer to Question 15 could evolve, so it would be good to revisit this recommendation regarding the number of executed batch records at the September 2013 CMC meeting.

2.4. Regulatory

Question 16: (b) (4)

(b) (4)

Question 17:

AbbVie acknowledges the Agency's comments in the 10 June 2013, correspondence regarding Breakthrough Therapy designation. Based on our understanding that this designation will provide for enhanced communication between FDA and AbbVie during both product development and NDA preparation/review, AbbVie respectfully requests the Agency's feedback on the following:

- In lieu of a formal meeting(s) with the Agency, are there other mechanisms to engage officials or subject matter experts within DAVP/FDA to receive timely feedback on key program issues?
- AbbVie is committed to development of a dossier that can be easily navigated and which will ensure an efficient FDA review. Due to the complexity of the dossier, which will consist of 2 dosage forms and 3 NMEs, AbbVie wishes to receive early feedback (prior to the presubmission meeting) on the appropriate presentation and integration of the 3-DAA data in the planned NDA. With reference to Question 6 above, AbbVie proposes to include a submission content plan and mock electronic datasets in a request for advice by August.

Can the Agency provide further clarification of the enhanced communication and the potential regulatory mechanisms for receiving timely feedback which will be provided by FDA to AbbVie during continued product development and NDA preparation/review, as described above?

DAVP response: You are welcome to request advice and feedback at any time and DAVP will respond in a timely manner. We acknowledge the complexity of this application and can review sample datasets and planned submission content prior to the pre-NDA meeting.

3.0 OTHER OUTSTANDING DEVELOPMENT ISSUES

On May 6, 2013, in response to the meeting request, DAVP sent you a correspondence asking you to address the following topics in your meeting background package:

1. The impact of the prohibition of estrogen-containing oral contraceptives in your clinical trials and responses to the information request (IR) you received on April 18, 2013.

   DAVP Response: DAVP acknowledges the response to the IR and your proposed oral contraceptive study.

   The proposed trial with combined oral contraceptives (trial M12-205) will evaluate the effect of the DAA regimen on Ortho-Cyclen (ethinyl estradiol + norgestimate). Based on the available information from DDI trials with strong CYP3A inhibitors (such as Reyataz and Stribild) and norgestimate containing oral contraceptives, it is expected that the concentrations of norelgestromin (active metabolite of norgestimate) will be significantly higher, thereby increasing the probability of norelgestromin related

adverse events. Depending on the results from trial M12-205, please consider evaluating drug-drug interaction with other combined oral contraceptives so that additional options may be available to women of child bearing potential.

Meeting Discussion:
AbbVie explained that based upon the results of M12-205, they may consider additional trials with other oral contraceptives. However, data from those trials will not be available for the NDA submission in April 2014. DAVP asked whether AbbVie could instead run an interim analysis of safety and PK from M12-205 and amend the ongoing trial to include other contraceptives. AbbVie clarified that so far, 9 subjects have enrolled in M12-205, and only half of those subjects have started co-dosing with the DAAs. AbbVie explained that the PK data for these subjects is not yet available; however, they have seen ALT elevations (Grade 1-2) in 4 of the 5 patients that have started co-dosing with the DAAs. Therefore, they may halt enrollment at 9 and consider another contraceptive regimen. DAVP asked if AbbVie knows which DAA is likely driving this effect, and AbbVie responded that they are currently looking into the mechanism for this toxicity but do not yet know. DAVP asked if co-dosing small numbers of patients with the single DAAs might help to identify the DAA driving the interaction. AbbVie responded that they did see a similar signal with ABT-450/ritonavir alone in Phase 1, although those data were not generated with concomitant dosing of oral contraceptives.

DAVP offered the assistance of the clinical pharmacology groups to work with AbbVie to identify contraceptive options that will be safe and effective for women on the AbbVie DAA regimen, as women of childbearing potential make up a significant portion of the population for whom treatment is needed.

2. Unresolved toxicology issues related to ABT-267 metabolites.

DAVP Response: DAVP acknowledges that this issue will be discussed at the upcoming CMC meeting in September.

Meeting Discussion:
DAVP explained that no further discussion is needed on this topic, as the pharmacology/toxicology team agrees with AbbVie's plans for evaluating the metabolites and the resulting data will be discussed as they become available.

3. The final to-be-marketed formulations including strengths of each DAA and ritonavir and the impact of changing formulations on interpreting drug-drug interaction studies. DAVP has noted you have made multiple changes in the formulation and delivery system, including the addition of ribavirin into a coformulated tablet. Please describe the studies used to bridge all relevant formulations administered in clinical trials or important clinical pharmacology trials.

DAVP Response: We do not agree with your analysis (b) (4)

(b) (4)

The following considerations may help to further assess the impact of higher ABT-450 exposures from the coformulated product on the magnitude of drug-drug interactions:

1) **Compare the extent of drug-drug interaction from trials where ABT-450 (b) (4) and the coformulated product were used with the same co-administered drug.**
2) **Use quantitative approaches (such as PBPK) to assess the impact of higher ABT-450 exposures.**
3) **Determine the need for extrapolating a given drug-drug interaction based on the proposed regimen(s). For example, DDI trial with gemfibrozil (M12-196) was conducted using the (b) (4) formulation; however, based on the results, you plan to contraindicate CYP2C8 inhibitors. Hence, if ABT-333 is part of the proposed regimen, gemfibrozil interaction may not need to be extrapolated.**
4) **Assess the impact of co-administered drug on ABT-450 exposures. For example, the results of DDI trial with rosuvastatin (trial M12-200; conducted using the (b) (4) tablet) indicates ~50 % increase in ABT-450 exposures. Even if a similar magnitude of interaction irrespective of the ABT-450 formulation used is assumed, ABT-450 exposures will be higher when the coformulated product is co-administered with rosuvastatin as compared to the ABT-450 exposures observed in trial M12-200.**

As data becomes available from ongoing and planned trials and the points outlined above are taken into consideration, we strongly encourage further discussions with DAVP about your approach on extrapolating the results of the DDI trials. In addition to drugs listed under "Concomitant medications that showed change in exposure (> 25 % change in AUC)" column in table 14 (Page 80), your plans of extrapolating results from trials conducted with narrow therapeutic index drugs (digoxin[M12-201] and warfarin [M12-198]) will be useful.

Meeting Discussion:

AbbVie explained that they will use quantitative approaches to bridge the DDI data, as recommended in DAVP's preliminary comments. They also plan to use in vitro data to support their rationale for extrapolating from the (b) (4) ((b) (4) tablet to the coformulated tablet formulation based upon the metabolic profile for each drug in the regimen. DAVP agreed with AbbVie's multi-pronged approach of using in vitro mechanistic and quantitative assessments to assess the impact of higher ABT-450 exposures from the coformulated product on the magnitude of drug interactions, However, DAVP responded that they do not agree with the company's rationale for extrapolating exposures for only those concomitant medications that showed a (b) (4) % change in AUC; rather, AbbVie should

predict the magnitude of interaction of all coadministered drugs where studies were conducted with the (b) (4) *formulation. AbbVie acknowledged this request and agreed that assessments can be performed for all DDI trials conducted with the* (b) (4) *formulation. AbbVie went on to describe their two quantitative approaches for bridging the DDI data. In the first approach, AbbVie described an analysis using a regression model to predict the magnitude of drug-drug interaction expected at exposures with the ABT-450 coformulated product and the second approach focused on predicting the magnitude of the DDI in a sub-set of subjects with mean exposures 63 % higher than the mean exposures observed in the DDI trial. DAVP recommended an additional analysis where the exposures of all subjects in a given DDI trial is increased by 63 % (to mimic the expected exposures with the coformulated product) and a mean exposure is computed which is then compared with the individual exposures observed in the DDI trial (using the* (b) (4) *formulation). In addition to the analysis planned by AbbVie, this analysis will also be helpful to predict the impact of higher ABT-450 exposures on the extent of the drug-drug interaction with the cofrmulated product. AbbVie agreed to conduct the analysis suggested by DAVP.*

DAVP also requested that AbbVie focus on the impact of the co-administered drugs on ABT-450 exposures and justify ABT-450 exposures that may exceed limits previously associated with increased risk of adverse events.

4. Clinical trials in patients with HIV/HCV co-infection and the post-transplant study.

   DAVP Response: DAVP acknowledges the recent submission of Protocol M14-004 for your co-infection study; it is currently under review. We acknowledge that the post-transplant trial is ongoing. Please provide an update on the status of enrollment at the meeting.

5. Expanded access programs including possible emergency/single-patient treatment INDs. Please include in your discussion the number of patients for whom expanded access has been requested and the number who have received treatment.

   DAVP Response: Please provide an update on your plans for expanded access to the three DAAs during the meeting.

4.0 ADDITIONAL COMMENTS

1. FDA encourages sponsors to submit a Pharmacovigilance (PV) Plan developed to detect new safety risks and to further evaluate identified safety risks with ABT-450/r/ABT-267 + ABT-333 following market approval. Information on PV Plans has been included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005) and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the PV plan is available, please include it in the NDA application in the appropriate module so that it can be reviewed accordingly.

2. We have recently reviewed your Pediatric Study Plan for the AbbVie DAA regimen and will be providing our comments on the PSP in the near future. However, we strongly encourage you to redesign your pediatric program to begin evaluation of the adolescent population (e.g., ages 12-18 years) using the "adult" formulations of your proposed regimen as soon as the regimen is agreed upon.

5.0 ADDITIONAL MEETING DISCUSSION

During the meeting, several additional topics not identified in the preliminary comments were discussed:

1. *AbbVie asked DAVP for any additional recommendations for the planned April 2014 NDA submission. DAVP inquired if the resistance data will be pooled across trials. AbbVie replied that they plan to submit an integrated resistance analysis, and questioned whether DAVP would like the resistance information presented separately for each trial, as well. DAVP replied that an integrated analysis and pooled resistance datasets are sufficient and that it is not necessary to submit the resistance datasets from different trials separately if all of the information is provided in the pooled datasets.*

2. 

bbVie agreed to work with the Division to determine an appropriate format for the meeting.

6.0 DATA STANDARDS FOR STUDIES

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

7.0 ISSUES REQUIRING FURTHER DISCUSSION

During the meeting, DAVP and AbbVie identified a number issues requiring further discussion, either informally or during subsequent meetings:

1. The need for AbbVie to submit SVR12 data from the placebo crossover arms of M11-646 and M13-098 (FDA will respond in writing).
2. The need for AbbVie to submit data from the 2-DAA combination program (M13-393) to help justify the inclusion of ABT-333 and ribavirin in the NDA for the 3-DAA combination, specifically for overlapping populations (to be discussed at the pre-NDA meeting).
3. The plans for further study of the interaction between the 3-DAA regimen and oral contraceptives, including possible modification of M12-205 to include additional contraceptive regimens.
4. The timing of GMP inspections relative to submission of the CMC module (to be discussed again at the September CMC meeting).
5. The number of executed batch records required for submission with the NDA (to be discussed again at the September CMC meeting).
6. The preferred presentation of bridging drug interaction data in the NDA.

8.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
FDA will respond to AbbVie regarding Question 3a and submission of placebo crossover arm SVR12 data from M11-646 and M13-098.	FDA	As soon as information is available.
AbbVie will provide additional data on 2-DAA combination in overlapping populations for discussion.	Sponsor	Prior to pre-NDA meeting
AbbVie will provide an update on plans for submission of sample datasets and the possibility of converting to standardized format.	Sponsor	As soon as information is available.
AbbVie will contact the Division regarding further plans for oral contraceptive interaction study(ies).	Sponsor	As soon as information is available.
AbbVie will contact the Division regarding plans for presenting bridging drug interaction data in the NDA.	Sponsor	As soon as information is available.
AbbVie will contact the Division to confirm that the non-clinical section of the NDA can be submitted as requested.	Sponsor	As soon as information is available.
AbbVie will submit the ISE statistical analysis plan.	Sponsor	August 2013
AbbVie will submit the second formative simulated-use test protocol for DMEPA review.	Sponsor	Mid-August 2013
(b) (4)	FDA	As soon as information is available.

9.0 ATTACHMENTS AND HANDOUTS

1. AbbVie slide presentation dated July 21, 2013
2. AbbVie preliminary responses to CMC comments, sent via email on July 19, 2013
3. DMEPA/DAVP response to Question 13 (human use factors studies) sent to AbbVie on July 19, 2013

38 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: July 19, 2013

TO: Janette J Meyer, RAC, Director, Regulatory Affairs - PPG

FROM: Stacey Min, Pharm.D., Regulatory Project Manager for Katherine Schumann, M.S., Regulatory Project Manager, DAVP

SPONSOR: AbbVie Inc.

SUBJECT: IND 103,526 / IND 108,434 / IND 101,636: July 22 Type B Meeting – Response to Question #13 regarding human factors studies

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Please refer to your Investigational New Drug Applications (INDs) for ABT-450, ABT-267 and ABT-333, and to your meeting package dated June 24, 2013, for your July 22, 2013 Type B Breakthrough Therapy multidisciplinary meeting. Please also refer to our Preliminary Comments of July 17, 2013, which stated that a response to Question #13 would be forthcoming.

DAVP and DMEPA have the following response regarding Question #13:

AbbVie Question #13:
Does the Agency agree with AbbVie's planned packaging/labeling design and development activities, as summarized?

AbbVie requests the opportunity to submit the summative simulated-use test protocol when available to DMEPA for pretest protocol review. What mechanism may be used to submit the summative simulated-use protocol to DMEPA for review?

FDA Response:
Response

We agree that a second formative simulated-use test and subsequent summative simulated-use test are required to confirm the use of the package and labeling is safe and effective. However, we have the following recommendations for the second formative simulated-use test and the labeling/packaging which should be included prior to conducting the second formative test to ensure that all aspects of potential user error have been studied prior to NDA submission.

Second Formative Simulated-Use Study:

- Healthcare practitioners (HCP's) are a defined intended user group. Therefore, it may be helpful to have their input as early as possible because they might have different failures which may add value to the second formative testing. Consider recruiting HCP's who are both familiar and unfamiliar with this patient population.

- We would like to review the Formative 2 Study Protocol prior to conducting the study. Please include in the protocol proposed iterations of the packaging that will be tested in Formative 2 study.

Labeling/Packaging:

A. [redacted] (b) (4) US Wallet Carton Labeling and Container Label:

a. The presentation of the established name is incorrect. Currently, the established name is presented to lead patients to believe that all of the drugs listed are contained in one tablet. We recommend the following presentation of the established name on all labeling and packaging prior to Formative Study 2:

Proprietary Name
veruprevir/ritonavir/ombitasvir Tablets
75 mg/50 mg/12.5 mg
and
dasabuvir Tablets
250 mg

b. As per CFR 201.10(g) ensure the size of the established name to be at least one-half as large as the letters comprising the proprietary name and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

c. Please provide evidence that each icon used on the labeling and packaging. (i.e. "AM" icon, "PM" icon, [redacted] (b) (4) is consistently understood with the intended meaning). In addition, add a question to test participants asking if the icons were understood with the intended meaning. In addition, consider removing the [redacted] (b) (4) as it does not add value to the instructions. As currently presented, the [redacted] (b) (4) resembles another pill and may confuse patients.

d. Consider testing to see if a time interval box needs to be placed on packaging so that patients will understand to not take the "AM" and "PM" dose too close together.

B. US [redacted] (b) (4) Wallet Carton Labeling:

a. The radio buttons on the cartons are labeled with days of the week. However, it was not discussed in the meeting packet any analysis of patients who may or may not begin therapy at the beginning of the week. Therefore, we recommend changing the days of the week (i.e. Monday-Sunday) to Days 1 to 7. This may help patients keep track if they do not start therapy on a Monday, and prevent patients from waiting to begin therapy until Monday.

b. Revise the "Contains" statement to present the daily quantity of tablets contained in each [redacted] (b) (4)/wallet and the weekly quantity of tablets contained in each carton on the principal display panel (PDP) such as the following:

Each carton contains 28 tablets in 7 [redacted] (b) (4)/wallets for 1 week of treatment.

Each [redacted] (b) (4)/wallet contains 4 tablets

(2 veruprevir/ritonavir/ombitasvir tablets and 2 dasabuvir tablets).

c. The proprietary name, established name, NDC number should be presented on the principal display panel (PDP) and top panel of the carton labeling.
d. The "Rx Only" statement is missing. Place the "Rx Only" statement on the principal display panel.
e. There is no usual dosage statement. Place a usual dosage statement on the side or back panel similar to the following: See package insert for full instructions.

C. (b) (4) US Wallet Container Label:

a. Ensure that the actual image of each tablet is presented instead of a mock image.
b. Remove the statements regarding (b) (4) This information can be confusing for patient (b) (4).

D. (b) (4)

a. (b) (4)

AbbVie requests the opportunity to submit the summative simulated-use test protocol when available to DMEPA for pretest protocol review. What mechanism may be used to submit the summative simulated-use protocol to DMEPA for review?

For summative simulated-use protocol submission, the summative simulated-use protocol should be submitted to DMEPA in Section 1.12 Other Correspondence in the eCTD.

Please respond via email to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 or Katherine.Schumann@fda.hhs.gov if you have any questions regarding the contents of this transmission.

Stacey Min for Katherine Schumann, M.S.
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/

STACEY MIN
07/19/2013

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

/s/

DEBRA B BIRNKRANT
08/13/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

INDs 103526, 108434, 101636

MEETING MINUTES

AbbVie, Incorporated
Attention: Janette Meyer
Associate Director, Regulatory Affairs-PPG
1 N. Waukegan Road, Dept. PA77/Bldg.AP30
North Chicago, IL 60064

Dear Ms. Meyer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABT-450/ritonavir/ABT-267 and ABT-333 coadministered with and without ribavirin (RBV).

We also refer to the teleconference between representatives of your firm and the FDA on April 3, 2013. The purpose of the meeting was to discuss and gain advice on drug substance-related development topics for the active ingredients, ABT-450, ABT-267 and ABT-333.

We refer to the request to revise the meeting minutes submitted by electronic mail on April 24, 2013. A copy of the revised official minutes of the teleconference is enclosed for your information.

If you have any questions, call Victoria Tyson, Regulatory Project Manager at (301) 796-0827.

Sincerely,

{See appended electronic signature page}

Rapti Madurawe, Ph.D.
Branch Chief
Division of New Drug Quality Assessment II
Office of New Drug Quality and Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2 CMC-Drug Substance
Meeting Date and Time:	April 3, 2013, 2:00-3:00 pm
Meeting Location:	White Oak, Building 22, Room 6396
Application Number:	INDs 103526, 108434,101636
Product Name:	ABT-450/r/ABT-267 and ABT-333
Indication:	treatment of genotype 1 chronic hepatitis C infection in adult patients who are treatment-naïve or who have been previously treated with pegIFN and RBV, including prior null responders, partial responders, and relapsers and those with compensated cirrhosis
Applicant Name:	AbbVie, Incorporated
Meeting Chair:	George Lunn, Ph.D.
Meeting Recorder:	Victoria Tyson

FDA Participants:

Name	**Title**
Stephen Miller, Ph.D.	Product Quality Team Leader, Office of New Drug and Quality Assessment (ONDQA)
George Lunn, PhD.	Product Quality Reviewer, ONDQA
Rapti Madurawe, Ph.D.	Branch Chief Preapproval CMC, ONDQA
Lin Qi, Ph.D.	Product Quality Reviewer, ONDQA
Fugiang Liu, Ph.D.	Product Quality Reviewer, ONDQA
Mark Seaton, Ph.D.	Nonclinical Reviewer, Division of Antiviral Products (DAVP)
Mark Powley, Ph.D.	Nonclinical Reviewer, DAVP
Hanan Ghantous, Ph.D., DABT	Nonclinical Team Leader, DAVP
Minerva Hughes, Ph.D.	Biopharmaceutics Reviewer, ONDQA
Russell Fleischer, PA-C, MPH,	Clinical Analyst, DAVP
Elizabeth Thompson, M.S.	Acting Chief, Project Management Staff, DAVP
Katherine Schumann, M.S.	Regulatory Project Manager, DAVP

AbbVie, Incorporated Participants:

Name	Title
Janette Meyer	Associate Director, Regulatory Affairs
Cheryl Pape, M.S.	Associate Director, CMC Regulatory Affairs
Kevin Fitzpatrick	Senior Director, CMC Regulatory Affairs
Sou-Jen Chang, Ph.D.	Associate Director, CMC Regulatory Affairs
Anutosh Saha, Ph.D.	Director, Global Regulatory Leader, Product Strategy, Regulatory
John Morris, Ph. D.	Director, CMC Project Management
Nancy Benz, Ph.D.	Director, Process Analytical Chemistry
Shailendra Bordawekar, Ph.D.	Director, Process Engineering
Seble Wagaw, Ph. D.	Associate Director, Process Chemistry
Thad Franczyk, Ph. D.	Associate Director, Process Chemistry and Catalysis
David Barnes, Ph. D.	Associate Director, Process Chemistry
Albert Thomas	Associate Director, Pharmaceutical Development
John Nicolette, M.S.	Principal Research Scientist, Pre-clinical Safety: Genetic Toxicology
Phillip Hajduk, Ph. D.	Director, Lead Discovery Technologies

1.0 BACKGROUND

AbbVie, Incorporated is evaluating the use of direct acting antivirals (DAAs) for use in combination with ritonavir, with or without ribavirin, for the treatment of genotype 1 chronic hepatitis C infection in adult patients who are treatment-naïve or who have been previously treated with pegylated interferon and ribavirin, including prior null responders, partial responders, and relapsers and those with compensated cirrhosis. This End of Phase 2 (EOP2) meeting was scheduled to discuss chemistry, manufacturing and control issues related to the drug substance, ABT-450/r/ABT-267 and ABT-333. In ongoing Phase 3 trials, AbbVie is evaluating a dosing regimen that includes an ABT-450/r/ABT-267 FDC film-coated tablet (two 75 mg/50 mg/12.5 mg tablets QD) and an ABT-333 film coated tablet (one 250 mg tablet BID) coadministered with and without weight-based RBV (1000 to 1200 mg in divided doses BID).

The specific objectives of the meeting are to discuss and gain advice on:

- designation of regulatory starting materials for ABT-267;
- the data package for the NDA to support approval of a second supplier of an ABT-33 drug substance intermediate;
- commercial drug substance specifications with respect to specifying (b) (4);
- control strategy for ABT-267 potential genotoxic impurities (GTI);
- control strategy for summing of structurally similar GTIs in the ABT-450 and ABT-267 drug substance used in the fixed dose combination ABT-450/r/ABT-267 tablets; and

- toxicity testing requirements for qualification of impurities for structurally similar compounds.

On March 29, 2013, the FDA issued preliminary responses to the questions posed in the March 4, 2013, meeting background package. AbbVie submitted a response to Question 1 on April 1, 2013 and provided slides on April 2, 2013, that consists of additional information and questions for discussion during the teleconference. AbbVie's questions are in bold font followed the discussion in regular font.

2.0 DISCUSSION

Control of Materials

Question 1. Based on the information provided in the original briefing document and the subsequent response to preliminary FDA comments to the CMC EOP2 meeting, does the Agency agree with AbbVie's proposal of the following Regulatory Starting Materials for ABT-267?

1. (b) (4)
2.
3.

Discussion:

FDA accepted (b) (4) as starting materials for the manufacture of ABT-267. Acceptability of the specifications and acceptance criteria for these starting materials will be determined upon NDA review. The FDA asked AbbVie to provide in the NDA submission justifications for the specifications and acceptance criteria of the starting materials, intermediates and drug substance. Appropriate acceptance criteria should not only consider the ability of the manufacturing process to reject impurities but also the manufacturing capability.

Control of Critical Steps and Intermediates-ABT-333

Question 2. Does the Agency concur with AbbVie's planned approach to qualify (b) (4) (b) (4) as an alternate supplier of the (b) (4)?

Discussion:

The proposal to qualify (b) (4) as an alternate supplier of the (b) (4) is reasonable. AbbVie committed to place three batches of drug substance made from the (b) (4) on their long-term stability program but no batch release or stability data for the drug substance made from the

[redacted] will be available at the time of submission of the NDA. The FDA informed AbbVie this is acceptable.

Question 3. Based on the information presented in the slides, AbbVie proposes to only maintain internal control for [redacted]. Does the Agency agree with this approach?

Discussion:

AbbVie provided a justification of specifications for [redacted], information on the formulation, manufacturing process, process development, stability and information on their experience with ritonavir in open dish stability studies for discussion. AbbVie is using [redacted], with a limit of detection of [redacted]%, and [redacted] to monitor for [redacted] FDA advised AbbVie to continue to monitor for [redacted] using these methods and stated that although physical methods, such as [redacted]

FDA stated that if AbbVie plans on [redacted]

Information from [redacted] will be important in the NDA submission to help support manufacturing process parameters, [redacted] limits, and storage conditions, and the need for any recommendations for handling by patients.

FDA asked AbbVie about their experience with correlating the [redacted] and suggested that including that type of knowledge in the NDA could be valuable.

ABT-267 (Genotoxic Impurity Controls)

Question 4. Does FDA agree with the proposed GTI control strategy for the ABT-267 drug substance?

Discussion

AbbVie confirmed that the [redacted] are indeed negative in the Ames test. The details of the assays will be provided in a future submission. A table (or alternative) that summarizes how each GTI is controlled, including those that are controlled by the process, will be included in the NDA submission. The FDA informed AbbVie that the proposal is acceptable.

AbbVie submitted the following information for discussion of Questions 5, 6 and 7:

Per ICH M7, AbbVie proposes that impurities in Table 1-3 (Appendix 5 of Briefing Document, pg. 120-128) containing no structural alerts and which would be given at or below 1 mg/day need no further qualification.

- ICH M7 Note 1 indicates that "for impurities below or above the qualification threshold that have been assessed per recommendations of the guideline and are not predicted to be mutagenic, no further qualification is required unless the daily dose of impurity exceeds 1 mg."
- Analysis by DEREK at AbbVie, several QSAR tools at the agency and structural similarity to their respective non-genotoxic investigational drugs show that the majority of the impurities in Tables 1, 2 and 3 in Appendix 5 have no concerns for mutagenicity.

Impurities with structural alerts or to be given above 1 mg/day would be assessed for genotoxic potential as outlined in ICHQ3A/B.

Questions 5, 6, 7. Does the Agency agree with AbbVie's application of the draft ICHM7 guideline with respect to qualification of non-alerting impurities?

Discussion:

The FDA agreed with AbbVie's proposal as outlined.

AbbVie submitted the following information for discussion and clarification regarding genotoxicity testing based on structural similarity coefficients:

AbbVie proposed that impurities above the ICHQ3A/B qualification thresholds with Tanimoto coefficients of similarity (b) (4) to their respective investigational drugs would be qualified from negative genotoxicity of those drugs.

1. Are Tanimoto coefficients of similarity (b) (4) not sufficient or appropriate in predicting mutagenicity outcome when compared against a substrate with known Ames result? All 3 drug substances have tested negative in Ames.
   - Similarity evaluation of >4000 compounds with Ames results showed a predictivity of 86% that compounds with (b) (4) coefficient of similarity to an Ames negative compound would also test negative.
2. Since Tanimoto coefficients of similarity of (b) (4) provide strong predictivity of both positive and negative Ames results, is it reasonable to conclude impurities with similarity coefficients of (b) (4) also be expected to have similar genetox outcome when compared against a substrate that is non-genotoxic?

- All 3 drug substances have been tested in a full battery of genetox tests per ICH S2(R1) and are considered non-genotoxic.

Discussion:

The FDA informed AbbVie that the structural similarity coefficients would be considered supportive information but do not replace the use of a 2nd (Q)SAR methodology as recommended in the draft ICH M7 guideline. AbbVie asked the FDA what level of evidence would be required to meet the guidelines. The FDA informed AbbVie that these are general scientific questions that are outside of the scope of this meeting and require further discussion internally. The FDA will discuss this issue internally and provide advice on how these questions should be submitted for review and feedback.

ABT-450 and ABT-267 (Summing of Structurally Similar GTIs)

Question 8. Does the Agency agree with AbbVie's approach for classifying genotoxic impurities into four groups with structural similarity and similar mechanism of action, and additionally agree with the proposed daily limit of (b) (4) µg/day for each group?

Discussion:

AbbVie requested clarification on whether the (b) (4) µg/day limit for individual mutagenic impurities and (b) (4) µg/day limit for total mutagenic impurities were applicable to the final combined drug product or individual drug substances. The FDA informed AbbVie that the limits can be applied to the individual drug substances.

3.0 PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).

- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

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. For additional guidance on submission of the PSP, including a PSP Template, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

4.0 DATA STANDARDS FOR STUDIES

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

5.0 ISSUES REQUIRING FURTHER DISCUSSION

The FDA will discuss the following issues internally and provide advice on how the questions below should be submitted for review and comment.

1. Are Tanimoto coefficients of similarity (b) (4) not sufficient or appropriate in predicting mutagenicity outcome when compared against a substrate with known Ames result? All 3 drug substances have tested negative in Ames.
   – Similarity evaluation of >4000 compounds with Ames results showed a predictivity of 86% that compounds with (b) (4) coefficient of similarity to an Ames negative compound would also test negative.

2. Since Tanimoto coefficients of similarity of (b) (4) provide strong predictivity of both positive and negative Ames results, is it reasonable to conclude impurities with similarity coefficients of (b) (4) also be expected to have similar genetox outcome when compared against a substrate that is non-genotoxic?
   - All 3 drug substances have been tested in a full battery of genetox tests per IC S2(R1) and are considered non-genotoxic.

6.0 ACTION ITEMS

- The FDA informed AbbVie that a discriminating dissolution method is critical to showing that the (b) (4) is maintained in the drug product made from (b) (4) When the dissolution method has been developed, AbbVie should use it to show that the (b) (4) is stable on drug product stability.

- AbbVie will submit the details of the assays used to control GTIs in a future submission.

- The FDA asked AbbVie to include the following information in the NDA:

  -a table summarizing how each GTI is controlled, including those controlled by the process;

  -justifications for the specifications and acceptance criteria of the starting materials, intermediates and drug substance;

  -information from (b) (4) to help support manufacturing process parameters, (b) (4) limits, and storage conditions, and the need for any recommendations for handling by patients; and

  -information about their experience with correlating the (b) (4)

7.0 ATTACHMENTS AND HANDOUTS

Slides

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

/s/

RAPTI D MADURAWE
04/25/2013

Benton, Sandra J

From: Benton, Sandra J
Sent: Friday, April 12, 2013 3:13 PM
To: Sherman, Rachel E; Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Thompson, Aliza; Farrell, Ann T
Cc: Bertha, Amy; Kim, Tamy; Fleischer, Russell D; Murray, Jeffrey S; Birnkrant, Debra B; Cox, Edward M; Raggio, Miranda; Brounstein, Daniel; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Tyson, Victoria; Lewis, Linda L (CDER); Schumann, Katherine; Ligon, Sharnell (CDER); Myers, Lauren; Vail, Victor H; Blount, Aprile; McCary, Barbara M
Subject: RE: April 17, 2013 - Medical Policy Council – Breakthrough Therapy Designation - Three INDs - Treatment of Hepatitis C Infection - AbbVie Inc

As the Council agrees with DAVP's recommendation to grant AbbVie Inc.'s breakthrough therapy request and do not believe a Council meeting is needed, I will cancel the meeting.

I appreciate the quick turnaround. Please let me know if you have any questions.

Sandy Benton
Senior Policy Analyst
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From: Benton, Sandra J
Sent: Friday, April 12, 2013 9:28 AM
To: Sherman, Rachel E; Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Thompson, Aliza; Farrell, Ann T
Cc: Bertha, Amy; Kim, Tamy; Fleischer, Russell D; Murray, Jeffrey S; Birnkrant, Debra B; Cox, Edward M; Raggio, Miranda; Brounstein, Daniel; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Tyson, Victoria; Lewis, Linda L (CDER); Schumann, Katherine; Ligon, Sharnell (CDER); Myers, Lauren; Vail, Victor H; Blount, Aprile; McCary, Barbara M
Subject: April 17, 2013 - Medical Policy Council – Breakthrough Therapy Designation - Three INDs - Treatment of Hepatitis C Infection - AbbVie Inc

Hi! I have scheduled a Medical Policy Council meeting on April 17 to discuss the breakthrough therapy designation request from AbbVie for its three INDs for treatment of Hepatitis C Infection.

IND 103526/ABT-450 (Ns3 Protease Inhibitor)
IND 101636/ABT-333 (NS5B Protease Inhibitor)
IND 108434/ABT-267 (NS5A Protease Inhibitor)

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.

OMP held a planning meeting with DAVP regarding this breakthrough therapy request. The request comes in at the time the regimen is in phase 3 development. All components of the regimen have been granted fast

track status and no additional development meetings are anticipated. The next major meeting anticipated will be the pre-NDA meeting; the NDA is expected in 2014. Therefore, DAVP has asked if this request can be reviewed by email.

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

- You agree with DAVP's recommendation to grant this breakthrough therapy request and you do not believe a Council meeting is needed.
- You agree with DAVP's recommendation to grant this breakthrough therapy request. However, you would like a Council meeting to discuss any questions you have.
- You disagree with DAVP's recommendation to grant this breakthrough therapy request.

If the Council agrees with bullet 1, I will cancel the April 17 Council meeting.

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

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<< File: 103526breakthrough.doc >> << File: IND 103526-108434-101636 breakthrough-request-hcv.pdf >>

Division Brief for Breakthrough Therapy Designation for ABT-450/RTV/ABT-267 + ABT-333 for Treatment of Genotype 1 Chronic Hepatitis C Patients

Introduction

The purpose of this Medical Policy Council meeting is to discuss the request by AbbVie for designation of the all oral drug combination of ABT-450/RTV/ABT-267 + ABT-333 with and without ribavirin (RBV) for the treatment of genotype 1 treatment-naïve and experienced patients with and without compensated cirrhosis with chronic hepatitis C (CHC) as breakthrough therapy under Section 903 of the Food and Drug Administration Safety and Innovation Act (FDASIA).

ABT-267 is an NS5A replication complex inhibitor, ABT-450 is a selective inhibitor of NS3 protease and ABT-333 is a selective non-nucleoside NS5B polymerase inhibitor (binds to the thumb domain of the HCV polymerase) of the hepatitis C virus (HCV). AbbVie states that, in accordance with the definition of breakthrough therapy in the legislation, the regimen of ABT-450/RTV[1]/ABT-267 + ABT-333 with or without RBV as an all oral triple regimen, treats CHC, which is a serious or life-threatening disease and preliminary clinical evidence indicates that the combination may provide substantial improvement over existing therapies on one or more clinically significant endpoints (efficacy and safety). ABT-450/RTV/ABT-267 have been developed into a fixed-dose combination.

Background

Approximately 3.2 million people in the United States have CHC, which can lead to cirrhosis and hepatocellular carcinoma, and is currently the most common reason for liver transplantation in the United States. At least six different HCV genotypes have been identified, numbered 1 to 6, with further breakdown into subtypes for several of the known genotypes (e.g., genotype 1 subtypes 1a and 1b). In the United States, genotype 1 is the most common (70 to 80 percent; mostly subtype 1a), followed by genotypes 2 and 3. The remaining genotypes occur uncommonly in the United States, but may predominate in other parts of the world.

The primary efficacy outcome of anti-HCV treatment is the achievement of a sustained virologic response (SVR), typically defined as unquantifiable HCV RNA 12 weeks following the completion of a course of treatment (i.e., “SVR12”), and generally considered a “virologic cure”. The current standard-of-care treatment for HCV genotype 1 infection is a combination of pegylated interferon alpha (Peg-IFNα), ribavirin (RBV), and one of two recently approved HCV NS3 protease inhibitors (boceprevir or telaprevir) administered for 24 to 48 weeks depending on the specific drug regimen and patient population. These regimens are associated with favorable efficacy (65-75% SVR12 rates) in treatment-naïve patients without severe liver complications of HCV infection, but have lower efficacy in certain difficult-to-treat populations, for example those with cirrhosis who respond poorly to Peg-IFNα/RBV. The regimens are difficult to administer (Peg-IFNα is given as a weekly injection, boceprevir and telaprevir are given 3 times daily with food restrictions) and are poorly tolerated in many patients, as each drug is

[1] Ritonavir (RTV) is a potent inhibitor of CYP3A4. Low doses of RTV are co-administered with ABT-450 to increase Cmax and maintain plasma half-life thereby increasing intracellular half-life and potentiating ABT-450’s antiviral activity.

associated with numerous serious and life-threatening toxicities including neuropsychiatric, autoimmune, ischemic and infectious disorders (Peg-IFNα), teratogenicity (RBV), anemia (RBV, telaprevir, boceprevir), bone marrow suppression (Peg-INFα, RBV) and severe rash (telaprevir- boxed warning). Furthermore, like many other HCV direct-acting antivirals (DAAs), boceprevir and telaprevir have relatively narrow genotype-specificity, and therefore are not approved for the treatment of non-genotype 1 HCV. Current standard-of-care for non-genotype 1 HCV is a 24- to 48-week duration of Peg-IFNα/RBV, which has limited efficacy in certain populations. Importantly, a significant proportion of HCV-infected patients are believed to be intolerant or ineligible (based on comorbitities or age) to use interferon-based therapies; these patients currently have no viable antiviral treatment options.

Because of the limitations of interferon-based therapies, there has been great interest in recent years in the development of all oral, interferon-free regimens consisting of combinations of multiple classes of HCV DAAs, which in some cases are dosed with RBV or with the PK enhancer ritonavir. After several years of development and optimization, several interferon-free, combination HCV DAA regimens being developed by various pharmaceutical sponsors are now being studied in pivotal Phase 3 clinical trials. It is widely anticipated that at least some of these regimens will have substantially improved efficacy over the current standard-of-care, particularly for HCV genotype 1, and with treatment duration possibly as short as 12 weeks. Most importantly, because these regimens do not require the use of interferon, they are expected to have substantially improved safety and tolerability over the current standard-of-care, and will be available to patients who cannot use interferon-based therapies.

Despite their promise, the use of interferon-free HCV DAA regimens will bring new treatment considerations and challenges. The breadth of HCV genotype coverage varies dramatically for different treatment regimens. For example, some HCV DAA regimens have poor efficacy for HCV genotype 1a relative to genotype 1b. For most HCV DAA-containing regimens, treatment failure is associated with the emergence of HCV resistance to the drug(s) and cross-resistance to other drugs in the same class(es), which can impact future treatment options. Drug-drug interactions will be an important consideration with the use of many regimens, particularly for patients coinfected with HIV who are on antiretroviral therapy. Furthermore, as noted above, certain regimens must still be dosed with RBV or with the PK enhancer ritonavir, which will bring additional safety and drug-drug interaction considerations.

Consideration of ABT-450/RTV/ABT-267/ABT-333 with and without RBV for Breakthrough Designation

Serious and Life-threatening Condition

As established in the background provided above, CHC is a serious or life-threatening disease. A recent CDC analysis of death certificate data found that HCV-attributable deaths increased significantly between 1999 and 2007. CDC estimates that there were 15,106 deaths caused by HCV in 2007. Simultaneously, HIV-related death rates have declined. In 2007, 12,734 people died of HIV/AIDS.[2] Death certificate information can be inaccurate; and, because a person other than the primary physician of the decedent often completed the death certificate, HCV was often not detected and thus not reported and therefore is likely under-represented in this analysis. The burden of HCV-related

[2] Ly, K., et al. Annals Of Internal Medicine, 2012. 156(4): p. 271-278.

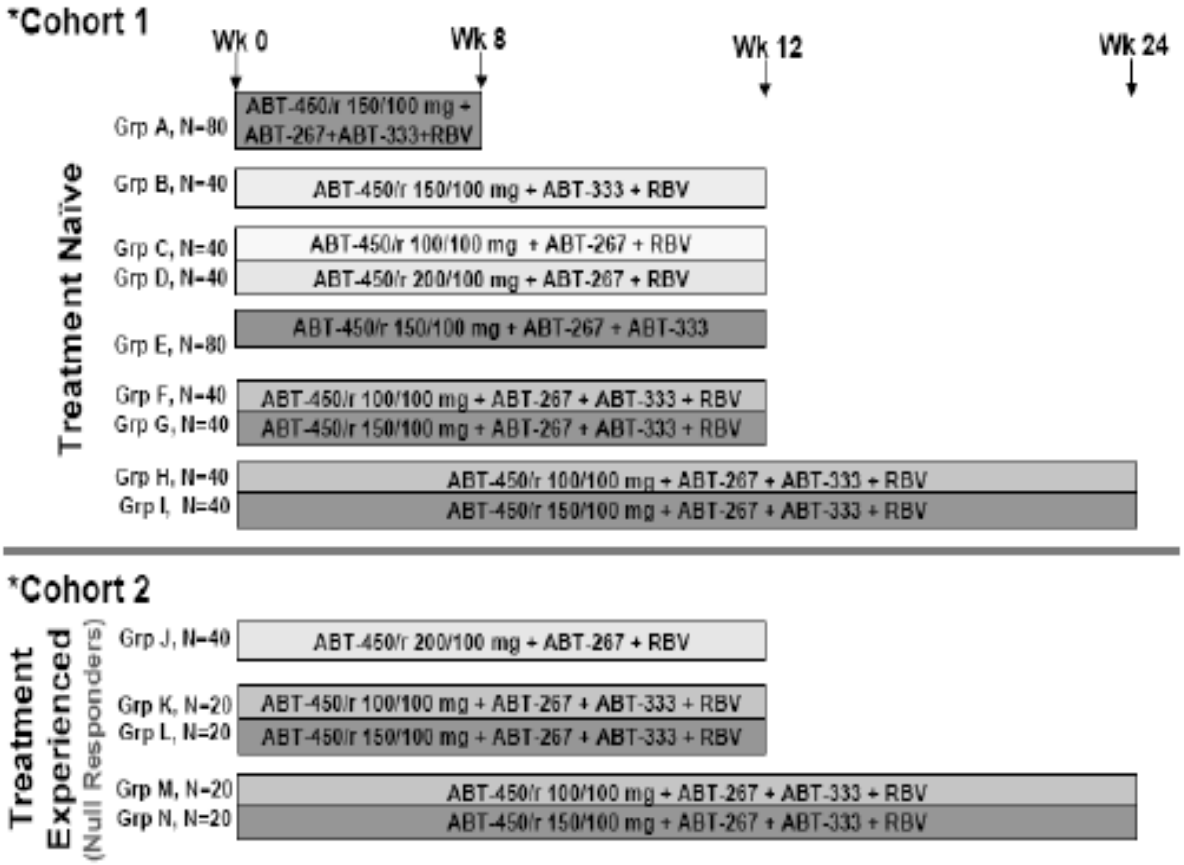
illness and death is high in the United States with an estimated 3.2 million people infected and mortality rate outpacing that of HIV/AIDS.

Data to Support Breakthrough Designation

The proposed regimen is being developed by AbbVie for treatment of genotype 1 HCV-infected, treatment-naïve adults, patients previously treated with Peg-IFNα/RBV, and patients with recurrent HCV post-liver transplantation. The currently available data to support this breakthrough therapy designation request are from multiple small and one large Phase 2 combination study.

Study M11-652 is an ongoing Phase 2 study evaluating various combinations of 8, 12, and 24 weeks of ABT-450/RTV/ABT-267 + ABT-333 ± RBV in treatment-naïve and experienced genotype 1 HCV-infected adults.

Figure 1 provides the study design for M11-652:



Efficacy Data from Phase 2

Demographically, groups were well balanced with 66% of the genotype 1 subjects infected with genotype 1a subtype who generally have lower rates of success with the approved therapeutic options.

Table 1. SVR12 rates in Study M11-652

Regimen	Wks	N	G1a	G1b
Treatment Naive				
Group A	8	80	48/56 (84)	23/24 (96)
Group B	12	41	23/29 (79)	12/12 (100)
Groups C and D	12	79	44/52 (85)	27/27 (100)
Group E	12	79	43/52 (83)	24/25 (96)
Groups F and G	12	79	52/54 (96)	25/25 (100)
Treatment Experienced				
Group J	12	45	21/26 (81)	18/18 (100)
Group K and L	12	45	25/28 (89)	17/17 (100)

As outlined in our 2013 (to be released) draft HCV Guidance for Industry, in order to progress from Phase 2 to Phase 3 trials we ask that all Sponsors provide SVR4 data on all subjects and all available SVR12 data for Phase 3 trial planning. Recently the Division met to discuss breakthrough therapy designation criteria that would provide satisfactory preliminary clinical evidence to indicate that a drug combination may provide substantial improvement over existing therapies on one or more clinically significant endpoints. We concluded SVR12 data would provide the evidence needed and would provide a consistent standard for breakthrough designation for HCV products. Although this trial does not have SVR12 data on all subjects from group1 (24 week regimen) breakthrough designation should be granted because we are satisfied with the available SVR12 results from the shorter duration regimen and no evidence of breakthrough or relapse in either treatment arm.

Safety Data

To date, >600 healthy and infected subjects have received some combination of ABT450/RTV, ABT-267, ABT-333 ± RBV for up to 12 weeks duration.

The most frequently reported treatment-emergent adverse events (occurring in >10% of subjects) include headache, fatigue, nausea, vomiting, diarrhea, insomnia, dizziness, pruritis, dry skin, and rash; all events were considered mild or moderate in severity.

The frequency of the following adverse events was higher among subjects who received concomitant RBV: nausea (23% vs. 13%), fatigue (27% vs. 20%), headache (27% vs. 18%), insomnia (18% vs. 8%), cough (9% vs. 2.5%), dyspnea (6.5% vs. 1%), pruritis (10.5% vs. 4%), dry skin (6.5% vs. 1%), rash (10.5% vs. 8%), and anemia (8% vs. 1%).

The most common laboratory abnormality has been aymptomatic transient elevations of total and indirect bilirubin, which were seen across multiple treatment arms, consistent with the known impact of ABT-450 on the bilirubin transporter OATP1B1.

In summary, the safety profile of ABT-450/RTV/ABT-267 + ABT-333 ± RBV is manageable and appears to have the advantages of a more tolerable safety profile compared to currently approved Peg-IFNα-based regimens. Use of this triple DAA all oral regimen will likely significantly decrease the high incidence of significant cytopenias (and subsequent use of blood transfusions, Granulocyte Colony Stimulating Factors and Erythropoiesis-Stimulating Agents), the worsening of depression or other mental health conditions, the incidence flu-like symptoms and will avoid injections and the potential for associated skin reactions.

Phase 3 Development Program

The regimen of ABT-450/RTV/ABT-267 + ABT-333 ± RBV is currently in Phase 3 of clinical development with over 1100 subjects in screening or treatment. An EOP2 meeting was held in October 2012 where the results of Study M11-652, and other smaller Phase 2 studies, and the design of Phase 3 studies were discussed.

AbbVie initially proposed to conduct four studies. However, DAVP raised various concerns about these studies and recommended revisions that would address specific regulatory and clinical issues. Instead of revising the protocols to address these questions, the sponsor initiated additional studies. The reason given was that the protocols had already been forwarded to IRBs and screening of subjects had already commenced, so it was not possible for the initial protocols to be revised.

The sponsor is now conducting six Phase 3 studies with the selected 3-DAA regimen administered with and without RBV in HCV genotype 1 infected subjects, including subjects with compensated cirrhosis. According to the sponsor, current enrollment projections indicate that the primary endpoints for the Phase 3 trials will be available by early 2014 to enable NDA submission in 2014.

Table 2. Ongoing AbbVie DAA combination Phase 3 trials.

Regimen	Study No.	Duration	Population	Study Design
3 DAA* + RBV	M11-646	12 wks	GT1 naïve	Placebo-controlled, randomized, double-blind, multicenter
	M13-098	12 wks	GT1 experienced	Placebo-controlled, randomized, double-blind, multicenter
	M13-099	12-24 wks	GT1 naïve and experienced with cirrhosis	Randomized, open-label study, multicenter
3 DAA* ± RBV	M13-961	12 wks	GT1b, naïve	Randomized, double-blind, multicenter
	M13-389	12 wks	GT1b, experienced	Randomized, open-label, multicenter
	M14-002	12 wks	GT1a, naive	Randomized, double-blind, multicenter

* 3 DAA = ABT-450/r/ABT-267 + ABT-333

In addition, ongoing or planned trials will evaluate the 3-DAA regimen in liver transplant subjects and subjects with HCV/HIV coinfection. However, a proposed HCV/HIV coinfection study was considered not safe to proceed due to unacceptable interactions between ABT-450 and HIV therapies.

Overall Summary and Division's Conclusion

Breakthrough therapy designation for ABT-450/RTV/ABT-267 + ABT-333 is supported by the following:

1. The three components of this triple regimen have novel mechanisms of action that represent previously untargeted pathways. Currently there are no other approved anti-HCV NS5A or NS5B inhibitors.
2. The Phase 2 SVR12 data provides evidence of substantial improvement in efficacy compared to the currently available standard of care. Additionally, improved efficacy was observed in "harder-to-treat" patients who are genotype 1a and those who had failed prior Peg-IFNα/RBV treatment.
3. The all oral regimen for a 12 week duration provided high rates of efficacy (SVR12 94%) compared to the historical rate up to 48 weeks of current boceprevir or telaprevir in combination with Peg-IFNα/RBV (SVR ~ 65-75%).
4. The safety profile of the triple regimen is promising. The regimen is Peg-IFNα free providing fewer cytopenias, no effect on depression, no flu-like prodrome and no injections.
5. Absence of interferon from the regimen will allow many patients with contraindications to interferon to receive an effective regimen.
6. The Phase 3 program is designed to determine safety and efficacy in a broad range of genotype 1 infected subjects: treatment naïve and experienced subjects with and without cirrhosis.

Based on the data presented, DAVP believes that ABT-450/RTV/ABT-267 + ABT-333 meets the definition of a breakthrough therapy for the treatment of genotype 1 treatment-naïve and experienced chronic hepatitis C patients as outlined in Section 903 of the Food and Drug Administration Safety and Innovation Act.

<u>Question</u>

1. Does the Medical Policy Council agree with DAVP's recommendation for breakthrough therapy designation for the AbbVie all oral DAA regimen for treatment of patients with CHC?

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

/s/

SANDRA J BENTON
04/15/2013

DEBRA B BIRNKRANT
04/15/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 103,526
IND 108,434
IND 101,636

MEETING MINUTES

AbbVie Inc.
Attention: Janette Meyer, RAC
Associate Director, Regulatory Affairs
1 N. Waukegan Road
North Chicago, IL 60064

Dear Ms. Meyer:

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABT-450, ABT-267 and ABT-333.

We also refer to the meeting between representatives of your firm and the FDA on October 1, 2012. The purpose of the meeting was to discuss your planned Phase 3 development program for the treatment of chronic hepatitis C virus (HCV) infection.

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 Katherine Schumann, M.S., Regulatory Project Manager at (301) 796-1182 or the Division's main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
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:	End of Phase 2
Meeting Date and Time:	October 1, 2012 9:30 AM – 11:00 AM EDT
Meeting Location:	White Oak, Building 22, Room 1309
Application Number:	IND 103,526 IND 108,434 IND 101,636
Product Name:	ABT-450 ABT-267 ABT-333
Indication:	Treatment of chronic hepatitis C virus (HCV) infection
Sponsor/Applicant Name:	AbbVie Inc.
Meeting Chair:	Russell Fleischer, PA-C, MPH
Meeting Recorder:	Katherine Schumann, MS

FDA ATTENDEES

1. Debra Birnkrant, M.D., Division Director, Division of Antiviral Products (DAVP)
2. Jeffrey Murray, M.D., MPH, Deputy Director, DAVP
3. Linda Lewis, M.D., Medical Team Leader, DAVP
4. Russell Fleischer, PA-C, MPH, Medical Reviewer, DAVP
5. Mary Singer, MD., Ph.D., Medical Team Leader, DAVP
6. Kimberly Struble, Pharm.D., Medical Team Leader, DAVP
7. Jules O'Rear, Ph.D., Clinical Virology Team Leader, DAVP
8. Patrick Harrington, Ph.D., Clinical Virology Reviewer, DAVP
9. Lisa Naeger, Ph.D., Clinical Virology Reviewer, DAVP
10. Guoxing Soon, Ph.D., Biostatistics Team Leader, Division of Biometrics IV, OB
11. Susan Zhou, Ph.D., Statistician, Division of Biometrics IV, OB
12. Vikram Arya, Ph.D., Clinical Pharmacology Reviewer, OCP
13. Shirley Seo, Ph.D., Acting Clinical Pharmacology Team Leader, OCP
14. Jeffry Florian, Ph.D., Pharmacometrics Reviewer, OCP
15. Karen Winestock, Chief, Project Management Staff, DAVP

16. Katherine Schumann, M.S., Regulatory Project Manager, DAVP

SPONSOR ATTENDEES

1. Scott C. Brun, M.D., Divisional Vice President, Virology, Global Pharmaceutical Research & Development (GPRD)
2. Barry M. Bernstein, M.D., Project Director, HCV Global Project Team, GPRD
3. Thomas J. Podsadecki, M.D., Senior Medical Director, Antiviral Clinical Project Team, GPRD
4. Sandeep Dutta, Ph.D., Director, Clinical Pharmacology and Pharmacometrics (CPPM)
5. Rajeev M. Menon, Ph.D., Associate Director, CPPM
6. Martin King, Ph.D., Director, Statistics, GPRD
7. Lois Larsen, Ph.D., Associate Director, Statistics, GPRD
8. Christine Collins, Ph.D., Director, Clinical Virology
9. Mark Goldberger, M.D., M.P.H., Division Vice President, Regulatory Policy and Intelligence
10. Andrew Storey, Head, US/Canada Area & Affiliate Strategy (A&AS), Regulatory Affairs
11. Margarita Aguilera, M.Sc., Senior Director, Regulatory Affairs, Global Product Strategy (GPS)
12. Alan McEmber, MS, RAC, Senior Direct, US/Canada, A&AS
13. Anutosh R. Saha, Ph.D., Director, Regulatory Affairs, GPS
14. Janette Meyer, RAC, Associate Director, Regulatory Affairs, A&AS

1.0 BACKGROUND

The purpose of this End-of-Phase 2 meeting is to discuss AbbVie's planned Phase 3 program for their direct-acting antiviral agent (DAA) combination regimen for the treatment of chronic hepatitis C virus (HCV) infection in HCV genotype-1 infected patients. The sponsor's proposed combination regimen consists of ABT-450/r (a protease inhibitor boosted with ritonavir), ABT-267 (an NS5A inhibitor), ABT-333 (an NS5B polymerase inhibitor) and ribavirin.

The proposed Phase 3 program consists of 4 trials (N = 1600) with a 4 drug regimen (a regimen containing the following 4 active drugs [ABT-450, ABT-267, ABT-333, and ribavirin] plus ritonavir for boosting) in treatment naïve, treatment experienced, cirrhotic and HIV-HCV co-infected patients, respectively. Two additional trials are proposed: one with a 3-drug regimen (a regimen with 3 active drugs; the same regimen as described above but without RBV) for HCV genotype subtype 1b patients only, and one long-term follow up study.

The primary data submitted in support of the proposed Phase 3 clinical program are derived from AbbVie's ongoing Phase 2 program, including trials M11-652, M12-267, M12-746 and M12-998.

AbbVie's desired outcome of the meeting is to gain agreement on the Phase 3 development program, including the combination regimen, target population(s), and design of the clinical trials.

DAVP sent preliminary comments to AbbVie on September 26, 2012.

On September 28, 2012, AbbVie provided a preliminary slide deck to DAVP and communicated that they would like to focus the meeting discussion on questions 2, 3, 9 and 13 and 17. On the morning of October 1, 2012, AbbVie provided the final version of their presentation (attached).

2. DISCUSSION

Questions submitted by the Sponsor are in **bold**, the Agency's preliminary comments are in regular font, and discussions during the October 1, 2012 meeting are in *italic* font.

AbbVie began the meeting by providing a summary of the data from their Phase 2 program that were submitted with the End-of-Phase 2 meeting package, as presented in the attached slide presentation.

2.1. NONCLINICAL

Question 1.
Does the Division agree that Abbott's nonclinical development program is adequate to support the planned NDA?

FDA Response to Question 1

Whereas we continue to be dissatisfied with the sponsor's decision to shorten the planned nine month dog study with ABT-267 to six months, given the lack of findings after six months of dosing, we do not feel an additional nine month dog study will add substantively to the nonclinical data set. We encourage Abbott, in future drug development plans, to adhere to M3(R2) guidance with respect to requirements for, and duration of nonclinical studies.

Regarding carcinogenicity studies, we ask that any final reports that have been reviewed by the Quality Assurance department be submitted with the NDA. All final reports of carcinogenicity studies should be submitted within one year of the NDA submission.

2.2. CLINICAL

Question 2. Rationale for Regimen, Dose, and Duration

2a. Does the Division agree with the selection of the above 3 DAA combination regimen administered with RBV for the pivotal Phase 3 studies and the studies in patients with compensated cirrhosis and HIV-1 coinfection?

2b. Does the Division agree with the selection of the 3 DAA combination regimen without RBV for evaluation in the Phase 3 study in treatment naïve HCV GT1b-infected subjects?

2c. Does the Division agree with the doses of ABT-450/r/ABT-267 and ABT-333 selected for the Phase 3 program?

2d. Does the Division agree that 12 weeks is the appropriate duration for the pivotal Phase 3 studies and the GT1b (± RBV) study?

2e. Does the Division agree with the duration ranging proposed for the studies in patients with compensated cirrhosis and HIV-1 coinfection?

FDA Response to Question 2

In general, we agree that the currently available data support evaluation of the 3-DAA + RBV combination regimen at the proposed doses in your Phase 3 program. However, while we recognize the concerns about multi-class DAA resistance among subjects who do not achieve SVR, we are not yet convinced that all 4 anti-HCV agents are absolutely necessary for certain patient populations that are predicted to respond favorably to treatment (i.e., treatment-naïve and treatment-experienced, non-cirrhotic genotype 1b subjects as well as treatment-naïve, non-cirrhotic genotype 1a subjects). Furthermore, there are safety and resistance-related risks to having a regimen that is too complicated or not well tolerated such that it leads to missed doses or premature discontinuation.

Due to the small number of subjects in the various treatment arms and the impact of non-virologic failures on overall SVR results in M11-652, it is difficult to discern treatment differences between the 3 DAAs + RBV treatment arms and treatment arms including 2-

DAAs + RBV or 3-DAAs (without RBV), even among HCV genotype 1a subjects. Furthermore, of the 159 genotype 1b subjects from M11-652, M12-267, M12-746 andM12-998 that were administered 3-DAAs, 3-DAAs + RBV, or 2-DAAs + RBV, there was one virologic failure (relapse) in the M11-652 8-week treatment arm and 1 virologic breakthrough in the M12-746 P/R-experienced arm, indicating that a 12-week, 3-DAA + RBV regimen is unlikely to be necessary for non-cirrhotic subjects with HCV genotype 1b infection. Therefore, it seems unnecessary to evaluate this regimen for genotype 1b subjects in three different studies of non-cirrhotic, HCV mono-infected subjects (M11-646, M13-098, and M13-961). We also do not believe the single instance of virologic relapse among HCV genotype 1b subjects in Group A of M11-652 precludes further investigation of this 8-week regimen in Phase 3 for HCV genotype 1b, if desired.

We believe there are other options for study designs that would address additional clinically relevant issues beyond your currently planned Phase 3 program. For example, the potential of removing RBV from a 3-DAA regimen without a significant decrease in efficacy for both genotype 1a and genotype 1b patients may result in fewer adverse events and the elimination of the required RBV-related pregnancy precautions. A study of ABT-450/r + ABT-267 + RBV versus 3-DAAs (without RBV) is also of interest to compare safety and efficacy of regimens including RBV or ABT-333. Conversely, a well powered trial confirming the necessity of the 3-DAA + RBV regimen for optimal treatment efficacy in genotype 1a patients would support its use in clinical practice.

Based on current results from your Phase 2 studies, and considering potential safety, tolerability, efficacy and drug resistance implications, we believe that the following treatments are viable options for study in non-cirrhotic, HCV mono-infected subjects:

1. ABT-450/r + ABT-267 + ABT-333 + RBV for 12 weeks (genotype 1a and genotype 1b, treatment-naïve and treatment-experienced)
2. ABT-450/r + ABT-267 + ABT-333 for 12 weeks (genotype 1a treatment-naïve; genotype 1b, treatment-naïve and treatment-experienced)
3. ABT-450/r + ABT-267 + RBV for 12 weeks (genotype 1a treatment-naïve; genotype 1b, treatment-naïve and treatment-experienced)
4. ABT-450/r + ABT-267 + ABT-333 + RBV for 8 weeks (genotype 1b, treatment-naïve and treatment-experienced)

There are multiple acceptable ways that these regimens could be incorporated into your planned Phase 3 development program. One reasonable and relatively straightforward approach would be to study non-cirrhotic HCV genotype 1a and 1b subjects independently, as outlined below.

<u>Genotype 1a, non-cirrhotic, HCV mono-infected</u>

- Limit the currently proposed M11-646 and M13-098 trials to genotype 1a subjects.
- M11-646 (treatment-naïve subjects) could study the following regimens:
    - ABT-450/r + ABT-267 + ABT-333 + RBV for 12 weeks
    - ABT-450/r + ABT-267 + ABT-333 + RBV placebo for 12 weeks
    - ABT-450/r + ABT-267 + RBV + ABT-333 placebo for 12 weeks

- M13-098 (P/R-experienced subjects) could study 3-DAAs + RBV for 12 weeks. This trial could include the all-placebo (deferred treatment) arm, if desired, to provide a safety comparison.

Genotype 1b, non-cirrhotic, HCV mono-infected subjects

- Include both treatment-naïve and P/R-experienced, HCV genotype 1b subjects in M13-961
- Some or all of the following regimens could be studied in M13-961:
  - ABT-450/r + ABT-267 + ABT-333 + RBV for 12 weeks
  - ABT-450/r + ABT-267 + ABT-333 + RBV placebo for 12 weeks
  - ABT-450/r + ABT-267 + RBV + ABT-333 placebo for 12 weeks
  - ABT-450/r + ABT-267 + ABT-333 + RBV for 8 weeks (with appropriate relapse-related futility criteria, particularly for P/R-experienced subjects)

The planned doses for each DAA are acceptable. Also, 12 weeks duration appears reasonable for the Phase 3 trials in treatment-naïve and treatment-experienced, non-cirrhotic, HCV mono-infected populations. As noted above, you may also consider evaluating the 8-week duration, ABT-450/r + ABT-267 + ABT-333 + RBV regimen in HCV genotype 1b, treatment-naïve, HCV mono-infected, non-cirrhotic subjects.

Compensated Cirrhosis (M13-099)

We agree with the 12- and 24-week durations proposed for study in subjects with compensated cirrhosis in M13-099.

(b) (4)

As currently designed, this study would not be safe to conduct. Please see the response to Question 7 for more information.

Meeting Discussion

AbbVie acknowledged that HCV genotype 1b subjects in Study M11-652 did well in all arms, while genotype 1a subjects had varied responses depending on the regimen and duration. AbbVie summarized the response rates in genotype 1a subjects in each arm, explaining that a greater percentage of subjects in the 12- week, 4 active drug arm (ABT-450/r, ABT-267, ABT-333 and RBV) achieved SVR_{12} than subjects in any other arm. AbbVie explained that most of the patients with virologic failure (not including those who did not achieve SVR_{12} for other reasons, such as loss to follow-up) had evidence of multi-class drug resistance, with the exception of some in the 8-week arm. DAVP asked if those subjects who failed had baseline mutations, but AbbVie replied that baseline mutations were rare, and only two have been identified to date. DAVP asked if the baseline analyses are still ongoing, and AbbVie responded that the analyses are currently ongoing, but most of the failures have been sequenced already. DAVP also pointed out that the sample size was relatively small for some of the arms in Study M11-652, and a one or two subject difference could potentially be driving the observed differences in SVR.

AbbVie continued by summarizing the safety data from M11-652 and emphasizing that better tolerability was seen in the RBV-free arms than those containing RBV. While removing the RBV-containing arms had a measureable effect on adverse event rates and lab parameters in naïve subjects, removal of ABT-333 did not. DAVP asked about the frequency of dose modification for patients with hemoglobin below 10g/dL. AbbVie replied that there were some patients with values below 10g/dL, but none below 8.5 g/dL. DAVP suggested a lower dose of ribavirin might be appropriate for study, if that was an option AbbVie was willing to pursue. DAVP also asked for the overall rate of fatigue across the arms in M11-652. AbbVie responded that they did not have the information immediately available, but would provide it following the meeting.

AbbVie then summarized the data from M11-652 as presented on Slide 11. DAVP asked if AbbVie's analyses identified any baseline factors that might be predictive of response. AbbVie replied that HCV genotype (1a versus 1b), IL28B status (CC or non-CC) and high baseline viral load were predictive of response across all arms, as was expected.

AbbVie next raised the issue of regimen selection for Phase 3 by presenting the challenges to adding additional arms to study either 2 DAAs with RBV or 3 DAAs without RBV in Phase 3. Particularly, AbbVie expressed concern that it would be difficult to demonstrate non-inferiority between the 3 DAA + RBV regimen and these reduced regimens within the same trial. DAVP then clarified that the preliminary comments provided were not meant to suggest that AbbVie show non-inferiority between their own regimens within their Phase 3 program. DAVP clarified that AbbVie's regimens should be noninferior to what is currently on the market (telaprevir plus pegylated interferon and ribavirin), but the company should still look at more than one regimen for GT-1a and 1b subjects in their Phase 3 program. Including the RBV-free regimen in Phase 3 trials of GT-1a and -1b subjects will help to determine if all 4 drugs are necessary for all sub-populations and possibly confirm the differences seen in M11-652. A RBV-free regimen may also provide an alternative for patients who would not be eligibile for a regimen containing RBV.

AbbVie expressed concern that GT-1a patients who fail on a 3 DAA regimen would not have many options left for treatment due to resistance. DAVP acknowledged the risk and responded that the initial recommendation was to look at one of the 3-drug regimens (either without RBV or without ABT-333) in GT-1a treatment-naïve subjects, and to investigate the 4-drug regimen in GT-1a treatment experienced subjects. AbbVie then asked if they could build in futility rules for virologic failure, in the event that GT-1a treatment-naïve patients do not respond well to a 3-drug regimen. DAVP replied that futility rules in these types of trials are typically used in Phase 2 when less is known about the regimen and potential response rates, and highly conservative futility rules are not recommended for Phase 3 to ensure differences in efficacy results are interpretable.

AbbVie asked for additional guidance on how to design a Phase 3 program looking at both a 4-drug regimen and a 3-drug regimen in multiple sub-populations, particularly with regard to the following considerations:

1. *Success criteria for the 4-drug and RBV-free regimens*
    a. *DAVP recommended that AbbVie confirm that the 4-drug and 3-drug regimens are as active as or more active than telaprevir + pegylated IFN and RBV (PR), based upon the upper bound of the confidence interval (not the point estimate). DAVP explained that the point estimate is not reliable due to inter-trial variability, given the difference in SVR rates observed in the placebo arms of the boceprevir and telaprevir trials. DAVP suggested that AbbVie should consider the variability in the point estimate in their trial design. DAVP pointed out that the populations in the AbbVie trials are likely to be different than those in the boceprevir and telaprevir programs anyway, given the enrollment restrictions necessary when administering pegylated IFN and RBV.*
    b. *AbbVie expressed concern that it would be difficult for a RBV-free regimen to reach the threshold seen with telaprevir + PR. DAVP indicated a willingness to consider the safety and tolerability benefits of a RBV-free regimen during review of an NDA for a regimen that did not meet this threshold. This consideration could also apply to the 4-drug regimen, given the significant potential benefit (again in terms of safety and tolerability) of a regimen without interferon.*
    c. *DAVP asked AbbVie to propose a revised statistical plan for their Phase 3 trials following the meeting.*
2. *If the 4-drug regimen arm has a significantly higher SVR rate (>10%) than the 3-drug (RBV-free) regimen following Phase 3, how would AbbVie move forward with submission of an NDA in terms of indication?*
    a. *DAVP reminded AbbVie that the indication would be a review issue, but also mentioned that a RBV-free regimen might be appropriate only for specific sub-populations (as distinguished by HCV genotype subtype and/or IL28B status), which could be specified in labeling.*
    b. *DAVP noted that if a drug is removed from the 4-drug regimen, elimination of RBV rather than ABT-333 is preferable given the safety/tolerability benefits, and resistance to the non-nucleoside-palm class is not as concerning as resistance to other classes of HCV DAAs.*
3. *If labeling specified different regimens for patients with different HCV genotype subtypes, would it be necessary to develop a companion diagnostic subtype assay?*
    a. (b) (4), (b) (5)

AbbVie expressed willingness to look at a 3 DAA regimen in Phase 3 in GT-1a naïve and GT-1b naïve and experienced subjects, but explained they would not be willing to limit

the 4-drug regimen for study in GT-1a subjects only. DAVP reiterated that, from M11-652, a 4-drug regimen appeared to be unnecessary for most GT-1b subjects. AbbVie explained that some countries outside of the United States may not have widely-available genotyping assays. A regimen that could be used for all patients would therefore be necessary and AbbVie would need data on the 4-drug regimen in GT-1b patients to support registration in those countries. DAVP asked if AbbVie has spoken with the EMA regarding this program. AbbVie replied that they have consulted with the EMA, but not regarding the issue of differing regimens for GT-1a and GT-1b patients. However, this consideration would not preclude AbbVie from including the 3 DAA(without RBV) regimen in their Phase 3 program, nor specifying different regimens for different sub-populations in the US prescribing information.

AbbVie proposed coming back to DAVP with a revised plan incorporating the 3 DAA (RBV free) regimen into M11-646 and M13-391. DAVP agreed that this would be appropriate and suggested scheduling a follow-up teleconference to discuss the revised trial designs and statistical plans.

Question 3. Combination Rule

Does the Division agree the data provided in Section 9.4.3.1 fulfill the requirements under the Combination Rule (21 CFR § 300.50) and demonstrate the individual contributions of ABT-450/r, ABT-267, ABT-333, and RBV to the 3 DAA combination regimen?

FDA Response to Question 3

Currently available efficacy and resistance data from nonclinical and clinical studies provide evidence that each agent in the 3-DAA + RBV regimen has anti-HCV activity and for certain patient populations likely contributes to the efficacy of the combination regimen. However, the formal assessment of the Combination Rule will be made during the NDA review. Because the efficacy differences between certain 2-DAA + RBV and 3-DAA ± RBV regimens have been relatively modest to date, it is important that the contribution of the individual drugs is addressed from multiple perspectives.

In addition to inclusion of additional arms in your pivotal Phase 3 trials as described in the response to Question 2, further support for the contribution of the individual drugs would be provided if you were to demonstrate that the addition of a third or fourth drug can limit the impact of a resistance-associated polymorphism that is predominant in a viral population at Baseline. We have the following recommendations to provide this supporting evidence:

(a) Analyze NS3 and NS5A Baseline sequences for all HCV genotype 1 subjects (including those who achieved SVR) in M12-998.

(b) Analyze NS3, NS5A and NS5B for Baseline samples from all subjects enrolled in M11-652, regardless of treatment arm and treatment outcome. The design of this trial provides an important opportunity to understand how Baseline resistance-associated polymorphisms impacted treatment responses, and whether their impact could be

minimized when additional drugs were included in the regimens. The comprehensive collection and analysis of Baseline sequence data from M11-652 will also help justify the collection of data from only a subset of SVR-achieving subjects in Phase 3 trials.

(c) Include summaries and datasets of Baseline resistance analyses from Phase 2 and Phase 3 trials at the time of NDA submission (see also response to Question 11).

Meeting Discussion

[redacted] (b) (4)

AbbVie replied that those trials have just been initiated and [redacted] (b) (4) *. AbbVie explained that their approach to date has been to minimize the possibility of resistance and maximize the SVR rates for all patients. Therefore, they have started with the number of drugs most likely to provide a virologic response for those patients that are most difficult to treat.*

DAVP noted that approximately 10-15% of subjects will likely have resistance-associated polymorphisms in at least one of the 3 drug targets, and analysis of baseline sequences from Phase 2 trials may help to demonstrate the contribution of a third DAA or RBV to provide added coverage to suppress these viral variants.

Question 4. Clinical Trial M11-646 (HCV genotype 1, treatment-naïve, non-cirrhotic)

4a. Does the Division agree with the proposed placebo-controlled design for Study M11-646 as described in Section 9.4.4.1?

4b. Does the Division agree with the overall patient population proposed for Study M11-646 as defined by the inclusion/exclusion criteria provided in the draft protocol?

4c. Does the Division agree with the proposed sample size (N = 600) for Study M11-646?

4d. Does the Division agree with the proposed randomization plan, including stratification factors?

4e. Does the Division agree with the proposed primary efficacy endpoint (SVR12) and proposed secondary efficacy endpoints and the definitions for success for each of these endpoints?

4f. Abbott proposes to test the primary and key secondary endpoints using the

prespecified hierarchical procedure by which the family-wise type I error rate will be controlled under 0.05. Does the Division agree?

FDA Response to Question 4
A placebo-controlled design is acceptable, but we have some recommendations regarding the overall design as described in our response to Question 2. Based on the available data from your Phase 2 studies, we do not believe a placebo-controlled group would be necessary to demonstrate a more robust assessment of efficacy.

Further, as described above, there are other options for study designs that would address important clinically relevant issues. For example, M11-646 could be revised to include only HCV genotype 1a subjects and they could be randomized in a double-blind manner to receive 12 weeks of either ABT-450/r + ABT-267 + RBV, all 3 DAAs without RBV, or all 3 DAAs with RBV. This design would allow you to determine the safety and efficacy impact of dropping RBV or ABT-333 in a better powered trial compared to M11-652. In particular, eliminating RBV from an all DAA regimen for both genotype 1a and 1b would result in reduced risk of RBV-related adverse events and elimination of the required RBV-related pregnancy precautions.

If you choose to conduct the originally designed study, we agree with the randomization and stratification plans for a placebo-controlled study. The sample size in the currently proposed design is acceptable, but this may need to be changed depending on how our response to Question 2 is addressed.

The primary efficacy endpoint is acceptable, provided that emerging follow-up data from M11-652 and other Phase 2 trials confirm the durability of SVR12 (see also Clinical Virology recommendations below). (b) (4) Please also see the DAVP response to Question 17.

You should be aware that your plan to submit the efficacy data from the placebo subjects subsequently treated with active therapy in the 120 day safety update is not acceptable; all relevant efficacy data must be submitted in the initial NDA.

Meeting Discussion
Please refer to the discussion under Question 2.

Question 5. Clinical Trial M13-098 (HCV genotype 1, P/R treatment-experienced, non-cirrhotic)

5a. Does the Division agree with the proposed placebo-controlled design for Study M13-098 as described in Section 9.4.4.1?

5b. Does the Division agree with the overall patient population proposed for Study

M13-098 as defined by the inclusion/exclusion criteria provided in the draft protocol?

5c. Does the Division agree with the proposed sample size (N = 400) for Study M13-098?

5d. Does the Division agree with the proposed randomization plan, including stratification factors?

5e. Does the Division agree with the plan to limit the number of prior relapsers to ≤ 30%?

5f. Does the Division agree with the proposed futility criteria?

5g. Does the Division agree with the proposed primary efficacy endpoint (SVR12) and proposed secondary efficacy endpoints and the definitions for success for each of these endpoints?

5h. Abbott proposes to test the primary and key secondary endpoints using the pre-specified hierarchical procedure by which the family-wise type I error rate will be controlled under 0.05. Does the Division agree?

FDA Response to Question 5

We agree with the placebo-controlled design, the sample size, randomization and stratification plans, the plan to limit prior relapsers to ≤30% of the population, and the proposed futility criteria. This study could be redesigned to include only subjects with HCV genotype 1a as described in the response to Question 2 above. It appears from the available, albeit limited, data in subjects with HCV genotype 1b, that even treatment-experienced, HCV genotype 1b subjects will have high response rates to ABT-450/r + ABT-267 + RBV, 3-DAAs alone, or 3-DAAs+RBV, and could be included in Study M13-961.

Regarding the proposed patient population, we agree with your plans to enroll subjects with a <1 $\log_{10}$ IU/mL HCV RNA response at Week 4 (who did not receive ~12 weeks of treatment) as P/R null responders. However, please limit these subjects to no more than ~25% of the total P/R null responder population so that adequate efficacy data are obtained from subjects identified by the more standard null responder definition, <2 $\log_{10}$ IU/mL HCV RNA decline at Week 12. Also, if there are sufficient numbers of subjects please conduct an analysis to compare treatment efficacy in these two subgroups of null responders. These two subgroups of subjects should be identifiable in virology and resistance datasets.

As in M11-646, the primary efficacy endpoint is acceptable provided emerging follow-up data from M11-652 and other Phase 2 trials confirm the durability of SVR12 (also see additional Clinical Virology recommendations below). Please see the response to Question 17 regarding secondary efficacy endpoints.

Please state whether the test of the second secondary efficacy endpoint EOTR will use the same threshold of 51%. For other comments please refer to comments in Question 4 above.

Meeting Discussion
Please refer to the discussion under Question 2.

Question 6. Clinical Trial M13-099 (HCV genotype 1, compensated cirrhosis)

6a. Does the Division agree with the proposed design of the study in compensated cirrhotic patients (Study M13-099) as described in Section 9.4.4.2?

6b. Does the Division agree that the number of subjects who were nonresponders to previous pegIFN/RBV treatment is adequate, that the limitation on the number of subjects who were relapsers to previous pegIFN/RBV treatment is acceptable, and number of required prior null responders is adequate?

6c. Does the Division agree with the proposed study population as defined by the inclusion/exclusion criteria in the draft protocol?

6d. Does the Division agree with primary and secondary endpoints proposed?

6e. Abbott has revised the futility criteria in accordance with the Division's preliminary comments dated 10 July 2012. Does the Division agree with the revised criteria?

FDA Response to Question 6
We generally agree with the proposed design, the plans for subject enrollment, and the virologic futility criteria.

As in M11-646, the primary efficacy endpoint is acceptable provided emerging follow-up data from M11-652 and other Phase 2 trials confirm the durability of SVR12 (also see additional Clinical Virology recommendations below). Please see the response to Question 17 regarding secondary efficacy endpoints.

Question 7. Clinical Trial (b) (4)

(b) (4)

FDA Response to Question 7

We do not agree with your proposed (b) (4) trial at the present time. (b) (4)

(b) (4)

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Because of these concerns and the lack of any Phase 2 safety and efficacy data in an HCV/HIV-1 coinfected population we do not believe it is appropriate to initiate (b) (4) at this time. We recommend that you conduct additional drug-drug interaction studies with other available ART agents, including atazanavir. Once these data are available, you should conduct a proof-of-concept study in which safety, efficacy, PK/PD and drug resistance data are carefully assessed in a smaller number of subjects representative of those who might enroll in a larger, subsequent Phase 3 study.

We also have the following recommendations for you to consider in your development program for HCV/HIV-1 coinfected patients:

(a) If feasible, for larger trial(s) please consider adding an arm of subjects who receive placebo during the first 12 or 24 weeks of anti-HCV DAA dosing to assess the rate of HIV-1 virologic breakthrough in the absence of any active HCV DAA treatment.

(b) Complete HIV-1 resistance testing should be conducted for anyone who experiences HIV-1 virologic failure during anti-HCV DAA treatment.

(c) Please identify the assay to be used for HIV-1 RNA viral load analyses in protocols.

(d) Please include at lease one additional HIV-1 RNA assessment for a visit between the end-of-treatment and Post-Treatment Week 12 visits (e.g., Post-Treatment Week 4).

(e) Subjects should have demonstrated HIV-1 RNA suppression for at least 24 weeks prior to initiating anti-HCV therapy.

(f) (b) (4)

(b) (4)
. Since HIV-co-infection accelerates the progression of HCV-related liver disease, we strongly recommend that any study of co-infected subjects include adequate numbers of subjects with cirrhosis.

(g) (b) (4)

Question 8. Clinical Trial M13-961 (HCV genotype 1b, treatment naïve)

8a. Does the Division agree with the proposed design of the parallel study (Study M13-961) to assess the RBV-free regimen in HCV GT1b-infected patients as described in Section 9.4.4.3?

8b. Does the Division agree with the proposed noninferiority margin as defined in the draft protocol synopsis?

8c. Does the Division agree with the proposed study population as defined by the inclusion/exclusion criteria in the draft protocol synopsis?

8d. Does the Division agree with the proposed futility criteria?

8e. Does the Division agree with the proposed randomization plan, including stratification factors?

8f. Does the Division agree with the proposed primary efficacy endpoint (SVR12) and proposed secondary efficacy endpoints and the definitions for success for each of these endpoints?

8g. Abbott proposes to test the primary and key secondary endpoints using the pre-specified hierarchical procedure by which the family-wise type I error rate will be controlled under 0.05. Does the Division agree?

FDA Response to Question 8
We generally agree with your rationale to explore a less intense treatment regimen in HCV genotype 1b infected subjects. Please also see our response to Question 2, as the design of M13-961 may change depending on how our response to Question 2 is addressed. As currently planned, we agree with the proposed study population, futility criteria, and randomization and stratification plans.

You should consider, however, evaluating a number of different regimens in this study that would assist with determination of the appropriate duration and safety of your DAAs. We do not believe the single instance of virologic failure (relapse) among HCV genotype

1b subjects in Group A of M11-652 precludes further investigation of this and other regimens in Phase 3 for HCV genotype 1b. To identify if a regimen including fewer drugs is viable in genotype 1b subjects, we recommend redesigning M13-961 and incorporating 3 or 4 active treatment arms:

- ABT-450/r + ABT-267 + ABT-333 + RBV for 8 weeks
- ABT-450/r + ABT-267 + ABT-333 + RBV for 12 weeks
- ABT-450/r + ABT-267 + ABT-333 or RBV for 12 weeks

It would also be possible to include treatment experienced subjects as the data from Study M11-652, albeit limited, suggests that even treatment-experienced HCV genotype 1b subjects may not require the full 12-week, 3-DAA+RBV regimen for optimal efficacy.

Therefore, such a design would allow you to determine if a shorter duration regimen or a 12 week regimen without RBV is a safe and effective option for this relatively easy to treat population.

The primary efficacy endpoint is acceptable provided emerging follow-up data from M11-652 and other Phase 2 trials confirm the durability of SVR12 (also see additional Clinical Virology recommendations below). Please also see the response to Question 17.

Question 9. Subgroup Enrollment in Phase 3 Studies

9a. Does the Division agree that the approach for enrollment of population subgroups in the Phase 3 NDA studies described in Section 9.4.4.4 is adequate?

FDA Response to Question 9
DAVP strongly recommends that the populations enrolled into your clinical studies be representative of the overall population of US subjects with chronic HCV infection.

We note your intention to target areas where there are substantial numbers of Black and Hispanic patients. Please describe what efforts you will undertake to ensure that adequate numbers of these subjects are enrolled.

We recommend that you not initiate enrollment of any subjects into any Phase 3 study until you have the final results of the methadone and buprenorphine drug interaction studies.

We agree with your inclusion criteria for subjects with bleeding disorders.

We do not agree with your exclusion of subjects for a single positive urine test for either opiates or alcohol. For example, methadone will give a false positive urine result for opiates.

Meeting Discussion

DAVP recommended that AbbVie enhance their recruitment plan to enroll population subgroups in the United States to include activities beyond placing sites in high prevalence areas. DAVP suggested that AbbVie engage in more active community outreach and work closely with local organizations to enroll these patients. AbbVie acknowledged this advice.

Question 10. Clinical Study M13-102 (long term follow-up)

10a. Does the Division agree with the design of the proposed long term follow-up study (Study M13-102)?

10b. Does the Division agree with the follow-up period of up to 3 years after the last dose of DAA in the prior Abbott study?

FDA Response to Question 10
In general we agree with the design of this study. Please comment on the long term follow-up data from SVR and non-SVR subjects who enrolled in Phase 2 trials that you expect will be available and submitted with the Original NDA. Ideally, data through at least ~48 weeks of follow-up will be included.

Please collect data on liver-related morbidity and mortality events.

Question 11. Virology Analysis Plan

11a. Does the Division agree that the resistance analysis plan will be adequate to support NDA approval?

11b. Does the Division agree with the proposed resistance analysis plan for the treatment-naïve and treatment-experienced subjects without cirrhosis or HIV-1 coinfection?

11c. Does the Division agree with the proposed resistance analysis plan for the cirrhotic and HIV-1 coinfected subjects?

FDA Response to Question 11
We do not agree. Your plan to provide sequence analysis results from matched Baseline samples from Phase 3 trials at the 4-month safety update is not acceptable. These data are important to understand the impact of Baseline resistance-associated polymorphisms on treatment outcome, and to support other analyses conducted to demonstrate the contribution of the individual drugs in the treatment regimens. **You should understand that the lack of adequate Baseline sequence data in the NDA could be a filing issue.**

It may be acceptable for you to analyze Baseline samples from only a subset of SVR-achieving subjects. However, for your trials in non-cirrhotic, HCV mono-infected subjects we are concerned that there will be too few subjects in certain subgroups who experience virologic failure that an equal number of SVR-achieving subjects will not be

sufficient to understand the impact of Baseline resistance polymorphisms on treatment response. Therefore, for all trials we strongly recommend analyzing Baseline samples from at least 2 SVR-achieving subjects for every 1 virologic failure subject (matched by HCV subtype, IL28B genotype, etc., to the extent possible) as currently planned for the trials in cirrhotic and HCV/HIV-1 coinfected subjects. Baseline samples from all subjects should be collected and stored in the event that additional analyses are needed.

We also have the following recommendations/requests regarding your resistance analysis and submission plans:

(a) When feasible, please conduct treatment-emergent resistance analyses for subjects who did not achieve SVR for reasons unrelated to virologic failure. These analyses are important to understand the potential resistance-related implications of poor adherence or poor tolerability leading to early treatment discontinuation.

(b) Please plan to conduct a meta-analysis of all subjects who have experienced virologic failure across all of your completed Phase 2 and Phase 3 trials to identify any potentially novel resistance-associated substitutions in NS3, NS5A or NS5B.

(c) Please provide a listing of substitutions/positions that are considered "signature" resistance-associated substitutions/positions for each DAA.

(d) Please plan to include complete resistance datasets from M11-652 in the NDA for independent review.

(e) Please comment on how you plan to submit data from clonal nucleotide sequence analyses. It may be reasonable to report all detected substitutions at a particular position in a single cell (i.e., as a mixture), with the understanding that these analyses will have a greater sensitivity to detect minority variants compared to population sequencing. Any analyses on the frequency of specific variants could be included separately.

(f) Please collect a blood sample at the time of virologic failure to evaluate pharmacokinetics; this may assist with an assessment of adherence.

Question 12. Clinical Safety Database

Does the Division agree that the proposed safety database and the proposed primary and supportive integrated safety analysis sets, as described in Section 9.4.5, will be adequate to support the proposed NDA?

FDA Response to Question 12

The safety database is likely to be adequate, even if some of the studies are redesigned as recommended.

Question 13. Clinical Pharmacology Program

Does the Division agree that Abbott's clinical pharmacology program will be adequate to support the proposed NDA?

FDA Response to Question 13
The clinical pharmacology plan is reasonable. As several drug-drug interaction trials are planned or currently ongoing, the need for additional assessments will depend on the outcome of ongoing/planned trials.

Please consider conducting a drug-drug interaction trial with a strong CYP3A inducer such as carbamazepine. The results from such a trial will help with providing dosing information when the DAA regimen is combined with CYP3A inducers.

Please conduct a drug-drug interaction trial of DAAs and atazanavir. The results from this trial will provide more information regarding the concomitant use of DAA combination and atazanavir in HIV/HCV co-infected patients.

In in vitro induction studies which will evaluate induction potential of DAA regimen on CYP1A2, CYP2B6, and CYP3A, please include hepatocyte preparations from at least 3 donors. This recommendation is in accordance with the 2012 Draft Guidance on "Drug Interaction Studies-Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations".

Question 14. Clinical Pharmacology Program
Does the Division agree with the doses selected and design of the thorough QTc study as described in Section 9.4.4.6.4 and the protocol synopsis provided in Appendix C?

FDA Response to Question 14
Protocols for QTc trials are reviewed by the IRT-QT group. Please submit the final protocol for review by the IRT-QT group.

Question 15. Labeling Considerations
Does the Division agree that successful completion (i.e., the clinical endpoints are met) of the pivotal Phase 3 pivotal studies in HCV GT1 infected treatment-naïve and treatment-experienced patients (Studies M11-646 and M13-098) and the additional Phase 3 studies in patients with compensated cirrhosis (Study M13-099) (b) (4) **provides an adequate basis for approval with the following indication?**

(b) (4)

FDA Response to Question 15

Given the recommendations regarding redesign of various studies, it is premature to agree to the specific language of an indication; the final wording will be a review issue and will be decided during review of the NDA.

We do not believe it is safe to conduct Study (b) (4) as currently designed, and it is unlikely that adequate data would be available and submitted in the NDA to support an indication in this population.

Question 16. Labeling Considerations

Does the Division agree that successful completion (i.e., the clinical endpoints are met) of the proposed Phase 3 Study (b) (4) would support the following additional indication (with modification to labeling included in Question 15, as appropriate)?

(b) (4)

FDA Response to Question 16

Again, it is premature to discuss the specifics of possible indications. (b) (4) Also see the response to Question 15.

(b) (4)

Question 17.

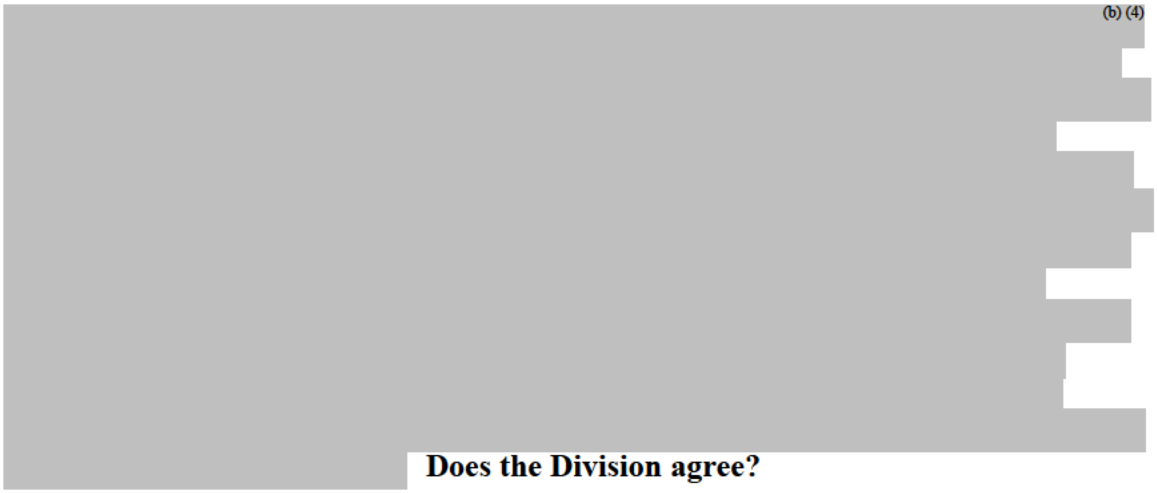
(b) (4) **?**

FDA Response to Question 17

(b) (4) .

It is possible that the results from clinically relevant subgroups could be included in the labeling. You will need to ensure there are adequate numbers in each subgroup to make assessments/comparisons. The final determination of appropriate subgroups for inclusion in labeling will be made during the NDA review.

Question 18.



Does the Division agree?

FDA Response to Question 18
Please see the response to Question 17.

2.3. REGULATORY

Question 19.
With reference to an Information Request letter dated June 29, 2010 from the Office of Clinical Pharmacology, Abbott is proposing to submit AIMS datasets per the template supplied in June 2010 to the IND. Resistance datasets according to revised template supplied on January 25, 2012 (courtesy copy of Draft Guidance, "Attachment to Guidance on Antiviral Product Development – Conducting and Submitting Virology Studies to the Agency"), analysis ready datasets, and electronic CRT datasets for all Phase 2b and Phase 3 studies will be submitted in the NDA. The electronic CRT and analysis-ready datasets will be standardized and consistent across studies, but will not be in CDISC format. However the analysis-ready datasets will utilize the ADSL data set and all analysis data sets will be as close to "one PROC away" as possible. Abbott is not planning to submit CRT data sets for Phase 1 studies. Does the Division Agree?

FDA Response to Question 19
These proposals are acceptable.

We agree with your plan to submit resistance data according to the January 2012 draft resistance template. We recommend submitting a mock resistance dataset for review prior to finalization and submission of datasets to address any possible formatting or submission problems in a timely matter.

2.4. ADDITIONAL COMMENTS

General Requests:

1. Please plan to discuss your plans and timeline for pediatric development.

2. Please plan to discuss your plans for evaluation of subjects with decompensated liver disease and subjects undergoing liver transplantation for HCV-related complications.

3. Please submit case summaries/narratives for all Grade 3 and 4 pancytopenia cases observed during clinical trials with ABT-450 plus any other agent.

Clinical Virology:

1. When you have collected data from M11-652 through the SVR24 endpoint, please summarize the numbers of subjects with HCV RNA <LLOQ Target Detected at Follow-up Weeks 4 or 12, and comment if such results were associated with subsequent virologic relapse (i.e., HCV RNA ≥LLOQ). These results are needed to support using the assay LLOQ for the SVR12 primary efficacy endpoints in your Phase 3 trials.

2. Please summarize available data from Phase 2 trials conducted to date on the impact of NS5B T390I or F415Y on treatment outcome for treatment arms that include ribavirin. Also, please summarize the frequency of treatment-emergent T390I or F415Y. These analyses should also be conducted for your Phase 3 trials.

3. Please comment on the proportion of subjects expected from U.S. and non-U.S. study sites for each Phase 3 trial. Also, please conduct phylogenetic analyses of Baseline HCV sequences from study subjects within each HCV subtype to compare the genetic relatedness of the DAA target sequences according to geographic region. These analyses may be conducted using pooled sequence data from your clinical development program that were generated for resistance analysis purposes.

4. Please conduct phylogenetic analyses of available Baseline sequence data for each drug target to characterize HCV genotype/subtype, and compare these results with those obtained with the Versant® HCV Genotype Inno-LiPA Assay v2.0. Again, these analyses may be conducted using pooled sequence data from your clinical development program that were generated for resistance analysis purposes.

5. Please include HCV RNA ≥LLOQ at end-of treatment, and virologic relapse during follow-up, in the protocol definitions of virologic failure for efficacy and resistance assessments.

6. Please specify the IL28B polymorphism (presumably rs12979860) to be used for stratification and subgroup analyses in clinical trials. Also, please provide a description of the assay to be used. Please also consider conducting retrospective analyses on the impact of other single-nucleotide polymorphisms near IL28B that have been associated with treatment response or natural clearance of HCV.

7. Regarding the phrase about HCV RNA analyses in clinical trial protocols, “results below LLOD are reported as ‘HCV RNA not detected,’” please confirm that results reported as HCV RNA not detected are based on a true “Target Not Detected” (i.e., no Ct value)

result and not based on a "<LLOD" result. HCV RNA levels <LLOQ cannot be accurately quantified, and levels below the assay limit of detection can still be detected by the assay at a certain frequency depending on the actual HCV RNA concentration. When you submit datasets that include HCV RNA data, please indicate whether results <LLOQ were reported as "Detected" or "Not Detected" (or "Target Not Detected").

8. The study reports for the primary efficacy analyses of your Phase 3 trials should include a preliminary assessment of the durability of SVR12 based on available data obtained after the SVR12 endpoint.

9. Please provide an update for your plans to enroll subjects in M13-393, Group 4 (HCV genotype 1a, ABT-450/r + ABT-267), considering emerging results from M11-652 and M12-998.

10. Please provide up-to-date table(s) of NS3/4A, NS5A and NS5B substitutions that have been evaluated for their impact on HCV susceptibility to ABT-450, ABT-267 or ABT-333 in biochemical or replicon studies, and indicate the fold-changes in EC_{50} and EC_{90} values in these assays. Please identify the HCV genotype/subtype background used in these assessments.

Statistical Comments:

The following comments apply should the proposed studies be conducted as currently designed. We strongly recommend you revise the studies as outlined above and once they are re-designed we may have additional statistical and analytical comments.

General

1. The sample sizes for studies M11-646, M13-098 and M13-099, appear to be adequate for the underlying assumptions, and based on the normal approximation of the binomial distribution in one-sample inference for superiority trials;

2. Provide statistical hypotheses for the primary efficacy endpoint and key secondary efficacy endpoints because these outcomes may be claimed as a result of using the fixed-sequence testing procedure (if considered clinically appropriate for labeling);

3. Provide statistical references for the sample size calculation and for fixed-sequence testing procedure;

4. SAPs should be submitted soon after any revisions to the study design for the four Phase 3 studies have occurred. For studies with similar designs, you may submit one SAP as long as the differences are clearly stated.

Studies M11-646 and M13-098

1. The efficacy goals for studies M11-646 and M13-098 are unclear. Preferably, these Phase 3 studies should demonstrate superiority or at least non-inferiority, based on historical comparison, to the current new standard of care (SOC) including either a boceprevir-containing or telaprevir-containing regimen, in a similar study population. In other words, the comparison of the primary efficacy endpoint from the current trial to the new SOC should take into account the variability in the effect size estimates as well as cross-trial variability. Cross-trial variability has been observed in the boceprevir and telaprevir trials, in which the SVR rate in the placebo arm of the telaprevir trial was 8% greater than that in the placebo arm of the boceprevir trial.

2. Confirm that there is no formal interim analysis on the primary efficacy assessment and no intention of stopping the trial earlier for an efficacy claim;

3. Describe the rationale for including Arm B in both M11-646 and M13-098;

4. Subgroup analysis of the primary efficacy endpoint SVR_{12} will be conducted for selected patients' demographics and baseline disease characteristics. For example, fourteen variables were selected for subgroup analysis in M11-646 or M13-098. For example, the M11-646 protocol states that "*Each subgroup analysis will be performed if there is an adequate number of subjects within each subgroup level. If the lower confidence bound of the 2-sided 95% confidence interval for a subgroup is > 66**%, then the regimen will be considered efficacious in the subgroup***. It does not appear that you plan to adjust the family-wise Type I Error for multiplicity. The efficacy of a drug is usually based on the overall population, supported by the consistency across subgroups.

Study M13-961

1. As currently designed, the sample size of 200 per arm for the non-inferiority study M13-961 appears to be slightly smaller than the DAVP reviewer's results. Please provide additional information including statistical references about how the sample size was derived.

2. Provide the justification for the -10.5% non-inferiority margin and statistical hypotheses for the primary and secondary efficacy endpoints.

3. Confirm that there is no formal interim analysis on efficacy assessment and no intention of stopping the trial earlier for efficacy claim.

4. Consider using randomization stratum-adjusted Mantel-Haenszel proportion and continuity-corrected variance by Koch et al (Koch, G.G., et al. (1989) Categorical Data Analysis. Chapter 13. Statistical Methodology in the Pharmaceutical Sciences. Marcel Dekker, New York, pp. 412-421) to estimate treatment differences in SVR_{12} and 95% CI for subgroup analyses.

Study M13-099

1. Provide the number of interim analyses and stopping rules for futility.

2. Consider reporting the randomization stratum-adjusted Mantel-Haenszel proportion with a continuity correction for the variance by Koch et al (Koch, G.G., et al. (1989) Categorical Data Analysis. Chapter 13. Statistical Methodology in the Pharmaceutical Sciences. Marcel Dekker, New York, pp. 412-421) in treatment differences between SVR_{12}(Arm A)- SVR_{12}(Arm B) and 95% CI, in addition to the unadjusted one.

3.0 PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

4.0 DATA STANDARDS FOR STUDIES

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

5.0 ISSUES REQUIRING FURTHER DISCUSSION

A follow-up teleconference will be held to discuss the following items:

1. The re-design of protocols M13-646 and M13-961 to include a 3-DAA regimen without ribavirin.

2. The revised, high-level statistical plans for the complete Phase 3 program.

6.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit revised Phase 3 program proposal, including trial design and high-level statistical plans, and request a follow-up teleconference with DAVP.	AbbVie Inc.	When available

Submit information on the rate of fatigue across all arms in M11-652.	AbbVie Inc.	As soon as possible

7.0 ATTACHMENTS AND HANDOUTS

Attached is the slide presentation from AbbVie Inc. dated October 1, 2012.

45 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

JEFFREY S MURRAY
10/31/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 103,526
IND 108,434
IND 101,636

MEETING MINUTES

Abbott Laboratories
Attention: Mary Konkowski
Associate Director, Regulatory Affairs
200 Abbott Park Road
Abbott Park, IL 60064-6188

Dear Ms. Konkowski:

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABT-450, ABT-267 and ABT-333.

We also refer to the meeting between representatives of your firm and the FDA on September 14, 2011. The purpose of the meeting was to discuss the planned Phase 2b clinical trial and overall development plan for your triple-drug combination with ABT-333, ABT-267 and ABT-450, without pegylated interferon alfa, for the treatment of HCV genotype 1 infection.

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, contact Katherine Schumann, M.S., at (301) 796-1182 or the Division's main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
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:	End of Phase 1
Meeting Date and Time:	September 14, 2011 2:30 PM – 4:00 PM EST
Meeting Location:	10903 New Hampshire Avenue Building 22, Room 1309
Application Numbers:	IND 103,526 IND 108,434 IND 101,636
Product Names:	ABT-450 ABT-267 ABT-333
Indication:	Treatment of chronic hepatitis C virus infection
Sponsor/Applicant Name:	Abbott Laboratories
Meeting Chair:	Linda Lewis, M.D.
Meeting Recorder:	Katherine Schumann, M.S.

FDA ATTENDEES

1. Debra Birnkrant, M.D., Division Director, Division of Antiviral Products (DAVP)
2. Jeffrey Murray, M.D., MPH, Deputy Director, DAVP
3. Linda Lewis, M.D., Medical Team Leader, DAVP
4. Russell Fleischer, PA-C, MPH, Medical Reviewer, DAVP
5. Mark Seaton, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
6. Jules O'Rear, Ph.D., Clinical Virology Team Leader, DAVP
7. Patrick Harrington, Ph.D., Clinical Virology Reviewer, DAVP
8. Damon Deming, Ph.D., Clinical Virology Reviewer, DAVP
9. Susan Zhou, Ph.D., Statistician, Division of Biometrics IV
10. Vikram Arya, Ph.D., Clinical Pharmacology Reviewer, OCP
11. Leslie Chinn, Ph.D., Clinical Pharmacology Reviewer, OCP
12. Jeffry Florian, Ph.D., Pharmacometrics Reviewer, OCP
13. Jianmeng Chen, Ph.D., Pharmacometrics Reviewer, OCP
14. Jingyu Yi, Ph.D., Pharmacometrics Reviewer, OCP
15. George Lunn, Ph.D., Product Quality Reviewer, ONDQA
16. Victoria Tyson, Chief, Project Management Staff, DAVP

17. Elizabeth Thompson, Regulatory Project Manager, DAVP
18. Katherine Schumann, Regulatory Project Manager, DAVP

SPONSOR ATTENDEES

1. Barry M. Bernstein, M.D., Project Director, HCV Global Project Team
2. Scott C. Brun, M.D., Divisional Vice President, Virology
3. Sandeep Dutta, Ph.D., Director, Clinical Pharmacology and Pharmacometrics
4. Thomas H Hassall, M.S, R.Ph., Senior Director, Regulatory Policy and Intelligence
5. Mary S. Konkowski, Associate Director, Regulatory Affairs
6. Lois M. Larsen, Ph.D., Associate Director, Statistics
7. Rajeev M. Menon, Ph.D., Associate Director, Clinical Pharmacology and Pharmacometrics
8. Thomas J. Podsadecki, M.D., Senior Medical Director, Antiviral Clinical Project Team
9. Nurit Rojstaczer, Ph.D., Director, Regulatory Affairs
10. Margarita Aguilera, M.Sc., Senior Director, Regulatory Affairs

1.0 BACKGROUND

Abbott Laboratories (Abbott) is developing three direct-acting antiviral (DAA) drugs for the treatment of chronic hepatitis C virus (HCV) infection: ABT-450, an NS3/4A protease inhibitor (being studied with ritonavir as a PK enhancer), ABT-333, a non-nucleoside NS5B palm-targeting polymerase inhibitor, and ABT-267, an NS5A inhibitor. Abbott is currently studying various combinations of these DAAs, with and without ribavirin (RBV), and without interferon, to identify an optimal regimen or regimens for this indication.

On July 8, 2011, Abbott submitted a request for an End-of-Phase 1 meeting with the Division to discuss the ongoing combination development program with ABT-450, ABT-267 and ABT-333, for the treatment of genotype 1, chronic HCV infection, including Protocol M11-652, a Phase 2b clinical trial in treatment-naïve and treatment-experienced HCV genotype 1-infected subjects. The Phase 2b trial is intended to support selection of a dosing regimen for subsequent Phase 3 trials in pegIFN-contraindicated and intolerant HCV-infected subjects.

The Division provided preliminary responses to Abbott's questions on September 9, 2011. Abbott responded with an email on September 13, 2011, providing a slide presentation to facilitate consideration of the questions identified for further discussion (Questions 5.3, 6, and 3, please refer to the attachments).

2. DISCUSSION

Questions submitted by the Sponsor are in **bold**, the Agency's preliminary comments are in *italics*, and discussions during the September 14, 2011 meeting are in regular font.

1. **Abbott intends to develop a combination of DAAs (with or without RBV) for treatment of chronic HCV infection.** (b) (4) **As such, Abbott proposes to conduct the clinical pharmacology development program (e.g., drug-drug-interaction [DDI] and special population studies) using only the DAA combination regimen and does not plan to conduct DDI and special population studies for the individual DAAs. Does FDA agree with this proposal?**

   The proposal to conduct the clinical pharmacology development program using only the DAA combination regimen is acceptable.

2. **Abbott proposes to conduct healthy volunteer DDI studies with the DAA combination regimen coadministered with commonly prescribed medications used in the HCV-infected population (e.g., antidepressants, statins, immunosupressants, hormonal oral contraceptives). For the commonly prescribed medications in HCV-infected patients, Abbott will choose a substrate/inhibitor that, based on in vitro data, may have an interaction with the DAA combination regimen based on metabolism/transport pathways. In addition, Abbott proposes to conduct DDI studies to evaluate the effects of the DAA combination regimen on a model cytochrome P450 (CYP) 3A substrate and the effect of a model CYP3A inhibitor on the DAA combination. A definitive list of DDI**

studies will be provided at a future meeting (e.g., End-of Phase 2 meeting). Does FDA agree with the proposed general study designs and the approach for selecting coadministered drugs for evaluation in DDI studies for the DAA combination regimen?

The approach of selecting the co-administered drugs for conducting drug-drug interaction trials seems reasonable. As described in the meeting package, the need for additional studies will be determined based on the information available from ongoing- and completed drug-drug interaction trials. The study design of the drug-drug interaction trials will depend on the objectives of the study and the pharmacokinetic properties of the drug(s) being evaluated. Therefore, specific feedback on the study design will be provided after review of the individual protocols.

3. **Abbott proposes to conduct the renal impairment study according to a reduced study design and is conducting the hepatic impairment study (Study M12-215) according to a full study design in non-HCV-infected subjects. Does FDA agree with the planned and ongoing studies and designs to characterize the pharmacokinetics of the DAA combination regimen in these special populations?**

The proposal to conduct the renal impairment trial following a "reduced design" and the hepatic impairment trial following a "full" design is acceptable.

Meeting Discussion:

DAVP agreed that it is appropriate to conduct the “reduced design” renal impairment trial in severe renal impairment subjects instead of end-stage renal disease subjects. DAVP reminded the sponsor that if any unexpected findings are observed in the renal impairment trial conducted using the reduced design, additional evaluation in other renal impairment groups will be needed.

4. **Abbott plans to conduct a thorough QT (TQT) study with the DAA combination regimen. Abbott does not plan to perform TQT studies with each individual DAA. The TQT study will assess therapeutic and supratherapeutic doses of the DAA combination regimen. Does FDA agree that the approach for the TQT study is appropriate to support the NDA of the proposed DAA combination regimen?**

If the sponsor intends to always use the selected compounds in combination at a fixed ratio (i.e., co-package) and there is no intention to develop or market each of the compound separately, it is acceptable to evaluate the QT effect under therapeutic and supratherapeutic doses of the DAA combination regimen. Should a signal be detected during the DAA combination TQT study, additional work may be necessary.

5.

5.1. Does FDA agree with the process and rationale to select:

- **Doses of ABT-450, ABT-267, and ABT-333?**
- **Treatment regimen and DAA combination?**
- **Duration of treatment, for subsequent studies, including Phase 3 studies?**

From an antiviral activity/durability perspective, the ideal ABT-450 exposure will be comparable or higher than that obtained with the 200/100 mg ABT-450/r dose evaluated in M11-602 (comparable to 250/100 mg tablet). However, we also recognize there are safety and PK considerations in your ABT-450 dose rationale, and emerging data from M12-267 and M12-746 indicate that the lower dose levels of ABT-450/r may be equally effective. In general, the ABT-450/r dose exploration planned in M11-652 seems reasonable, although clear differences in SVR rates may not be observed due to the relatively small size of the arms and the contributions of other DAAs and RBV in the study regimens.

Based on the lack of an obvious dose-response relationship for ABT-333, your plan to study the 400 mg BID dose level going forward is reasonable.

For ABT-267, we agree that any interaction that reduces ABT-450 exposure should be avoided, and maximizing ABT-450 exposure should be the priority for optimal antiviral activity and durability. Therefore, your rationale to study the 25 mg QD dose level for ABT-267 is reasonable.

We expect that data from the ongoing drug-drug interaction trial M12-221 will be useful to help inform dose selection of the DAAs in M11-652. Please provide an update on the status of this trial.

5.2. Does the Agency agree that the modified factorial design of Study M11-652, along with data from other supportive studies, will adequately demonstrate that each component of the DAA combination regimen contributes to the desired effect of treatment for genotype 1 HCV infection?

We generally agree that M11-652 will be informative for identifying promising regimens and durations to carry forward, and possibly understanding the role of RBV. However, as discussed below, we are concerned that data from M11-652 and other studies conducted to date may not be adequate to demonstrate the individual contribution of ABT-333 or ABT-267 in the planned combination regimens. Please see the next section for additional comments and recommendations.

5.3. Does FDA agree that the proposed program will also meet the requirement set forth in FDA's combination drug policy, which is articulated in 21 CFR 300.50, Fixed-combination prescription drugs for humans, in regard to the need to demonstrate the contribution of each agent to the treatment regimen?

Based on the favorable results obtained thus far from M12-267 and M12-746, we are concerned that results from M11-652 will not demonstrate the contribution of ABT-333 or ABT-267 to the proposed combination regimens, potentially requiring further exploration of different DAA combinations or treatment durations. Furthermore, results of the 24 week treatment duration arms (Arms H/I) in the current design can only be interpreted in the event that Arms F/G from the 12 week treatment duration display an

increased response relative to all other 12 week treatment arms.

One strategy that may help demonstrate the individual contributions of ABT-333 and ABT-267 would be to study the 8-week duration in M11-652 in a factorial design incorporating strict cohort stopping rules to identify early failures or relapse. We believe the 24-week regimens for the treatment-naïve cohort may not be necessary, and could be replaced with two other regimens, for example:

- *Arm H (8 weeks): ABT-450/r + RBV + ABT-267*
- *Arm I (8 weeks): ABT-450/r + RBV + ABT-333*

Efficacy data from these arms would be compared with data from Arm A to obtain a better understanding of the contributions of ABT-333 and ABT-267. The 24 week treatment duration arms in the treatment experienced population (Arms M/N) should still be included, but the number of subjects in each of these arms could be increased to better discriminate whether 24 weeks of treatment with 3 DAAs with RBV may be necessary in a subset of patients.

If necessary, other potential strategies to address this concern could be designed building on results from M11-652 in subsequent trials. For example, if favorable data continue to emerge from your combination DAA program you could consider exploring the efficacy of an ABT-450/r + RBV regimen in a carefully designed trial, with an appropriate patient population, futility rules, and treatment rescue strategies to reduce resistance-related risks for study subjects.

Efficacy and safety data from M11-652 and other planned and ongoing studies will need to be reviewed to determine whether sufficient information is available to support a Phase 3 program. If additional treatment strategies need to be explored, it is unclear at this point if they would first need to be addressed in Phase 2, or if they could be addressed in Phase 3.

We can discuss alternative trial designs and/or modifications to the design of Study M11-652 with you during the meeting.

Meeting Discussion:

Abbott began by providing a justification for the design of Study M11-652 as proposed. Abbott reiterated that the trial is designed around a core duration of 12 weeks of DAA treatment. Abbott explained that the company's modeling and simulation efforts, as well as preliminary clinical data with the DAAs, suggest that 12 weeks of therapy is the optimal duration. Additional therapy up to 24 weeks is not anticipated to confer any added benefit. Similarly, modeling suggests that treatment for 8 weeks may results in slightly lower SVR rates than treatment for 12 weeks.

(b) (4)

(b) (4)

Abbott then asked why DAVP had suggested possibly looking at ABT-450 and ribavirin alone, given the risk of resistance. DAVP explained that this was just one possible option to address the Division's main concern that Abbott will not be able to demonstrate the contribution of each DAA in the combination if the 2 DAA and 3 DAA arms in M11-652 are equally successful. Since preliminary data indicate that ABT-450 is the most potent and durable of the three DAAs, the Division is particularly interested in determining the additional contribution of ABT-333 and ABT-267 to the proposed combination regimens. The Division noted that the ABT-450 plus ribavirin option could be considered in a future trial if emerging data continue to be favorable, and the contribution of the individual agents is still unclear. However, the Division concurred with Abbott's concerns about the resistance barrier in such a regimen, and also noted that observations of virologic breakthrough in other trials (as noted below) may change this recommendation.

Abbott then presented slides 14-17, containing preliminary clinical data from trials M12-267 and M12-746, emphasizing that although the data in treatment naïve patients look very positive, they have observed virologic breakthrough in two subjects during the initial weeks of therapy in the treatment-experienced cohort (M12-746 Group 3, Slide 17; note that data from the second breakthrough subject was obtained recently and not included in slide).

DAVP asked Abbott if breakthrough was confirmed for the two treatment-experienced patients in M12-746 Group 3. Abbott responded that they did not have confirmation of breakthrough in these patients yet. The Division mentioned the work of Doug Bartels on selection of F415Y by ribavirin (http://regist2.virology-education.com/2011/6HEPC/docs/08_Bartels.pdf) and commented that the impact of this substitution on efficacy of regimens containing ABT-333 and/or ribavirin for treatment experienced subjects should be assessed.

(b) (4)

The Division indicated that Abbott should return for an End-of-Phase-2 meeting for further discussion after the planned Phase 2 program is completed.

Abbott asked if the Division agreed with the proposed criteria on Slide 4 to select regimen(s) for further development if those studied in M11-652 result in similar SVR rates. DAVP suggested that Abbott might want to add "persistence of resistant variants" and "differential activity against genotype 1a versus 1b" to the criteria already listed. The Division also suggested Abbott might also consider metabolism and drug interactions when selecting final regimen(s). DAVP cautioned that the appropriate criteria for selection will likely depend upon the results of M11-652.

Finally, DAVP reminded Abbott to try to enroll subjects of diverse racial and ethnic backgrounds in their planned trials.

6. **Abbott plans to conduct parallel Phase 3 programs for a DAA combination regimen in both pegIFN treatment-naïve and -experienced patients as well as pegIFN-contraindicated and -intolerant HCV patients.** (b) (4)

We generally agree that your plan to conduct parallel Phase 3 programs in pegIFN treatment-naïve and -experienced patients as well as pegIFN-contraindicated and -intolerant HCV patients is reasonable based on the current state of the field. Please be aware that the definitions of these populations will need to be further negotiated to ensure the broadest representation of at-risk subjects.

(b) (4)

Meeting Discussion:

(b) (4), (b) (5) While Abbott's general approach appears to be reasonable, the Division will likely have specific recommendations once these discussions are concluded, in time for Abbott to implement them in their Phase 3 program.

(b) (4) DAVP reminded Abbott that they should include a broad representation of contraindicated patients in their trials. DAVP also cautioned that the intolerant patient may be more difficult to define and require additional documentation to confirm eligibility.

(b) (4)

(b) (4)

Abbott asked if the Division could comment on the required size of the trials. DAVP replied that it was too early to discussion the trial size, but that the safety database should follow the recommendation in DAVP's draft guidance, "Chronic Hepatitis C Virus Infection: Development Direct-Acting Antiviral Agents for Treatment." (b) (4) Therefore, DAVP would expect to see the higher number specified in the guidance (1,000-1,500 patients exposed to the proposed dose and duration). DAVP agreed that Phase 2 data with the appropriate regimen can supplement the safety database.

7. **Abbott plans to copackage the components of the approved DAA regimen as a single presentation under 1 Trade Name and 1 Package Insert to assure the safe and effective use of the product in accord with approved labeling.** (b) (4)

Does FDA agree with this proposal?

The acceptability of the final packaging configuration will depend upon data from the ongoing combination program. However, we encourage you to submit your proposed copackaging presentation for review early in the development process.

Meeting Discussion:

DAVP suggested that Abbott consider initiating long-term stability studies of the products in possible copackaging configurations as soon as possible, so that adequate stability data are available for submission with the NDA. DAVP also noted that the choice of copackaging configuration should take into account the number of drugs chosen for the final combination. (b) (4)

(b) (4)

Abbott agreed to take these comments into consideration and mentioned that they are also looking at coformulation options at this time.

Additional Discussion:

At the end of the meeting, DAVP provided general recommendations to the sponsor regarding the combination development program. DAVP advised Abbott to being thinking about conducting trials in special populations, such as HIV/HCV co-infected patients, pediatric patients and elderly patients. Abbott responded that they had already begun thinking about these populations. DAVP also mentioned that Abbott should exercise caution in administering ritonavir to HIV/HCV co-infected patients.

The Division also suggested that Abbott submit a new IND for the combination, once a final regimen has been chosen. DAVP and Abbott agreed that it would be premature to submit a combination IND at this stage in development, before the final combination is selected.

Additional Comments:

Clinical Pharmacology:

1. Please describe your plans for assessing the effect of CYP3A4 inducers on the pharmacokinetics of DAAs.

2. Based on the available drug-drug interaction data, please provide a summary table of anticipated ABT-450 exposures (e.g. C_{trough} and AUC) for the different treatment arms that are being evaluated in M11-652. This table will aid us in assessing the proposed ABT-450/r doses and determine if further dose exploration is warranted.

Clinical Virology:

3. Please provide an update on virologic response data from ongoing trials M12-267 and M12-746. We are particularly interested in virologic responses observed for M12-746 subjects who have completed the trial through at least Follow-up Week 4. Having preliminary SVR and relapse data from this trial may help guide some of the discussion of your clinical development program.

4. Please summarize the effect of common NS3 Q80 polymorphisms on ABT-450 anti-HCV activity in cell culture, the impact of baseline Q80 polymorphisms on ABT-450 antiviral activity in monotherapy studies, and whether treatment-emergent substitutions are observed at NS3 Q80.

5. Your resistance analyses for ABT-450-treated subjects thus far have focused on substitutions at NS3 positions R155, A156 and D168. Please provide a listing of all positions where treatment-emergent substitutions have been observed in more than one subject exposed to ABT-450.

6. As previously communicated to you, please continue to consider ribavirin in your resistance assessments. We specifically request you assess the impact of baseline HCV genotype 1a NS5B F415Y on the efficacy of your DAA+RBV combination regimens, which should be possible for trials that include subjects who previously failed treatment with Peg-IFNα/RBV.

3.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data

in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

4.0 ISSUES REQUIRING FURTHER DISCUSSION

At the conclusion of the meeting, there were no issues requiring further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Provide feedback regarding definition of pegIFN-contraindicated and –intolerant populations	FDA	As available
Submit data from M11-652 and additional ongoing trials for Agency review	Sponsor	As available

6.0 ATTACHMENTS AND HANDOUTS

Attached is an email from the sponsor, dated September 13, 2011, in response to FDA's preliminary comments of September 9, 2011. The slide presentation attached to that email is also provided.

From: Mary S Konkowski
To: Schumann, Katherine;
Subject: RE: IND 103,526 Question Regarding EOP1 Meeting
Date: Tuesday, September 13, 2011 3:25:22 PM
Attachments: FDA Meeting September 14 2011.ppt

Hi Katie,

As a follow-up to our conversation yesterday, I would like to provide you with an update.

Abbott confirms that we do not have any further comments regarding FDA preliminary responses for Question 1, 2, and 4. In addition to discussing, FDA's preliminary comments for Questions 5.3 and 6, Abbott has added a clarifying question for the Agency regarding Question 3.

Abbott has prepared a few slides to facilitate tomorrow's discussion of Questions 5.3, 6 and 3. The slides also provide an update on the data from M12-221 (Question 5.1) and M12-746 (Additional Comment 3).

Additional Comments:
For 1 and 2, Abbott will provide the requested information by September 30.
For 4 and 5, Abbott will provide the requested information in November.
With regard to Additional Comment 6, we will comply with your request.

Please feel free to contact me if you have any questions before the meeting. My cell is (b) (6)

Kind regards,

Mary

Mary Konkowski
Associate Director
Regulatory Affairs
Pharmaceutical
Products Group

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mary.konkowski@abbott.
com

From: "Schumann, Katherine" <Katherine.Schumann@fda.hhs.gov>
To: 'Mary S Konkowski' <mary.konkowski@abbott.com>
Date: 09/12/2011 02:54 PM
Subject: RE: IND 103,526 Question Regarding EOP1 Meeting

Thank you, Mary. Your summary below is in agreement with my understanding of our telephone conversation.

I look forward to meeting you on Wednesday,

Katie
(301) 796-1182

From: Mary S Konkowski [mailto:mary.konkowski@abbott.com]
Sent: Monday, September 12, 2011 3:53 PM
To: Schumann, Katherine
Subject: Re: IND 103,526 Question Regarding EOP1 Meeting

Hi Katie,

Based on current discussions with the Abbott team, we are not planning to send preliminary comments ahead of the Wednesday meeting. As we discussed on the telephone this afternoon:

- Abbott wishes to focus the meeting the discussion on the Agency's responses to Question 5.3 and Question 6.
- I will let the Abbott team know the Agency would like to open the meeting with a brief discussion of Question 7.

- Prior to the meeting, Abbott will provide an update on status of the M12-221 trial (as requested in the Agency's response to Question 5.1) and will provide an update on virologic response data from ongoing trial M12-746 (as requested in Additional Comments - Clinical Virology #3. We are targeting to have this information to you tomorrow afternoon.
- The Abbott team will be traveling tomorrow. I expect to have email access in the afternoon.
- If you need to get a hold of me by telephone, I can be contacted via cell phone at (b) (6)

I look forward to the meeting. Please feel free to contact me if I can be of further assistance.

Kind regards,

Mary

Mary Konkowski
Associate Director
Regulatory Affairs
Pharmaceutical
Products Group

Abbott
Laboratories
200 Abbott Park
Road
AP30-1E, Dept
PA76
Abbott Park, IL
60064-6157

Tel: (847) 938-3063
mary.konkowski@abbott.com

From: "Schumann, Katherine" <Katherine.Schumann@fda.hhs.gov>
To: 'Mary S Konkowski' <mary.konkowski@abbott.com>
Date: 09/12/2011 01:41 PM
Subject: IND 103,526 Question Regarding EOP1 Meeting

Hi Mary,

I know you've only had the preliminary responses since Friday afternoon, but do you have any idea at this time if you will be sending us a list of the preliminary responses you'd like discuss ahead of the meeting on Wednesday afternoon?

Thanks,

Katie

Katherine Schumann, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6237
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

DEBRA B BIRNKRANT
10/04/2011

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206619

LATE-CYCLE MEETING MINUTES

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

Dear Dr. ZumBrunnen:

Please refer to your New Drug Application (NDA) dated April 21, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets, 12.5 mg/75 mg/50 mg, copackaged with dasabuvir tablets, 250 mg).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 20, 2014.

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 Katherine Schumann, M.S., Regulatory Project Manager, at (301) 796-1182.

Sincerely,

{See appended electronic signature page}

Linda L. Lewis, M.D.
Cross-Discipline 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: October 20, 2014, 2:00 – 3:30 PM EDT
Meeting Location: Teleconference

Application Number: NDA 206619
Product Name: VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets)
Applicant Name: AbbVie, Inc.

Meeting Chair: Linda Lewis, M.D.
Meeting Recorder: Katherine Schumann, M.S.

FDA ATTENDEES

Office of Antimicrobial Products
John Farley, Deputy Director

Division of Antiviral Products
Debra Birnkrant, Division Director
Jeffrey Murray, Deputy Director,
William Tauber, Acting Deputy Director for Safety
Linda Lewis, Medical Team Leader
Russell Fleischer, Medical Reviewer
Mark Seaton, Pharmacology/Toxicology Reviewer
Jules O'Rear, Clinical Virology Team Leader
Patrick Harrington, Clinical Virology Reviewer
Elizabeth Thompson, Chief, Project Management Staff
Katherine Schumann, Regulatory Project Manager

Office of Biostatistics
Joy Mele, Biostatistician, DB IV
Guoxing Soon, Biostatistics Team Leader, DB IV

Office of Clinical Pharmacology
Islam Younis, Clinical Pharmacology Team Leader, DCP IV
Vikram Arya, Clinical Pharmacology Reviewer, DCP IV
Dhananjay Marathe, Pharmacometrics Reviewer, DPM

Office of New Drug Quality Assessment
Caroline Strasinger, CMC Reviewer
Stephen Miller, CMC Lead, DNDQA II

Office of Surveillance and Epidemiology
Felicia Duffy, Risk Management Analyst, DRISK

EASTERN RESEARCH GROUP ATTENDEES
(b) (6), Independent Assessor

APPLICANT ATTENDEES
Nihar Baxi, Associate Director, Regulatory Strategic Planning
Barry M. Bernstein, Vice President, Infectious Disease Development
Scott Brun, Vice President, Clinical Development
Christine Collins, Director, HCV Clinical Virology
Juliana Correa Leite, Director, Regulatory Affairs, Latin America
Barbara Da Silva-Tillmann, Senior Medical Director, HCV Product Safety Lead
Melanie Gloria, Associate Director, Clinical Program Development
Martin King, Director, Statistics
Lois Larsen, Director, Statistics
Rajeev M. Menon, Director, Clinical Pharmacology and Pharmacometrics
John Morris, Director, CMC Project Management
Cheryl Pape, Director, Regulatory Affairs, CMC
Nancy Peterson, Associate Director, Global Project Management
Tami Pilot-Matias, Senior Principle Research Scientist, Clinical Virology
Thomas J. Podsadecki, Project Director, Antiviral Clinical Project Team
Ron Robison, Vice President, Regulatory Affairs
Sarah Rogers, Manager, Regulatory Affairs
Anutosh R. Saha, Director, Regulatory Affairs, GPS
Drew Sansone, Senior Director, Regulatory Affairs, US and Canada
Michael Severino, Executive Vice President, Research and Development
Imran Shah, Director, Regulatory Affairs, GPS
Nancy Shulman, Senior Medical Director, Antiviral Clinical Project Team
Andrew Storey, Vice President, Regulatory Affairs, US and Canada
Bruce Trela, Director, PCS Scientific Projects
Mary Voth, Associate Director, Regulatory Affairs, Labeling
Wangag Xie, Senior Manager, Statistics
Troy ZumBrunnen, Director, Regulatory Affairs, US and Canada

1.0 BACKGROUND

NDA 206619 was submitted on April 21, 2014 for VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets).

Proposed indication: Treatment of genotype 1 chronic hepatitis C virus infection, including patients with compensated cirrhosis.

PDUFA goal date: December 21, 2014

FDA issued a Background Package in preparation for this meeting on October 9, 2014.

AbbVie, Inc. provided a document responding to the following substantive review and labeling issues identified in the Background Package on October 15, 2014.

- Duration of therapy for GT1a cirrhotic subjects
- Monitoring for hepatotoxicity
- Clinical recommendations related to the use of VIEKIRA PAK with estrogen containing products

2.0 DISCUSSION

1. Introductory Comments

DAVP explained that the purpose of a Late-cycle Meeting (LCM) was to share and discuss any substantive review issues that have been identified to date and the plans for the remainder of the review.

DAVP noted that this application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

2. Discussion of Substantive Review Issues

Clinical

- Duration of therapy for GT1a cirrhotic subjects

Discussion:
DAVP opened the discussion by confirming receipt of AbbVie's labeling proposal to include a footnote under Table 1 (dosing recommendations) stating that a (b) (4) **. DAVP noted that the Division and AbbVie have previously discussed the most appropriate duration of therapy for genotype 1a patients with cirrhosis, and reiterated DAVP's goal of providing optimal treatment for the largest number of subjects. DAVP is specifically concerned that when the product is used in a broader patient population, SVR rates are likely to decrease. DAVP then turned the discussion over to AbbVie to go through the October 15 response regarding this issue.**

(b) (4)

(b) (4)

AbbVie then responded to some of the statistical concerns raised by DAVP

(b) (4)

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- (b) (4)
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-

(b) (4)

DAVP acknowledged that with a recommendation of 24 weeks for all GT1a cirrhotic patients, some patients will receive a longer duration of therapy than needed. However, this should give all patients the best chance at virologic response, especially in a real-world setting where SVR rates are likely to be lower.

(b) (4)

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DAVP further explained the shortcomings of the analyses used to support the dosing proposal.

(b) (4)

(b) (4)

However, DAVP does not have sufficient evidence that these parameters, prospectively, are good predictors of outcome.

DAVP reiterated that all analyses were post-hoc and of a secondary endpoint, relapse. Relapse was named in the protocol as a descriptive outcome with no plans for making inferences based on this outcome. DAVP pointed out that for similar analyses of relapse shown in the HARVONI labeling, the full randomized population was analyzed and the results were consistent with results for SVR. DAVP acknowledged that subgroup analyses defined by the laboratory parameters of AFP, platelet count and albumin were pre-specified in the SAP (not the protocol), but only one month before the last patient visit in this open-label trial.

AbbVie reiterated that relapse is the outcome that is affected by duration, and stated that the signal is all contained with the relapsers. DAVP agreed that most of the reasons for not achieving an SVR were due to relapse.

DAVP stated that an agreement was unlikely to be reached during the teleconference, and that the issue would be further considered by the review team. DAVP's primary concern is to maximize successful outcomes because patients who fail are unlikely to have viable re-treatment options, especially as re-treatment with intereferon will probably not be acceptable to patients and clinicians. DAVP explained that the differences in adverse reactions between the 12 and 24 week arms were very modest, and that the Division is not convinced

(b) (4)

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DAVP confirmed that 24 weeks for all GT1a patients with cirrhosis is still preferred, but offered to go back and review the data from M13-099 and earlier labeling proposals. DAVP emphasized that no additional analyses from AbbVie are needed to consider this issue.

- Monitoring for hepatotoxicity

Discussion:

DAVP began the discussion by explaining that recent labeling comments regarding the Warnings and Precautions (W&P) section were made to align with labeling regulations and guidance. The W&P section should describe a clinically significant adverse reaction or risk and include the following information: risk factors, incidence, outcome, steps to prevent, reduce or monitor risk, and management strategies.

DAVP explained that elevated ALT meets the criteria for inclusion in the W&P section. DAVP's concern is that some events were assessed as drug induced hepatocellular injury, and DAVP does not agree with the idea of (b) (4) **. DAVP believes that clinicians should be aware of the issue and closely monitor patients at initiation of therapy, Week 2, Week 4 and then as clinically appropriate. DAVP considers this an important safety issue.**

(b) (4)

DAVP disagreed with this assessment, (b) (4) **Having very specific parameters for stopping treatment in labeling, such as those that DAVP has proposed, will assist providers by ensuring that they do not discontinue therapy inappropriately because they are lacking guidance.**

AbbVie agreed that providers will likely be monitoring as part of clinical practice, (b) (4) **AbbVie pointed out that the Adverse Reactions sections of labeling does describe the characteristics of ALT elevations seen during the clinical program. AbbVie proposed** (b) (4)

DAVP agreed that unnecessary interruption of therapy is not desirable, but did not agree that (b) (4) **ALT elevations are considered a safety issue and DAVP is concerned that when this product gets out into the general population, the Agency may receive reports of serious liver injury. It is possible that more significant events will occur post-marketing than were seen in the clinical trials.**

AbbVie offered to submit a proposal (b) (4) **DAVP agreed to review the proposal, but emphasized that the DAVP believes the monitoring schedule previously proposed will capture the most significant events and already aligns with the monitoring timelines in AASLD**

guidelines and the ribavirin prescribing information. DAVP acknowledged AbbVie's concern that bilirubin elevations early in treatment might contribute to a clinician's decision to discontinue treatment, but pointed out that bilirubin elevations are part of the profile of ABT-450.

3. Information Requests

Product Quality

- The Quality Information submitted on September 25, 2014 and September 30, 2014 is currently under review and no additional information is needed from the Applicant at this time. Whether a PMC is necessary is currently under discussion within the CMC review team.

Inspection Issues

- Satisfactory FDA 483 response with adequate corrective actions and evidence will be required to meet regulatory compliance.

Discussion:
DAVP noted the items listed above. No additional discussion occurred.

4. REMS or Other Risk Management Actions

Discussion:
AbbVie commented that the draft Medication Guide would be submitted later in the week. Post-meeting note: The draft Medication Guide was received on 10/24/14.

5. Postmarketing Requirements/Postmarketing Commitments

Discussion:
AbbVie commented that proposed dates for the PMC/PMRs listed in the meeting background package would be provided later in the week. Post-meeting note: the proposed dates were received 10/23/14.

6. Major Labeling Issues

Clinical Pharmacology

- Clinical recommendations related to the use of VIEKIRA PAK with estrogen containing products, immunosuppressants, and omeprazole.

Discussion:

Estrogen-containing products

DAVP explained that internal discussions are ongoing regarding AbbVie's proposal (b) (4) and that the next round of labeling comments will provide the Division's response. (b) (4) Specific language will be provided with the next version of labeling.

Immunosuppressants

Regarding the immunosuppressants tacrolimus and cyclosporine, DAVP is in general agreement with AbbVie's analysis submitted on October 1. DAVP will address the issue with subsequent labeling comments.

Omeprazole

DAVP has requested input from colleagues in the Division of Gastroenterology and Inborn Errors Products. Once that advice is provided, DAVP will address the issue with subsequent labeling comments.

Section 14 Clinical Studies

DAVP mentioned that AbbVie's response to the re-organization of Section 14 Clinical Studies is currently under review, and the Division is still trying to determine if the data from the 12 week arm for GT1a subjects with cirrhosis will be included.

DAVP pointed out that the (b) (4) are unlikely to be retained because they lengthen the label without showing any meaningful information, as efficacy among these subjects was so universally successful. DAVP mentioned that the information regarding the post-transplant and HIV co-infected trials will be moved (b) (4) to Section 14.

7. Review Plans

   - Continue with labeling review and discussions
   - Discuss and finalize PMR/PMCs

Discussion:
DAVP noted the items listed above.

8. Wrap-up and Action Items

Discussion:
DAVP agreed to follow up with AbbVie after the meeting regarding the timing of additional labeling comments.

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/s/

LINDA L LEWIS
11/17/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206619

LATE CYCLE MEETING
BACKGROUND PACKAGE

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

Dear Dr. ZumBrunnen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ombitasvir, paritaprevir, and ritonavir tablets, 12.5 mg/75 mg/50 mg copackaged with dasabuvir tablets, 250 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for October 20, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Katherine Schumann, M.S., Regulatory Project Manager, at (301) 796-1182.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	October 20, 2014, 2:00 – 3:30 PM EDT
Meeting Location:	Teleconference
Application Number:	NDA 206619
Product Name:	VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets)
Indication:	Treatment of genotype 1 chronic hepatitis C virus infection
Sponsor/Applicant Name:	AbbVie Inc.

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

Discipline Review Letters

No Discipline Review letters have been issued to date.

Substantive Review Issues

The following substantive review issues have been identified to date:

Clinical

1. Duration of therapy for GT1a cirrhotic subjects:

DAVP recommends that all GT1a cirrhotic subjects be treated for 24 weeks regardless of prior treatment history or changes in specific laboratory parameters. DAVP remains concerned that once VIEKIRA PAK is approved, the SVR rates will likely be lower than those observed in the controlled clinical trial setting. DAVP's recommendation for a single duration of treatment for all GT1a cirrhotic subjects is couched in the desire to: (1) provide a simplified regimen, (2) avoid confusion when there are discrepancies in laboratory parameters (e.g., high alpha-fetoprotein with normal platelet count and albumin level), and (3) provide the best chance of virologic cure to all patients as those who fail treatment with VIEKIRA PAK will have extremely limited options for re-treatment.

DAVP also acknowledges your response and proposal (based on post-hoc analyses) for considering (b) (4) . However, DAVP does not find the evidence you have provided sufficient for identifying a subgroup of GT1a cirrhotic patients that will uniquely benefit from longer treatment. DAVP believes that the clinical reasons outlined above are further supported by statistical evidence favoring treating all GT1a cirrhotic patients for 24 weeks for the following reasons:

- Subgroup analyses we have performed do not provide statistical evidence of differential treatment effects showing any particular subgroup benefits more from longer treatment.
    - All tests for interaction yield p-values >0.15.
    - All subgroups show higher SVR rates when treatment is for 24 weeks compared to treatment for 12 weeks.

- (b) (4) , the data does not support that these values identify subgroups of patients that may uniquely benefit from longer treatment. (b) (4)

Study M13-099 SVR_{12} results

	3DAA+RBV 12 weeks	3DAA+RBV 24 weeks	24 wks-12 wks Trt diff (95%CI)	p-value for Int.[1]
Overall	191/208 92%	166/172 96%	+5% (+0.07%, +10%)	
By GT				
1a	124/140 89%	115/121 95%	+6% (-0.6%, +13%)	
1b	67/68 98.5%	51/51 100%	+1% (-6%, +8%)	>0.3

(b) (4)

2. Monitoring for hepatotoxicity:

   DAVP (b) (4) recommends patients have liver chemistries measured pre-dose, at weeks 2 and 4 and then as clinically indicated. Although the frequency of ALT elevations in the Phase 3 trials was low, and estradiol-containing medications are being contraindicated, there remains a concern that some patients may have an event of hepatotoxicity that would go unrecognized. Further, the recent version of the AASLD/IDSA guidelines recommends monitoring liver chemistries in all patients every 4 weeks during treatment.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

POSTMARKETING REQUIREMENTS/POSTMARKETING COMMITMENTS

The following are a list of preliminary PMRs and PMCs under consideration by the Division. Additional correspondence regarding these PMRs and PMCs will be provided following the meeting.

Pediatric Postmarketing Requirements (PREA)

1. Evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak) in pediatric subjects 3 to less than 18 years of age with chronic hepatitis C virus infection.

   Final Protocol Submission: July 31, 2015
   Trial Completion: April 30, 2019
   Final Report Submission: August 31, 2019

2. Collect and analyze long-term safety data for subjects enrolled in the pediatric ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak) pharmacokinetic, safety, and antiviral efficacy study(ies). Data collected should include at least 3 years of follow-up in order to characterize the durability of response to ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak) and the long-term safety including growth assessment, sexual maturation, and characterization of resistance associated substitutions in viral isolates from subjects failing therapy.

   Final Protocol Submission: July 31, 2015
   Trial Completion: April 30, 2022
   Final Report Submission: August 30, 2022

Postmarketing Requirements

Clinical Virology

3. Conduct the following site-directed mutant HCV replicon phenotype analyses:

   - Sofosbuvir activity against HCV replicons carrying NS5B substitutions associated with dasabuvir resistance: C316Y (GT1a and GT1b) and S556G (GT1a).

   - Dasabuvir activity against HCV replicons carrying the following NS5B substitutions: L159F (GT1a and GT1b), V321A (GT1a and GT1b), M423I (GT1a), I482T (GT1a) and A486V (GT1b).

   - Paritaprevir activity against HCV replicons carrying substitutions in the NS3 helicase (e.g., P334S, S342P, V406A/I, T449I, P470S) that emerged in virologic failure subjects treated with the 3-DAA +/- RBV regimen; evaluate the impact of these substitutions alone and in combination with other key resistance-associated substitutions (e.g., R155K or D168x) that were often detected in combination.

Postmarketing Commitments

Clinical

4. Submit final clinical study reports and datasets for the following ongoing Phase 3 clinical trials: M11-646, M13-098, M13-099, M13-961, M13-389 and M14-002.

5. Submit a final clinical study report and datasets for a clinical trial in subjects with end-stage renal disease (M14-226).

6. Submit a final clinical study report and datasets for a clinical trial in subjects with decompensated (Child-Pugh B) hepatic impairment (M14-227).

7. Submit a final clinical study report and datasets for a clinical trial in subjects with recurrent HCV infection following liver transplantation (M12-999).

8. Submit a final clinical study report and datasets for a clinical trial in subjects with HIV/HCV co-infection (M14-004).

9. Submit a final clinical study report and datasets for a clinical trial to determine if ribavirin (RBV) is necessary in GT1b subjects with cirrhosis (M14-490).

10. Submit a complete report for ongoing clinical study M13-102, "A Follow-up Study to Assess Resistance and Durability of Response to AbbVie Direct-Acting Antiviral Agent (DAA) Therapy in Subjects Who Participated in Phase 2 or 3 Clinical Studies for the Treatment of Chronic Hepatitis C Virus (HCV) Infection."

    Comment to AbbVie: Please propose dates for submission of the CSRs listed in items 4 - 10 above.

REMS OR OTHER RISK MANAGEMENT ACTIONS

As discussed during the Mid-Cycle Communication on July 14, 2014, the Agency does not anticipate the need for a Risk Evaluation and Mitigation Strategy (REMS).

As discussed at the same meeting, the Patient Package Insert (PPI) should be converted to a Medication Guide to address the risk of hepatotoxicity and the need to temporarily discontinue estradiol-containing medications. The Agency requests that a draft Medication Guide accompany the next version of the draft prescribing information (PI) that is submitted to the NDA.

PRESCRIBING INFORMATION

Your proposed PI must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

A response to your October 1, 2014 submission of revised draft labeling will be provided prior to the LCM.

LCM AGENDA

1. Introductory Comments – 5 minutes (Katie Schumann/Linda Lewis)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 30 minutes

   Each issue will be introduced by FDA and followed by a discussion.

   Clinical

   - Duration of therapy for GT1a cirrhotic subjects
   - Monitoring for hepatotoxicity

3. Information Requests – 5 minutes

   Product Quality

   - The Quality Information submitted on September 25, 2014 and September 30, 2014 is currently under review and no additional information is needed from the Applicant at this time. Whether a PMC is necessary is currently under discussion within the CMC review team.

   Inspection Issues

   - Satisfactory FDA 483 response with adequate corrective actions and evidence will be required to meet regulatory compliance.

4. REMS or Other Risk Management Actions – 5 minutes

5. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

6. Major labeling issues – 20 minutes

   Clinical Pharmacology

   - Clinical recommendations related to the use of VIEKIRA PAK with estrogen containing products, immunosuppressants, and omeprazole.

7. Review Plans – 5 minutes

   - Continue with labeling review and discussions
   - Discuss and finalize PMR/PMCs

8. Wrap-up and Action Items – 5-10 minutes

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/s/

JEFFREY S MURRAY
10/09/2014