CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206619Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 206619
Product Name: Viekira Pak

PMC #1 Description: 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.

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	12/31/2016
Other:	

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.*USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALY REPORTABLE**

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

   ☐ Need for drug (unmet need/life-threatening condition)
   ☐ Long-term data needed (e.g., stability data)
   ☐ Only feasible to conduct post-approval
   ☒ Improvements to methods
   ☐ Theoretical concern
   ☐ Manufacturing process analysis
   ☐ Other

The Applicant currently has incorporated a test method for detection of [redacted] in the ombitasvir, paritaprevir, ritonavir tablets in the drug product specification. The sensitivity of the current method is as follows:

[redacted]

The PMC is being requested for the Applicant to continue to develop a more sensitive method for [redacted] detection of [redacted]% for life-cycle management of drug product quality. The increased sensitivity is not required for preapproval because a method with [redacted]% detection limit has been instituted, and the Applicant has provided data supporting that [redacted] is of low probability and has not been observed to date.

2. Describe the particular review issue and the goal of the study.

A detection limit of [redacted]% is in line with current FDA practices [redacted]

The goal is for the Applicant to develop a more sensitive method. If at the end of the PMC period amethod with the requested sensitive level cannot be obtained, the Applicant should submit information to demonstrate reasonable efforts were made, the lowest detection limit achieved, and provide justification that the [redacted] at the lowest detection level achieved remains low risk.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues

☒ Other

Describe the agreed-upon study:

The Applicant should continue to develop a method with increased sensitivity (LOD (b) (4) %) for the detection of (b) (4).

5. To be completed by ONDQA/OBP Manager:

☒ Does the study meet criteria for PMCs?
☒ Are the objectives clear from the description of the PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs only)

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

/s/

ALTHEA CUFF
12/18/2014

STEPHEN MILLER
12/18/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 206619
Product Name: Viekira Pak (ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets)

PMR/PMC Description: Evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response as the primary endpoint) of ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak) in pediatric subjects 3 to less than 18 years of age with chronic hepatitis C virus infection.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	07/31/2015
Study/Trial Completion:	04/30/2019
Final Report Submission:	08/31/2019
Other:	

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

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

   Adult studies are completed and ready for approval. The review team met with the Pediatric Review Committee (PeRC) on October 15, 2014. The PeRC agreed with the Division to grant a deferral for pediatric patients aged 3 to less than 18 years because the product is ready for approval in adults.

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

The study is a deferred pediatric trial under PREA to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak) for the treatment of chronic hepatitis C virus (HCV) infection in pediatric subjects 3 to less than 18 years of age. The Division is in general agreement with the Applicant's overall initial pediatric study plan (agreed iPSP).

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

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

One or more trials will be conducted to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response as the primary endpoint) of ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak) in pediatric subjects 3 to less than 18 years of age with chronic hepatitis C virus infection. The PK study will assess exposure of all 3 active DAAs and confirm PK profile is similar to that observed in adults. PK may be evaluated in a stand-alone trial or as the initial phase of the safety and efficacy trial. Safety and efficacy will be evaluated in an open-label clinical trial and compared to a well-characterized historical control group in the same age group and to the larger adult trials of Viekira Pak.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

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

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 206619
Product Name: Viekira Pak (ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets)

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	12/31/2015
	Study/Trial Completion:	04/30/2022
	Final Report Submission:	08/30/2022
	Other:	

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

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

Adult studies are completed and ready for approval. This PMR will provide long-term safety data and characterize the durability of response in pediatric subjects treated in the pharmacokinetic, safety and efficacy study of ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak).

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

The study is a deferred pediatric study under PREA for the treatment of chronic hepatitis C virus (HCV) infection in pediatric subjects 3 to less than 18 years of age. The study will 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.

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

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Multi-year observational follow-up study in pediatric subjects 3 to less than 18 years of age. The study will 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.

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

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

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	206619
Product Name:	Viekira Pak (ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets)

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A already ongoing
	Study/Trial Completion:	
	Final Report Submission:	02/28/2015
	Other:	

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

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

The information to be gained applies to patients who have failed treatment with Viekira Pak or other HCV direct-acting antiviral therapies. The study will provide information that may inform future treatment options for patients failing this treatment. The information has minimal initial impact on the patient populations to be recommended for treatment with Viekira Pak.

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

This study will provide additional information regarding the drug resistance and cross-resistance characteristics of Viekira Pak to better understand the potential drug resistance-related risks of treatment failure. The study will generate data that may help predict the efficacy of re-treatment with Viekira Pak and other therapies with overlapping drug resistance pathways. Also, the study will evaluate the potential impact of sofosbuvir treatment-emergent NS5B substitutions on the activity of the NS5B inhibitor dasabuvir included in Viekira Pak, which could help predict whether prior sofosbuvir treatment failure impacts the efficacy of Viekira Pak.

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

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Non-clinical virology studies in HCV replicon system

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

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

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?

☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	206619
Product Name:	Viekira Pak (ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets)

PMR/PMC Description: Submit a final report for ongoing observational 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."

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A already ongoing
	Study/Trial Completion:	10/31/2016
	Final Report Submission:	10/31/2017
	Other:	

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

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

This is a long-term follow-up observational study of subjects who have completed previous and ongoing trials of the direct-acting antiviral agents (DAAs) included in Viekira Pak.

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

The current NDA review determined that although few subjects failed treatment with Viekira Pak, those who failed did so because of emergence of resistance to multiple drugs in the regimen. It is not known how long the emergent resistance substitutions may persist and how this may impact future treatment options. The purposes of this long term follow-up study are to (1) characterize the evolution of drug resistant viral populations in patients who failed treatment with Viekira Pak (and the DAA components of Viekira Pak) in clinical trials, and (2) monitor the durability of virologic response in subjects who were effectively treated with Viekira Pak (and the DAA components of Viekira Pak) in clinical trials . Subjects are to be followed for up to 3 years following completion of their parent Phase 2 or 3 trial.

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

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Long-term observational follow-up study. All subjects will have completed treatment in an earlier protocol and will not receive any treatment as part of this study.

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

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

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	206619
Product Name:	Viekira Pak (ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets)
PMR/PMC Description:	Conduct an observational study to investigate the safety and efficacy of ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak) in a sufficient number of Blacks/African Americans with and without cirrhosis compared to whites/Caucasians.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	07/31/2015
	Study/Trial Completion:	06/30/2019
	Final Report Submission:	12/31/2020
	Other:	

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

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

Blacks/African Americans are disproportionately affected by chronic hepatitis C infection and historically have poor response to treatment compared to Caucasians. The clinical trials of Viekira Pak enrolled a very small number of Blacks/African Americans (~6% of overall Phase 3 trial enrollment). Although these subjects appeared to benefit from Viekira Pak, they could potentially be at more risk for adverse reactions due to the increased prevalence in this population of other underlying co-morbidities such as diabetes, hypertension and anemia.

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

The goal of this study is to further characterize Viekira Pak safety and efficacy in Black/African American patients, including those with cirrhosis.

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

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☒ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This is an observational study that will collect data from 250-300 Black/African American patients, including a cohort with cirrhosis, and compare response rates to those in non-Black/African America patients, also including cirrhotic patients. The study will measure the proportion of subjects achieving Sustained Virologic Response (SVR12) after 12 or 24 weeks of treatment and also compare the general safety profile and adverse reactions of interest, such as rash, anemia, and liver toxicity.

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

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

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	206619
Product Name:	Viekira Pak (ombitasvir, paritaprevir, ritonavir tablets; dasabuvir tablets), co-packaged for oral use
PMR/PMC Description:	Submit the final report and datasets for the ongoing clinical Trial M14-227 entitled "An Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 and ABT-333 with Ribavirin in Adults with Genotype 1 Chronic Hepatitis C Virus Infection and Decompensated Cirrhosis."

PMR/PMC Schedule Milestones:	Final Protocol Submission:	N/A already ongoing
	Study/Trial Completion:	12/31/2016
	Final Report Submission:	12/31/2017
	Other:	

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

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

   Study M14-227 is an ongoing trial that will assess the safety and efficacy of ombitasvir/paritaprevir/ritonavir + dasabuvir (VIEKIRA PAK) +/- ribavirin in subjects with varying degrees of hepatic impairment in a cohort with decompensated cirrhosis.

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

VIEKIRA PAK can be administered to patients with Childs Pugh A hepatic impairment, but it is unknown if it can be administered safety to patients with Childs-Pugh B impairment as a clinical pharmacology study indicated that these patients may have increased drug exposures. Increased drug exposure has been associated with increased risk of liver toxicity. Patients with more advanced liver impairment need safe and effective therapies to potentially avoid further progression to hepatic failure.

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

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☒ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☒ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     X Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Open label, safety and efficacy trial in patients with varying degrees of hepatic impairment (focusing on those with Child-Pugh B cirrhosis). Pharmacokinetics in this population will be evaluated and PK parameters will be correlated with any observed liver toxicity.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

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

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	206619
Product Name:	Viekira Pak (ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets)

PMR/PMC Description: Submit a final report and datasets for the ongoing clinical Trial M14-226 entitled "An Open-Label Study to Evaluate the Safety and Efficacy of Ombitasvir/ABT-450/Ritonavir and Dasabuvir with or without Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection, with Severe Renal Impairment or End-Stage Renal Disease."

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A already ongoing
	Study/Trial Completion:	05/31/2016
	Final Report Submission:	05/31/2017
	Other:	

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

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

   Study M14-226 is an ongoing, open label clinical trial that will assess the safety and efficacy of ombitasvir/paritaprevir/ritonavir + dasabuvir (VIEKIRA PAK) with ribavirin in patients with varying degrees of renal impairment.

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

The natural history of HCV in patients with advanced renal impairment (on dialysis or not) is not fully elucidated, but an adverse effect of HCV on survival has been noted. It has been recommended that the decision to treat HCV in patients with chronic kidney disease be based on the potential benefits and risks of therapy, including life expectancy, candidacy for kidney transplant, and comorbidities (dialysis dependent or not). Use of interferon/ribavirin based therapies is challenging due to significant side effects. Direct acting antiviral treatment may forestall the increased risk of progressive liver disease, which may lead to increased life expectancy.

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

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

X Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Open label safety and efficacy trial in patients with chronic HCV infection and varying degrees of renal impairment.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

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

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	206619
Product Name:	Viekira Pak (ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets)

PMR/PMC Description: Submit the final report and datasets for the ongoing Phase 3 clinical Trial M11-646 entitled "A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection."

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A already ongoing
	Study/Trial Completion:	12/31/2014
	Final Report Submission:	10/31/2015
	Other:	

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

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

M11-646 is a multicenter, randomized, double-blind, placebo controlled Phase 3 trial in treatment naive adults used to support the initial approval of Viekira Pak. Subjects initially randomized to placebo were offered open-label active study drugs following completion of the double-blind treatment period. A follow-up analysis is occurring after subjects who received open label active treatment complete post-treatment week 12; analysis was not included in the NDA submission.

All subjects administered active study drugs are being followed for 48 weeks post-treatment to test for durability of SVR12 and emergence or persistence of resistance.

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

SVR24 and SVR48 data from the open label active treatment group will be reviewed to further confirm safety and efficacy. Long-term post-treatment week 48 data will be reviewed to monitor the durability of virologic response.

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

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Long-term open-label observational data will be submitted following a primary clinical trial.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other

Open-labe, long-term post-treatment follow-up data will be submitted from a primary clinical trial.

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

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	206619
Product Name:	Viekira Pak (ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets)
PMR/PMC Description:	Submit the final report and datasets for the Phase 3 clinical Trial M13-098 entitled "A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Experienced Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection."

PMR/PMC Schedule Milestones:	Final Protocol Submission:	N/A already ongoing
	Study/Trial Completion:	12/31/2014
	Final Report Submission:	10/31/2015
	Other:	

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

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

   M13-098 is a multicenter, randomized, double-blind, placebo controlled Phase 3 trial in treatment experienced adults used to support the initial approval of Viekira Pak. Subjects initially randomized to placebo were offered open-label active study drugs following completion of the double-blind treatment period. A follow-up analysis is occurring after subjects who received open label active treatment complete post-treatment week 12; this data was not included in the NDA submission.

   All subjects administered active study drugs are being followed for 48 weeks post-treatment to test for durability of SVR12 and emergence or persistence of resistance.

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

SVR12 data from the open label active treatment group will be reviewed to further confirm safety and efficacy. Long-term post-treatment week 48 data will be reviewed to monitor the durability of virologic response.

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

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Long-term, open-label observational data will be submitted from a primary clinical trial.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other

Open-label and long-term post-treatment follow-up data will be submitted from a primary clinical trial.

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

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	206619
Product Name:	Viekira Pak (ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets)
PMR/PMC Description:	Submit the final report and datasets for the Phase 3 clinical Trial M13-099 entitled "A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT- 333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis."

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A already ongoing
	Study/Trial Completion:	12/31/2014
	Final Report Submission:	09/30/2015
	Other:	

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

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

M13-099 is a randomized, open-label trial Phase 3 trial conducted in treatment naïve and pegIFN/RBV experienced subjects with compensated cirrhosis used to support the initial approval of Viekira Pak. The study results were submitted after all subjects had completed 12 weeks of post-treatment follow-up and were assessed for the primary endpoint, SVR12.

All subjects will be followed through post-treatment week 48 to assess safety, durability of SVR, and the emergence and persistence of resistant viral variants.

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

Observational data through post-treatment week 48 will be submitted and reviewed to confirm safety and monitor the durability of virologic response in subjects with compensated cirrhosis. Emergence and persistence of resistance will be assessed in subjects failing treatment.

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

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Long-term follow-up data will be submitted from a primary clinical study in subjects with compensated cirrhosis.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
Long-term post-treatment data will be submitted from a primary clinical trial.

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

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	206619
Product Name:	Viekira Pak (ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets)
PMR/PMC Description:	Submit the final report and datasets for the Phase 3 clinical Trial M13-961 entitled "A Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With and Without Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection."

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A already ongoing
	Study/Trial Completion:	12/31/2014
	Final Report Submission:	09/30/2015
	Other:	

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

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

   M13-961 is a randomized, double-blind, controlled Phase 3 in treatment-naïve adults with genotype 1b chronic HCV infection used to support the initial approval of Viekira Pak. The trial evaluated Viekira Pak with ribavirin and Viekira Pak alone. The primary analysis occurred after all enrolled subjects completed the post-treatment week 12 visit or prematurely discontinued the study.

   All subjects administered at least one dose of study drug will be followed through post-treatment week 48 to assess safety, durability of SVR, and the emergence and persistence of resistant viral variants.

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

Observational data through post-treatment week 48 will be submitted and reviewed to confirm safety and monitor the durability of virologic response of Viekira Pak with and without ribavirin in treatment naïve subjects with GT1b HCV infection. Emergence and persistence of resistance will be assessed in subjects failing treatment.

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

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   Long-term follow-up data will be submitted from a primary clinical study in treatment naïve subjects with GT1b HCV infection.

   Required

   ☐ Observational pharmacoepidemiologic study
   ☐ Registry studies

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
Long-term post-treatment data will be submitted from a primary clinical trial.

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

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	206619
Product Name:	Viekira Pak (ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets)

PMR/PMC Description: Submit the final and datasets for the Phase 3 clinical Trial M13-389 entitled "A Randomized, Open-Label, Multicenter Study to Evaluate the Safety and Antiviral Activity of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With and Without Ribavirin in Treatment-Experienced Subjects with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection."

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A already ongoing
	Study/Trial Completion:	12/31/2014
	Final Report Submission:	10/31/2015
	Other:	

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

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

   M13-389 is a randomized, open-label Phase 3 in treatment-experienced subjects with GT1b chronic HCV infection used to support the initial approval of Viekira Pak. The trial evaluated Viekira Pak with ribavirin and Viekira Pak alone for 12 weeks. The primary analysis occurred after all enrolled subjects completed the post-treatment week 12 visit or prematurely discontinued the study.

   All subjects administered at least one dose of study drug will be followed for 48 weeks post-treatment to assess safety, durability of SVR, and the emergence and persistence of resistant viral variants.

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

Observational data through post-treatment week 48 will be submitted and reviewed to confirm safety and monitor the durability of virologic response of Viekira Pak with and without ribavirin in treatment experienced subjects with GT1b HCV infection. Emergence and persistence of resistance will be assessed in subjects failing treatment.

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

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Long-term follow-up data will be submitted from a primary clinical study in treatment experienced subjects with GT1b HCV infection.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
Long-term post-treatment data will be submitted from a primary clinical trial.

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

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	206619
Product Name:	Viekira Pak (ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets)

PMR/PMC Description: Submit the final and datasets for the Phase 3 clinical Trial M14-002 entitled "A Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With and Without Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1a Chronic Hepatitis C Virus (HCV) Infection."

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A already ongoing
	Study/Trial Completion:	12/31/2014
	Final Report Submission:	09/30/2015
	Other:	

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

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

M14-004 is a randomized, double-blind Phase 3 trial in treatment-naive subjects with GT1a chronic HCV infection used to support the initial approval of Viekira Pak. The trial evaluated Viekira Pak with ribavirin and Viekira Pak alone for 12 weeks. The primary analysis occurred after all enrolled subjects completed the post-treatment week 12 visit or prematurely discontinued the study.

All subjects administered at least one dose of study drug will be followed for 48 weeks post-treatment to assess safety, durability of SVR, and the emergence and persistence of resistant viral variants.

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

Observational data through post-treatment week 48 will be submitted and reviewed to confirm safety and monitor the durability of virologic response in treatment-experienced subjects with GT1a HCV infection. Emergence and persistence of resistance will be assessed in subjects failing treatment.

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

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Long-term follow-up data will be submitted from a primary clinical study in treatment naive subjects with GT1a HCV infection.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
Long-term post-treatment data will be submitted from a primary clinical trial.

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

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	206619
Product Name:	Viekira Pak (ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets)
PMR/PMC Description:	Submit the final report and datasets for the ongoing clinical Trial M12-999 entitled "Open-label, Phase 2 Study to Evaluate the Safety and Efficacy of the Combination of ABT-450/ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With or Without Ribavirin (RBV) in Adult Liver Transplant Recipients with Genotype 1 Hepatitis C Virus (HCV) Infection."

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A already ongoing
	Study/Trial Completion:	09/30/2016
	Final Report Submission:	09/30/2017
	Other:	

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

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

   Study M12-999 is an ongoing trial. Treatment of subjects more than 3 years post liver transplant with recurrent hepatitis C virus infection with mild fibrosis and normal hepatic function with VIEKIRA PAK has demonstrated high response rates. The revised trial investigates other populations of subjects with post-transplant recurrence.

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

Recurrence of hepatitis C virus infection is nearly universal following liver transplantation, and can lead to hepatic failure and in some cases require re-transplantation. There are currently no interferon-free options approved to treat post-transplant recurrent hepatitis C virus infection. Viekira Pak has been shown to be effective in clinically stable post-liver transplant patients with mild fibrosis and normal hepatic function. The revised trial will expand evaluation of Viekira Pak treatment to post-transplant subjects with more severe recurrent HCV liver disease.

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

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Open label, safety and efficacy trial in post-liver transplant patients with more severe recurrent HCV-related liver disease.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
X Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

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

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	206619
Product Name:	Viekira Pak (ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets)
PMR/PMC Description:	Submit the final report and datasets for the ongoing clinical Trial M14-004 entitled "A Randomized, Open-label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Human Immunodeficiency Virus, Type 1 (HIV-1) Coinfection."

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A already ongoing
	Study/Trial Completion:	06/30/2017
	Final Report Submission:	06/30/2018
	Other:	

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

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

   There are currently no interferon-free direct acting antiviral drugs approved for treatment of the HIV/HCV coinfected population.

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

This trial (currently ongoing) would provide safety and efficacy information on the combination of ombitasvir/paritaprevir/ritonavir + dasabuvir (VIEKIRA PAK) with ribavirin in the population of HIV-HCV co-infected patients. Individuals co-infected with HIV/HCV have a greater risk of progression to cirrhosis or decompensated liver disease than HCV-mono-infected patients. This accelerated rate is magnified in HIV/HCV-co-infected patients with low CD4 counts.

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

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Open label, safety and efficacy trial in HIV/HCV co-infected patients.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
X Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

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

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	206619
Product Name:	Viekira Pak (ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets)
PMR/PMC Description:	Submit the final report and datasets for the ongoing clinical Trial M14-490 entitled "An Open-Label, Single-Arm Study to Evaluate the Safety and Efficacy of Ombitasvir/ABT-450/Ritonavir and Dasabuvir in Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis."

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A already ongoing
	Study/Trial Completion:	11/30/2015
	Final Report Submission:	11/30/2016
	Other:	

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

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

   Study M14-490 is evaluating a ribavirin-free regimen for subjects with genotype 1b infection. In the registration trial submitted with the NDA, subjects with GT1b infection and cirrhosis received a regimen that included RBV. It appeared that subjects with GT1b infection with compensated cirrhosis may not require ribavirin as part of their treatment regimen.

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

This trial will determine if ribavirin can safely be removed from the VIEKIRA PAK regimen in subjects with cirrhosis and GT1b HCV infection without sacrificing antiviral efficacy.

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

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Open label treatment trial in subjects with cirrhosis and GT1b HCV.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
X Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

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

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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/s/

KATHERINE SCHUMANN
12/16/2014

WILLIAM B TAUBER
12/16/2014

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

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

Memorandum

Date: **December 5, 2014**

To: **Katherine Schumann, M.S., Senior Regulatory Project Manager**
Division of Antiviral Products

From: Jessica Fox, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: **NDA 206619 – VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets) co-packaged for oral use**

As requested in the Division of Antiviral Products' (DAVP) consult dated May 1, 2014, the Office of Prescription Drug Promotion (OPDP) has reviewed the VIEKIRA PAK prescribing information, medication guide, and carton and container labeling.

OPDP's comments on the prescribing information are provided below in the proposed substantially complete version of the labeling received via email from DAVP on November 25, 2014.

OPDP reviewed the draft carton and container labeling submitted to the EDR on October 22, 2014, and has no comments at this time.

The Division of Medical Policy Programs and OPDP provided a single, consolidated review of the medication guide on December 5, 2014.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Jessica Fox at (301) 796-5329 or at Jessica.Fox@fda.hhs.gov.

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/s/

JESSICA M FOX
12/05/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 4, 2014
To:	Debra Birnkrant, MD Director **Division of Antiviral Products (DAVP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Jessica Fox, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name) Dosage Form and Route:	VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets) co-packaged for oral use
Application Type/Number:	NDA 206-619
Applicant:	AbbVie Inc.

1 INTRODUCTION

On April 21, 2014, AbbVie Inc. submitted for the Agency's review the last portion of a rolling submission for an Original New Drug Application (NDA) 206-619 for VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), co-packaged for oral use. The proposed indication for VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets) is for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on May 1, 2014 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), co-packaged for oral use.

2 MATERIAL REVIEWED

- Draft VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), co-packaged for oral use Medication Guide (MG) received on October 24, 2014 and further revised on November 13, 2014, revised by the Review Division and received by DMPP and OPDP on November 14, 2014.
- Draft VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets) Prescribing Information (PI) received on April 21, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 14, 2014 and November 25, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed comments regarding the "How should I take VIEKIRA PAK?" section of the PPI, are collaborative comments from DMPP and DMEPA.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
12/04/2014

JESSICA M FOX
12/04/2014

BARBARA A FULLER
12/05/2014

LASHAWN M GRIFFITHS
12/05/2014

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 6, 2014
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 206619
Product Name and Strength:	Viekira Pak (ombitasvir, paritaprevir, ritonavir copackaged with dasabuvir)
Submission Date:	October 22, 2014
Applicant/Sponsor Name:	Abbvie, Inc.
OSE RCM #:	2014-822-1
DMEPA Primary Reviewer:	Mónica Calderón, PharmD, BCPS
DMEPA Associate Director:	Irene Chan, PharmD BCPS

1 PURPOSE OF MEMO

Abbvie, Inc. has submitted the revised container label and carton labelings (Appendix A) for the Viekira Pak wallet (b) (4). However, since the submissions, Abbvie has informed FDA that it only intends to market the wallet configuration (confirmed via email October 23, 2014). Thus, the Division of Antiviral Products (DAVP) requested that we review the revised label and labeling for the wallet to determine if it is acceptable from a medication error perspective.

2 CONCLUSIONS

The revised container label and carton labeling are acceptable from a medication error perspective.

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/s/

MONICA M CALDERON
11/06/2014

IRENE Z CHAN
11/06/2014

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF ANTIMICROBIAL PRODUCTS
DIVISION OF ANTIVIRAL PRODUCTS

MEMORANDUM

Date: October 6, 2014

From: Poonam Mishra, MD
Medical Officer, DAVP

Through: Debra Birnkrant, MD
Division Director, DAVP

To: NDA 206619
Russell Fleischer, PA-C, MPH, Clinical Reviewer
Linda Lewis, MD, CDTL

Subject: Recommendations for On-Treatment Hepatic Monitoring Post-Approval

---

General Information:

Applicant:	AbbVie, Inc.
Drug Name:	paritaprevir, ombitasvir, and dasabuvir
Trade Name:	Viekira Pak™
Drug Class:	ABT-450 (paritaprevir) is an NS3/4 protease inhibitor, ABT-267 (ombatasvir) is an NS5A inhibitor, and ABT-333 (dasabuvir) is a non-nucleoside NS5b inhibitor
Proposed Indication:	Treatment of chronic hepatitis C virus genotype 1 infection in adults
Materials Reviewed:	Primary Clinical Review archived on September 18, 2014
	Relevant sections of NDA submission dated April 21, 2014 (eCTD#0003)
	Liver Safety Assessment Report by the Expert Hepatic Panel convened by the Applicant

Introduction and Background

AbbVie has submitted NDA 206619 which evaluated ABT-450/ritonavir + ABT-267 + ABT-333 (referred to as 3-DAA) combination administered with and without ribavirin (RBV) for treatment of chronic hepatitis C virus (HCV) genotype 1 infection in adults. The efficacy and safety of the 3-DAA ± RBV regimen was demonstrated in the Phase 3 trials conducted by the Applicant to support the marketing application.

As per the request by the primary review team, this memorandum focuses specifically on the recommendations regarding the hepatic monitoring during therapy with 3-DAA regimen in clinical settings post-approval. It should be noted that no independent analyses of efficacy and safety data has been done by this reviewer. The recommendations in this memo are based on the review of the pertinent findings reported by the Applicant, safety analyses and findings discussed in Primary Clinical Review and the ongoing discussions with the review team. For detailed hepatic evaluation of the clinical trial data including details on the specific cases, please refer to Clinical Review by Russell Fleischer, PA-C, MPH archived in DARRTS on September 18, 2014.

Globally, it is estimated that 170-200 million persons are infected with HCV, and it affects about 3-5 million people in the United States (US). (http://www.epidemic.org/thefacts/theepidemic/worldPrevalence/). HCV infection is a major public health problem and a leading cause of chronic liver disease in the US. The natural history of chronic hepatitis C (CHC) involves progression to cirrhosis, hepatocellular carcinoma, liver failure, and death. CHC is currently the most common reason for liver transplantation in the US. The ultimate goal of CHC treatment is to reduce the occurrence of end-stage liver disease and its complications including decompensated cirrhosis, liver transplantation and hepatocellular carcinoma. Treatment success is measured by the attainment of sustained virological response (SVR), a reliable predictor of long-term clearance of HCV infection. Multiple observational cohorts have shown correlations between SVR and improvements in clinical outcomes such as development of hepatocellular carcinoma, hepatic events, fibrosis, and all-cause mortality (Veldt 2007; Singal, 2010; Backus 2011; Van der Meer 2012).

The treatment options for CHC are rapidly evolving. Two direct-acting antiviral agents (DAAs), boceprevir and telaprevir (HCV NS3/4A protease inhibitors), were approved in May, 2011 for use in combination with pegylated interferon and RBV for the treatment of chronic HCV genotype 1 infection. More recently, another HCV NS3/4A protease inhibitor, simeprevir was approved in November, 2013. Recent approval of sofosbuvir, a nucleotide analog inhibitor of HCV NS5B polymerase (first-in-class), in December, 2013

has also transformed the landscape of CHC treatment with sustained viral response rates reaching 90 percent. The field is progressing towards interferon/ribavirin free therapeutic options with simpler, shorter duration treatment regimens with improved efficacy and safety profiles.

Drug-induced liver injury (DILI) is the most frequently reported adverse event that leads to a regulatory action such as failure to approve drug for marketing, added label warnings, withdrawal of drug from the market based on postmarketing reports of serious and/or fatal hepatotoxicity. DILI is the leading cause of acute liver failure in the US (Ostapowicz 2002).

Diagnosis of DILI remains to be a major diagnostic challenge as there is presently no specific diagnostic biomarker. Moreover, the clinical presentation is heterogeneous and it can mimic any form of hepatobiliary disease, from non-specific changes in liver enzymes to fatal hepatic necrosis (Kaplowitz & DeLeve 2003). Some drugs may show several different patterns (Kaplowitz & DeLeve 2003).

Since the probability of identifying overt liver injury in clinical trials is low, any signals for serious hepatotoxicity such as incidence of asymptomatic serum alanine aminotransferase (ALT) and bilirubin elevations observed during drug development program warrants further evaluation. Higher incidence of hepatocellular injury (ALT and/or AST > 3x ULN) in drug group rather than in control or placebo group and the presence of Hy's Law cases (Hy's Law Case Definition: Subject with ALT > 3xULN and TB > 2x ULN without initial findings of cholestasis (ALP <2xULN); No evidence of another cause) is used by FDA to identify drugs potentially capable of causing severe liver injury.

Application of Hy's law in the trial population of chronic hepatitis C patients with pre-existing liver disease is challenging as these patients often have elevated liver enzymes at baseline. However, with DAA use, the decline in viral load usually is associated with decline or normalization of liver enzymes. Any elevations after the nadir values are reached on-treatment should indicate a drug-associated effect or a viral breakthrough.

One of the major concerns which is often voiced is that clinical trial inclusion or exclusion criteria are too stringent and do not reflect the wide range of patients who will receive treatment in "real-world" setting. Hence, it is prudent that any signal of potential severe liver injury identified during clinical trials is adequately monitored in clinical practice after drug approval and marketing.

Discussion of Pertinent Findings

Elevated Liver Enzymes

The liver enzyme elevations observed in the clinical trials of 3-DAA regimen to date are concerning. Grade 3 and Grade 4 ALT elevations were observed in multiple subjects. As noted in Section 7 (Review of Safety) of the Clinical Review, "The most important clinically relevant treatment-emergent adverse effect (TEAE) related to treatment with the 3-DAAs was elevated transaminase levels." These liver enzyme abnormalities are considered a potential signal for serious hepatotoxicity.

Hepatotoxicity cases observed in the 3-DAA clinical trials were evaluated by an independent hepatic expert panel convened by the Applicant. The expert panel included three hepatologist (Drs. (b) (4)) who independently performed their assessments. The assessment performed by the panel is provided in Table 58 of the Applicant's Integrated Summary of Safety (ISS). Please also refer to Liver Safety Assessment Report included in the Applicant's submission for detailed assessment of the findings.

Table 29 of the Clinical Review provides in-depth discussion of the hepatotoxicity cases including Expert Panel Assessment/comments and Clinical Reviewer's assessment/comments. Of note, there were three hepatotoxicity cases (# 114504, M13-961; #440305, M13-098; and #606111, M13-099) in which the Clinical Reviewer's assessment differed from that of Expert Panel assessment. Two of these cases were scored as "Unlikely DILI" and one as "possible DILI" by the expert panel.

The following excerpt from the Clinical Review summarizes the observed findings of elevated liver enzymes in clinical trials evaluating 3-DAA regimens.

> "ALT elevations were observed in Phase 2 and Phase 3 trials. Treatment with 3-DAA ± RBV generally resulted in a rapid decrease from baseline in ALT levels consistent with the reduction in viral load and hepatic inflammation caused by HCV infection in most patients. Approximately 1% of 3-DAA + RBV-treated subjects experienced a post-baseline ALT elevations of ≥Grade 3. These ALT elevations were generally asymptomatic and occurred during the first 28 days of study drug treatment. There were no Hy's law cases based on review by an independent hepatic expert panel. Most subjects experienced improvement or resolution by the Final Treatment Visit or by PTW 4 *(posttreatment week 4)*, and in most cases, the ALT elevation resolved with continued DAA treatment; and, a risk factor of concomitant systemic estrogen-containing medication use was identified ALT elevations."

As noted in the clinical review, "The mean time to ALT elevation was 20 days (range 8-57)."

The table below (excerpt from Table 26 of the Clinical Review) shows the number of subjects with ALT elevations by grades. It should be noted that the grading system used in these trials was Common Terminology Criteria for Adverse Events v4.0 (CTCAE) grading system in which Grade 3 ALT includes > 5.0 – 20.0 ULN and Grade 4 ALT elevations include values >20xULN.

Table 26 Maximum post-baseline on-treatment CTCAE Grade 1, 2, 3, and 4 LFT elevations

N (%)	3-DAA + RBV X 12 weeks Non-cirrhotic n=1171	3-DAA X 12 weeks Non-cirrhotic N=509	PBO* N=255	3-DAA + RBV X 12 weeks Cirrhotic N=208	3-DAA + RBV X 24 weeks Cirrhotic N=172
ALT					
-Grade 1 (>3.0 x ULN)	190(16)	101 (20)	180 (70)	93 (45)	84 (49)
-Grade 2 (>3-5 x ULN)	13 (1)	8 (2)	31 (12)	4 (2)	0
-Grade 3 (>5-20 x ULN)	9 (<1)	1 (<1)	3 (2)	4 (2)	0
-Grade 4 (>20 x ULN)	3 (<1)	0	0	2 (1)	0

Source: Excerpt from Clinical Review by Russel Fleischer, PA-C, MPH archived on September 18, 2014

As shown in the table, there were five subjects with Grade 4 ALT elevations in the 3-DAA + RBV treatment arms compared to none in the placebo arm. There were 14 subjects with Grade 3 ALT elevations in the 3-DAA + RBV treatment arms compared to 3 subjects in the placebo arm.

It should be noted that the frequency of ALT elevations was higher in Phase 2 trials evaluating higher doses of ABT-450. As noted in the Clinical Review, "The frequency of ALT elevations was higher in subjects who received ABT-450/r 200/100 mg (5%) compared to those who received a 150 or 100 mg dose (<1%). One subject with a Grade 2 ALT elevation discontinued treatment due to cholestatic hepatitis."

The following excerpts from the Applicant's Summary of Clinical Safety further summarize the findings observed in the clinical trials.

> "Among all subjects in the All Treated Analysis Set, a low percentage experienced postbaseline ALT values of at least grade 2 (2.2%) or at least grade 3 (1.0%) and most of these subjects received the 3-DAA + RBV regimen. A similar pattern of results was observed for AST. Six (0.2%) subjects (all 3-DAA + RBV) had a postbaseline grade 4 ALT value. One of these 6 subjects also had a postbaseline grade 4 AST value.
>
> The Kaplan-Meier curve of the time to onset of grade 3+ ALT elevations for the All Treated Analysis Set showed that the majority of grade 3+ ALT elevations occurred within the first 28 days of treatment."

> An independent hepatic expert panel reviewed hepatic laboratory and clinically relevant data from all subjects whose ALT and total bilirubin values were in the Hy's quadrant of an eDISH plot, and any subject with a postbaseline serum ALT > 5 × upper limit of normal (ULN) without a total bilirubin elevation ≥ 2 × ULN (subset of Temple's corollary quadrant). The panel adjudicated cases to determine whether they were consistent with Hy's law, and assigned a Drug Induced Liver Injury Network (DILIN) score for all cases reviewed.
>
> Twenty (0.8%) subjects had ALT and total bilirubin values that were in the Hy's quadrant of an eDISH plot, and 13 (0.5%) subjects with a postbaseline serum ALT > 5 × upper limit of normal (ULN) without a total bilirubin elevation ≥ 2 × ULN (subset of Temple's corollary quadrant).
>
> The panel concluded that none of these 32 subjects met criteria for Hy's law. The panel determined that the elevations in total bilirubin in these cases were temporally inconsistent with Hy's law in that they preceded the peak serum ALT elevations, a result consistent with inhibition of bilirubin transporters by ABT-450. Moreover, the peak total bilirubin elevations were predominantly indirect bilirubin, a finding inconsistent with Hy's law, and again consistent with inhibition of bilirubin transporters and exacerbation by RBV-induced hemolysis.
>
> Although none of the 32 cases was adjudicated as consistent with Hy's law, the hepatic panel assigned a DILIN score of at least "possible" for the majority (n = 25) of these 32 subjects, indicating that the 3-DAA regimen may be associated with the observed laboratory abnormalities in these cases. The hepatic panel also reviewed the data for 10 subjects who received placebo; 3 of these 10 subjects received a DILIN score of at least "possible". In all cases that received a DILIN score of at least "possible," ALT elevations were asymptomatic.
>
> The majority of these 32 subjects completed study drug with ALT levels that had declined from the peak value and that were normal or grade 1 by the Final Treatment Visit or by Post-Treatment Week 4.
>
> Of the 32 subjects evaluated by the independent hepatic expert panel, treatment-emergent adverse events led to interruption of study drug in 3 subjects and discontinuation of study drug in 2 subjects. In all cases, serum ALT improved or resolved by end of treatment."

Furthermore, as noted in the Liver Safety Assessment Report, "…*the majority of elevations in serum ALT > 3 X ULN occurred between 1-2 weeks on active treatment and that the frequency of these events falls substantially thereafter*." The panel also tried to assess "for a characteristic or "signature" presentation" in the cases evaluated. The report noted that, "*Although the typical signature event observed was an early rise in serum ALT/AST peaking at 2 weeks with subsequent resolution despite continued drug treatment, variations on this theme were observed in cases considered by*

consensus among the hepatologists to be at least probably due to study drug." A secondary rise at about 6 weeks was also noted in at least two cases which was attributed to the study drug by the hepatologists in the panel.

As noted in the panel report, one of the subjects (enrolled in Trial M13-393, Subject 30300) had an ALT elevation noted at Treatment week 6, accompanied by a rise in serum total bilirubin. The panel noted that, "….experienced a secondary rise in serum total bilirubin which preceded the spike in aminotransferase levels but continued to rise during resolution of the aminotransferases. At this time, the conjugated bilirubin concentration exceeded that of the unconjugated bilirubin. This is a confusing case and since the bilirubin rise preceded the onset of ALT elevations, the consensus of the hepatologists was that it should not be considered a Hy's Law Case."

Medical Officer Comments

This case is concerning as the ALT elevations were noted at Treatment Week 6 concomitantly with an increase in bilirubin levels.

Another case (M12-998, Subject 3183) was noted to have marked elevations in ALT values at TW10 ("linked to insertion and subsequent of cervical a ring that delivers estrogens"). These elevations in transaminase values were accompanied with elevations in bilirubin levels as well. The study drugs were continued for 12 weeks with resolution by PTW4.

Of the 32 subjects (N=2632) evaluated by the independent hepatic expert panel, the panel assigned a DILIN score of "highly likely" for six subjects, 14 subjects were assigned as "probable" and 5 subjects as "possible". The expert hepatic panel made the following points in their discussion of the findings*, "Although the liver safety experience with the 3 DAA regimen is generally reassuring, it cannot at this time be concluded that the treatment associated elevations in serum aminotransferases will always have a benign course, particularly in women (and possibly men) receiving estrogens. Although this risk appears to be greatest in subjects treated with estrogens, subject 30300 (receiving ABT-450/r, ABT 267, and RBV) was not receiving concomitant treatment with estrogens yet experienced many of the features of a Hy's Law case while receiving an ABT/r containing regimen. It is therefore possible that the 3-DAA regimen could result in clinically important liver injury in patients not receiving estrogens."*

As noted in the FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, "More difficult to detect is toxicity that is not predictable or clearly dose-related that occurs at doses well tolerated by most people, but seems to depend on individual susceptibilities that have not as yet been characterized." Furthermore the

guidance notes that, “There are no good data to predict how great this excess incidence of AT elevations should be compared to controls to suggest an increased risk of DILI.”

It should be noted that increased risk of liver enzyme elevations, including an SAE of acute hepatitis, was observed in subjects with concomitant systemic estrogen-containing medication use during clinical trials. In addition, serum ALT elevations were also observed in a healthy volunteer study evaluating estrogen-containing oral contraceptive.

Medical Officer Comments

Transient elevations in ≥ Grade 3 ALT were observed in 1% of subjects treated with 3-DAA, and were not associated with deterioration of other liver functions. Of note, the liver enzymes improved spontaneously even with the continued use of the investigational 3-DAA drugs indicating apparent “adaptation” to the treatment regimen. The majority of subjects completed the treatment as planned with very few subjects with study drug interruption or drug discontinuation. The elevated bilirubin elevations were observed due to transporter effect and concomitant ribavirin use and preceded the serum transaminases elevations. (b) (4)

Elevated Bilirubin Values

Paritaprevir is a known inhibitor of OATP1B1 and OATP1B3 transporters. Transient elevations of total and indirect bilirubin levels observed in clinical trials were attributed to the ABT-450’s inhibition of the bilirubin transporters. Bilirubin was predominantly indirect, it occurred early during treatment (by day 8-15), was generally not associated with signs or symptoms, stabilized and returned to baseline or near baseline levels by end of treatment or PTW4. Mean bilirubin levels were higher among subjects treated with 3-DAA + RBV compared to those who did not receive RBV. Approximately 2% of study subjects had jaundice or scleral icterus or both. One subject interrupted DAA treatment for a few days, but no subject discontinued DAAs due to elevated bilirubin levels.

Another protease inhibitor, simeprevir, is also known to inhibit hepatic transporters OATP1B1 and MRP2. The approved USPI for Simeprevir includes the following:

> Elevations in bilirubin were predominately mild to moderate (Grade 1 or 2) in severity, and included elevation of both direct and indirect bilirubin. Elevations in bilirubin occurred early after treatment initiation, peaking by study Week 2, and were rapidly reversible upon cessation of OLYSIO. Bilirubin elevations were generally not associated with elevations in liver transaminases.

Medical Officer Comments

Reversible increase in serum bilirubin was observed in a proportion of patients without evidence of associated hepatocellular toxicity or cholestasis. This information needs to be adequately conveyed in the PI.

Of note, paritaprevir was shown in preclinical animal studies to cause gall bladder erosions, and there were five subjects with SAEs related to gall bladder disease. As noted by the Clinical Reviewer, "It was not possible to rule out a relationship between these events and the DAAs, and post-marketing surveillance for these types of events is recommended."

Medical Officer Comments

I agree that these findings of SAEs related to gall bladder disease need to be monitored as part of the postmarketing surveillance.

Conclusions and Recommendations

The observed findings from clinical trial data indicate that subjects with potential DILI were identified and managed appropriately in clinical trial settings. However, if the same will hold true in the real-world setting needs to be seen.

The following excerpt from an article by Abboud and Kaplowitz, addresses how to identify signals of liver toxicity in clinical trials and then monitoring in clinical practice.

> "Mitigating the potential for drug-induced liver injury is achieved by the identification of toxicity signals during clinical trials and the monitoring of liver tests in clinical practice. There are three signals of liver toxicity in clinical trials: (i) a statistically significant doubling (or more) in the incidence of serum alanine aminotransferase (ALT) elevation >3 x the upper limit of normal (ULN); (ii) any incidence of serum ALT elevation >8-10 x ULN; and (iii) any incidence of serum ALT elevation >3 x ULN accompanied by a serum bilirubin elevation >2 x ULN. Monitoring of liver tests in clinical practice has shown unconvincing efficacy, but where a benefit-risk analysis would favour continued therapy, monthly monitoring may have some benefit compared with no monitoring at all."

The following excerpt from the LiverTox website further addresses some of the dilemmas of the management of the liver enzyme elevations.

> "The appearance of serum enzyme elevations during drug therapy often leads to the decision to decrease the dose or stop the medication, but the level or duration of elevations that calls for such a decision is often unclear. The occurrence of symptoms or jaundice should lead to prompt discontinuation. In addition, any elevation of ALT above 10 times the ULN and persistent elevations above 3 times the ULN are appropriate criteria to stop a medication, particularly if it has been implicated in causing severe drug induced liver injury or is a new medication with uncertain potential for hepatotoxicity."
> http://livertox.nih.gov/Phenotypes_enzy.html [accessed on September 23, 2014].

Causality assessment for DILI in these cases with pre-existing liver disease is challenging due to presence of multiple confounding factors such as elevated baseline liver enzymes in chronic HCV patients, elevated indirect bilirubin levels due to inhibition of enzyme and inhibition of hepatic transporter associated with drug use. Natural flares of serum ALT values in CHC patients are not very well-defined.

There is no consensus on what level of liver enzymes elevations without associated symptoms or jaundice should lead to drug discontinuation. Furthermore, it remains unclear whether monitoring of liver tests is effective in avoiding the clinically significant hepatotoxicity.

A concern was raised that "routine monitoring may result in the unnecessary discontinuation of treatment in the majority of patients experiencing ALT elevations." Liver enzyme elevations should serve as an indicator to monitor more closely and should not necessarily lead to discontinuation of therapy. Risk benefit assessment for an individual patient by the treating physician should determine the further course of management. The health care providers need to assess whether potential benefit of continuing drug therapy (maximizing the chance to achieve SVR) outweighs the potential DILI risk (which might be mitigated by close monitoring).

It is crucial that health care providers are well informed of the profile of the liver enzyme elevations observed in the clinical trials. This information needs to be adequately conveyed in the prescribing information to mitigate any potential risks associated with markedly elevated liver enzymes by routine monitoring of the patients in the clinical setting. Early monitoring should allow the wider access of drug in the intended population while minimizing the risk of hepatic adverse events.

Signal for DILI related to investigational agent was identified in clinical trials and thus careful monitoring is warranted in post-marketing setting to potentially mitigate the serious risk associated with drug-induced hepatotoxicity.

AASLD/IDSA hepatitis C Guidance entitled, “Recommendations for Testing, Managing, and Treating Hepatitis C” developed by AASLD and IDSA in collaboration with the International Antiviral Society – USA (IAS-USA) recently issued an update, “Monitoring Patients Who Are Starting Hepatitis C Treatment, Are in Treatment, or Have Completed Therapy (available at http://www.hcvguidelines.org). The following recommendations regarding monitoring during antiviral therapy have been made.

Recommended monitoring during antiviral therapy

CBC count, creatinine level, calculated GFR, and hepatic function panel are recommended every 4 weeks during antiviral therapy. TSH is recommended every 12 weeks for patients on IFN. More frequent assessment for drug-related toxic effects (eg, CBC count for patients receiving RBV) is recommended as clinically indicated.

Rating: Class I, Level B

Quantitative HCV viral load testing is recommended after 4 weeks of therapy, at the end of treatment, and at 12 weeks following completion of therapy.

Rating: Class I, Level B
(http://www.hcvguidelines.org accessed on September 26, 2014)

In my opinion, this 3-DAA drug regimen with its potential for severe DILI will need more frequent assessment in addition to every 4 weeks routine monitoring as recommended by the HCV guidelines panel.

This reviewer defers to the primary review team regarding the final overall risk/benefit assessment for the proposed indication and the final text for the PI, pending drug approval. Any signals of hepatotoxicity should be monitored adequately during post-marketing setting. The goal of monitoring is to identify and characterize the liver injury to further determine whether the observed findings are transient or are progressing.

The following recommendations for your consideration are noted below:

- *The information about the observed elevated liver enzymes and the potential for severe liver injury should be adequately conveyed in the prescribing information so that patients and health care providers are vigilant for any signs or symptoms of liver injury.*

- *The information about the elevated bilirubin values due to inhibition of transporters should be conveyed in the PI as well.*

- *Agree with the assessment that the use of the drug regimen with concomitant use of estrogen-containing hormonal contraceptives should be contraindicated.*

- *Recommend adequate monitoring of liver enzymes and synthetic liver functions in clinical practice for early detection and optimal management of drug-induced liver injury.*

- *Recommend appropriate laboratory testing prior to initiating treatment, at Weeks 2 and 4, and then additional testing should be performed periodically during the duration of therapy. If elevated liver enzymes are observed at any timepoint or symptoms of hepatitis such as fatigue, weakness, nausea, poor appetite, right upper abdominal pain, or jaundice develop, more frequent monitoring is recommended as clinically indicated.*

- *Discontinuation of drug should be considered in any patient with confirmed elevation of ALT above 10 times the ULN. Drug should be discontinued in the presence of symptoms of hepatitis or hepatic dysfunction.*

- *Need for additional laboratory testing at on-treatment week 6, needs to be further discussed with the review team as there were few cases in which a second spike of ALT rise was seen around Treatment Week 6 and in one subject the ALT elevation was observed at TW6.*

- *Postmarketing surveillance will be crucial in identifying any serious DILI cases. After the approval, observational cohorts such as HCV-TARGET may provide additional information that may be helpful in further characterizing the hepatic injury due to the 3-DAA regimen.*

These recommendations are meant to be flexible and may be revised upon further discussions with the primary review team or emergence of any new safety findings.

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/s/

POONAM MISHRA
10/06/2014

ADDENDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 18, 2014
Requesting Office or Division:	Division of Antiviral Products
Application Type and Number:	NDA 206619
Product Name and Strength:	Viekira Pak (ombitasvir, paritaprevir, ritonavir copackaged dasbuvir) Tablets, 12.5 mg/75 mg/50 mg
Submission Date:	July 21, 2014
Applicant/Sponsor Name:	Abbvie
OSE RCM #:	2014-822
DMEPA Primary Reviewer:	Mónica Calderón, PharmD, BCPS
DMEPA Associate Director:	Irene Chan, PharmD, BCPS

1 PURPOSE OF ADDENDUM

DMEPA previously completed a review (OSE Review #2014-822, dated September 10, 2014) which provided recommendations for Viekira Pak carton labeling to replace the days of the week with "Day 1, Day 2, etc." in order to mitigate the potential for delay in therapy.[1] However, after this review was finalized, the Division of Antiviral Products (DAVP) review team did not feel a delay in therapy would be a cause for clinical concern and that the days of the week for this particular packaging configuration may be a better tool for reminding a patient as to when they took their medication. The review team believed that keeping the days of the week instead of changing to "Day 1, Day 2, etc." would be less error prone. Upon further consideration, we believe that errors may occur with either presentation. Thus, we will align with DAVP's request to maintain the days of the week on the carton labeling.

[1] Calderon, M. Label and Labeling Review for Viekira Pak (NDA 206619). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 09 10. 32 p. OSE RCM No.: 2014-822.

2 CONCLUSIONS

We align with DAVP's request to maintain the days of the week on the carton labeling. We have no additional recommendations at this time.

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/s/

MONICA M CALDERON
09/19/2014

LUBNA A MERCHANT
09/19/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
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Pediatric and Maternal Health Staff Memorandum

Date: September 12, 2014 **Date Consulted**: July 11, 2014

From: Miriam Dinatale, D.O., Medical Officer
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP, Acting Labeling AD
Pediatric and Maternal Health Staff

Lynne P. Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff

To: Division of Antiviral Products (DAVP)

Drug: Viekira Pak (ombitasivir/paritaprevir/ritonavir copackaged with dasabuvir)

NDA: 206619

Applicant: AbbVie, Inc

Subject: Pregnancy and Lactation labeling, Risk Management Pregnancy and Prevention Planning

Materials Reviewed: Viekira Pak product labeling, Sponsor clinical and nonclinical study reports

Consult Question:
Please recommend ways to effectively communicate the risk of hepatotoxicity with concomitant use of systemic estrogen-containing medications and Viekira Pak in Viekira Pak labeling and the need for effective contraception while on ribavirin.

INTRODUCTION

On April 21, 2014, AbbVie, Inc. submitted a 505(b)(1) New Drug Application (NDA 206619) to obtain approval to market Viekira Pak (ombitasivir/paritaprevir/ritonavir copackaged with dasabuvir) for the proposed indication of the treatment of chronic hepatitis C virus genotype-1 (GT1) infection in adults, including those with compensated cirrhosis, who are either treatment-naïve or previously treated with pegylated interferon (pegIFN) and ribavirin. Viekira Pak is used in combination with ribavirin in certain patient populations.

The Division of Antiviral Products (DAVP) consulted the Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) on July 11, 2014, to recommend ways to effectively communicate the risk of hepatotoxicity with concomitant use of systemic estrogen-containing medications and Viekira Pak while emphasizing the need for effective contraception if Viekira Pak is taken in combination with ribavirin, a drug that has demonstrated teratogenicity in all animal species studied. At a labeling meeting held on August 14, 2014, DAVP also requested that PMHS-MHT revise the Viekira pregnancy and nursing mothers section of the label using the proposed Pregnancy and Lactation Labeling Rule format. See Appendix A for the sponsor's proposed Viekira Pak Pregnancy and Nursing Mothers subsections of labeling.

BACKGROUND

Hepatitis C Virus (HCV) is a serious and life-threatening condition that can lead to advanced fibrosis, cirrhosis and extra-hepatic manifestations (renal disease, cryoglobulinemia, lymphoma, thyroiditis). Viekira Pak consists of: 1) a non-nucleoside inhibitor of nonstructural protein 5B (NS5B) RNA polymerase (dasabuvir); 2) a nonstructural protein 3 (NS3) protease inhibitor (paritaprevir) combined with; 3) ritonavir to enhance systemic exposures; and 4) a nonstructural protein 5A (NS5A) inhibitor (ombitasivir).[1] Viekira Pak is used in combination with ribavirin in certain patient populations. (b) (4)

[redacted]

DISCUSSION

Hepatitis C and Pregnancy

Chronic hepatitis C virus infection is seen in 0.15%- 2.4% of pregnant women in the U.S. In pregnant women with chronic HCV infection, there is a reduction in mean ALT levels with rebound in the postpartum period. This is thought to be due to several factors including: the release of endogenous interferon from the placenta during pregnancy, immune tolerance and sex hormones, which might result in modulation of the immune response against HCV. Overall, reports of obstetric complications of mothers infected with HCV are limited. A few studies have been done to investigate the effect of HCV on pregnancy outcomes. In a population-based cohort study from 2003 to 2005, 506 HCV-positive mothers, 2022 randomly selected HCV-negative mothers and 1439 drug-using HCV negative mothers were studied. This study showed that infants born to HCV-positive women were more likely to

[1] Executive CAC Meeting Minutes, July 22, 2014: pg 1.
[2] Applicant proposed Viekira Pak label, 2014.

have low birth weight, be small for gestational age, be admitted to the intensive care unit, or require assistance with ventilation. [3]

In another study, birth certificate records of 1,670,369 pregnancies from 1998 to 2007 were reviewed and demonstrated that infants born to HCV infected women were more likely to have low birth weight, be born preterm and have a congenital anomaly (did not list what types). This study, however, had several limitations and did not provide an association with variables, such as tobacco, alcohol or drugs.[4]

In a study done by Reddick *et al* records of pregnancy-related discharge between 1995 and 2005 were reviewed. Of the 297,664 pregnancy–related discharges, 555 had HCV. After excluding women with pre-gestational diabetes, the incidence and risk of gestational diabetes (GDM) was evaluated. Compared to non-infected controls, GDM was higher in HCV-infected women ($p=0.049$), but the results may have been due to the small sample size.[5]

Overall, population-based and case-control studies have inconsistently uncovered independent associations of maternal HCV infection with gestational diabetes, preterm delivery, low birth weight, small for gestational age, and cholestasis of pregnancy. It is not known why prematurity, low birth weight, SGA outcomes are seen in pregnant women with HCV. Dr. Prasad and Dr. Honegger[6] suggest that this may be due to inadequately controlled effects of maternal substance use, but they did note that a study done by Hurtado *et al,* which looked at placental immunity in HCV infection, suggested that alterations of placental Natural killer T cells (increased cytotoxicity) may account for the increased risk of preterm delivery.[7]

The overall rate of mother-to-child transmission of HCV from HCV-infected, HIV-negative mothers is about 3-5%. The risk of perinatal transmission is increased with: HIV co-infection, HCV RNA levels (viral titers over 10^5 to 10^6), HCV genotype, amniocentesis, and prolonged membrane rupture over six hours. Elective cesarean section has not been shown to reduce vertical transmission.[8] Overall, the U.S. Preventative Services Task Force has concluded that there is no clearly demonstrated intervention that will reduce the risk for mother-to-infant HCV transmission. [9]

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[3] Pergam SA, Wang CC, Gardella CM, Sandison TG, Phipps WT, Hawes SE. Pregnancy complications associated with hepatitis C: data from a 2003–2005 Washington state birth cohort. American journal of obstetrics and gynecology. 2008;199:38, e1–9

[4] Connell et al. "Maternal hepatitis B and hepatitis C carrier status and perinatal outcomes." Liver International. 2011. 1163-1170.

[5] Reddick KL, Jhaveri R, Gandhi M, James AH, Swamy GK. Pregnancy outcomes associated with viral hepatitis. Journal of viral hepatitis. 2011;18:e394–8.

[6] Prasad, M and Honegger, J. "Hepatitis C Virus in Pregnancy." American Journal of Perinatology.2013; 30(2): 1-20.

[7] Hurtado CW, Golden-Mason L, Brocato M, Krull M, Narkewicz MR, Rosen HR. Innate immune function in placenta and cord blood of hepatitis C--seropositive mother-infant dyads. PloS one. 2010;5:e12232.

[8] Arshad, M et al. "Hepatitis C virus infection during pregnancy and the newborn period-are they opportunities for treatment?" Journal of Viral Hepatitis. 2011. 18: 229-236.

[9] Cottrell, E et al. "Reducing Risk of Mother-to-Infant Transmission of Hepatitis C virus: A Systemic Review for the U.S. Preventative Services Task Force." Annals of Internal Medicine. 2013; 158(2): 109-113.

Current HCV treatment includes the use of pegylated interferon and ribavirin which can be harmful if used in pregnancy. Pegylated interferon has psychiatric side effects (depression and suicidal behavior) and ribavirin is a known teratogen and should not be used in pregnancy.[10]

Viekira Pak and Pregnancy

A search of published literature was performed, and there are no available published data with dasabuvir, ombitasivir or paritaprevir use in pregnant women. Ritonavir is currently indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. The following information is in ritonavir labeling regarding use in pregnancy:

> As of January 2012, the Antiretroviral Pregnancy Registry (APR) has received prospective reports of 3860 exposures to ritonavir containing regimens (1567 exposed in the first trimester and 2293 exposed in the second and third trimester). Birth defects occurred in 35 of the 1567 (2.2%) live births (first trimester exposure) and 59 of the 2293 (2.6%) live births (second/third trimester exposure). Among pregnant women in the U.S. reference population, the background rate of birth defects is 2.7%. There was no association between ritonavir and overall birth defects observed in the APR.[11]

Additionally, no evidence of impaired fertility, teratogenicity, or embryo-fetal toxicity was observed in animal reproduction studies with the administration of dasabuvir, ombitasivir or paritaprevir/ritonavir (the components of Viekira Pak) to rats, rabbits or mice during organogenesis. PMHS agrees with the sponsor that a pregnancy category B is the appropriate classification for Viekira Pak labeling because animal reproduction studies failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.[12] Please refer to the DAVP Nonclinical review for a comprehensive review of the animal reproduction studies.

In addition, AbbVie [redacted] (b) (4); however, Viekira Pak does not include ribavirin. It should be noted that ribavirin is labeled a pregnancy category X based on the significant teratogenic and embryocidal effects observed in rat and rabbit offspring in animal reproduction and developmental toxicity studies. Ribavirin caused malformations of the skull, palate, eye, jaw, limbs, skeleton and gastrointestinal tract in all species studied.[13] There is an on-going pregnancy registry established to collect pregnancy exposure data in women exposed to ribavirin during pregnancy. The data in this registry are limited and are not currently adequate to characterize the risk to the embryo or fetus via maternal or paternal exposure to ribavirin.[14] Ribavirin labeling includes a Boxed Warning for teratogenicity, a contraindication for use in

[10] Arshad, M et al. "Hepatitis C virus infection during pregnancy and the newborn period-are they opportunities for treatment?" Journal of Viral Hepatitis. 2011. 18: 229-236.
[11] See Norvir (ritonavir) labeling, November 7, 2013
[12] Pregnancy Category B: Animal reproduction studies have not shown an adverse effect on the fetus and there are no adequate and well-controlled studies in pregnant women, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no adequate and well controlled studies in humans
[13] See 2014 PMHS-MHT Ribavirin Pregnancy Registry Review
[14] See 2013 PMHS-MHT Ribavirin Pregnancy Registry Review, DAARTS Reference ID 3377289

pregnancy, and contraception information for females and males of reproductive potential using the drug.[15]

PMHS recommends that information regarding ribavirin be excluded from Viekira Pak labeling because the product does not contain ribavirin. (b) (4) [redacted]. A reference statement to ribavirin labeling would be appropriate in Viekira Pak labeling to ensure prescribers are aware to refer to ribavirin labeling for all of the important safety information when the products are used concomitantly. We also note that Viekira Pak was submitted and filed as a 505(b)(1) application; (b) (4) [redacted]

Hepatitis C and Lactation

HCV RNA has been detected in breast milk and colostrum. Although transmission is possible, the viral count in breast milk is very low and likely becomes inactivated in the infant's digestive tract. The risk of HCV transmission is higher if the mother has cracked or bleeding nipples. Mothers who are co-infected with HIV and HCV are recommended to follow current guidelines for prevention of HIV transmission.[17] Cottrell, *et al*., reviewed fourteen cohort studies (2971 mother-infant pairs) and found no association between breastfeeding by women infected with HCV and risk for transmission to infants. Most infants were followed for one year. Overall, the U.S. Preventative Services Task Force has concluded that avoidance of breastfeeding is not indicated for reducing transmission risk of HCV.[18]

Viekira Pak and Lactation

The Drugs and Lactation Database (LactMed)[19] was searched for available lactation data on the use of dasabuvir, ombitasivir or paritaprevir, and no information was found. The applicant provided data from a pre- and post-natal animal developmental study in rats that demonstrated the presence of each drug in rat milk and showed no adverse effects in nursing pups. See the DAVP Nonclinical review for a review of this data.

Ritonavir is present in human milk, and LactMed includes the following lactation data on ritonavir:

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[15] See current approved ribavirin labeling

[16] See 21 CFR 314.3

[17] Arshad, M et al. "Hepatitis C virus infection during pregnancy and the newborn period-are they opportunities for treatment?" Journal of Viral Hepatitis. 2011. 18: 229-236.

[18] Cottrell, E et al. "Reducing Risk of Mother-to-Infant Transmission of Hepatitis C virus: A Systemic Review for the U.S. Preventative Services Task Force." Annals of Internal Medicine. 2013; 158(2): 109-113.

[19] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

> Thirty mother/infants pairs (ten each at 6, 12 or 24 weeks postpartum) were enrolled in a lactation study. Each mother was taking ritonavir 100 mg twice daily by mouth starting at delivery. On the study day, at a median of 14.9 hours after the previous evening's dose, maternal plasma and breastmilk samples were obtained prior to the morning dose and 2, 4 and 6 hours after the dose. One hundred twelve of the 121 breastmilk samples contained detectable quantities (10 mcg/L or greater) of ritonavir, with a median breastmilk concentration of 79 mcg/L over the 6 hours. Infant plasma samples were obtained before their mother's first dose and at 2, 4 and 6 hours after the mother's dose. Infants were allowed to breastfeed *ad libitum* during the study period. Ritonavir was undetectable (<10 mcg/L) in all of the 115 infant plasma samples.[20]

In another lactation study, ritonavir was measured in 117 breastfed (90% exclusive) infants whose mothers were taking lopinavir plus ritonavir for HIV infection during pregnancy and postpartum. At 8 and 12 weeks postpartum, none of the infants had detectable ritonavir in their plasma; 91% of infants had detectable ritonavir in their hair samples at 12 weeks postpartum at a mean concentration of 0.15 ng/mg of hair (range 0.03 to 0.42 ng/mg). The authors concluded that infants receive negligible exposure to ritonavir during breastfeeding.[21]

(b) (4)

however, no information was submitted to justify this recommendation. Human lactation data are available only for ritonavir in which only negligible amounts of the drug were detected in breast milk. Lactation data from animal studies (rats) demonstrated the presence of drug in milk with no adverse effects observed in nursing pups.

(b) (4)

The American Academy of Pediatrics (AAP) considers breastfeeding to be the ideal method of feeding and nurturing infants.[22] In addition, human milk is the most complete form of nutrition for infants and offers a range of health benefits for lactating women and breastfed infants. Breastfeeding should not be discouraged with drug use unless appropriately justified. The PLLR will require the following lactation risk and benefit statement:

> The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for (name of drug) and any potential adverse effects on the breastfed child from (name of drug) or from the underlying maternal condition.

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[20] Corbett AH, Kayira D, White NR et al. Antiretroviral pharmacokinetics in mothers and breastfeeding infants from 6 to 24 weeks postpartum: results of the BAN Study. Antivir Ther. 2014.

[21] Gandhi M, Mwesigwa J, Aweeka F et al. Hair and plasma data show that lopinavir, ritonavir, and efavirenz all transfer from mother to infant in utero, but only efavirenz transfers via breastfeeding. J Acquir Immune Defic Syndr. 2013;63:578-84.

[22] American Academy of Pediatrics Policy Statement. "Breastfeeding and the Use of Human Milk." Pediatrics. 2012; 129: e827-e841

Systemic estrogen-containing medications and Viekira Pak

In Phase 3 clinical trials with Viekira Pak, elevations of ALT greater than five times the upper limit of normal occurred in some subjects. The rate of ALT elevations was seen more frequently in women who were using Viekira Pak with estrogen-containing medications, such as combined oral contraceptives, vaginal rings and hormone replacement. Increased rates of Grade 3 or higher ALT elevations were seen both in healthy subjects and in subjects with chronic hepatitis C. In some cases of concomitant Viekira Pak and estrogen administration, ALT elevations persisted with ongoing therapy; in these cases, ALT elevations resolved following discontinuation of the hormonal contraceptive. Additionally, there was no correlation seen between exposures to study drugs and transaminitis, nor did the use of estrogen-containing products increase exposure of study drugs. These effects were not observed with topical vaginal estrogen products. Refer to the DAVP Clinical Pharmacology review for a comprehensive review of this data.

(b) (4)

There are no recommendations for the use of effective contraception with the use of Viekira Pak because no signal for teratogencity was observed in animal reproduction studies with the drugs that comprise Viekira Pak. However, we note that the use of effective contraception is necessary for females of reproductive potential using ribavirin; therefore, the division should consider updating ribavirin labeling to add appropriate methods of effective contraception with the use of concomitant medications in which estrogen-containing products are contraindicated or not recommended.

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing Mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. A brief description of an available pregnancy exposure registry or pregnancy surveillance program that monitors or evaluates pregnancy outcomes with exposure of a drug during pregnancy should be placed in the pregnancy subsection. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in human milk is noted and presented in the label, not the amount. Additionally, information on pregnancy testing,

contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.
PMHS-MHT notes that pregnancy categories will be eliminated with the publication of the PLLR and replaced with clinically relevant information to assist prescribers with benefit/risk decision making for using a drug during pregnancy.

RECOMMENDATIONS
PMHT-MHT recommends a pregnancy category B classification for Viekira Pak since animal reproduction studies failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.[23] The pregnancy subsection of Viekira Pak labeling was structured in the spirit of the proposed PLLR, while complying with the current pregnancy labeling regulations (see 21 CFR 201.57(c)(9)(i).

(b) (4)

A reference statement to ribavirin labeling would be appropriate in Viekira Pak labeling to ensure prescribers are aware to refer to ribavirin labeling for all of the important safety information when the products are used concomitantly. We also note that Viekira Pak was submitted and filed as a 505(b)(1) application; (b) (4)

PMHS-MHT VIEKIRA PAK LABELING
PMHS-MHT recommends the following revision to the Pregnancy and Nursing Mothers subsections of Viekira Pak labeling. Final labeling will be negotiated with DAVP and may not fully reflect changes suggested here.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Category B

Risk Summary
Adequate and well controlled studies with VIEKIRA PAK have not been conducted in pregnant women. In animal reproduction studies, no evidence of teratogenicity was observed with the administration of ombitasvir (mice and rabbits), paritaprevir/ritonavir (mice and rats), or dasabuvir (rats and rabbits) at exposures higher than the recommended clinical dose *[see Data]*. Because animal reproduction studies are not always predictive of human response, VIEKIRA PAK should be used during pregnancy only if clearly needed.

[23] Pregnancy Category B: Animal reproduction studies have not shown an adverse effect on the fetus and there are no adequate and well-controlled studies in pregnant women, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no adequate and well controlled studies in humans
[24] See 21 CFR 314.3

If VIEKIRA PAK is administered with ribavirin, [redacted] (b) (4)

Reviewer Comment: A pregnancy risk statement (Risk Summary)that is based on animal data should and usually includes the number and type(s) of species studied, timing of exposure, animal doses expressed in terms of human dose or exposure equivalents and outcomes for pregnant animals and offspring. However, due to the number of drugs contained in Viekira Pak and the separate animal reproduction studies conducted, we recommend placing a brief summary statement that reflects the animal reproduction data with a cross-reference to the Data subheading where a complete description of animal data is described.

Data

Animal data

In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals treated throughout pregnancy with ombitasvir and its major inactive human metabolites (M29, M36), paritaprevir/ritonavir, or dasabuvir. For ombitasvir, the highest dose tested produced exposures equal to 28-fold (mouse) or 4-fold (rabbit) the exposures in humans at the recommended clinical dose. The highest doses of the major, inactive human metabolites similarly tested produced exposures approximately 26 times higher in mice than in humans at the recommended clinical dose. For paritaprevir/ritonavir, the highest doses tested produced exposures equal to 98-fold (mouse) or 8-fold (rat) the exposures in humans at the recommended clinical dose. For dasabuvir, the highest dose tested produced exposures equal to 48-fold (rat) or 12-fold (rabbit) the exposures in humans at the recommended clinical dose.

8.3 Nursing Mothers

It is not known whether any of the components of VIEKIRA PAK or their metabolites are present in human milk. Unchanged ombitasvir, paritaprevir and its hydrolysis product M13, and dasabuvir were the predominant components observed in the milk of lactating rats, and no adverse effects were observed in nursing pups. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Viekira Pak and any potential adverse effects on the breastfed child from Viekira Pak or from the underlying maternal condition.

If VIEKIRA PAK is administered with ribavirin, the nursing mothers information for ribavirin also applies to this combination regimen (See prescribing information for RIBAVIRIN).

APPENDIX A- Sponsor's Proposed Viekira Pak Pregnancy and Nursing Mothers Labeling

(b) (4)

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/s/

MIRIAM C DINATALE
09/12/2014

JEANINE A BEST
09/12/2014

LYNNE P YAO
09/18/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 9, 2014
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 206619
Product Name and Strength:	Viekira Pak (ombitasvir, paritaprevir, ritonavir copackaged with dasabuvir) Tablets, 12.5 mg/75 mg/50 mg and 250 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Abbvie, Inc.
Submission Date:	July 21, 2014
OSE RCM #:	2014-822
DMEPA Primary Reviewer:	Mónica Calderón, PharmD, BCPS
DMEPA Associate Director:	Irene Chan, PharmD, BCPS

1 REASON FOR REVIEW

Abbvie, Inc. is developing Viekira Pak for the treatment of genotype 1 Chronic Hepatitis C infection under NDA 206619. Thus, the Division of Antiviral Products (DAVP) requested that DMEPA evaluate the Applicant's proposed wallet [redacted] (b) (4) pack labels and labeling, full prescribing information (FPI) and patient package insert (PPI) for areas of vulnerability that could lead to medication errors. Additionally, Abbvie conducted a human factors validation study to evaluate the proposed wallet [redacted] (b) (4) packs. We evaluated the results from the validation study.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C (N/A)
Human Factors Study	D
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 "3-DAA REGIMEN HUMAN FACTORS REPORT"

Abbvie, Inc. reported that 17 out of 18 (94%) of study participants were successful in using the wallet pack configuration [redacted] (b) (4) We agree with Abbvie, Inc. that these failures are unlikely to represent a pattern of potentially harmful dosing errors, and we believe the risk for errors has been minimized to an acceptable level. We believe that the proposed packaging can be introduced safely and be used correctly intended users for its intended uses and use environments.

3.2 WALLET [redacted] PACK LABELS AND LABELING

The wallet [redacted] pack labels and labeling submitted for our review were slightly modified from those used in the validation study to include the established name "parataprevir", formerly noted as ABT-450, the proprietary name "Viekera Pak", and a toll free number to provide patient support. We note the wallet [redacted] pack weekly carton labeling can be improved to mitigate a possible delay in therapy based on the days of the week presented on the carton. The patient may interpret starting their treatment on a Monday versus the day they receive their medication which may be a different day of the week. While we expect Sponsors to validate a product with the intended-to-market interface, we do not expect the proposed changes to the carton to significantly alter the risk profile from a usability perspective. Thus, we we believe the proposed change can be implemented for the carton without requiring another validation study.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the study report entitled "3-DAA Human Factors Report" determined that Abbvie, Inc. has adequately demonstrated usability of the proposed wallet [redacted] pack configurations. We have recommendations for improvements to the weekly wallet [redacted] pack cartons in order to mitigate the potential for delay in therapy. This change does not require validation in another usability study. See Section 4.1, below, for our recommendation.

4.1 RECOMMENDATIONS FOR ABBVIE, INC.

A. Weekly [redacted] Wallet Pack Carton Labeling

1. Replace the days of the week with "Day 1, Day 2, etc." in order to prevent a possible delay in therapy since not all patients will necessarily begin treatment on a Monday.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Viekira Pak that Abbvie, Inc. submitted on July 21, 2014.

Table 2. Relevant Product Information for Viekira Pak	
Active Ingredient	ombitasvir, paritaprevir, ritonavir copackaged with dasabuvir
Indication	Treatment of Hep C genotype 1 infection.
Route of Administration	Oral
Dosage Form	Tablet
Strength	ombitasvir, paritaprevir, ritonavir 12.5 mg/75 mg/50 mg dasabuvir 250 mg
Dose and Frequency	Morning: Two tablets of ombitasvir, paritaprevir, ritonavir + One tablet of dasabuvir with food (in the morning) Evening: One tablet of dasabuvir with food
How Supplied	Monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs. Each child resistant daily dose pack contains four tablets: two ombitasvir, paritaprevir, ritonavir tablets, 12.5 mg/75 mg/50 mg and two tablets of dasabuvir 250 mg
Storage	Store at or below 30°C (86°F)

APPENDIX D. HUMAN FACTORS STUDY

D.1 Objective

The Human Factors (HF) validation testing was intended to assess the safe and effective use of the Viekira Pak wallet [redacted] configurations by the intended user group to administer the Abbvie 3-DAA regimen through two tasks:

- Simulate consumption of AM dose
- Verbalizing comprehension of consumption of PM dose

Abbvie's intention is to market the wallet co-packaging configuration; however, the [redacted] was included as a contingency in the event approval is granted before the new packaging line for the wallet configuration is qualified. Abbvie is currently anticipating the packaging line for the wallet configuration to be ready by mid-October 2014, prior to the Division's action date.

D.2 Study Population

The study included 39 patient participants, all diagnosed with HCV (treated, not treated, or failed treatment):

- 18 received the wallet configuration
- [redacted]
- Five (5) participants were without a high school diploma or equivalent, of Hispanic of African American descent, and with a household income of less than $30,000

D.3 Study Design

Participants did not receive formal training on proper use of the [redacted] wallet pack configurations. Participants were asked to complete tasks in a lab-based environment as if they were at home or in a non-clinical setting. Moderators were present and directly observed all activities, but did not intervene while participants attempted tasks unless it was necessary such as in the even that a participant initiated a potentially hazardous action. Each participant was presented with a monthly carton which contained four weekly cartons, each of which contained seven daily dosing packs of [redacted] wallet pack configuration. Each monthly carton also contained a document similar to the intended USPI. A phone was available in the testing room for participants to use in case they decided to utilize the help line without moderator interference or probing. The use-error evaluation of the product was objective (performance-based, simulated-use evaluations).

D.4 Results

Participant performance was scored as an overall success or failure based only on participant's ability to successfully complete two critical tasks, the AM dose task and the PM dose task.

- AM dose task
    - Simulating taking 3 pills (two ombitasvir, paritaprevir, ritonavir tablets and one dasabuvir tablet) for AM dose.
    - Verbalizing comprehension to administer med with food.
- PM dose task
    - Verbalizing comprehension to take one pill (dasabuvir) more than 6 hours after taking the AM dose.
    - Verbalizing comprehension to administer med with food.

Table 4. Summary of Critical Step Successes

	AM Dose Task		PM Dose Task		
	Dose (Two ABT-450/r/ABT-267 and One ABT-333)	Food	Dose (One ABT-333; > 6 hrs after AM dose)	Food	Overall Success
Wallet N = 18	17 (94%)	18 (100%)	18 (100%)	18 (100%)	17 (94%)
[redacted]					(b) (4)

1. Success with operational difficulty

- Participant 24 (P24) struggled to open the weekly carton and the daily dosing wallet to remove the pills. She used the available phone during the test and successfully completed all critical steps. Root cause analysis discovered she struggled due to negative transfer, her current medication dispenser is pre-filled and her medication would "pop out" when she pressed a button. She believed the daily log indicators were actually buttons that would dispense the medication b/c they looked similar to the buttons she was familiar with on her medication dispenser.

2. Success with Notes

- [redacted] (b) (4)
- P36 completed all steps and had an overall success rating, but attempted to open the carton from the bottom.

3. Failures

All four participants that failed overall had failed to take the AM dose correctly; however, all participants were able to verbalize that they intended to administer their AM dose with food, a critical step.

- Three (3) participants took one ombitasvir, paritaprevir, ritonavir tablet as their AM dose.
- One (1) participant took one ombitasvir, paritaprevir, ritonavir tablet and two dasabuvir tablets as their AM dose.
- Three (3) of the four (4) participants that failed had self-identified their error and successfully completed the PM task.
- Three (3) of the four (4) failures were attributed to negative transfer and one (1) failure was attributed to patient inattentiveness.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Viekira Pak labels and labeling submitted by Abbvie, Inc. on August 15, 2014.

- Wallet Pack labels and labeling
- (b) (4)
- Full Prescribing Information
- Patient Package Insert

G.2 Label and Labeling Images

Daily Wallet Pack

(b) (4)

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[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MONICA M CALDERON
09/10/2014

IRENE Z CHAN
09/10/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 28, 2014

TO: Katherine Schumann, MS, Senior Regulatory Project Manager
Russell Fleischer, PA-C, MPH, Senior Clinical Analyst
Division of Antiviral Products

FROM: Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 206-619

APPLICANT: AbbVie Inc.

DRUG: Viekira Pak

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority review (Breakthrough Therapy Designation)
INDICATION: Treatment of genotype-1 chronic HCV-infection including patients with cirrhosis
CONSULTATION REQUEST DATE: April 25, 2014
DIVISION ACTION GOAL DATE: December 19, 2014

PDUFA DATE: November 5, 2014

INSPECTION SUMMARY DUE DATE: October 1, 2014

I. BACKGROUND:

The Applicant conducted four pivotal trials in support of approval of a combination of ombitasvir/ABT-450/ritonavir co-packaged with dasabuvir tablets because of a need for new compounds that may overcome the disadvantages of current HCV therapy. The combination products are designed as NME/ Breakthrough Therapy Designation and are currently being reviewed in support of an application for HCV infected treatment naïve and subjects with cirrhosis.

The Applicant sponsored four pivotal clinical studies: Protocols M11-646, M13-099, M13-389, and M13-961 were conducted to support the pending application.

Protocols: M11-646 entitled "A Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-Administered with Ribavirin (RBV) in Treatment- Naïve Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (SAPPHIRE-I)",

M13-099 entitled "A Randomized, Open-Label Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-Administered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (TURQUOISE-II)",

M13-389 entitled "A Randomized, Open-Label, Multicenter Study to Evaluate the Safety and Antiviral Activity of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 with and Without Ribavirin (RBV) in Treatment- Experienced Subjects With Genotype 1b Chronic Hepatitis C Virus (HCV) Infection (PEARL-II)", and

M13-961 entitled "A Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With and Without Ribavirin (RBV) in Treatment-Naïve Adults With Genotype 1b Chronic Hepatitis C Virus (HCV) Infection (PEARL-III)".

Protocol M11-646

The objectives of this study were: 1) to show the non-inferiority in SVR12 rates (the percentage of subjects achieving a 12-week sustained virologic response, SVR12, (HCV RNA<LLOQ12) weeks following therapy) of 12 weeks of treatment with ABT-450/rABT-267 and ABT-333 co-administered with RBV (DAA combination regimen) to historical SVR rate of telaprevir plus pegIFN and RBV therapy, and 2) to assess the safety of DAA

combination regimen versus placebo for 12 weeks in HCV genotype-1-infected adults without cirrhosis.

The secondary objectives of this study were: 1) to measure the effect of the DAA combination regimen compared to placebo for 12 weeks on normalizing alanine aminotransferase (ALT) levels, and 2) to demonstrate the effect of the DAA combination regimen on SVR12 in subjects with HCV genotype 1a and genotype 1b infection, and on HCV RNA levels during and after treatment as measured by the co-treatment virologic failure and post-treatment relapse, respectively.

This protocol was a multi-national, randomized, double-blind, placebo-controlled, multicenter study evaluating ABT-450/rABT-267 and ABT-333 co-administered with RBV in treatment-naïve, non-cirrhotic HCV genotype 1-infected adults. The plan was to include a total of 600 HCV genotype 1-infected subjects. Treatment-naive subjects were randomized to two arms A and B in 3:1 ratio in the double-blind treatment period at approximately 80 sites.

- Arm A: ABT-450/r/ABT-267 150mg/100mg/25mg QD +ABT-333 250 mg BID+RBV for 12 weeks
- Arm B: Placebo for (ABT-450/rABT-267 150mg/100mg/25mgQD+ ABT-333 250mg BID+RBV) for 12 weeks followed by ABT-450/r/ABT-267 150mg/100mg/25mg QD +ABT-333 250mg BID + RBV for 12 weeks.

The duration of the study was 72 weeks long (not including a screening period of up to 35 days) consisting of three periods: The double-blind (DB) Treatment period, the Open-label (OL) Treatment Period (for subjects randomized to Placebo/Arm B), and the Post-Treatment (PT) Period (for all subjects who received active study drugs)

Protocol M13-099

The objectives of this study were: 1) to assess the safety and to compare the SVR12 rates (the percentage of subjects achieving a 12-week sustained virologic response, SVR12, (HCV RNA<LLOQ12) weeks following therapy) of 12 weeks of treatment with ABT-450/rABT-267 and ABT-333 co-administered ABT-450, ribavirin and ABT-267 (ABT-450/r/ABT-267), and 2) ABT-333 co-administered with ribavirin (RBV) for 12 or 24 weeks to historical SVR rate of telaprevir plus pegIFN and RBV therapy in HCV genotype-1-infectd adults with compensated cirrhosis.

The secondary objectives of this study were: 1) to compare the SVR12 rates between the 12 and 24-week treatment arms, and 2) to assess the percentage of subjects with virologic failure during treatment and the percentage of subjects with relapse post-treatment.

This protocol was a phase 3, randomized, open-label, multicenter study evaluating the safety and efficacy of ABT-450/rABT-267 and ABT-333 co-administered with RBV for 12 or 24 weeks in HCV genotype 1, treatment-naïve, and previous pegIFN/RBV treatment experienced adults with compensated cirrhosis. The plan was to enroll a total of 580 HCV genotype 1-infected subjects. Treatment-naive subjects were randomized to two arms A and B as follows:

- Arm A: ABT-450/r/ABT-267 150mg/100mg/25mg QD +ABT-333 250 mg BID+RBV* for 12 weeks
- Arm B: ABT-450/rABT-267 150mg/100mg/25mgQD+ ABT-333 250mg BID+RBV) for 12 weeks followed by ABT-450/r/ABT-267 150mg/100mg/25mg QD +ABT-333 250mg BID + RBV* for 24 weeks.
- RBV will be administered weight-based 1000-1200 mg divided twice daily

RBV* subjects were administered weight-based 1000-1200mg divided twice daily

Subjects meeting eligibility criteria were randomized to the 12-and 24-week treatment arms until approximately 380 subjects are enrolled at approximately 75 sites.

Protocol M13-389

The Primary objectives of this study were: 1) to evaluate the safety of 12 weeks of treatment with ABT-459/r/ABT-267 and ABT-333 with and without RBV, and 2) to show the inferiority in SVR12 rates (the percentage of subjects achieving a 12-week sustained virologic response, SVR12, (HCV RNA < LLOQ 12 weeks following therapy) of both arms to historical SVR rate of telaprevir plus pegIFN and RBV.

This was a phase 3, open-label, randomized, combination treatment study of ABT-450 /r/ABT-267 and ABT-333 with or without RBV enrolling approximately 210 subjects at about 45 sites. Treatment included pegIFN/RBV treatment-experienced, non-cirrhotic, **HCV sub-genotype 1b-infected subjects.**

Subjects were randomized at a ratio of 1:1 to Arm1 and Arm 2.

- Arm 1: ABT-450/r/ABT-267 150mg/100mg/25mg QD +ABT-333 250 mg BID+RBV* for 12 weeks
- Arm 2: ABT-450/rABT-267 150mg/100mg/25mg QD+ ABT-333 250mg BID for 12 weeks.

  RBV* subjects were administered weight-based 1000-1200 mg divided twice daily per local label (e.g. <75kg=1000mg daily divided BID or >75kg=1200mg daily divided BID)

Protocol M13-96.

The primary objectives of this study were: 1) to compare the safety of the combination of ABT-459/r/ABT-267 and ABT-333 administered with and without RBV for 12 weeks, and 2) to show the non-inferiority in SVR12 rates (the percentage of subjects achieving a 12-week sustained virologic response, SVR12, (HCV RNA < LLOQ 12 weeks following therapy) of 12 weeks treatment with ABT-450/rABT-267and ABT-333 administered with and without RBV compared to historical SVR rate of telaprevir plus pegIFN and RBV therapy in treatment –

naïve HCV genotype (GT) **1b** infected adults without cirrhosis.

This was a phase 3, randomized, double-blind, controlled, multicenter study evaluating the combination of ABT-450 /r/ABT-267 and ABT-333 with or without RBV in treatment naïve HCV GT 1b-infected adults without cirrhosis. Approximately 400 HCV GT 1b-infected subjects without cirrhosis were randomized to Arm A and Arm B in a 1:1 ratio at approximately 60 sites as follows:

- Arm A: ABT-450/r/ABT-267 150mg/100mg/25mg QD +ABT-333 250 mg BID+RBV* for 12 weeks
- Arm B: ABT-450/rABT-267 150mg/100mg/25mg QD+ ABT-333 250mg BID + Placebo for RBV* for 12 weeks.

RBV* subjects were administered weight-based 1000-1200 mg divided twice daily per local label (e.g. <75kg=1000mg daily divided BID or >75kg =1200mg daily divided BID).

The review division requested inspection of eight clinical investigators for the pivotal studies noted above because data from the studies are considered essential to support the approval of NDA 206-619: two domestic sites (LA and NY) for Protocol M11-646, one domestic (TX and one foreign (France) for protocol M13-099, two foreign sites (Turkey and Italy for Protocol M13-389, and two foreign site (Romania and Israel) for Protocol M13-961 which enrolled a large number of subjects in support of this application. These sites were targeted to evaluate the various regimens and population proposed for inclusion in labeling. It was for these reasons that it was critical that international sites be included in the inspection. This would be the first approval of these new drugs and most of the limited experience with foreign data. In addition, the sponsor was inspected because the combination products were designated as an NME; a Breakthrough Therapy. Note: Site # 47627/Yaacov Baruch/Israel was cancelled due to travel restriction at the time the site was scheduled for inspection.

II. RESULTS (by protocol/site):

Name of CI, Location, and Site #	Protocol and # of subjects randomized	Inspection Dates	Final Classification
Huberto Aguilar, M.D. Shreveport, LA 71103 Site #42730	Protocol M11-646 Number of subjects: 13	5/20-23/2014	NAI
Samuel Sigal, M.D. New York, NY 10016 Site# 39549	Protocol M11-646 Number of subjects: 14	June 10-18/ 2014	NAI
Christophe, Hezode, M.D Cretell , France Site# 44318	Protocol M13-099 Number of subjects: 24	August 18-21/2014	Pending (preliminary classification VAI)
Fred Poordad, M.D. San Antonio, TX Site #37739	Protocol M13-099 Number of subjects: 17	June 9-19/2014	NAI
Iftihar Koskal, M.D Trabzon, Turkey Site #48811	Protocol M13-389 Number of subjects: 11	August 18-21/2014	Pending (preliminary classification NAI)
Massimo Columbo, M.D. Milan, Italy Site #39008	Protocol M13-389 Number of Subjects 14	August 11-14/2014	Pending (preliminary classification VAI
Florin Caruntu, M.D. Buchrest, Romania Site#47495	Protocol M13-961 Number of subjects 16	August 11-15/2014	Pending (preliminary classification NAI
AbbVie Inc. North Chicago, IL 60064	All Protocols listed above (Eight sites)	May 29-June 6/2014	Pending (preliminary classification NAI)

Key to Classifications
NAI = No deviations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on e-mail communication from the field; the Establishment Inspectional Report (EIR) has not been received from the field and complete review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

1. **Huberto Aguilar, M.D.**
   Shreveport, LA 71103

   a. **What Was Inspected:** This inspection was performed as a data audit for NDA 206-619 Study Protocol M13-646. At this site, a total of 21 subjects were screened, eight subjects were reported as screen failures, 13 subjects were randomized into the study, and all 13 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

   The medical records/source data for 21 subjects were reviewed and compared to data listings. The review included drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, financial disclosure, sponsor and monitor audit activities prior and current medications, and adverse events. Source documents for all subjects were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings. No deficiencies were noted.

   b. General Observations/Commentary: At the conclusion of the inspection, a one item Form FDA 483 was issued to Dr. Aguilar regarding the missing laboratory results to ensure two subjects met inclusion criteria. The clinical investigator was able to obtain copies of the laboratory results from the clinical laboratory to document that the subjects did in fact qualify for enrollment into the study.

   Overall, the medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

   c. **Assessment of Data Integrity:** The data generated by this site are considered reliable and appear acceptable in support of the pending application.

2. **Samuel Sigal, M.D.**
   New York, NY 10016

   a. **What Was Inspected:** This inspection was performed as a data audit for NDA 206-619 and inspected Study Protocol M13-646. At this site, a total of 19 subjects were screened, five subjects were reported as screen failures, 14 subjects were randomized into the study, and 14 subjects completed the study. Fourteen subjects achieved undetectable HCV RNA levels at Week 12. The blind was broken for Subjects 127209 and 127213 after consultation with the medical monitor due to adverse events of anemia; anemia is an expected side effect of study drugs. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed informed consent forms prior to enrollment.

   The medical records/source documents for 16 subjects were reviewed. The medical records/source documents for enrolled subjects for certain visits were reviewed including drug accountability records, vital signs, IRB files, financial disclosures,

inclusion/exclusion criteria, prior and concomitant medications, and adverse events reporting. The field investigator compared the source documents/endpoint values to the data listings for primary efficacy endpoints, and no discrepancies were noted.

b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Sigal. The medical records reviewed were found to be in order and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

c. **Assessment of Data Integrity:** The data in support of the clinical efficacy and safety at Dr. Sigal's site are considered reliable and may be used in support of the pending applications

3. Christophe Hezode, M.D.
Cretell 94010, France

a. What Was Inspected: This inspection was performed as a data audit for NDA 206-619 and inspected Study Protocol M13-099. At this site, a total of 29 subjects were screened, 24 subjects were randomized into the study, and two subjects experienced serious adverse events (Subject 382123 died due to complication from liver transplant and Subject 382117 was hospitalized after falling from a ladder and suffering head trauma). Three subjects relapsed and five subjects were reported as screen failures with the reason(s) not documented. Six subjects continued in the follow-up treatment, and 13 subjects completed treatment. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for 29 subjects were reviewed for primary/secondary endpoints, informed consent including drug accountability records, vital signs, IRB records, financial disclosure, prior and current medications, and inclusion/exclusion criteria. Source documents for all subjects were compared to data listings for primary efficacy endpoints and adverse events listing. There was no evidence of under-reporting of adverse events at this site. Drug accountability records were incomplete in that the number of tablets returned by the subjects was not documented or known. Errors were made when issuing test kits or performing tests outside the established window were not documented or explained. In addition, monitoring visits were not conducted for certain dates and the monitoring visit logs were contemporaneous.

b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Hezode. However, minor deficiencies as stated above were discussed with the clinical investigator who agreed with the observations and promised correction.

The medical records reviewed were verifiable based on the information available at the site. There were no known limitations to the inspection. There were no deaths and no evidence of under-reporting of adverse events at this site.

c. **Assessment of Data Integrity:** Although minor deviations were noted at this site, the findings appear to be isolated instances, and it is unlikely that these findings would significantly impact the outcome of the study. Overall, the data submitted in support of the clinical efficacy and safety from this site are considered reliable and may be used in support of the pending applications.

4. **Fred Poordad, M.D.**
   San Antonio, TX 78215

   a. **What Was Inspected:** This inspection was performed as a data audit for NDA 206-619 Study Protocol M13-099. At this site, a total of 30 subjects were screened, 13 subjects were reported as screen failures, 17 subjects were randomized into the study, and 17 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

      The medical records/source data for 17 subjects were reviewed and compared to data listings. The review included consent forms, drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, financial disclosures, sponsor correspondence, prior and current medications, and adverse events. Source documents for all subjects were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings. There was no evidence of in accuracy of data captured.

   b. **General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Poordad. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

   c. **Assessment of Data Integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable and may be used in support of the pending application.

5. **Iftikar Koksal, M.D.**
   Trabzon, Turkey

   a. **What was Inspected**: This inspection was performed as a data audit for NDA 206619 and inspected Study M13-389. At this site, a total of 16 subjects were screened, five subjects were reported as screen failures, 11 subjects were randomized into the study, and all 11 subjects completed the study. Review of the Informed Consent Documents for all subjects verified that all subjects signed informed consent forms prior to enrollment.

      The medical records/source documents for 11 subjects enrolled were reviewed. The review included the six screen failures, drug accountability records, vital signs, IRB files, inclusion/exclusion criteria, study procedures, monitoring procedures, and use of

concomitant medications. Source documents were compared to CRFs and data listings, to include primary efficacy endpoints and adverse events. No deficiencies were noted.

b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Koksal. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

c. Assessment of Data Integrity: The data generated in support of the clinical efficacy and safety at this site are considered reliable and may be used in support of the pending applications.

6. Massimo Columbo, M.D.
Milan, 20122 Italy

a. What was Inspected: This inspection was performed as a data audit for NDA 206-619 and inspected Study M13-389. At this site, a total of 15 subjects were screened, one subject was reported as a screen failure, 14 subjects were randomized into the study, and 14 subjects completed the study. Review of the Informed Consent Documents for all subjects verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for all subjects were reviewed. The medical records for 15 subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, inclusion/exclusion criteria, study procedures, monitoring procedures, financial disclosure, and use of concomitant medications. Source documents were compared to CRFs and data listings, to include primary efficacy endpoints and adverse events reporting.

b. General Observations/Commentary: At the conclusion of the inspection, a one-item Form FDA 483 was issued to Dr. Columbo citing failure to adhere to the investigational plan in that 7 of 14 subjects enrolled had their blood drawn prior to having their electrocardiograms (ECG) performed as required by the protocol. Further, our field investigator discussed with the clinical investigator the fact that three subjects returned fewer tablets than they were supposed to have returned. The observations were presented and discussed with the clinical investigator who agreed with the findings and promised to provide a written response to FDA within 15 days.

The medical records reviewed were found adequate and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

c. Assessment of Data Integrity: Although minor deviations were noted at the above site, the findings appear to be isolated instances, and it is unlikely that these findings significantly impacted the outcome of the study. Overall, the data generated at this site in support of the clinical efficacy and safety are considered reliable and may be used in support of the pending applications.

7. Florin Carunta, M.D.
Bucharest, Romania

a. **What was Inspected**: This inspection was performed as a data audit for NDA 206-619 and inspected Study M13-961. At this site, a total of 17 subjects were screened, one subject was reported as a screen failure, 16 subjects were randomized into the study, and all subjects completed the study. Review of the Informed Consent Documents for all subjects verified that all subjects signed informed consent forms prior to enrollment.

   The medical records/source documents for all subjects were reviewed. The medical records were reviewed in depth, including drug accountability records, vital signs, IRB files, inclusion/exclusion criteria, study procedures, monitoring procedures, and use of concomitant medications. Source documents were compared to CRFs and data listings, to include primary efficacy endpoints and adverse events reporting.

b. **General Observations/Commentary:** At the conclusion of the inspection, no Form Form FDA 483 was issued to Dr. Caruntu. However, the missing hard copies of the laboratory results confirming positive hepatitis C was not available during the inspection to ensure two subjects met inclusion criteria. The clinical investigator was able to obtain copies of the laboratory results from the primary care physician to confirm the presence of hepatitis C prior to inspectional close out. The medical records reviewed were found adequate and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

c. **Assessment of Data Integrity:** Overall, the data generated at this site in support of the clinical efficacy and safety are considered reliable and may be used in support of the pending applications.

8. AbbVie Inc.
North Chicago, IL 60064

a. **What was Inspected**: The inspection audited the four protocols and focused on the clinical investigators listed above during the course of this sponsor monitor inspection. In addition, the audit included two additional sites due to noncompliance uncovered by the monitor audits. However, two sites noncompliance were brought into compliance and none of the sites needed to be closed.

   The inspection reviewed the following: Company history and officer responsibilities, training program, manufacturing/design operations, selection of clinical investigators, quality assurance, study monitoring procedures, data review and reports, protocol adherence, computerization, participating clinical investigators, and adverse event reporting.

b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to the Firm. The inspection found that the sponsor adhered to their SOPs regarding proper monitoring of their clinical investigators. The activities included, but not limited to, trial drug records, subject records, electronic database for entry of study data, protocol adherence, case report forms/source documents and adverse events reporting medical records reviewed were found adequate and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were sufficient and well organized records. Monitoring of clinical investigator sites was thorough and appeared adequate. There was no evidence of under-reporting of adverse events or protocol deviations.

d. Assessment of Data Integrity: The sponsor monitoring procedures appears to have been conducted adequately and the data submitted by the sponsor may be used in support of the respective indication. In general, the data appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Eight clinical investigator sites were inspected in support of this application. The inspection of the eight clinical investigators listed above revealed no regulatory violations. The final classification for Drs. Aguilar, Sigal and Poordad sites are No Action Indicated (NAI). The preliminary classification for Drs. Hezode and Columbo sites are Voluntary Action Indicated (VAI), and for Dr. Koskal and the Sponsor, AbbVie, Inc. are No Action Indicated (NAI). For the prelminary classifications, a summary addendum will be generated if conclusions change upon receipt and review of the EIRs. Overall, the data submitted from these six sites are considered acceptable and may be used in support of any future resubmission.

{See appended electronic signature page}

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/s/

ANTOINE N EL HAGE
09/09/2014

SUSAN D THOMPSON
09/09/2014

KASSA AYALEW
09/09/2014

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	206619
Generic Name	ABT-450/ritonavir Ombitasvir (ABT-267) Dasabuvir (ABT-333)
Sponsor	AbbVie, Inc.
Indication	Treatment of genotype 1 chronic hepatitis C infection, including patients with cirrhosis
Dosage Form	Oral tablet and capsule
Drug Class	NS3 protease inhibitor, NS5A inhibitor, NS5B polymerase inhibitor
Therapeutic Dosing Regimen	ABT-450 200 mg, ritonavir 150 mg, ABT-267 25 mg, and ABT-333 250 mg
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	ABT-450 350 mg, ritonavir 150 mg, ABT-267 50 mg, and ABT-333 500 mg
Submission Number and Date	004 / 4/21/2014
Review Division	DAVP

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect for a combination of ABT-450 with ritonavir plus ABT-267 and ABT-333 was detected in this TQT study. Using Individual corrected QT (QTcF) interval, the largest upper bounds of the 2-sided 90% CI for the mean differences between therapeutic dose and placebo, and between supratherapeutic dose and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 2, indicating that assay sensitivity was established.

In this randomized, double-blind, 4-period, placebo-and positive-controlled, 60 subjects received a combination of ABT-450, ritonavir, ABT-267, and ABT-333, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for a combination of ABT-450, ritonavir, ABT-267, and ABT-333 and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment Group	Time (h)	ΔΔQTcF (ms)	90% CI (ms)
Regimen Y: Therapeutic Dose	5	3.7	(1.7, 5.7)
Regimen Z: Supratherapeutic Dose	5	5.9	(4.0, 7.9)
Regimen D: Moxifloxacin 400 mg	2	10.8	(8.9, 12.7)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 8.3 ms.

C_{max} values of ABT-450, ABT-267, ABT-333 following therapeutic doses (ABT-450 200 mg + ABT-267 25 mg + ABT-333 250 mg + ritonavir 200 mg), are comparable or higher than those at steady state in healthy volunteers. The supratherapeutic doses (ABT-450 300 mg + ABT-267 50 mg + ABT-333 500 mg + ritonavir 200 mg) produce C_{max} values high enough to provide adequate margins for the predicted worst scenarios including higher exposures due to drug interactions, hepatic or renal impairment, and Asian subjects. And at these concentrations there are no detectable prolongations of the QT interval.

2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL

Effects on Electrocardiogram

THE EFFECT OF A COMBINATION OF ABT-450, ABT-267, RITONAVIR, AND ABT-333 ON QTC INTERVAL WAS EVALUATED IN A RANDOMIZED, DOUBLE BLIND, PLACEBO AND ACTIVE-CONTROLLED (MOXIFLOXACIN 400 MG) 4-WAY CROSSOVER THOROUGH QT STUDY IN 60 HEALTHY SUBJECTS (b) (4)

2.2 QT-IRT'S PROPSED LABEL

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

Effects on Electrocardiogram

The effect of a combination of ABT-450, ABT-267, ritonavir, and ABT-333 on QTc interval was evaluated in a randomized, double blind, placebo and active-controlled (moxifloxacin 400 mg) 4-way crossover thorough QT study in 60 healthy subjects. At concentrations approximately 6, 1.8 and 2 times the phase 3 therapeutic concentrations of ABT-450, ABT-267 and ABT-333, the combination did not prolong QTc to any clinically relevant extent.

3 BACKGROUND

3.1 PRODUCT INFORMATION

ABT-267 is an inhibitor of hepatitis C nonstructural protein 5A (NS5a). It is intended to be used with ABT-450 (inhibitor of NS3 and NS4a) and ABT-333 (inhibitor of NS5B) to treat with patients with HCV infection.

3.2 MARKET APPROVAL STATUS

ABT-267, ABT-450, and ABT-333 are not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

At a large multiple of the clinical exposure, ABT-267 showed some hERG blockade. At lower, but still large multiples of the clinical exposure, ABT-267 had no discernible effects on hemodynamics or cardiac electrophysiological parameters in anesthetized or conscious dogs.

3.4 PREVIOUS CLINICAL EXPERIENCE

Several hundred subjects have received relevant multiple doses of ABT-267 in studies. Cardiac signs, symptoms, and adverse events have not been prominent. No ECG abnormalities have been noted.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of ABT-450, ABT-267, ABT-333 and ritonavir's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 103,526. The sponsor submitted the study report M12-680 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

Placebo- and Active-Controlled Cross-Over Study of the Potential for Cardiac Repolarization Effects Following a Combination of ABT-450 with Ritonavir Plus ABT-267 and ABT-333 in Healthy Adult Subjects

4.2.2 Protocol Number

M12-680

4.2.3 Study Dates

First Subject First Visit: 12 February 2013
Last Subject Last Visit: 27 June 2013

4.2.4 Objectives

The objective of this study was to determine the potential for QTc prolongation following a combination of ABT-450, ritonavir, ABT-267, and ABT-333 in healthy adults.

4.2.5 Study Description

4.2.5.1 Design

This is a Phase 1, double-blinded, 4-period, placebo and active controlled, randomized study designed to evaluate the potential for QTc prolongation due to ABT-450, ritonavir, ABT-267, and ABT-333 in combination in healthy adults.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

For purposes of blinding at the site with respect to the Direct Acting Anti-viral Agents (DAA) regimens and the placebo regimen, the study drugs (ABT-450, ritonavir, ABT-267, and ABT-333 or placebo) corresponding to each of Regimens A, B, and C were not identified; however, Regimen A was one of the following Treatments X, Y or Z and each of Regimens B and C were also one of the three treatments. The moxifloxacin administration was un-blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Study drugs were administered in the morning on Study Day 1 under non-fasting conditions of each period as follows:

Treatment X (Regimen A):
Single dose of placebo, the placebo dose consisted of:
2 tablets of placebo for 25 mg ABT-267,
7 tablets of placebo for 50 mg ABT-450,
2 capsules of placebo for 25 mg ritonavir,
1 capsule of placebo for 100 mg ritonavir, and
2 tablets of placebo for 250 mg ABT-333

Treatment Y (Regimen B):
Single dose consisting of:
1 tablet ABT-267 25 mg and 1 tablet placebo for ABT-267 25 mg
4 tablets ABT-450 50 mg and 3 tablets placebo for ABT-450 50 mg
2 capsules ritonavir 25 mg and 1 capsule ritonavir 100 mg
1 tablet ABT-333 250 mg and 1 tablet placebo for ABT-333 250 mg

Treatment Z (Regimen C):
Single dose consisting of:
2 tablets of ABT-267 25 mg

7 tablets of ABT-450 50 mg
2 capsules ritonavir 25 mg and 1 capsule ritonavir 100 mg
2 tablets ABT-333 250 mg

Regimen D:
Single dose of 1 tablet moxifloxacin 400 mg

4.2.6.2 Sponsor's Justification for Doses

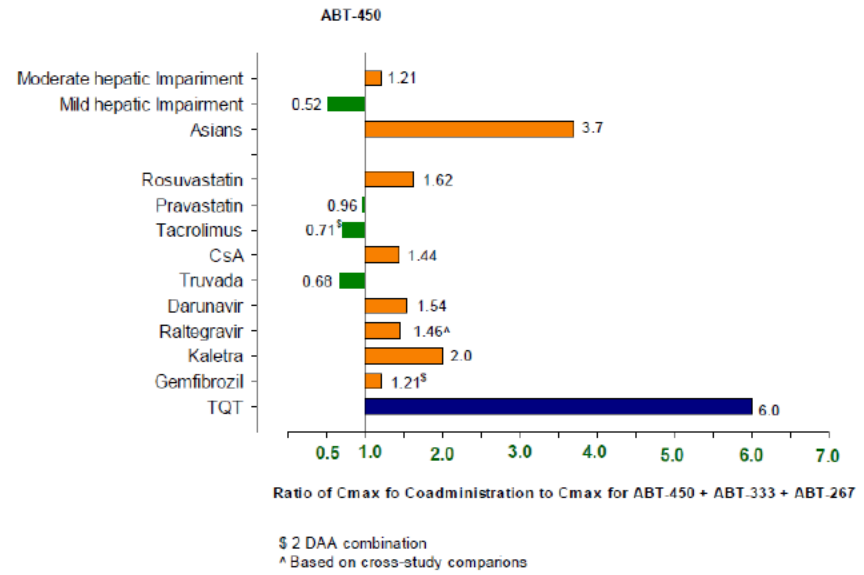
The sponsor evaluated four different compounds as part of a combination regimen in the TQT study. Based on accumulation and drug-drug interaction data, the sponsor selected the following doses for the therapeutic and supratherapeutic scenario for each of the four compounds:

ABT-450

The proposed therapeutic dose of ABT-450 is 150 mg coformulated with ritonavir 100 mg and ABT-267 25 mg. However, the ABT-450 200 mg dose from the (b) (4) tablet (Phase 2b formulation) was used as the therapeutic dose in this study since it was expected to provide exposures comparable to the ABT-450 150 mg coformulated tablet (Phase 3 formulation) at steady state.

Coadministration of ABT-450 with lopinavir/ritonavir resulted in ~100% higher exposures (C_{max}) and C_{max} in Asian subjects was approximately 3-fold of Caucasian subjects (Figure 1). Thus, the ABT-450 350 mg (b) (4) tablet, was expected to provide ~6-fold higher exposures than therapeutic steady state exposures when co-dosed with ritonavir 150 mg, was used as the supratherapeutic dose.

Figure 1. ABT-450 Exposures



Ritonavir

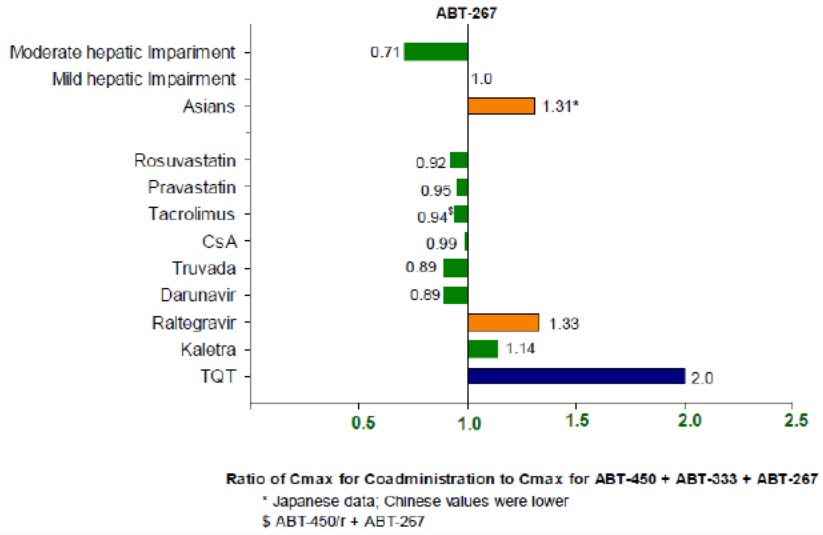
The proposed dose of ritonavir 100 mg was coformulated with ABT-450 150 mg and ABT-267 25 mg. However, a 150 mg dose of the ritonavir capsule was used as a

therapeutic dose in this study since it was expected to provide exposures comparable to the ritonavir 100 mg coformulated tablet at steady state. Furthermore, ritonavir exposures are not significantly affected by other inhibitors. Hence, the ritonavir 150 mg dose was also used as the supratherapeutic dose.

ABT-267

A single 25 mg dose of ABT-267 was expected to provide exposure comparable to steady state ABT-267 exposure (single dose to steady state C_{max} ratio of 0.85 to 0.9) and thus can be used as the therapeutic dose in this study. Furthermore, since less than 2-fold increase in ABT-267 exposure was expected based on available data (Figure 2), drug interaction and special population a dose that provides 2 × therapeutic exposures i.e., 50 mg, was used as the supratherapeutic dose.

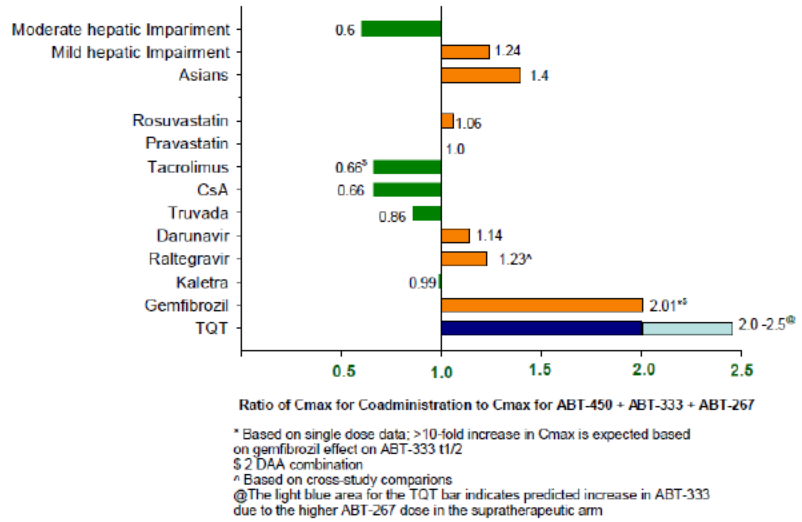
Figure 2. ABT-267 Exposures



ABT-333

ABT-333 shows minimal to no accumulation at doses less than 1000 mg BID. A single 250 mg dose of ABT-333 was expected to provide exposure comparable to steady state ABT-333 exposures and thus used as the therapeutic dose for this study. Furthermore, since greater than 2-fold increase in ABT-333 exposure was not expected based on available data (Figure 3), a supratherapeutic dose of 500 mg (2 × therapeutic doses) was used.

Figure 3. ABT-333 Exposures



Moxifloxacin

The recommended therapeutic dose for moxifloxacin is 400 mg. A single dose of 400 mg moxifloxacin appears to prolong QTc by approximately 5 to 12 ms on average, which is consistent with the ICH E14 guideline recommendation that the positive control should have an effect on the mean QT/QTc interval of about 5 ms.

Reviewer's Comment: The sponsor's dose selection is acceptable. As shown in the table below, the drug exposures for ATB-450, ritonavir, ABT-267, ABT-333, and ABT-333 M1 metabolite following therapeutic doses in the TQT study resulted in higher or similar exposures as those using the Phase 3 formulation. And the drug exposures following supratherapeutic doses covered the worst scenarios due to drug interactions, hepatic or renal impairment, or Asian subjects.

Table 16. C_{max} Values for DAAs (Least Square Means or Geometric Means)

	ABT-450	RTV	ABT-267	ABT-333	ABT-333 M1
	C_{max} in ng/mL				
M12-680 Therapeutic Dose	2970	2340	135	1120	726
M12-680 Supratherapeutic Dose	9200	2190	232	2090	1320
Mean in Healthy Volunteers (Phase 2 formulation)[a]	991	1731	117	1120	701
Mean in Healthy Volunteers (Phase 3 formulation)[b]	1467	1598	127	1028	660
Ratio: Supratherapeutic/Phase 3 formulation in Healthy Volunteers	6.3	1.4	1.8	2.0	2.0
Maximum-fold increase following drug interaction[c]	2.19	1.31[d]	1.14	1.18	1.18

a. Geometric Mean for 3 DAA combination, Formulation (Dose): (b) (4) (150 mg) ABT-450, SGC (100 mg) RTV, (b) (4) (25 mg) ABT-267, Tablet (400 mg) ABT-333, 10 study arms (96 subjects) for ABT-450, RTV and 16 study arms (162 subjects) for ABT-267, ABT-333 and M1 [R&D14/0050].[17]

b. Geometric Mean for 3 DAA combination, Dose and Formulation: 150/100/25 mg ABT-450/r/ABT-267 co-formulated tablet, 250 mg ABT-333 regimen, 8 study arms (97 subjects) [R&D14/0050].[17]

c. Ratio of 3DAA + Concomitant medication/3 DAA.

d. Interaction for a 100 mg dose of RTV.

4.2.6.3 Instructions with Regard to Meals

Subjects received a standardized diet, providing approximately 40% of the daily calorie s from fat and up to 45% of daily calories from carbohydrates (approximately 2,200 total calories/day), for all meals during confinement. Starting with lunch on Study Day –2 until after the 24-hour blood collection on Study Day 2 in each period, the subjects consumed only the scheduled meals provided in the study and water to quench thirst. The subjects abstained from all other food and beverage.

On Study Day –1, subjects were served meals at approximately the same time as Study Day 1. On Study Day 1 of each period, subjects were served breakfast approximately 30 minutes prior to dosing, lunch approximately 4 hours after dosing, dinner approximately 5 hours after lunch, and a snack approximately 3 hours after dinner. The subject's meal times on Study Day –1 and Study Day 1 in each period were to be identical to minimize any variation caused by differences in the meal times in relation to ECG assessment times on Study Day –1 and Study Day 1 in each period.

On Study Day 2 in each period, an optional breakfast was to be served following collection of the 24-hour blood sample and completion of the scheduled study procedures.

The meal content was identical on Study Day –1 through Study Day 2 (through the ECG recording portion) of all four periods. The composition (protein, fat, carbohydrate, and total calories) of these meals was determined by a dietician and a record was kept with the source documents. The sequence of starting meals on the dosing days was maintained

such that the time intervals between dosing and meals were essentially the same for all subjects in each period. Subjects did not consume:

- tobacco or nicotine-containing products within the 6-month period prior to any study drug administration,
- alcohol within the 72-hour period prior to any study drug administration,
- grapefruit or grapefruit products, Seville oranges, starfruit and quinine/tonic water within the 72-hour period prior to study drug administration, or
- caffeine during confinement.

Reviewer's Comment: The (b) (4) *(* (b) (4) *tablet formulation for ABT-450,* (b) (4) *(* (b) (4) *formulation for ritonavir,* (b) (4) *(* (b) (4) *tablet formulation for ABT-267, and tablet formulation for ABT-333 were used in the TQT study and administration with food is acceptable.*

The food effects of the ABT-267 (b) (4) *Ritonavir SGC, and ABT-333 tablet formulations have been evaluated and summarized in the Clinical Pharmacology Highlights. The food effect of the ABT-450* (b) (4) *formulation has not been evaluated. However, study subjects were instructed that all medications should be administrated with food in the Phase 1 and II studies where this formulation was administrated.*

4.2.6.4 ECG and PK Assessments

A 12-lead resting ECG was obtained at the time points listed in triplicate, approximately 2 minutes apart, with the exception of those in the list specified as single ECGs:

- Screening (single)
- Study Day –2 of each period (single)
- Study Day –1 time matched to prior to dose (0 hour) on Study Day 1
- Study Day –1 at times matched to the times of the scheduled ECGs obtained at 2, 3, 4, 5, 8 and 12 hours post-dose on Study Day 1
- Prior to dosing (0 hour) on Study Day 1 of each period
- Study Day 1 at 2, 3, 4, 5, 8, 12, and 24 hours after the dose in each period
- Upon subject discontinuation (single)
- Clinically as needed (single)

Blood samples for all 4 regimens were collected at the following times: prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 8, 12, and 24 hours after dosing in each study period.

Reviewer's Comment: The timings of ECG and PK assessments are adequate to capture C_{max} *of the four compounds and delayed effect over 24 hours.*

4.2.6.5 Baseline

The sponsor used time-matched pre-dose QTc values on Day 1 as baselines.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Sixty adult male (N=28) and female (N=32) subjects ages between 18 and 55 years enrolled the study and all completed the study.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was time-matched baseline-adjusted mean differences between combination of ABT-450, ritonavir, ABT-267, and ABT-333 and placebo in ΔQTcF. The sponsor used a mixed model and the results were presented in Table 2. The model included baseline values as a covariate; period, time, treatment, time-by-treatment interactions as fixed effect; and subjects as random effect. The upper limits 2-sided 90% CI for therapeutic and supratherapeutic dose groups were below 10 ms.

Table 2: Sponsor Results ΔΔQTcF for combination of ABT-450, ritonavir, ABT-267, and ABT-333 and Moxilfoxacin 400 mg

	LS Means of Change from Baseline		Difference of Change	95% Upper
Time (hr)	Placebo	Drug	From Placebo	Confidence Bound
Moxifloxacin vs. Placebo				
2	–4.3	5.0	9.3	11.0
3	–2.5	8.3	10.8	12.6
4	–0.3	10.3	10.6	12.3
5	0.8	10.7	9.9	11.7
8	0.9	9.3	8.4	10.1
12	0.1	5.3	5.2	7.0
24	–2.0	1.6	3.7	5.4
Therapeutic vs. Placebo				
2	–4.3	–4.2	0.0	1.8
3	–2.5	0.3	2.9	4.7
4	–0.3	2.0	2.3	4.1
5	0.8	4.4	3.6	5.4
8	0.9	3.7	2.8	4.6
12	0.1	1.0	0.9	2.7
24	–2.0	–2.9	–0.9	0.9
Supratherapeutic vs. Placebo				
2	–4.3	–2.7	1.6	3.3
3	–2.5	1.9	4.4	6.2
4	–0.3	5.0	5.2	7.0
5	0.8	6.7	5.9	7.7
8	0.9	5.8	4.9	6.7
12	0.1	1.5	1.5	3.3
24	–2.0	–2.1	–0.1	1.7

Note: The average of three replication measurements at each scheduled time point was used for the analysis. The analysis model had effects for period, sequence, regimen, time, regimen by time and period by time.

Source: Clinical Study Report No., Table 11-2, page 86/7184

Reviewer's Comments: We will provide our independent analysis result in Section 5.1. Our analysis results are similar with the sponsor's results of QTcF.

4.2.8.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the ΔQTcF effect for moxifloxacin. The results were presented in Table 2. Sponsor's provide the upper bounds of the 90% CI. We provide our independent analysis result in Section 5.1. The largest unadjusted 90% lower confidence interval for moxifloxacin 400 mg is 8.9 ms. Thus, assay sensitivity in this thorough QTcF study was established.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc ≤450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms, and changes from

baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. No subject's absolute QTc > 480 ms and ΔQTc >60 ms.

4.2.8.3 Clinical Pharmacology

4.2.8.3.1 Pharmacokinetic Analysis

The PK results are presented in Table 3-6 for ABT-450, ritonavir, ABT-267, ABT-333, and ABT-333 M1 metabolite respectively. Compared with the therapeutic doses of 25 mg ABT-267, 200 mg ABT-450, 150 mg ritonavir, and 250 mg ABT-333, which would provide similar drug exposures at steady state of intended clinical doses, Cmax and AUC following administration of the supratherapeutic doses of 50 mg ABT-267, 350 mg ABT-450, 150 mg ritonavir, and 500 mg ABT-333 were higher —3.1 to 4.1-fold for ABT-450, 1.7- to 1.8-fold for ABT-267, 1.9- to 2.1-fold for ABT-333, 1.8- to 2.4-fold for ABT-333 M1 metabolite, and similar (90-110%) for ritonavir.

Table 3: Sponsor Results for Pharmacokinetic Parameters for ABT-450

Pharmacokinetic Parameters (units)		ABT-450 200 mg (Regimen Y) N = 57	ABT-450 350 mg (Regimen Z) N = 59
T_{max}	(hr)	4.7 ± 1.1	4.6 ± 1.3
C_{max}	(ng/mL)	3880 ± 2600	10100 ± 3950
AUC_t	(ng•h/mL)	22300 ± 15800	79100 ± 39400
AUC_∞	(ng•h/mL)	22900 ± 16100[a]	80600 ± 40200[a]
$t_{1/2}$[b]	(hr)	3.52 ± 0.63[a]	3.42 ± 0.58[a]

Note: Regimen Y: ABT-267 25 mg, ABT-450 200 mg, ritonavir 150 mg, ABT-333 250 mg (Therapeutic Dose).
Regimen Z: ABT-267 50 mg, ABT-450 350 mg, ritonavir 150 mg, ABT-333 500 mg (Supratherapeutic Dose).

a. Ns varied for estimates of AUC_∞, and $t_{1/2}$, as β could not be determined using 3 concentration timepoints from the terminal elimination phase in a few subjects in these regimens.

b. Harmonic mean ± pseudo-standard deviation.

Table 4: Sponsor Results for Pharmacokinetic Parameters for Ritonavir

Pharmacokinetic Parameters (units)		Ritonavir 150 mg (Regimen Y) N = 57	Ritonavir 150 mg (Regimen Z) N = 59
T_{max}	(hr)	5.3 ± 3.1	6.1 ± 4.0
C_{max}	(ng/mL)	2510 ± 1020	2330 ± 759
AUC_t	(ng•h/mL)	20100 ± 10100	21400 ± 8270
AUC_∞	(ng•h/mL)	19700 ± 9890[a]	21000 ± 8240[a]
$t_{1/2}$[b]	(hr)	3.72 ± 0.70[a]	4.01 ± 0.80[a]

Note: Regimen Y: ABT-267 25 mg, ABT-450 200 mg, ritonavir 150 mg, ABT-333 250 mg (Therapeutic Dose).
Regimen Z: ABT-267 50 mg, ABT-450 350 mg, ritonavir 150 mg, ABT-333 500 mg (Supratherapeutic Dose).

a. Ns varied for estimates of AUC_∞, and $t_{1/2}$, as β could not be determined using 3 concentration timepoints from the terminal elimination phase in a few subjects in these regimens.

b. Harmonic mean ± pseudo-standard deviation.

Table 5: Sponsor Results for Pharmacokinetic Parameters for ABT-267

Pharmacokinetic Parameters (units)		ABT-267 25 mg (Regimen Y) N = 57	ABT-267 50 mg, (Regimen Z) N = 59
T_{max}	(hr)	4.9 ± 0.8	4.9 ± 1.1
C_{max}	(ng/mL)	138 ± 27.9	239 ± 52.1
AUC_t	(ng•h/mL)	1340 ± 269	2390 ± 488
AUC_∞	(ng•h/mL)	1610 ± 357[a]	2900 ± 640[a]

Note: Regimen Y: ABT-267 25 mg, ABT-450 200 mg, ritonavir 150 mg, ABT-333 250 mg (Therapeutic Dose).
Regimen Z: ABT-267 50 mg, ABT-450 350 mg, ritonavir 150 mg, ABT-333 500 mg (Supratherapeutic Dose).

a. Ns varied for estimates of AUC_∞, as β could not be determined using 3 concentration timepoints from the terminal elimination phase in these regimens.

Table 6: Sponsor Results for Pharmacokinetic Parameters for ABT-333

Pharmacokinetic Parameters (units)		ABT-333 250 mg (Regimen Y) N = 57	ABT-333 500 mg (Regimen Z) N = 59
		ABT-333	
T_{max}	(hr)	3.9 ± 1.2	4.0 ± 1.4
C_{max}	(ng/mL)	1190 ± 428	2230 ± 833
AUC_t	(ng•h/mL)	10200 ± 3890	20100 ± 7410
AUC_∞	(ng•h/mL)	11100 ± 4420[a]	23200 ± 9390[a]
$t_{1/2}$[b]	(hr)	5.56 ± 0.84[a]	6.56 ± 1.38[a]
		ABT-333 M1 Metabolite	
T_{max}	(hr)	4.5 ± 1.1	4.5 ± 1.4
C_{max}	(ng/mL)	763 ± 232	1370 ± 365
AUC_t	(ng•h/mL)	6610 ± 2240	14400 ± 3850
AUC_∞	(ng•h/mL)	7080 ± 2390[a]	16200 ± 4320[a]
$t_{1/2}$[b]	(hr)	4.50 ± 0.63[a]	5.45 ± 1.34[a]

Note: Regimen Y: ABT-267 25 mg, ABT-450 200 mg, ritonavir 150 mg, ABT-333 250 mg (Therapeutic Dose).
Regimen Z: ABT-267 50 mg, ABT-450 350 mg, ritonavir 150 mg, ABT-333 500 mg (Supratherapeutic Dose).

a. Ns varied for estimates of AUC_∞, and $t_{1/2}$, as β could not be determined using 3 concentration timepoints from the terminal elimination phase in a few subjects in these regimens.

b. Harmonic mean ± pseudo-standard deviation.

4.2.8.3.2 Exposure-Response Analysis

No exposure-response analysis was conducted by the sponsor.

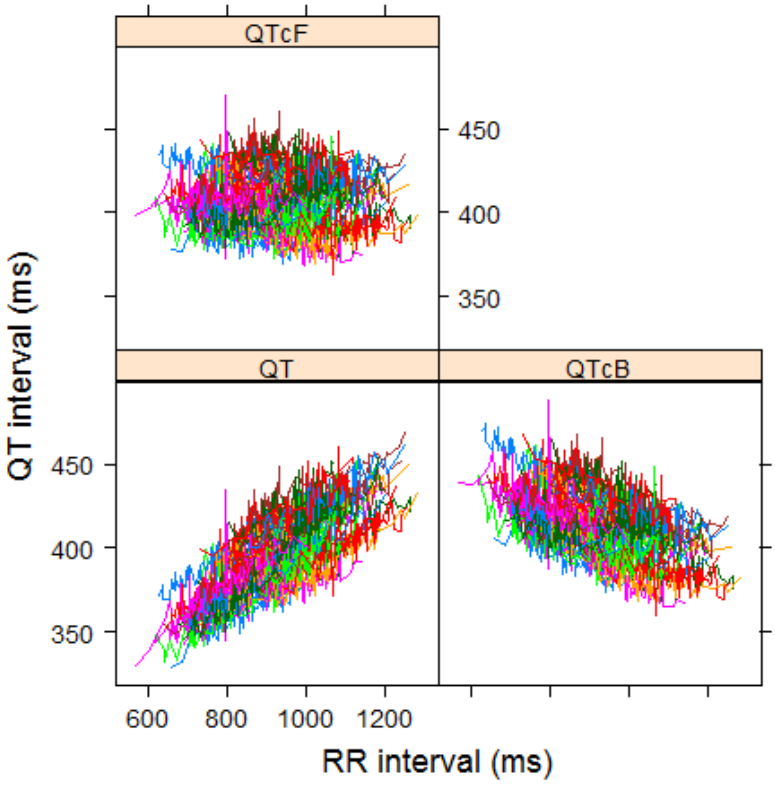
Reviewer's Analysis: There are inherent difficulties in relating drug exposure to an observed QT prolongation signal given the concurrent administration of four compounds. Since combination regimen at both therapeutic and supratherapeutic doses did not meet the threshold for QT prolongation, the absence of exposure-response analysis is acceptable. We will provide our independent analysis result in Section 5.2.

5 REVIEWERS' ASSESSMENT

This review did not evaluate of the QT/RR correction method because the sponsor provided QTcB and QTcF correction intervals. This reviewer chooses to present QTcF for the primary statistical analysis.

The QT-RR interval relationship between different correction methods and RR is presented in Figure 1

Figure 1: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.1 STATISTICAL ASSESSMENTS

5.1.1 QTc Analysis

5.1.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 7. The largest upper bounds of the 2-sided 90% CI for the mean differences between therapeutic dose and placebo, between supratherapeutic dose and placebo are 5.7 ms and 7.9 ms, respectively.

Table 7: Analysis Results of ΔQTcF and ΔΔQTcF for a combination of ABT-450, ritonavir, ABT-267, and ABT-333 and Moxifloxacin 400 mg

	Placebo	Regimen D: Moxifloxacin 400 mg					Regimen Y: Therapeutic Dose				Regimen Z: Supratherapeutic Dose			
	ΔQTcF	ΔQTcF		ΔΔQTcF			ΔQTcF		ΔΔQTcF		ΔQTcF		ΔΔQTcF	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	Adj. 90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
2	-4.3	59	5.0	9.3	(7.4, 11.3)	(6.7, 12.0)	57	-4.1	0.2	(-1.8, 2.2)	59	-2.7	1.6	(-0.3, 3.6)
3	-2.6	59	8.3	10.8	(8.9, 12.7)	(8.3, 13.4)	56	0.4	3.0	(1.1, 4.9)	59	1.9	4.5	(2.6, 6.3)
4	-0.3	59	10.3	10.6	(8.6, 12.6)	(7.9, 13.4)	57	2.1	2.4	(0.4, 4.5)	59	5.0	5.3	(3.3, 7.3)
5	0.8	59	10.7	9.9	(7.9, 11.8)	(7.2, 12.5)	56	4.5	3.7	(1.7, 5.7)	58	6.7	5.9	(4.0, 7.9)
8	0.8	59	9.2	8.4	(6.7, 10.1)	(6.1, 10.8)	57	3.7	2.9	(1.1, 4.6)	59	5.8	5.0	(3.3, 6.7)
12	-0.0	59	5.3	5.3	(3.6, 7.1)	(2.9, 7.8)	57	1.0	1.0	(-0.8, 2.8)	58	1.7	1.7	(-0.1, 3.5)
24	-2.1	59	1.8	3.8	(2.1, 5.5)	(1.5, 6.1)	57	-2.9	-0.8	(-2.5, 0.9)	59	-2.1	-0.0	(-1.7, 1.7)

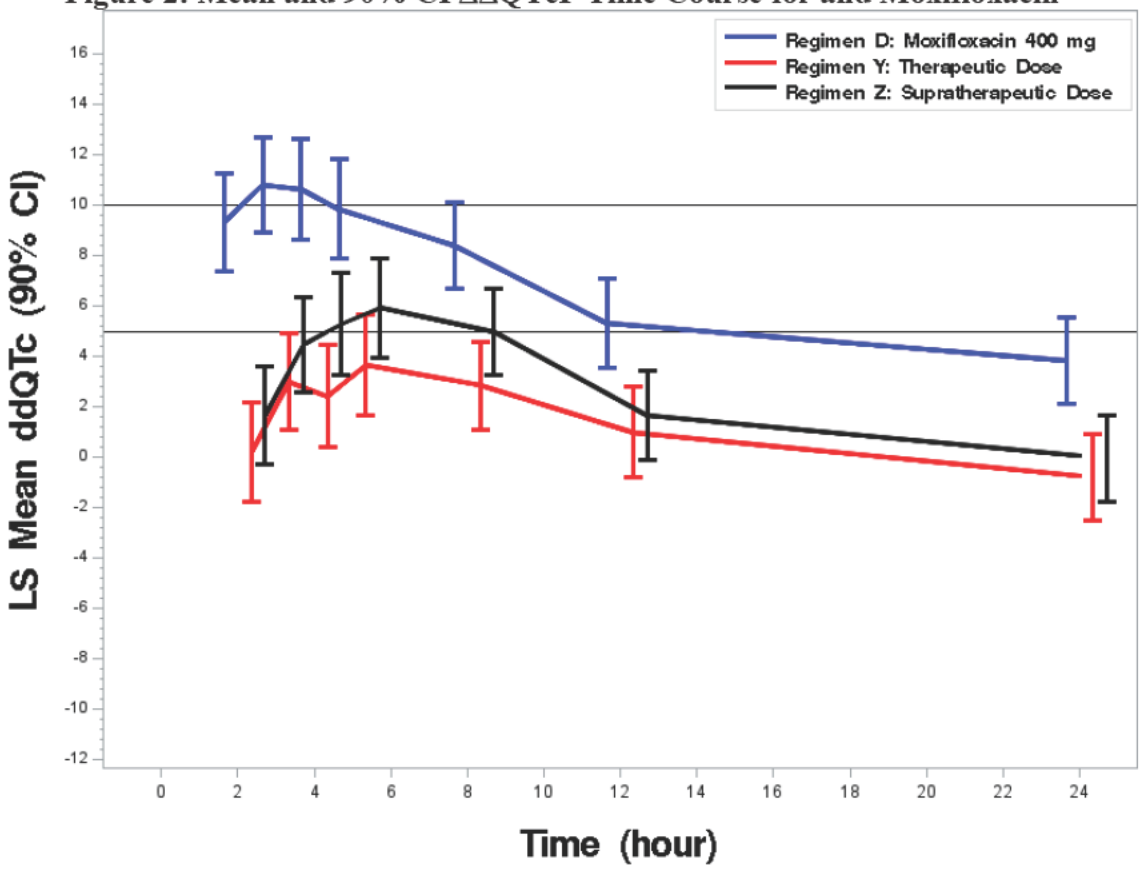
5.1.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 7**Error! Reference source not found.**. The largest unadjusted 90% lower confidence interval for moxifloxacin 400 mg is 8.9 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 8.3 ms, which indicates that an at least 5-ms QTcF effect of moxifloxacin can be detected from the study.

5.1.1.3 Graph of ΔΔQTcF Over Time

Figure 2 displays the time profile of ΔΔQTcF for different treatment dose groups and moxifloxacin 400 mg.

Figure 2: Mean and 90% CI ΔΔQTcF Time Course for and Moxifloxacin



5.1.1.4 Categorical Analysis

Table 8 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, and between 480 ms and 500 ms. No subject's QTcF is above 480 ms.

Table 8: Categorical Analysis for QTcF

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms
Regimen D: Moxifloxacin 400 mg	59	58 (98.3%)	1 (1.7%)
Regimen X: Placebo	59	58 (98.3%)	1 (1.7%)
Regimen Y: Therapeutic Dose	57	57 (100%)	0 (0.0%)
Regimen Z: Supratherapeutic Dose	59	59 (100%)	0 (0.0%)

Table 9 lists changes from baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. No subject's change from baseline is above 60 ms.

Table 9: Categorical Analysis for ΔQTcF

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms
Regimen D: Moxifloxacin 400 mg	59	58 (98.3%)	1 (1.7%)
Regimen X: Placebo	59	59 (100%)	0 (0.0%)
Regimen Y: Therapeutic Dose	57	57 (100%)	0 (0.0%)
Regimen Z: Supratherapeutic Dose	59	59 (100%)	0 (0.0%)

5.1.2 HR Analysis

The statistical reviewer used the same mixed model to analyze the ΔHR effect. The model includes treatment as fixed effect and baseline values as a covariate. The results are presented in Table 10. The largest upper bounds of the 2-sided 90% CI for the mean differences between therapeutic dose and placebo, between supratherapeutic dose and placebo are 1.6 bpm and 2.7 bpm, respectively. Table 11 presents the categorical analysis of HR. One subjects who experienced HR interval greater than 100 bpm is in therapeutic dose group.

Table 10: Analysis Results of ΔHR and ΔΔHR for a combination of ABT-450, ritonavir, ABT-267, and ABT-333 and Moxifloxacin 400 mg

		Regimen D: Moxifloxacin 400 mg				Regimen Y: Therapeutic Dose				Regimen Z: Supratherapeutic Dose			
	Placebo	ΔHR		ΔΔHR		ΔHR		ΔΔHR		ΔHR		ΔΔHR	
Time(h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
2	-1.1	59	-0.8	0.3	(-1.2, 1.8)	57	-1.0	0.1	(-1.4, 1.6)	59	-1.3	-0.2	(-1.7, 1.3)
3	-1.1	59	-0.4	0.7	(-0.6, 1.9)	56	-0.7	0.3	(-0.9, 1.6)	59	-0.1	0.9	(-0.3, 2.2)
4	-1.5	59	-1.3	0.2	(-1.1, 1.5)	57	-1.6	-0.1	(-1.4, 1.3)	59	-0.2	1.3	(0.0, 2.7)
5	-1.5	59	-1.5	-0.1	(-1.4, 1.2)	56	-1.5	-0.0	(-1.4, 1.3)	58	-1.2	0.3	(-1.1, 1.6)
8	0.8	59	0.4	-0.4	(-2.0, 1.2)	57	-0.1	-0.9	(-2.5, 0.7)	59	-0.2	-1.0	(-2.6, 0.6)
12	0.9	59	0.1	-0.8	(-2.2, 0.7)	57	-0.6	-1.5	(-2.9, -0.0)	58	0.3	-0.6	(-2.0, 0.9)
24	2.8	59	2.5	-0.3	(-1.8, 1.2)	57	2.5	-0.3	(-1.8, 1.2)	59	2.4	-0.5	(-2.0, 1.0)

Table 11: Categorical Analysis for HR

Treatment Group	Total N	HR <=100 ms	HR >100 ms
Regimen D: Moxifloxacin 400 mg	59	59 (100%)	0 (0.0%)
Regimen X: Placebo	59	59 (100%)	0 (0.0%)
Regimen Y: Therapeutic Dose	57	56 (98.2%)	1 (1.8%)
Regimen Z: Supratherapeutic Dose	59	59 (100%)	0 (0.0%)

5.1.3 PR Analysis

The statistical reviewer used the same mixed model to analyze the ΔPR effect. The model includes treatment as fixed effect and baseline values as a covariate. The results are presented in Table 12. The largest upper bounds of the 2-sided 90% CI for the mean differences between therapeutic dose and placebo, between supratherapeutic dose and placebo are 5.6 ms and 3.8 ms, respectively. Table 13 presents the categorical analysis of PR. Five subjects who experienced PR interval greater than 200 ms are in both therapeutic and supratherapeutic dose groups.

Table 12: Analysis Results of ΔPR and ΔΔPR for a combination of ABT-450, ritonavir, ABT-267, and ABT-333 and Moxifloxacin 400 mg

	Placebo	Regimen D: Moxifloxacin 400 mg				Regimen Y: Therapeutic Dose				Regimen Z: Supratherapeutic Dose			
	ΔPR	ΔPR		ΔΔPR		ΔPR		ΔΔPR		ΔPR		ΔΔPR	
Time(h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
2	0.4	59	0.6	0.1	(-1.6, 1.9)	57	1.4	1.0	(-0.8, 2.8)	59	0.1	-0.3	(-2.1, 1.5)
3	1.0	59	0.9	-0.1	(-1.9, 1.7)	56	1.6	0.7	(-1.2, 2.5)	59	0.5	-0.4	(-2.2, 1.4)
4	0.2	59	-0.2	-0.4	(-2.3, 1.5)	57	2.5	2.3	(0.4, 4.2)	59	1.4	1.2	(-0.7, 3.0)
5	-0.1	59	-1.8	-1.7	(-3.6, 0.1)	56	3.6	3.7	(1.9, 5.6)	58	1.9	2.0	(0.2, 3.8)
8	1.1	59	-0.8	-1.9	(-3.8, 0.1)	57	1.4	0.3	(-1.7, 2.2)	59	1.5	0.4	(-1.5, 2.4)
12	0.0	59	-1.2	-1.2	(-3.0, 0.6)	57	1.1	1.1	(-0.7, 2.9)	58	1.6	1.6	(-0.2, 3.4)
24	-0.7	59	-1.5	-0.8	(-2.7, 1.0)	57	-1.2	-0.5	(-2.4, 1.4)	59	-1.7	-1.0	(-2.9, 0.8)

Table 13: Categorical Analysis for PR

Treatment Group	Total N	PR <=200 ms	PR >200 ms
Regimen D: Moxifloxacin 400 mg	59	56 (94.9%)	3 (5.1%)
Regimen X: Placebo	59	56 (94.9%)	3 (5.1%)
Regimen Y: Therapeutic Dose	57	55 (96.5%)	2 (3.5%)
Regimen Z: Supratherapeutic Dose	59	56 (94.9%)	3 (5.1%)

5.1.4 QRS Analysis

The statistical reviewer used the same mixed model to analyze the ΔQRS effect. The model includes treatment as fixed effect and baseline values as a covariate. The results is presented in Table 14. The largest upper bounds of the 2-sided 90% CI for the mean differences between therapeutic dose and placebo, between supratherapeutic dose and placebo are 1.0 ms and 1.5 ms, respectively. Table 15 presents the categorical analysis of QRS. Three subjects who experienced QRS interval greater than 110 ms are in both therapeutic and supratherapeutic dose groups.

Table 14: Analysis Results of ΔQRS and ΔΔQRS for a combination of ABT-450, ritonavir, ABT-267, and ABT-333 and Moxifloxacin 400 mg

	Placebo	Regimen D: Moxifloxacin 400 mg				Regimen Y: Therapeutic Dose				Regimen Z: Supratherapeutic Dose			
	ΔQRS	ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS	
Time(h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
2	-0.0	59	0.3	0.3	(-0.4, 1.0)	57	-0.4	-0.3	(-1.0, 0.3)	59	0.3	0.3	(-0.3, 1.0)
3	-0.1	59	0.3	0.4	(-0.2, 1.0)	56	-0.0	0.1	(-0.5, 0.7)	59	0.4	0.6	(-0.0, 1.2)
4	-0.1	59	0.1	0.2	(-0.3, 0.8)	57	0.0	0.1	(-0.5, 0.7)	59	0.5	0.6	(0.0, 1.2)
5	0.1	59	0.1	0.0	(-0.6, 0.6)	56	0.1	0.0	(-0.6, 0.6)	58	0.9	0.8	(0.2, 1.4)
8	-0.6	59	0.0	0.7	(0.0, 1.3)	57	-0.3	0.3	(-0.4, 1.0)	59	0.2	0.8	(0.2, 1.5)
12	-0.0	59	-0.2	-0.2	(-0.9, 0.5)	57	-0.2	-0.2	(-0.9, 0.5)	58	0.0	0.0	(-0.7, 0.8)
24	-0.0	59	0.2	0.2	(-0.3, 0.7)	57	-0.3	-0.3	(-0.8, 0.3)	59	-0.3	-0.3	(-0.8, 0.3)

Table 15: Categorical Analysis for QRS

Treatment Group	Total N	QRS <=110 ms	QRS >110 ms
Regimen D: Moxifloxacin 400 mg	59	58 (98.3%)	1 (1.7%)
Regimen X: Placebo	59	57 (96.6%)	2 (3.4%)
Regimen Y: Therapeutic Dose	57	55 (96.5%)	2 (3.5%)
Regimen Z: Supratherapeutic Dose	59	58 (98.3%)	1 (1.7%)

5.2 Clinical Pharmacology Assessments

The mean ABT-450, ritonavir, ABT-267, ABT-333, and ABT-333 M1 metabolite concentration-time profiles are illustrated in Figure 3-7.

Figure 3: Mean ABT-450 concentration-time profiles for therapeutic dose (blue line) and supratherapeutic dose (red line)

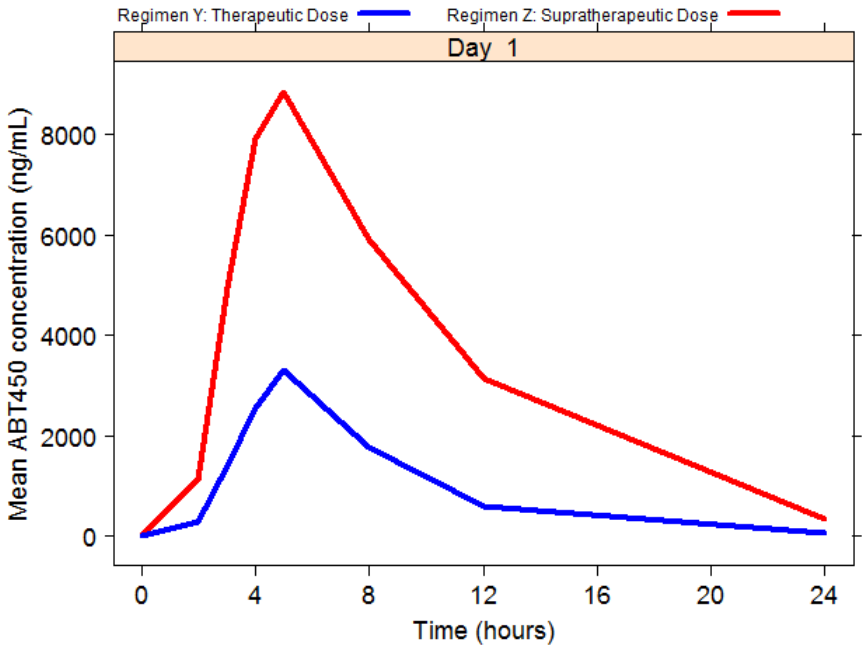


Figure 4: Mean Ritonavir concentration-time profiles for therapeutic dose (blue line) and supratherapeutic dose (red line)

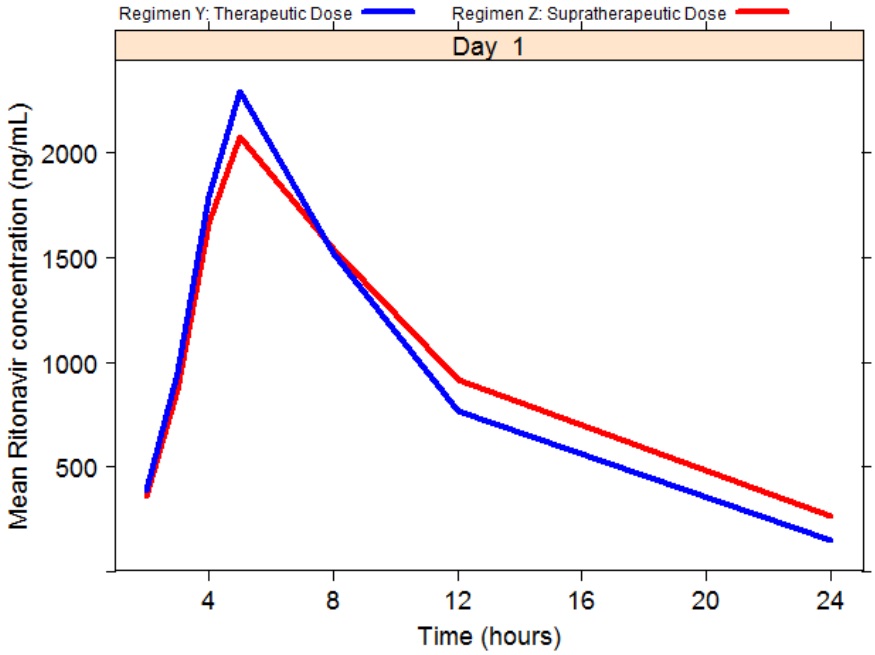


Figure 5: Mean ABT-267 concentration-time profiles for therapeutic dose (blue line) and supratherapeutic dose (red line)

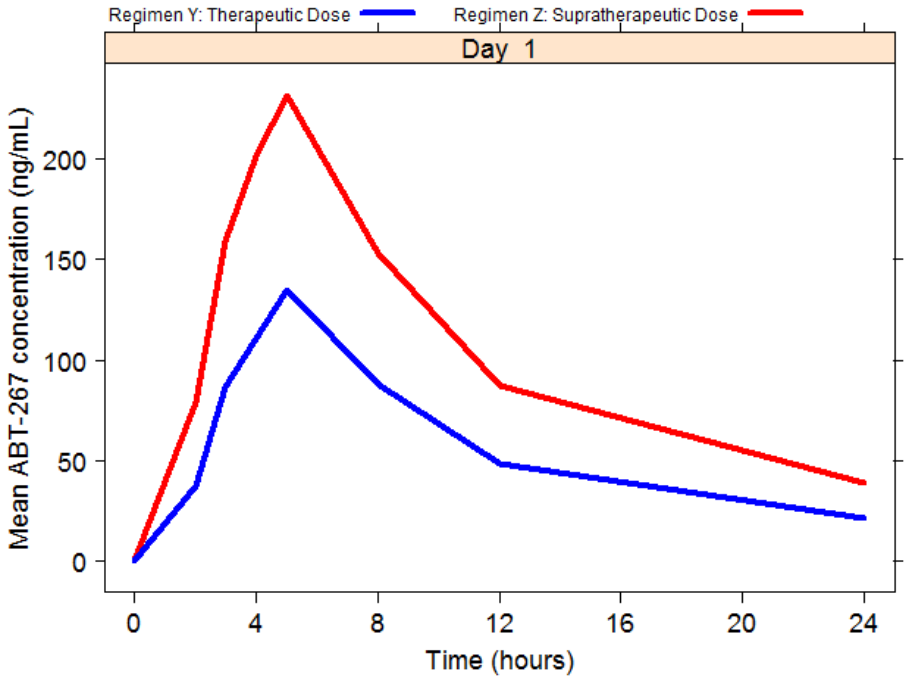


Figure 6: Mean ABT-333 concentration-time profiles for therapeutic dose (blue line) and supratherapeutic dose (red line)

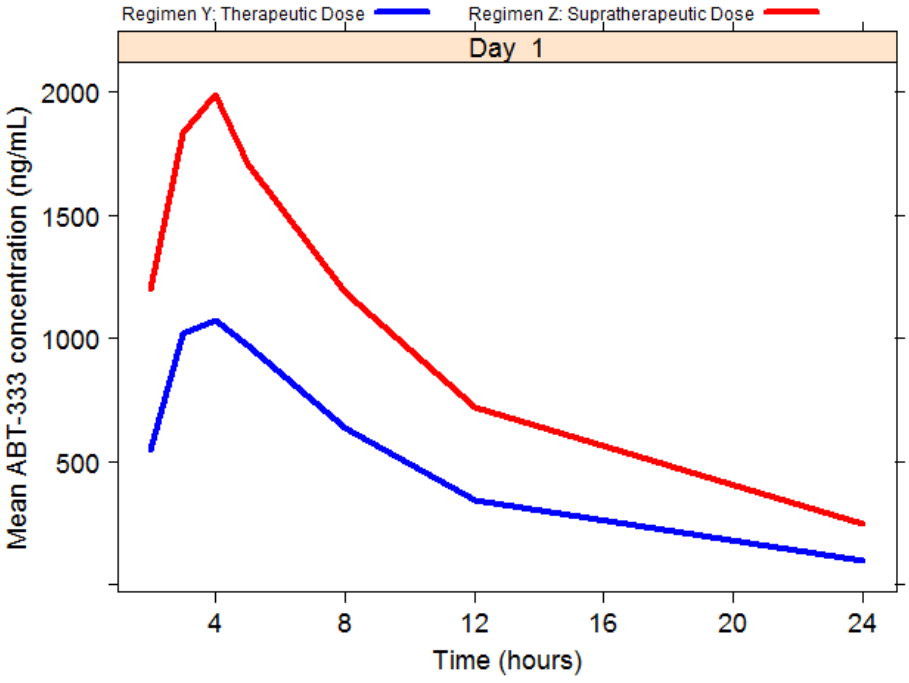
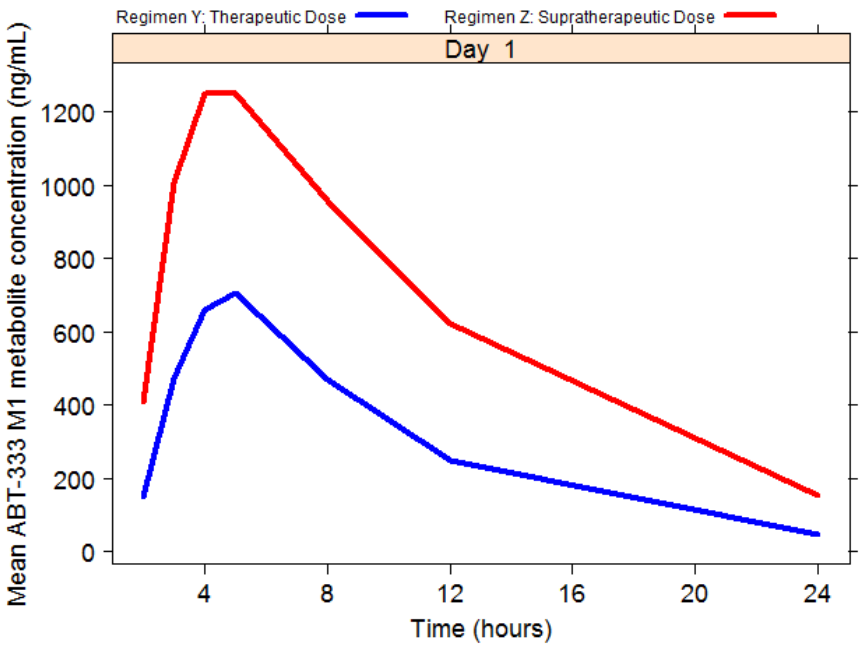


Figure 7: Mean ABT-333 M1 metabolite concentration-time profiles for therapeutic dose (blue line) and supratherapeutic dose (red line)



The relationship between **ΔΔ** QTcF and ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite concentrations are visualized in Figures 8-12. Significant concentration-**ΔΔ** QTcF relationships are observed for all the compounds with positive slopes for all three models as shown in the figures. However, due to the complex nature of concurrent administration of the therapeutics, it is difficult to determine which therapeutic contribute more to the positive exposure response relationship. Based on the observed concentration-QTc relationships, it is unlikely the combination therapy will cause clinical significant QT prolongation even at the supra-therapeutic exposure level.

Figure 8: ΔΔ QTcF vs. ABT-450 concentration

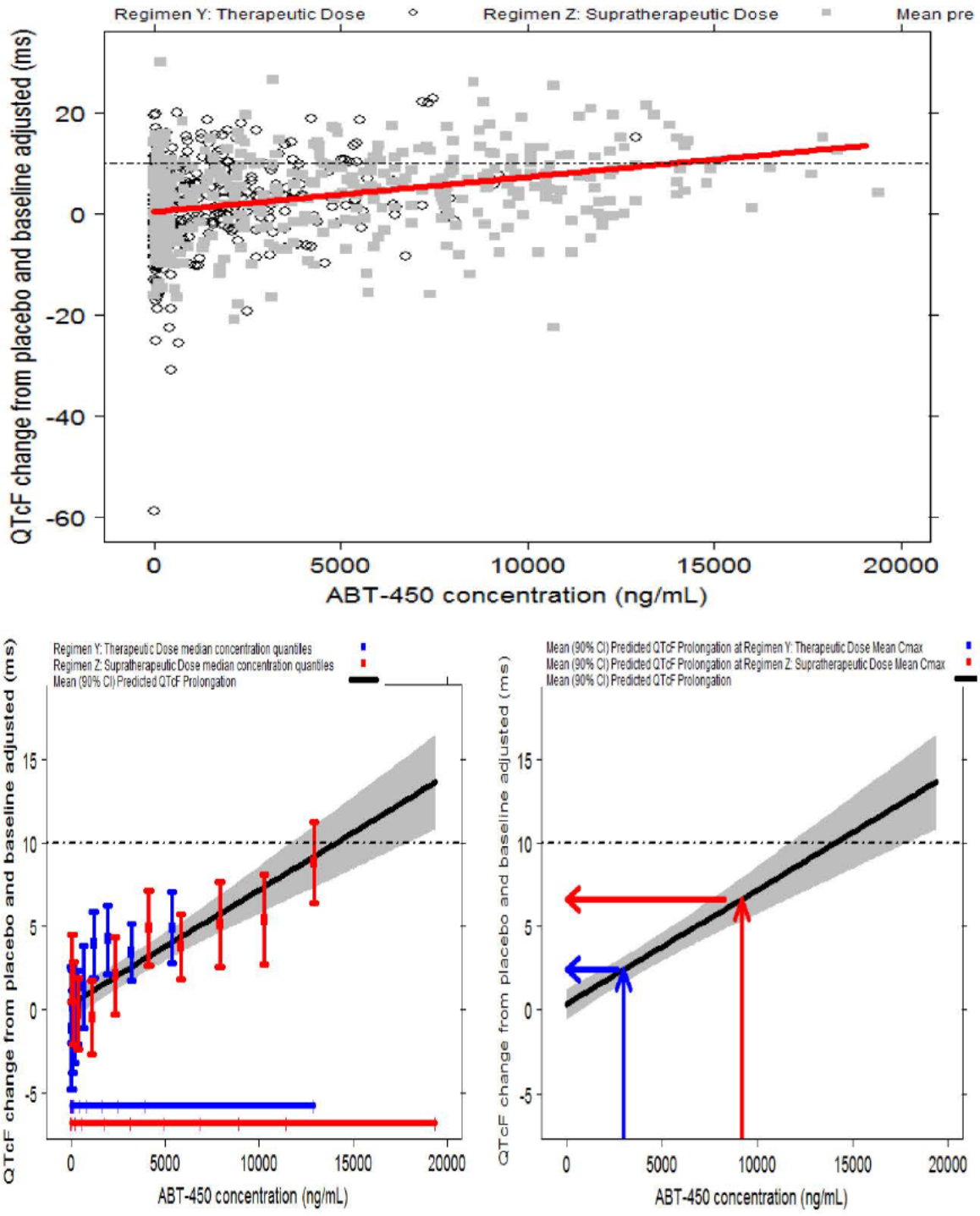


Figure 9: ΔΔ QTcF vs. ritonavir concentration

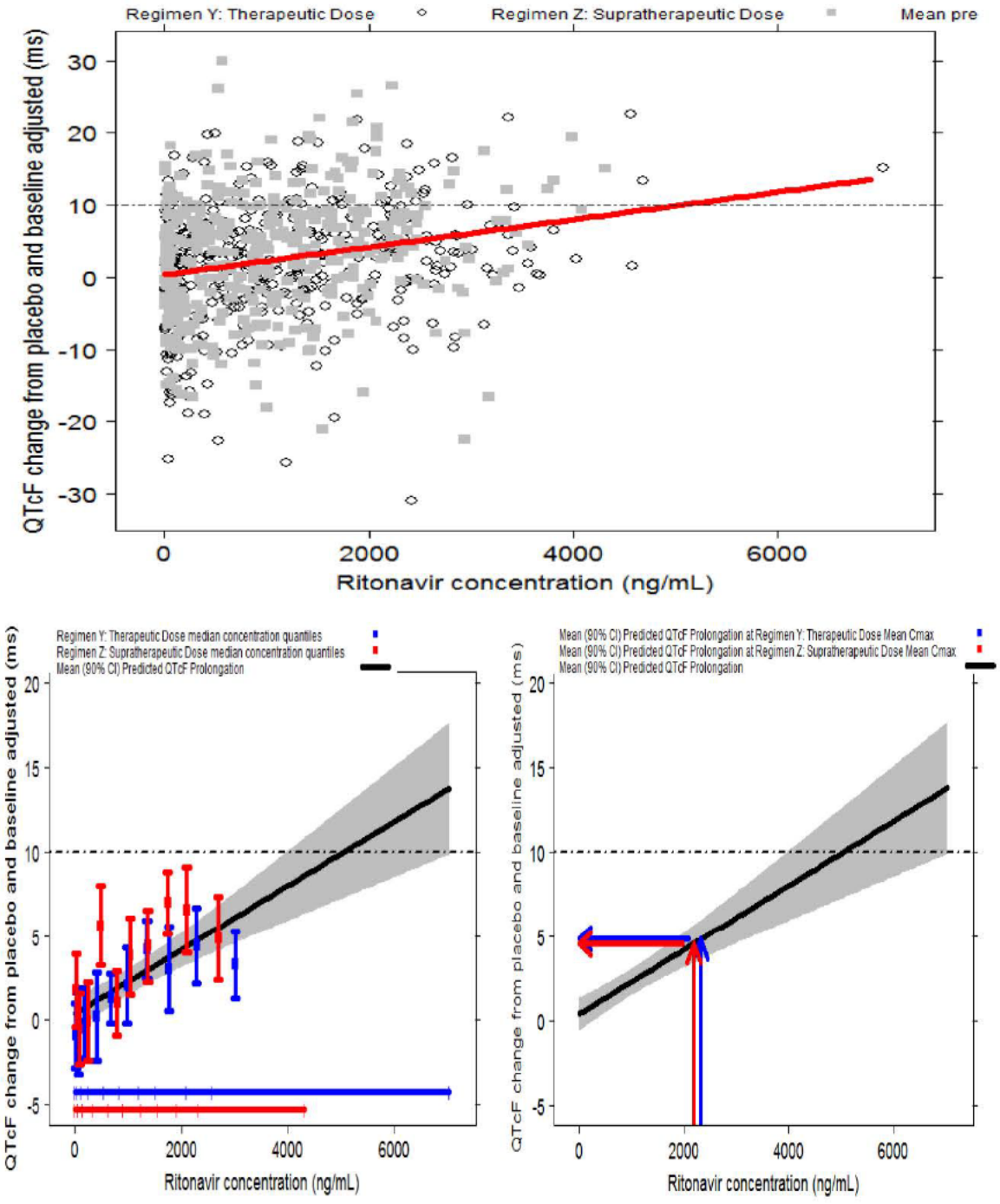


Figure 10: ΔΔ QTcF vs. ABT-267 concentration

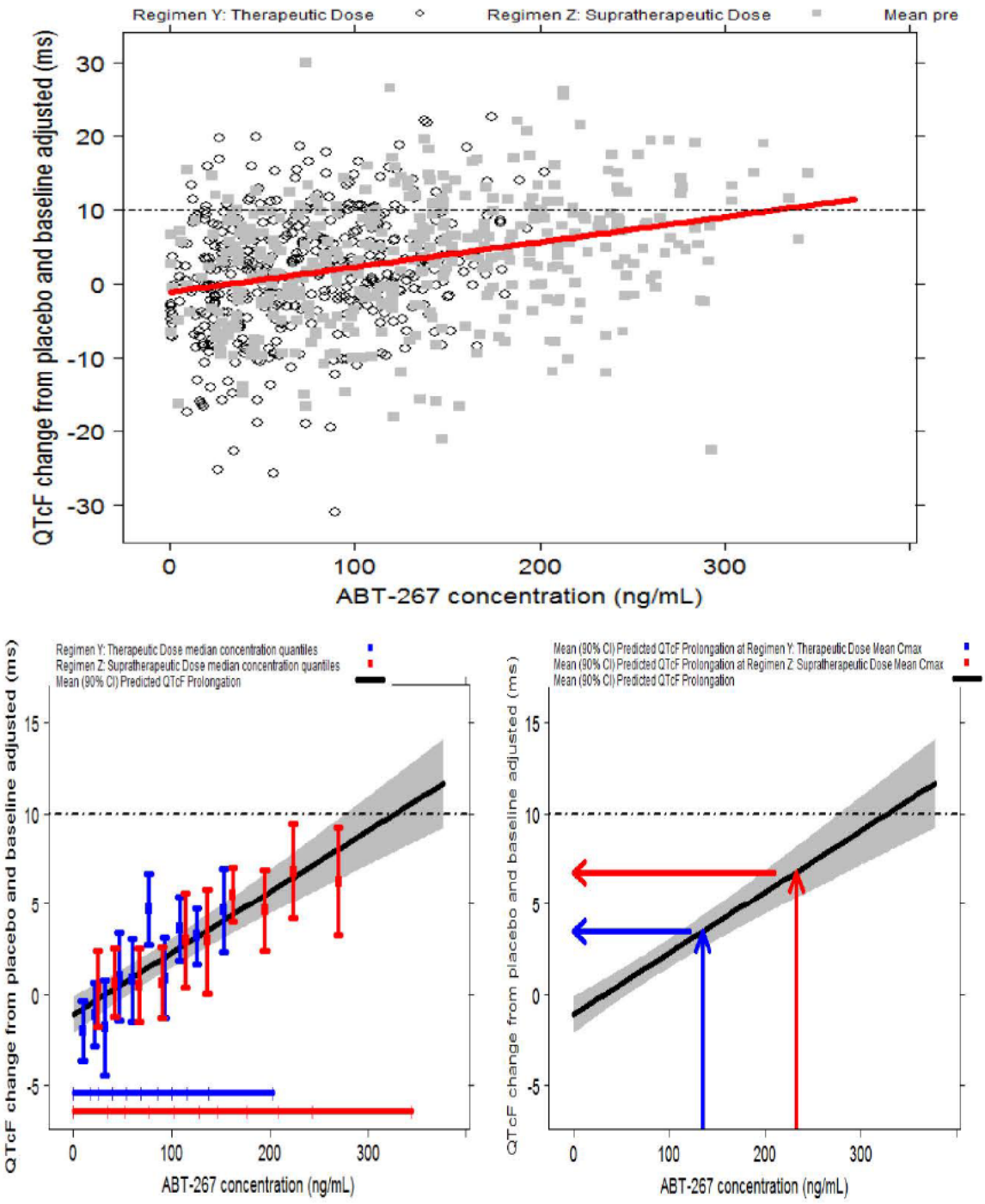


Figure 11: ΔΔ QTcF vs. ABT-333 concentration

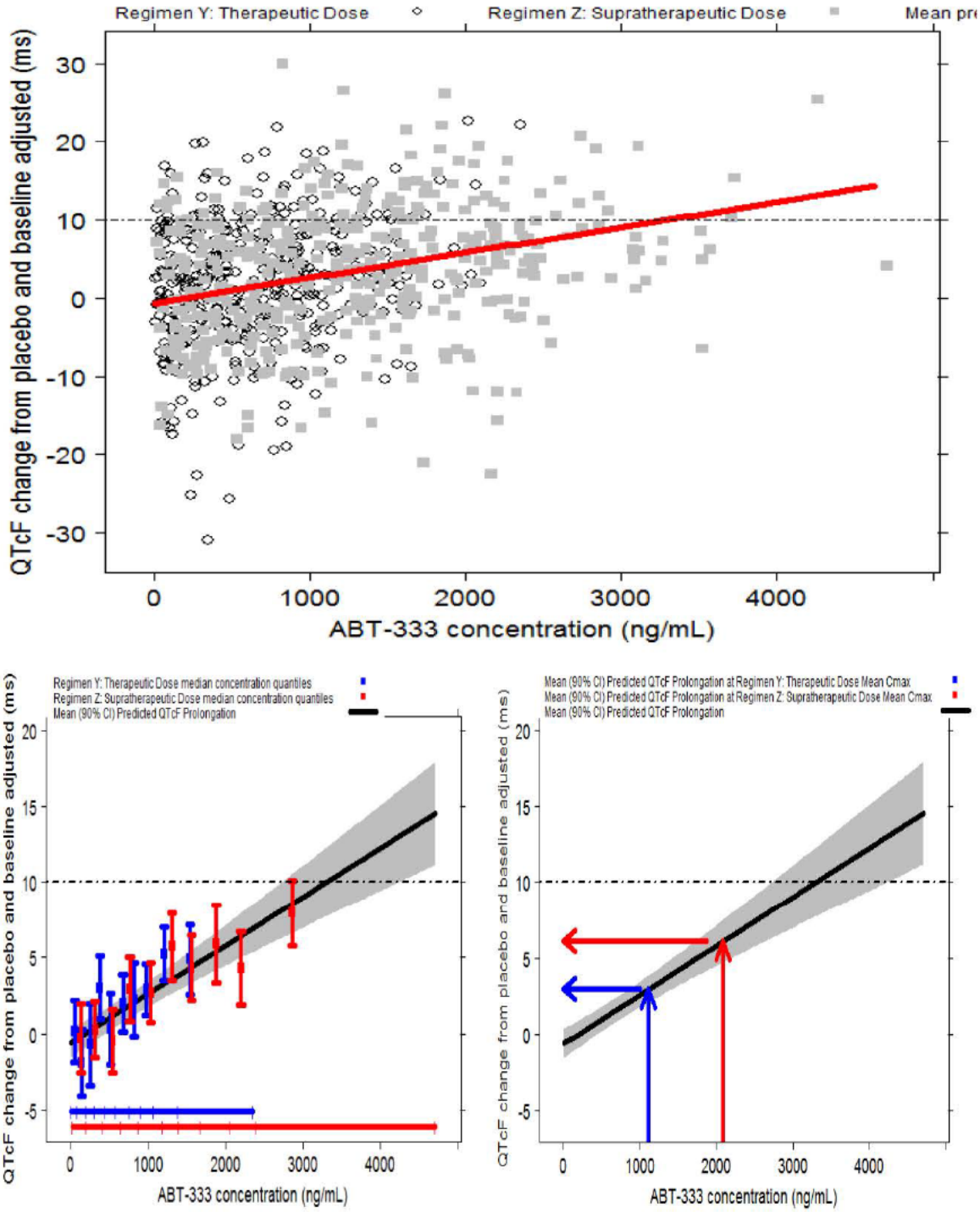
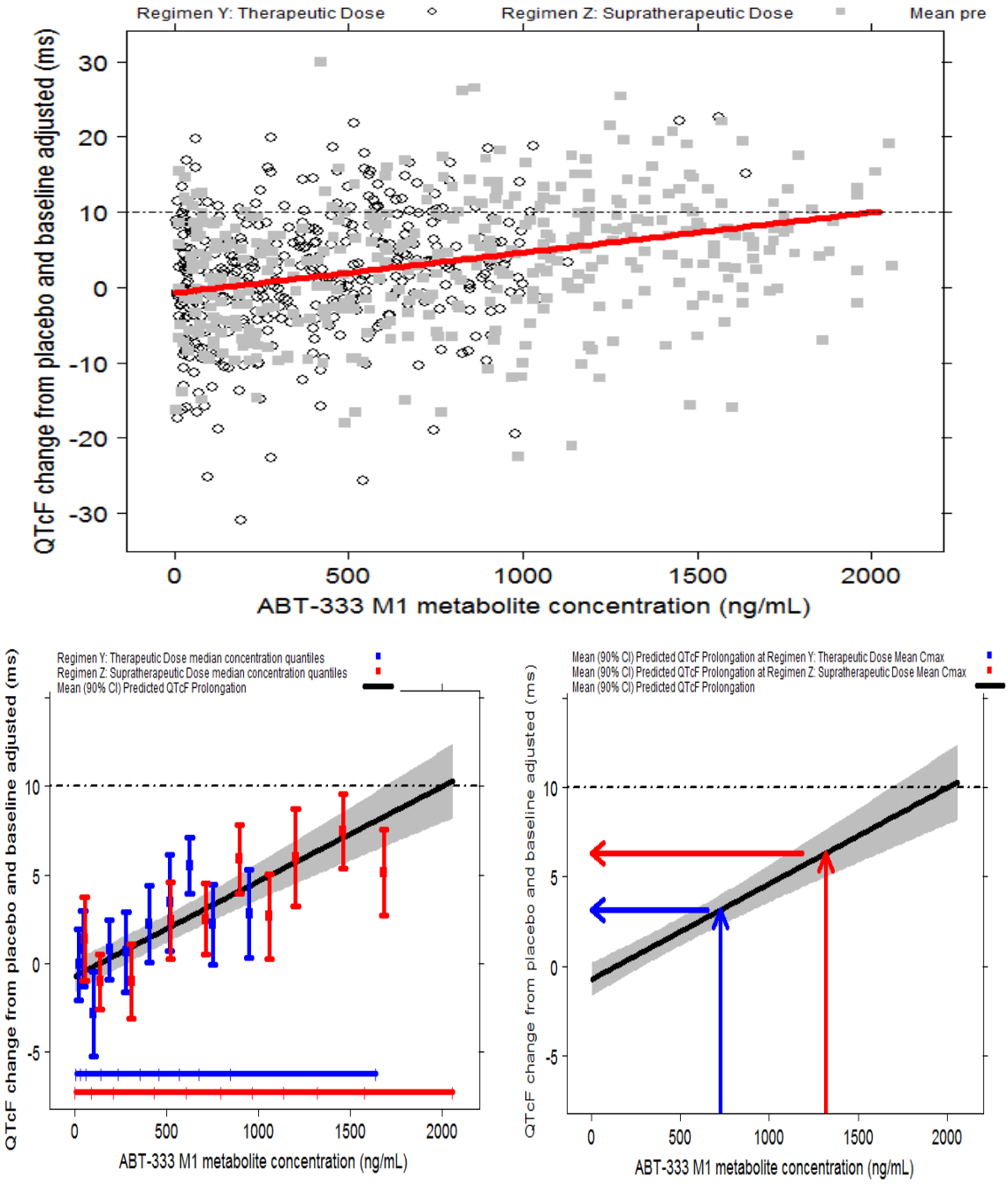


Figure 12: ΔΔ QTcF vs. ABT-333 M1 metabolite concentration



5.3 CLINICAL ASSESSMENTS

5.3.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines--i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death--occurred in this study.

5.3.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.3.3 PR and QRS Interval

There were no clinically relevant effects on PR or QRS.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Key Information on the Clinical Pharmacology of ABT-450 Administered as ABT-450/r

ABT-450 is co-administered with ritonavir (r) to increase exposure and prolong half-life. All data for ABT-450 presented below are following co-administration with ritonavir 100 mg. Four different formulations of ABT-450 have been evaluated in humans: (b) (4) (b) (4) used in interferon-free Phase 2 studies), ABT-450 + ritonavir co-formulated tablet (ABT-450/r co-formulated tablets) and ABT-450 + ritonavir +ABT-267 co-formulated tablet (ABT-450/r/ABT-267 co-formulated tablets, Phase 3 formulation).

Therapeutic Dose	150 mg with 100 mg ritonavir Compared to the SDD tablets used in Phase 2 studies, ABT-450 AUC and C_{max} were 63% and 93% higher, respectively, with ABT-450/r/ABT-267 co-formulated tablets (Phase 3 formulation).	
Maximum Tolerated Dose (MTD)	MTD was not reached in the Single Ascending Dose (SAD) or Multiple Ascending Dose (MAD) studies. Maximum administered doses were: ABT-450 HGC/r: 400/100 mg in SAD study and 300/100 mg QD in MAD study	
Principle Adverse Events	Multiple dose Phase 1 study (in combination with ritonavir): fatigue, blood bilirubin increase, headache, diarrhea, ALT increase, abdominal pain, muscle spasms, and presyncope in > 1 of 30 subjects. Phase 2 studies evaluated ABT-450 in combination with pegylated-interferon (pegIFN) + Ribavirin (RBV) or with other DAAs (discussed under combination DAAs).	
Maximum Dose Tested	Single dose	ABT-450 (b) (4) /r: 400/100 mg ABT-450 (b) (4) tablets/r: 300/100 mg ABT-450/r/ABT-267 co-formulated tablets: 200/100/25 mg
	Multiple dose	ABT-450 (b) (4) /r: 300/100 mg QD for 14 days ABT-450 (b) (4) tablets/ r: 250/100 mg QD for 14 days

Exposure Achieved at Maximal Tested Dose	Single dose mean (%CV)	ABT-450 (b) (4)/r 400/100 mg: ABT-450 AUC_∞ = 81078 ng•h/mL (76%) and C_{max} = 10267 mg/mL (50%) ABT-450 (b) (4) tablets/r 300/100 mg: ABT-450 AUC_∞ = 21151 ng•h/mL (64%) and C_{max} = 4757 ng/mL (59%) ABT-450/r/ABT-267 co-formulated tablets 200/100/25 mg: ABT-450 AUC_∞ = 10700 ng•h/mL (97%) and C_{max} = 2010 ng/mL (101%)
	Multiple dose mean (%CV)	ABT-450 (b) (4)/r 300/100 mg QD: ABT-450 AUC_∞ = 38391 ng•h/mL (39%) and C_{max} = 7311 ng/mL (41%) ABT-450 (b) (4) tablets/r 250/100 mg QD: ABT-450 AUC_∞ at steady-state ranged from 12200 to 21200 ng•h/mL. %CV ranged from 72% to 92%.ABT-450 C_{max} at steady-state ranged from 2690 to 4850 ng/mL. %CV ranged from 51% to 88%.
Range of Linear PK	Non-linear PK across all of the doses and formulations administered.	
Accumulation at Steady State	2.4-fold (100% CV) for C_{max} and 1.95-fold (98% CV) for AUC with ABT-450 (b) (4)/r 200/100 mg QD.	
Metabolites	ABT-450 was the predominant circulating species in plasma (~90% of radioactivity). Co-administration with the CYP3A inhibitor ritonavir inhibits the metabolism of ABT-450. Five metabolites were identified in human plasma, including M2, M29, and trace levels of M3, M13 and M6.	
Absorption	Absolute bioavailability	Not determined.
	T_{max}	ABT-450 (b) (4) tablets/r: Mean T_{max} ranged from 3.3 to 7.1 h following single dose. %CV ranged from 18% to 46%. ABT-450/r/ABT-267 co-formulated tablets: Mean T_{max} ranged from 4.2 to 4.3 h following single dose. %CV ranged from 19% to 29%.
Distribution	Vd/F	ABT-450 (b) (4) tablets /r 150/100 mg: Mean Vd/F ranged from 608 to 774 L following single dose. %CV ranged from 68% to 79%. ABT-450/r/ABT-267 co-formulated tablets 150/100/25 mg: 446 L (68%) following single dose.
	% bound	> 97% bound to human plasma proteins.

Elimination	Route	ABT-450 was predominantly eliminated in the feces (88% of radioactive dose) with urinary elimination accounting for < 8.8% of the total radioactivity recovered.
	Terminal $t_{1/2}$	ABT-450 (b) (4) tablets/r: Mean $t_{1/2}$ ranged from 4.9 to 7.3 h following single dose. %CV ranged from 11% to 31%. ABT-450/r/ABT-267 co-formulated tablets: Mean $t_{1/2}$ ranged from 5.4 to 5.5 h following single dose. %CV ranged from 24% to 27%.
	CL/F	ABT-450 (b) (4) tablets/r 150/100 mg: Mean CL/F ranged from 65.7 to 87.1 L/h across 2 groups following single dose. %CV ranged from 62% to 66%. ABT-450/r/ABT-267 Co-formulated tablets 150/100/25 mg: Mean CL/F was 51.7 L/h with 62% CV following single dose.
Intrinsic Factors	Age, Sex, and Race	See data sheet for combination dosing.
	Hepatic and renal impairment	Not conducted for individual DAAs. See data sheet for combination dosing.
Extrinsic factors	Drug interactions	Ritonavir 100 mg increased the mean C_{max} and AUC of ABT-450 300 mg dose by approximately 28- and 48-fold, respectively.
	Food effect	ABT-450 (b) (4) ritonavir capsules at 200/100 mg: ABT-450 C_{max} and AUC were 19% and 11% higher, respectively, with a moderate fat meal. See data sheet for combination dosing for effect on final formulation.
Expected High Clinical Exposure Scenario	See data sheet for combination dosing.	

Key Information on the Clinical Pharmacology of ABT-450 Administered as ABT-450/r in Combination with ABT-267 and ABT-333

Therapeutic Dose	150 mg with 100 mg ritonavir	
Maximum Tolerated Dose (MTD)	Dose escalation was not conducted for the 3-DAA combination of ABT-450/r + ABT-267 + ABT-333.	
Principle Adverse Events	Adverse events in Phase 3 studies (including ribavirin) based on Placebo-Controlled and Regimen Controlled Analysis Sets: Pruritus, Fatigue, Nausea, Asthenia, Insomnia, Anemia.	
Maximum Dose Tested	Single dose	ABT-450 (b) (4) tablets/r: 400/100 mg (with ABT-333 800 mg and ABT-267 100 mg)
	Multiple dose	ABT-450 (b) (4) tablets/r: 250/100 mg QD for 21 days (with ABT-333 400 mg BID and ABT-267 200 mg QD)
Exposure Achieved at Maximal Tested Dose	Single dose mean (%CV)	ABT-450 (b) (4) tablets/r 400/100 mg (with ABT-333 800 mg and ABT-267 100 mg): ABT-450 AUC = 76560 ng•h/mL (54%) and C_{max} = 10225 ng/mL (39%)
	Multiple dose mean (%CV)	ABT-450 (b) (4) tablets/r 250/100 mg (with ABT-333 400 mg BID and ABT-267 25 mg QD): ABT-450 AUC = 7390 ng•h/mL (57%) and C_{max} = 1430 ng/mL (67%)
Range of Linear PK	Supraproportional increase in exposure with dose.	
Accumulation at Steady State	When administered in combination with ABT-267, ABT-333 or ABT-267 + ABT-333, ABT-450 accumulation was ~2-fold and comparable to that of ABT-450 with ritonavir only. When ABT-450/r/ABT-267 QD was administered with ABT-333 BID, ABT-450 reached steady state within 7 to 11 days after dosing.	
Metabolites	Expected to be same as ABT-450/r alone.	
Absorption	Absolute/relative bioavailability	Not determined.
	T_{max}	ABT-450/r/ABT-267 co-formulated tablets: arithmetic mean T_{max} = 4 h
Distribution	Vd/F	ABT-450/r/ABT-267 co-formulated tablets: geometric mean Vd/F = 169 L
	% bound	Expected to be the same as ABT-450/r alone.

Elimination	Route	Expected to be the same as ABT-450/r alone.
	Terminal $t_{1/2}$	ABT-450/r/ABT-267 co-formulated tablets: median of harmonic means $t_{1/2}$=5.5 h.
	CL/F	ABT-450/r/ABT-267 co-formulated tablets: geometric mean CL/F = 20 L/h.
Intrinsic Factors	Age, Sex, and Race	See Table 1 for significant covariates.
	Hepatic and renal impairment	See Table 2 and Table 3.
Extrinsic factors	Drug interactions	See Figure 1 to Figure 5.
	Food effect	See Table 4.
Expected High Clinical Exposure Scenario	See Table 5.	

Key Information on the Clinical Pharmacology of Ritonavir Administered as ABT-450/r

Therapeutic Dose	100 mg co-administered with ABT-450 150 mg Compared to the ritonavir capsules co-administered with ABT-450 (b) (4) tablets in Phase 2 studies, ritonavir AUC and C_{max} were only 16% and 23% higher, respectively, with the ABT-450/r/ABT-267co-formulated tablets (Phase 3 formulation).	
Maximum Tolerated Dose (MTD)	MTD was not reached in the SAD or MAD studies. Maximum administered doses were: ABT-450 (b) (4)/r: 100/200 mg in SAD study and 300/100 mg QD in MAD study	
Principle Adverse Events	Multiple dose Phase 1 study (in combination with ABT-450): fatigue, blood bilirubin increase, headache, diarrhea, ALT increase, abdominal pain, muscle spasms, and presyncope in > 1 of 30 subjects. Phase 2 studies evaluated ABT-450/r either in combination with pegIFN + RBV or with other DAAs (presented under combination DAAs).	
Maximum Dose Tested	Single dose	ABT-450 (b) (4)/r: 100/200 mg
	Multiple dose	ABT-450 (b) (4)/r: 300/100 mg QD for 14 days
Exposure Achieved at Maximal Tested Dose	Single dose mean (%CV)	ABT-450 (b) (4)/r 100/200 mg: Ritonavir AUC_{∞} = 23301 ng•h/mL (53%) and C_{max} = 2925 ng/mL (50%)
	Multiple dose mean (%CV)	ABT-450 (b) (4)/r 300/100 mg QD: Ritonavir AUC_{∞} = 7476 ng•h/mL (24%) and C_{max} = 7311 ng/mL (41%)
Range of Linear PK	Non-linear PK across 50 to 200 mg doses administered with ABT-450.	
Accumulation at Steady State	Following multiple QD dosing of ritonavir with ABT-450 in healthy subjects, 1.5- to 2-fold accumulation was observed at steady state.	
Metabolites	Most of the radioactivity circulating in plasma after a 600-mg oral liquid dose of ^{14}C-ritonavir was due to parent drug. M-2 was the primary metabolite in feces and urine (more than 3% of the AUC for parent).	
Absorption	Absolute bioavailability	Not determined.
	T_{max}	ABT-450 (b) (4) tablets/r: Mean T_{max} ranged from 3.8 to 8.1 h following single dose. %CV ranged from 12% to 73%. ABT-450/r/ABT-267 co-formulated tablets: Mean T_{max} ranged from 4.0 to 4.4 h following single dose. %CV range from 18% to 25%.

Distribution	Vd/F	ABT-450 (b) (4) tablets/r 150/100 mg: Mean Vd/F ranged from 150 to 157 L following single dose. %CV ranged from 56% to 57 %. ABT-450/r/ABT-267 co-formulated tablets 150/100/25 mg: Mean Vd/F was 89.15 L with 47% CV following single dose.
	% bound	> 99% bound in humans
Elimination	Route	A total of 97.6% of a 600-mg dose of ^{14}C-ritonavir was eliminated in the urine and feces of humans within ~6 days (148 hours). Fecal excretion was the major route of elimination, accounting for 86.4% of the dose. Urinary excretion accounted for 11.3% of the dose.
	Terminal $t_{1/2}$	ABT-450 (b) (4) tablets/r: Mean $t_{1/2}$ ranged from 4 to 5.6 h following single dose. %CV ranged from 8% to 28% ABT-450/r/ABT-267 co-formulated tablets: Mean $t_{1/2}$ ranged from 4.4 to 4.5 h following single dose. %CV ranged from 18% to 24%
	CL/F	ABT-450 (b) (4) tablets/r 150/100 mg: Mean CL/F ranged from 22.5 to .22.9 L/h following single dose. %CV ranged from 49% to 57% ABT-450/r/ABT-267 co-formulated tablets 150/100/25 mg: Mean CL/F was 13.2 L/h with 40% CV following single dose.
Intrinsic Factors	Age, Sex, and Race	See data sheet for combination dosing.
	Hepatic and renal impairment	See data sheet for combination dosing for the effect of hepatic impairment on ritonavir administered with DAAs.
Extrinsic Factors	Drug interactions	Not applicable.
	Food effect	ABT-450 (b) (4) / ritonavir capsules at 200/100 mg: ritonavir C_{max} and AUC were 30% and 14% lower, respectively, with a moderate fat meal. See data sheet for combination dosing for effect on final formulation.
Expected High Clinical Exposure Scenario	See data sheet for combination dosing.	

Key Information on the Clinical Pharmacology of Ritonavir Administered as ABT-450/r in Combination with ABT-267 and ABT-333

Therapeutic Dose	100 mg with ABT-450 150 mg	
Maximum Tolerated Dose (MTD)	Dose escalation for ritonavir was not performed during combination dosing of ABT-450/r + ABT-267 + ABT-333.	
Principle Adverse Events	Adverse events in Phase 3 studies (including ribavirin) based on Placebo-Controlled and Regimen Controlled Analysis Sets Pruritus, Fatigue, Nausea, Asthenia, Insomnia, Anemia.	
Maximum Dose Tested	Single dose	ABT-450 (b) (4) tablets/r 400/100 mg (with ABT-333 800 mg and ABT-267 100 mg)
	Multiple dose	ABT-450 (b) (4) tablets/r 250/100 mg QD for 21 days (with ABT-333 400 mg BID and ABT-267 200 mg QD)
Exposure Achieved at Maximal Tested Dose	Single dose mean (%CV)	ABT-450 (b) (4) tablets/r 400/100 mg (with ABT-333 800 mg and ABT-267 100 mg): ritonavir AUC = 11990 ng•h/mL (36%) and C_{max} = 1340 ng/mL (24%)
	Multiple dose mean (%CV)	ABT-450 (b) (4) tablets/r 250/100 mg QD (with ABT-333 400 mg BID and ABT-267 200 mg QD): ritonavir AUC = 10300 ng•h/mL (21%) and C_{max} = 1420 ng/mL (25%)
Range of Linear PK	Not applicable	
Accumulation at Steady State	Accumulation with the 3-DAA combination was comparable to that with ABT-450 plus ritonavir alone, which is 1.5- to 2-fold accumulation at steady state.	
Metabolites	Expected to be same as ritonavir alone.	
Absorption	Absolute/relative bioavailability	Not determined.
	T_{max}	~ 4 h
Distribution	Vd/F	59 L
	% bound	Expected to be same as ritonavir alone.
Elimination	Route	Expected to be same as ritonavir alone.
	Terminal $t_{1/2}$	3.73 h
	CL/F	11L/h
Intrinsic Factors	Age, Sex, and Race	See Table 1 for significant covariates.
	Hepatic and renal impairment	See Table 2 and Table 3.
Extrinsic Factors	Drug interactions	See Figure 1 to Figure 5.
	Food effect	See Table 4.
Expected High Clinical Exposure Scenario	See Table 5.	

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Key Information on the Clinical Pharmacology of ABT-267 Dosed Alone and in Combination with ABT-333 and ABT-450/r

ABT-267 Dosed Alone

Therapeutic Dose	25 mg	
Maximum Tolerated Dose (MTD)	MTD was not reached in the SAD or MAD studies. Maximum administered dose was 350 mg and 200 mg in the SAD and MAD studies, respectively.	
Principle Adverse Events	Multiple dose Phase 1 study: rash in 2 of 32 subjects. Phase 2 studies evaluated ABT-267 in combination with pegIFN + RBV or with other DAAs (presented under combination DAAs).	
Maximum Dose Tested	Single dose	(b) (4) tablet ((b) (4) 200 mg (b) (4) ((b) (4) 350 mg
	Multiple dose	(b) (4) 100 mg for 7 days (b) (4) 200 mg for 7 days
Exposure Achieved at Maximal Tested Dose	Single dose mean (%CV)	(b) (4) and (b) (4) Mean C_{max} ranged from 236 to 617 ng/mL (%CV: 20 to 23) and Mean AUC ranged from 2810 to 6910 ng•h/mL (%CV: 28% to 29%)
	Multiple dose mean (%CV)	(b) (4) and (b) (4) Mean C_{max} ranged from 156 to 581 ng/mL (%CV: 31 to 33) and Mean AUC ranged from 1670 to 5470 ng•h/mL (%CV: 27% to 31%)
Range of Linear PK	Single dose: 1.5 to 350 mg Multiple doses: 5 to 200 mg	
Accumulation at Steady State	The mean ABT-267 AUC_{0-24} accumulation ratio ranged from 1.3 to 1.7 following 10 days of multiple dosing for doses ranging from 5 mg to 100 mg QD.	
Metabolites	Following oral administration of a single dose of ABT-267 alone to humans, M23, M29, M36 and M37 were the main metabolites in plasma, representing approximately 93% of total plasma radioactivity along with the parent compound. At least nine metabolites were observed at either low or trace levels.	
Absorption	Absolute bioavailability	Not determined.
	T_{max}	25 mg single dose ((b) (4) and (b) (4) mean T_{max} ranged from 3.5 to 4.8 hours across 5 studies. %CV was 13% to 40%.
Distribution	Vd/F	25 mg single dose ((b) (4) and (b) (4) mean Vd/F ranged from 1198 L to 1884 L across 2 studies. %CV was 21% to 36%
	% bound	99.9%

Elimination	Route	Following a 25 mg dose of ABT-267, approximately 90.2% of the radioactivity was recovered in feces with limited radioactivity (1.91%) in urine. Unchanged parent drug accounted for 87.8% of total radioactivity recovered in feces and 0.03% in the urine.
	Terminal $t_{1/2}$	25 mg single dose ((b) (4) and (b) (4) mean ranged from 20 to 24 hours across 3 studies. %CV was 20 to 28%
	CL/F	25 mg single dose ((b) (4) and (b) (4) mean ranged from 36 to 69 L/hr across 3 studies. %CV was 27% to 37%
Intrinsic Factors	Age, Sex, and Race	See data sheet for combination dosing.
	Hepatic and renal impairment	Not conducted for individual DAAs. See data sheet for combination dosing.
Extrinsic Factors	Drug interactions	Ritonavir increased exposure of ABT-267 5 mg by 60% to 70%.
	Food effect	The 25 mg (b) (4) formulation showed 93% increase in C_{max} and 62% increase in AUC when dosed with a moderate fat meal. See data sheet for combination dosing for effect on final formulation
Expected High Clinical Exposure Scenario	See data sheet for combination dosing.	

ABT-267 in Combination with ABT-450/r and ABT-333: 25 mg ABT-267 (b) (4) Formulation Data

Therapeutic Dose	25 mg	
Maximum Tolerated Dose (MTD)	Dose escalation was not conducted for the combination. The maximum dose of ABT-267 evaluated for the combination was 200 mg with ABT-450/r 250/100 mg and ABT-333 400 mg BID.	
Principle Adverse Events	Adverse events in Phase 3 studies (including ribavirin) based on Placebo-Controlled and Regimen Controlled Analysis Sets: Pruritus, Fatigue, Nausea, Asthenia, Insomnia Anemia.	
Maximum Dose Tested	Single dose	200 mg (with ABT-333 400 mg and ABT-450/r 250/100 mg QD) [Day 1 of the multiple dose study]
	Multiple dose	200 mg QD for 21 days (with ABT-333 400 mg BID and ABT-450/r 250/100 mg QD)
Exposure Achieved at Maximal Tested Dose	Single dose mean (%CV)	Study M12-187, Arm 4, Day 1 C_{max}: 418 ng/mL (25%), AUC: 4260 ng•h/mL (27%)
	Multiple dose mean (%CV)	Study M12-187, Arm 4, Day 21 C_{max}: 367 ng/mL (25%), AUC: 4680 ng•h/mL (29%)
Range of Linear PK	Not applicable	
Accumulation at Steady State (least square mean ratio)	Accumulation at the 25 mg dose administered as the 3-DAA combination was minimal (0.90 to 1.03).	
Metabolites	Parent drug accounted for 51.9% of the drug-related material, followed by M29 (19.9%), M36 (13.1%), M37 (9.3%) and M23 (5.8%).	
Absorption	Absolute/relative bioavailability	Not determined.
	T_{max}	~ 5 h
Distribution	Vd/F	412 L
	% bound	Expected to be the same as ABT-267 dosed alone.
Elimination	Route	Expected to be the same as ABT-267 dosed alone.
	Terminal $t_{1/2}$	21.1 h
	CL/F	13 L/h
Intrinsic Factors	Age, Sex, and Race	See Table 1 for significant covariates.
	Hepatic and renal impairment	See Table 2 and Table 3.
Extrinsic Factors	Drug interactions	See Figure 1 to Figure 5.
	Food effect	See Table 4.
Expected High Clinical Exposure Scenario	See Table 5.	

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Key Information on the Clinical Pharmacology of ABT-333 Dosed Alone and in Combination with ABT-267 and ABT-450/r

ABT-333 Dosed Alone

Therapeutic Dose	400 mg of Phase 1 and 2 formulation equivalent to 250 mg of Phase 3 formulation (used in the TQT study)	
Maximum Tolerated Dose (MTD)	MTD was not reached in the SAD or MAD study. Maximum administered dose was 2000 mg (capsule) and 1600 mg (tablet) BID in the single ascending and multiple ascending dose studies, respectively.	
Principle Adverse Events	Multiple dose Phase 1 studies: nausea, fatigue, diarrhea in > 1 of 47 subjects. Phase 2 studies evaluated ABT-333 in combination with pegIFN + RBV or with other DAAs (presented under combination DAAs).	
Maximum Dose Tested	Single dose	2000 mg in capsule; 1600 mg in tablet.
	Multiple dose	1000 mg BID in capsule for 10 days; 1600 mg BID in tablet for 7 days.
Exposure Achieved at Maximal Tested Dose	Single dose mean (%CV)	Capsule: AUC = 18046 ng•h/mL (27%), C_{max} = 2296 ng/mL (25%); Tablet: AUC = 16601 ng•h/mL (49%), C_{max} = 2220 ng/mL (41%)
	Multiple dose mean (%CV)	Capsule: AUC = 18038 ng•h/mL (48%) C_{max} = 2768 ng/mL (44%); Tablet: AUC=30144 ng•h/mL (46%) C_{max} = 4239 ng/mL (37%)
Range of Linear PK	Single dose: 10 to 1200 mg for capsule and 400 to 1600 mg for tablet; Multiple doses: up to 1000 mg BID for capsule and 1600 mg BID for tablet	
Accumulation at Steady State	R_{AUC}: 1.23 (44% CV) for 400 mg BID R_{Cmax}: 1.06 (49% CV) for 400 mg BID	
Metabolites	Following oral administration of a single dose of [^{14}C]ABT-333 to humans, unchanged parent drug was the most abundant radioactive component in plasma (58.1% of total plasma radioactivity). Among seven metabolites identified in human plasma, M1 was characterized as a major metabolite (21.4% of total plasma radioactivity), while the other six were minor metabolites, each accounting for less than 10% of total radioactivity in plasma. When ABT-333 was administered alone in healthy subjects, the M1 metabolite to parent AUC ratio at steady state ranged from 0.23 to 0.31.	
Absorption	Absolute bioavailability	Absolute bioavailability: approximately 50% from the 400 mg tablet.
	T_{max}	2.9 to 3.3 h for parent (%CV: 18% to 28%); 3.3 to 3.8 h for the M1 metabolite (%CV: 13% to 18%); after a single 400 mg tablet
Distribution	Vd/F mean (%CV)	Tablet 400 mg single dose: 761 L (54%)

	% bound	> 99%
Elimination	Route	Following a single dose of 400 mg [^{14}C]ABT-333, the total radiolabeled material was predominantly eliminated in the feces (94.4% of radioactive dose) with urinary elimination accounting for approximately 2% of the total radioactivity recovered.
	Terminal $t_{1/2}$	6.6 to 7.0 h for parent (%CV were 14% to 20%); 5.4 to 6.0 hr for M1 metabolite (%CV were 17% to 24%); following single 400 mg single dose.
	CL/F	Tablet 400 mg single dose: 69 L/h (35%)
Intrinsic Factors	Age, Sex, and Race	See data sheet for combination dosing.
	Hepatic and renal impairment	Not conducted for individual DAAs. See data sheet for combination dosing.
Extrinsic Factors	Drug interactions	Co-dosing ABT-333 at steady state with ketoconazole resulted in only a modest 50% to 60% increase in ABT-333 C_{max} and AUC.
	Food effect	C_{max} and AUC ratios were 0.93 and 1.11 for the 100 mg capsule formulation. There were no statistically significant differences ($p > 0.05$) between the nonfasting and fasting regimens in C_{max}, AUC_t and AUC_∞.
Expected High Clinical Exposure Scenario	See data sheet for combination dosing.	

Formulations: capsule 5 and 50 mg

Tablet used in Phase 1 and Phase 2 studies: 400 mg

Tablet used in Phase 3 and Thorough QT (TQT): 250 mg

The 1 × 250 mg tablet is comparable to 1 × 400 mg tablet (C_{max} and AUC are bioequivalent)

ABT-333 Dosed in Combination with ABT-450/r and ABT-267: ABT-333 400 mg BID (Tablet Formulation)

Therapeutic Dose	400 mg of Phase 1 and 2 formulation equivalent to 250 mg of Phase 3 formulation (used in the TQT study)	
Maximum Tolerated Dose (MTD)	Dose escalation was not conducted for the combination. The maximum dose of ABT-333 evaluated for the combination was 800 mg with ABT-450/r 400/100 mg and ABT-267 100 mg.	
Principle Adverse Events	Adverse events in Phase 3 studies (including ribavirin) based on Placebo-Controlled and Regimen Controlled Analysis Sets :Pruritus, Fatigue, Nausea, Asthenia, Insomnia, Anemia	
Maximum Dose Tested	Single dose	800 mg (with ABT-450/r 400/100 mg and ABT-267 100 mg)
	Multiple dose	400 mg BID for 21 days (with ABT-450/r 250/100 mg QD and ABT-267 200 mg QD)
Exposure Achieved at Maximal Tested Dose	Single dose mean (%CV)	AUC: 32200 ng•h/mL (29%), C_{max}: 3050 ng/mL (22%)
	Multiple dose mean (%CV)	AUC: 10100 ng•h/mL (27%), C_{max}: 1420 mg/mL (26%)
Range of Linear PK	Not applicable.	
Accumulation at Steady State (least square mean ratio)	Minimal to no accumulation was observed at doses of 200 mg BID to 600 mg BID, 65% accumulation was observed at the 1000 mg BID doses, and approximately 2-fold accumulation was seen at doses > 1000 mg BID. The 400 mg dose of ABT-333 when administered with ABT-450, ritonavir and ABT-267 did not accumulate with Day 21: Day 1 C_{max} and AUC ratios of 0.84 and 0.96, respectively.	
Metabolites	The M1 metabolite to parent AUC ratio at steady state is higher when ABT-333 is administered as part of the 3-DAA combination, and was 0.57 at steady state in healthy subjects.	
Absorption	Absolute/relative bioavailability	Not determined.
	T_{max}	~ 4 h (for 250 mg tablet).
Distribution	Vd/F	183 L (for 250 mg tablet)
	% bound	Expected to be the same as ABT-333 dosed alone

Elimination	Route	Expected to be same as ABT-333 dosed alone
	Terminal $t_{1/2}$	5.88 h (for 250 mg tablet)
	CL/F	21 L/h (for 250 mg tablet).
Intrinsic Factors	Age, Sex, and Race	See Table 1 for significant covariates.
	Hepatic and renal impairment	See Table 2 and Table 3.
Extrinsic Factors	Drug interactions	See Figure 1 to Figure 5.
	Food effect	See Table 4.
Expected High Clinical Exposure Scenario	See Table 5.	

Table 1. Population Pharmacokinetic Model Estimated Effect on Significant Covariates

Compound	Population Parameters	Effect on AUC
ABT-450	76 kg, 54 year-old, non-cirrhotic male without concomitant use of opioids and anti-diabetics C_{max}: 97 ng/mL $AUC_{24,ss}$: 1130 ng•h/mL $C_{min,ss}$: 18 ng/mL	Female: 95% higher 54 ± 10 years of age: ≤ 17% change Cirrhosis: 140% higher Anti-diabetics: 46% higher Opioid Use: 56% higher 76 ± 10 kg body weight: No change
Ritonavir	Male, normal renal function, genotype 1a C_{max}: 396 ng/mL $AUC_{24,ss}$: 3400 ng•h/mL $C_{min,ss}$: 56 ng/mL	Female: 15% higher Mild Renal Impairment (75 mL/min CL_{cr}): 13% higher Genotype 1b: 25% lower
ABT-267	76 kg, 54 year-old, non-cirrhotic male C_{max}: 49 ng/mL $AUC_{24,ss}$: 857 ng•h/mL $C_{min,ss}$: 22 ng/mL	Female: 54% higher 54 ± 10 years of age: < 10% change Cirrhosis: 10% lower 76 ± 10 kg body weight: < 10% change
ABT-333	76 kg, 54 year-old, non-cirrhotic male with normal renal function C_{max}: 533 ng/mL $AUC_{24,ss}$: 8150 ng•h/mL $C_{min,ss}$: 162 ng/mL	Female: 21% higher 54 ± 10 years of age: No change Mild Renal Impairment (75 mL/min CL_{cr}): 8% higher Cirrhosis: 41% higher 76 ± 10 kg of body weight: No change (≤ 4% change)
Ribavirin	Non-cirrhotic male with normal renal function C_{max}: 1450 ng/mL $AUC_{24,ss}$: 38200 ng•h/mL $C_{min,ss}$: 1690 ng/mL	Female: 29% higher Mild Renal Impairment (75 mL/min CL_{cr}): 8% higher Cirrhosis: Similar (6% lower)

Table 2. Effect of Hepatic Impairment on C_{max} and AUC of DAAs from the 3-DAA Combination (Study M12-215)

	Parameter	ABT-450	Ritonavir	ABT-267	ABT-333
Mild Impairment (Child Pugh A)	C_{max}	↓ 48%	↓ 40%	↔	↑ 24%
	AUC	↓ 29%	↓ 34%	↔	↔
Moderate Impairment (Child Pugh B)	C_{max}	↑ 26%	↓ 33%	↓ 29%	↓ 39%
	AUC	↑ 62%	↓ 30%	↓ 30%	↔
Severe Impairment (Child Pugh C)	C_{max}	↑ 3.2-fold	↓ 35%	↓ 68%	↑ 34%
	AUC	↑ 9.5-fold	↔	↓ 54%	↑ 3.3-fold

↑ = increase; ↓ = decrease; ↔ = less than 20% change.

Results shown are based on comparisons to subjects with normal hepatic function.

Fold increase (e.g., 3.2-fold indicates 320% increase or ratio of 4.2).

Table 3. Effect of Renal Impairment on C_{max} and AUC of DAAs from the 3-DAA Combination (Study M12-193)

	Parameter	ABT-450	Ritonavir	ABT-267	ABT-333
Mild Impairment (CL_{cr}: 60 – 89 mL/min)	C_{max}	↔	↑ 26%	↔	↔
	AUC	↔	↑ 42%	↔	↑ 21%
Moderate Impairment (CL_{cr}: 30 – 59 mL/min)	C_{max}	↔	↑ 48%	↔	↔
	AUC	↑ 33%	↑ 80%	↔	↑ 37%
Severe Impairment (CL_{cr}: 15 – 29 mL/min)	C_{max}	↔	↑ 66%	↔	↔
	AUC	↑ 45%	↑ 114%	↔	↑ 50%

↑ = increase; ↔ = less than 20% change

Results shown are based on regression analyses of C_{max} or AUC versus CL_{cr} and comparison to subjects with normal renal function.

Table 4. The Effects of Food on the Phase 3 Dosage Formulation (Least Squares Mean Ration [90% CI] for Non-Fasting Versus Fasting Dosing Conditions)

	Effect of Moderate-Fat Food		Effect of High-Fat Food	
Total Calories	~ 600 Kcal		~ 1000 Kcal	
Fat (% Calories)	20% to 30%		55% to 60%	
	C_{max}	**AUC_{inf}**	**C_{max}**	**AUC_{inf}**
	Study M11-389: ABT-450/r/ABT-267 150/100/25 mg Co-formulated Tablet			
ABT-450	4.674 (3.036 – 7.195)	3.108 (2.164 – 4.463)	4.003 (2.600 – 6.161)	2.798 (1.948 – 4.018)
Ritonavir	1.632 (1.300 – 2.048)	1.486 (1.232 – 1.793)	1.502 (1.197 – 1.886)	1.437 (1.191 – 1.733)
ABT-267	2.273 (1.974 – 2.618)	1.817 (1.608 – 2.053)	2.061 (1.789 – 2.373)	1.760 (1.557 – 1.988)
	Study M13-330: ABT-333 at 250 mg			
ABT-333	1.527 (1.190 – 1.959)	1.295 (1.080 – 1.552)	1.416 (1.104 – 1.817)	1.215 (1.013 – 1.457)
ABT-333 M1	1.497 (1.189 – 1.886)	1.301 (1.085 – 1.560)	1.172 (0.931 – 1.476)	1.10 (0.922 – 1.326)

ABT-450/r/ABT-267 co-formulated tablets at 150/100/25 mg dose.

ABT-333 250 mg tablet at 250 mg dose.

Table 5. Summary of DAA Exposures (C_{max}) Observed in Phase 1, 2, and 3 Studies

	C_{max} (ng/mL) (Least Squares Means or Geometric Means)				
	ABT-450	**Ritonavir**	**ABT-267**	**ABT-333**	**ABT-333 M1**
Study M12-680 Therapeutic Dose	2970	2340	135	1120	726
Study M12-680 Supra-therapeutic dose	9200	2190	232	2090	1320
Mean in Healthy Volunteers (Phase 2 formulation)[a]	991	1731	117	1120	701
Mean in Healthy Volunteers (Phase 3 formulation)[b]	1470	6000	127	1030	660
Ratio: Supra-therapeutic/Phase 3 formulation in Healthy Volunteers	6.3	1.4	1.8	2.0	2.0
Maximum fold-increase in Hepatic Impairment	1.26	0.67	0.85	1.33	0.68
Maximum fold-increase in Renal Impairment	1.01	1.66	0.96	1.12	0.83
Maximum fold-increase in Asians	1.70	1.23	1.00	1.00	1.00
Maximum fold-increase following drug interaction[c]	2.19	1.31[d]	1.14	1.18	1.18

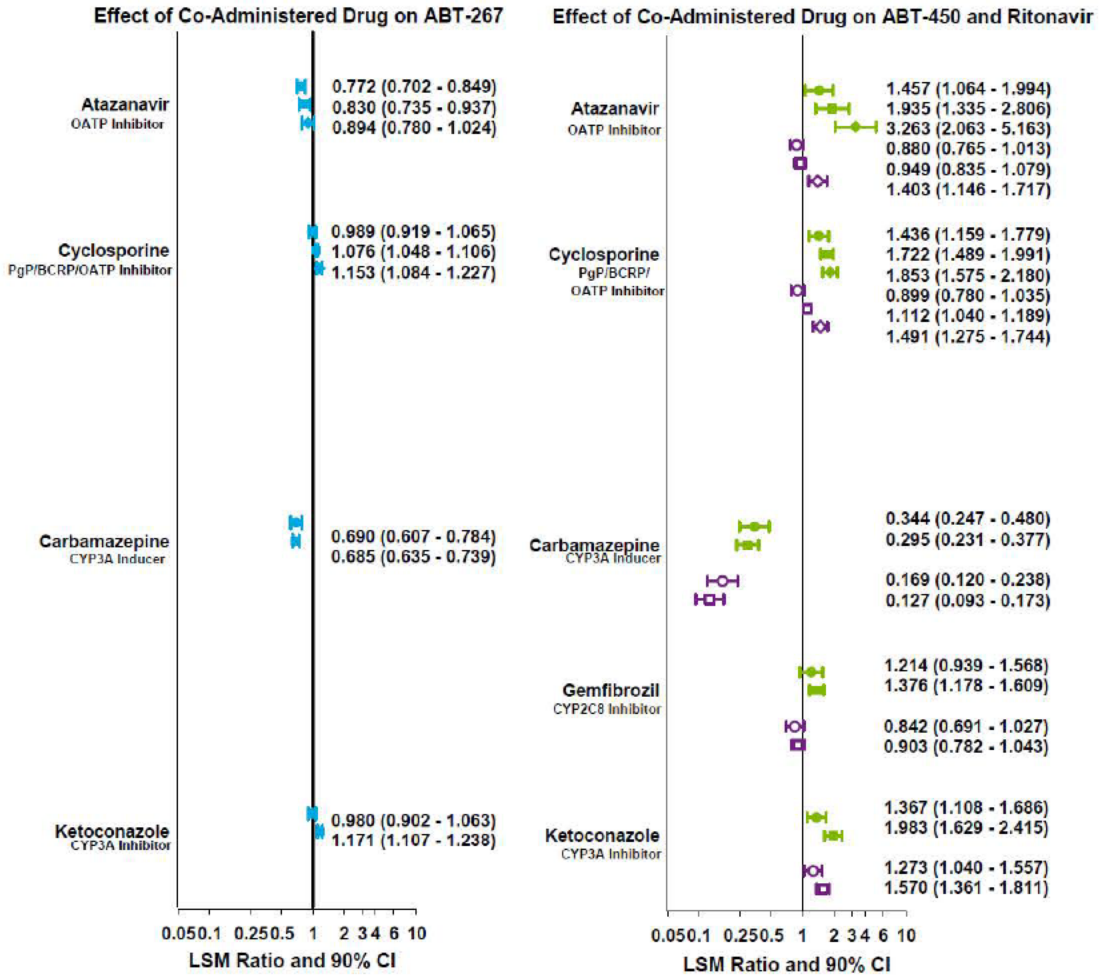
a. Geometric means for 3-DAA combination. Formulation (Dose): (b) (4) (ABT-450 150 mg), capsule (ritonavir 100 mg), (b) (4) (ABT-267 25 mg) and tablet (ABT-333 400 mg). Across 10 study arms (96 subjects) for ABT-450 and ritonavir, and across 16 study arms (162 subjects) for ABT-267, ABT-333 and ABT-333 M1.

b. Geometric means for 3-DAA combination. Formulation (Dose): Co-formulated tablet (ABT-450/r/ABT-267 150/100/25 mg) and tablet (ABT-333 250 mg). Data from across 8 study arms (97 subjects).

c. Ratio of 3-DAAs + concomitant medications/3-DAAs.

d. Interaction for a 100 mg dose of ritonavir.

Figure 1. Interactions with DAAs as Substrates of Metabolic Enzymes and Transporters (LSM Ratio and 90% CI)



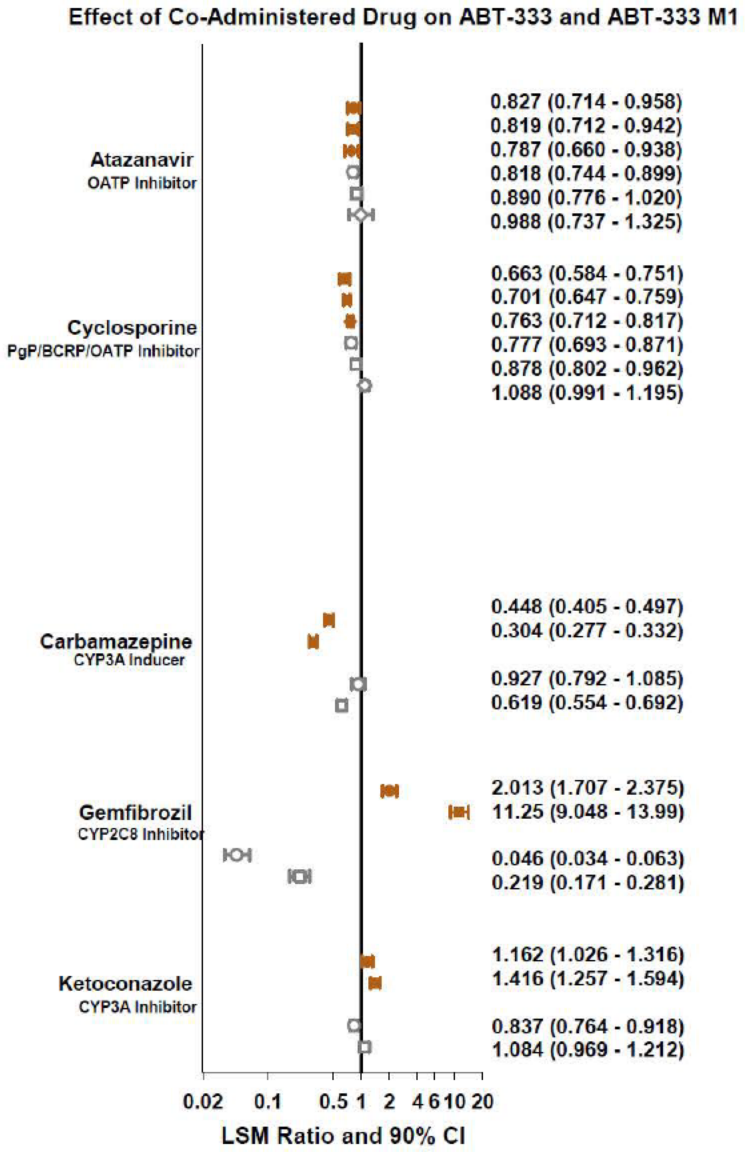
Circle = C_{max}; square = AUC; diamond = C_{trough}.

Solid symbol = ABT-267 or ABT-450; open symbol = ritonavir.

LSM ratio and 90% CI are for DAA + co-administered drug over DAA alone.

Ketoconazole is also a P-gp inhibitor.

Figure 1. **Interactions with DAAs as Substrates of Metabolic Enzymes and Transporters (LSM Ratio and 90% CI) (Continued)**



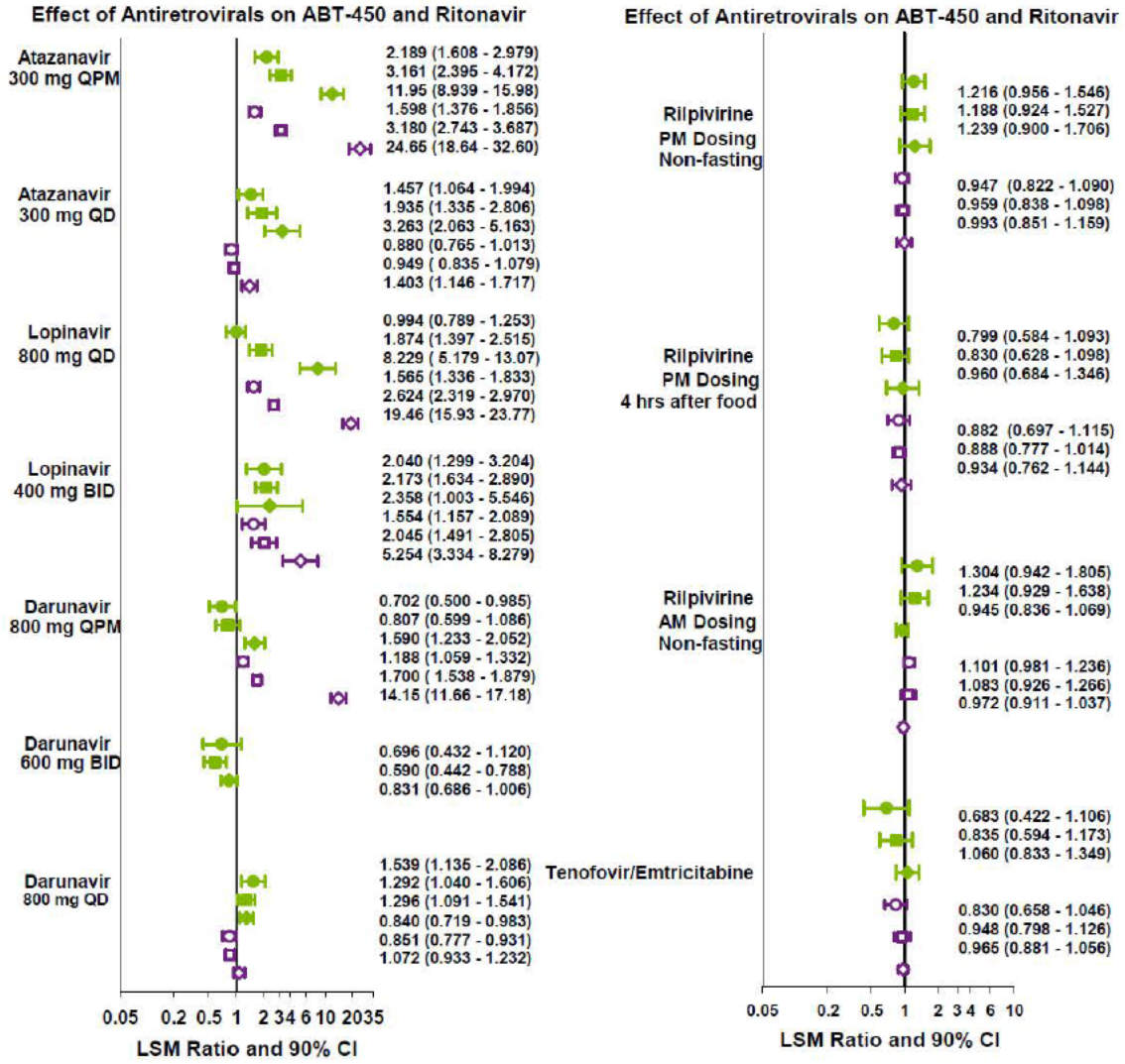
Circle = C_{max}; square = AUC; diamond = C_{trough}.

Solid symbol = ABT-333; open symbol = ABT-333 M1.

LSM ratio and 90% CI are for DAA + co-administered drug over DAA alone.

Ketoconazole is also a P-gp inhibitor.

Figure 3. Effect of Antiretroviral Agents on C_{max}, AUC and C_{trough} of DAAs and Ritonavir (LSM and 90% CI) (Continued)



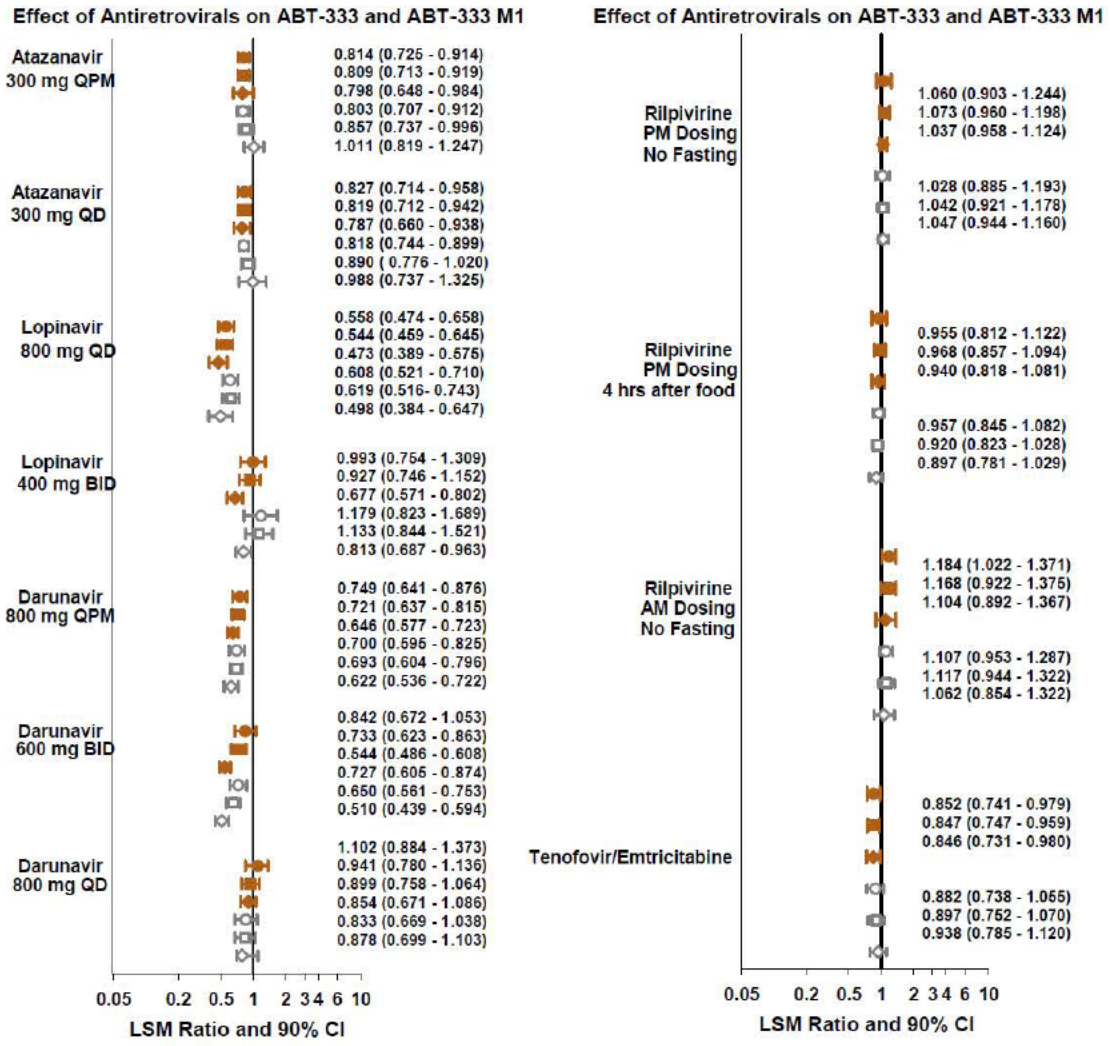
Circle = C_{max}; square = AUC; diamond = C_{trough}.

Solid symbol = ABT-450; open symbol = ritonavir.

Ritonavir comparisons for lopinavir BID and QD is 300 mg versus 100 mg; for darunavir QPM, darunavir BID and atazanavir QPM is 200 mg versus 100 mg.

LSM ratio and 90% CI are for DAA + co-administered drug over DAA alone.

Figure 3. Effect of Antiretroviral Agents on C_{max}, AUC and C_{trough} of DAAs and Ritonavir (LSM and 90% CI) (Continued)

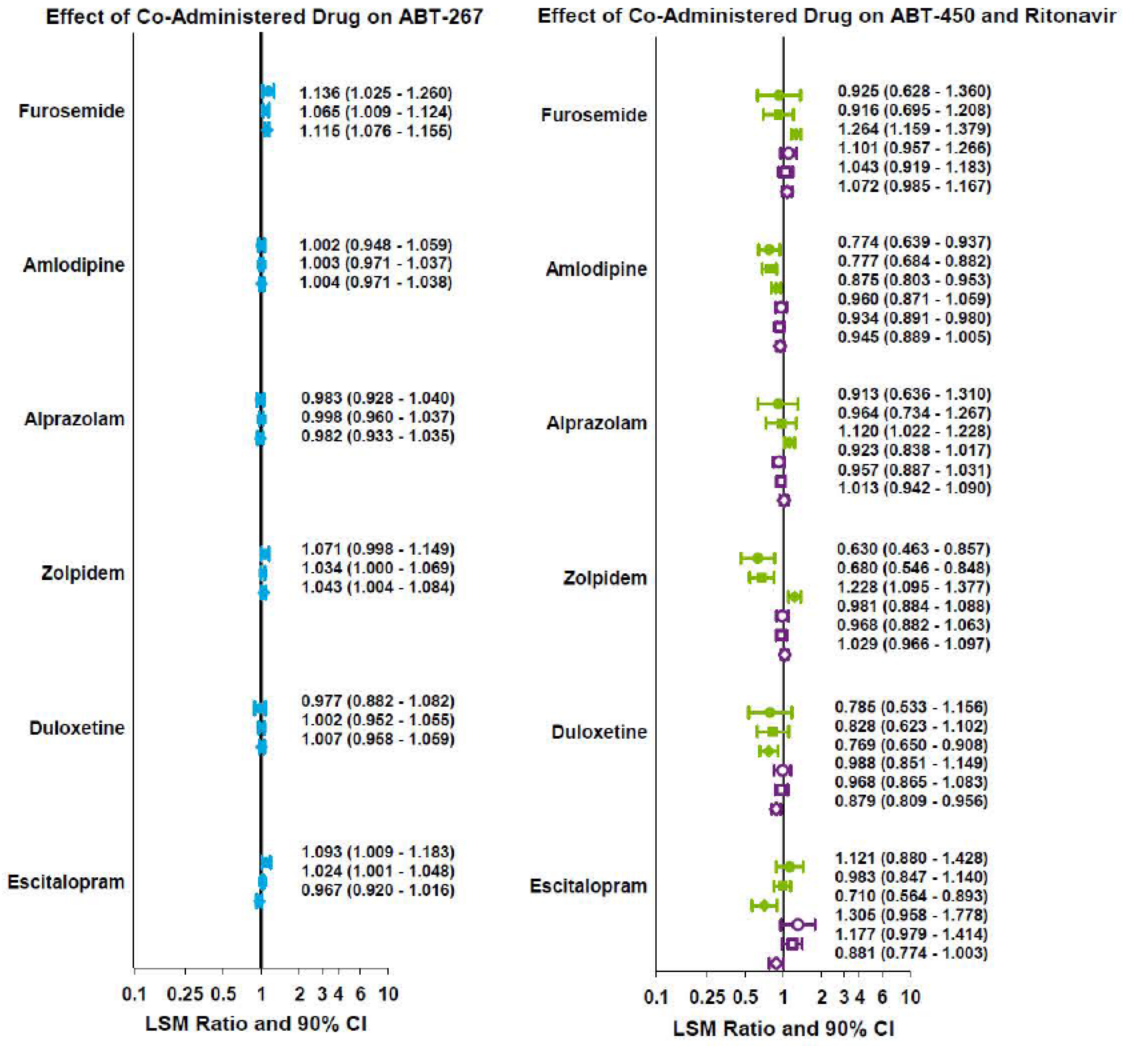


Circle = C_{max}; square = AUC; diamond = C_{trough}.

Solid symbol = ABT-333; open symbol = ABT-333 M1.

LSM ratio and 90% CI are for DAA + co-administered drug over DAA alone.

Figure 4. Pharmacokinetic Interactions with Commonly Used Medications (LSM and 90% CI)

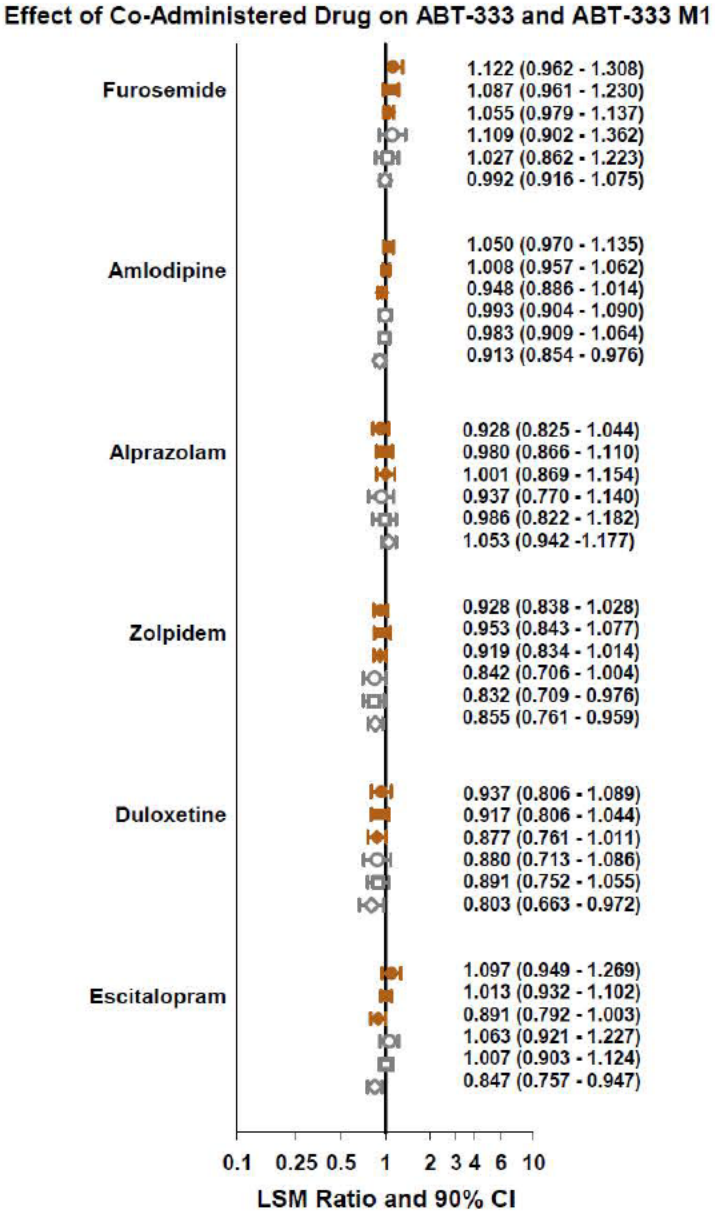


Circle = C_{max}; square = AUC; diamond = C_{trough}.

Solid symbol = ABT-267 or ABT-450; open symbol = ritonavir.

LSM ratio and 90% CI are for DAA + co-administered drug over DAA alone.

Figure 4. **Pharmacokinetic Interactions with Commonly Used Medications (LSM and 90% CI) (Continued)**

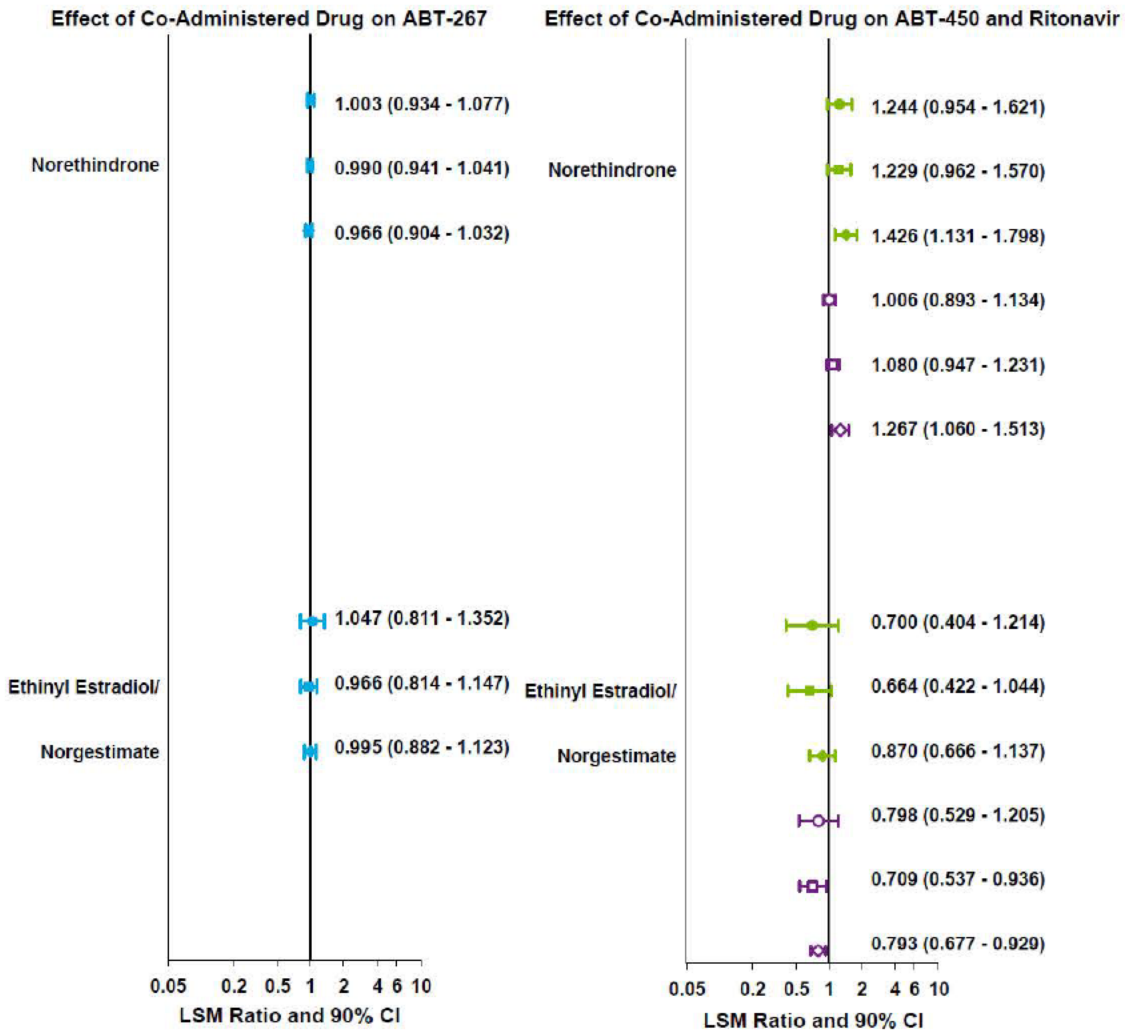


Circle = C_{max}; square = AUC; diamond = C_{trough}.

Solid symbol = ABT-333; open symbol = ABT-333 M1.

LSM ratio and 90% CI are for DAA + co-administered drug over DAA alone.

Figure 5. Pharmacokinetic Interactions with Oral Contraceptives (LSM and 90% CI)

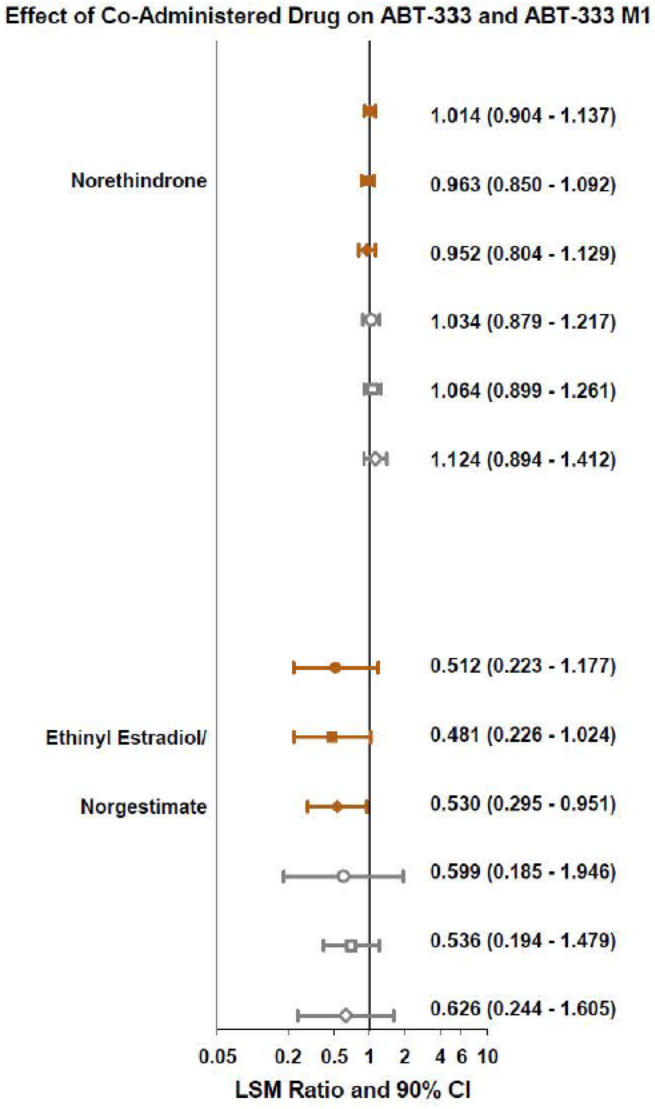


Circle = C_{max}; square = AUC; diamond = C_{trough}.

Solid symbol = ABT-267 or ABT-450; open symbol = ritonavir.

LSM ratio and 90% CI are for DAA + co-administered drug over DAA alone.

Figure 5. **Pharmacokinetic Interactions with Oral Contraceptives (LSM and 90% CI) (Continued)**

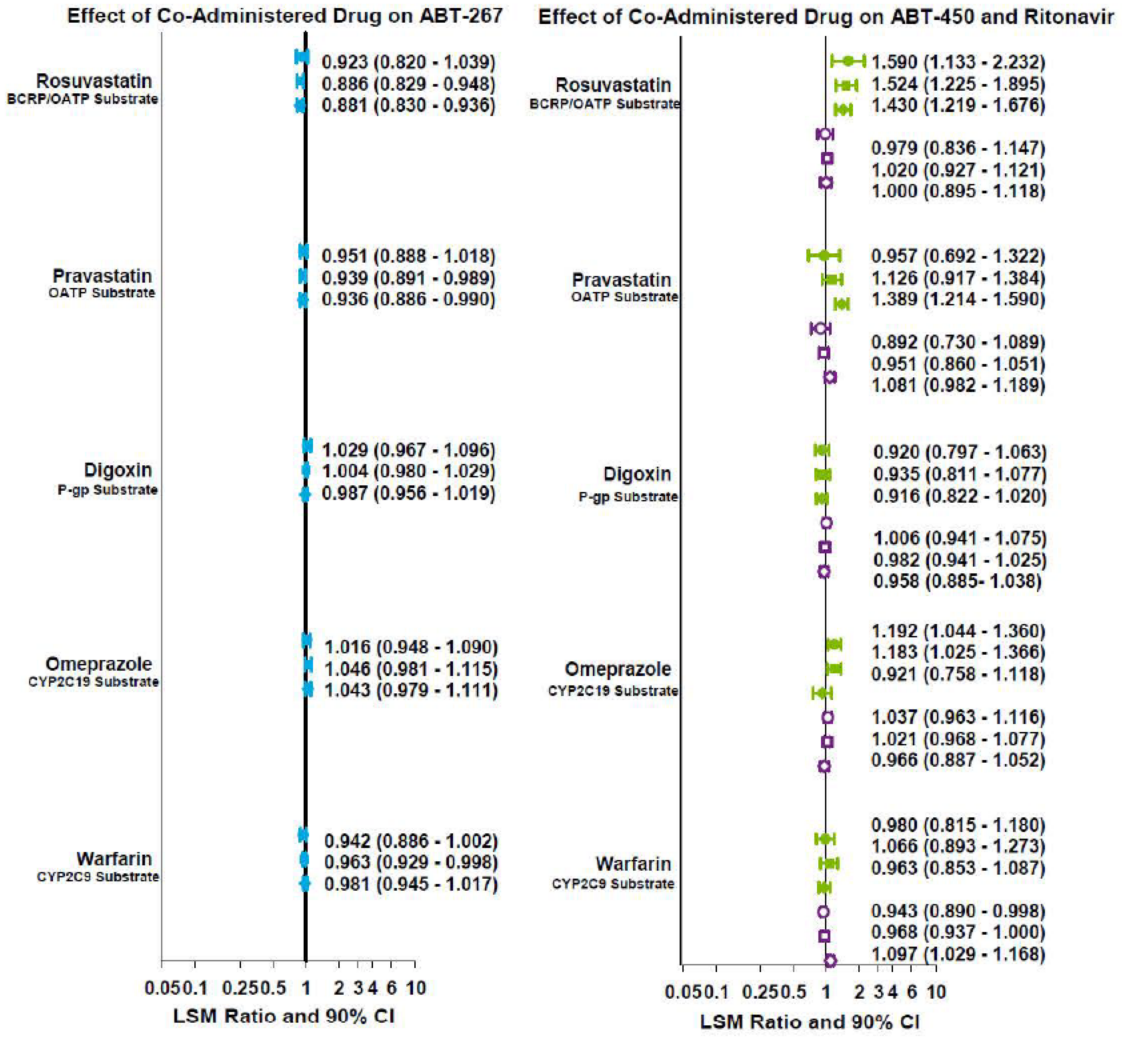


Circle = C_{max}; square = AUC; diamond = C_{trough}.

Solid symbol = ABT-333; open symbol = ABT-333 M1.

LSM ratio and 90% CI are for DAA + co-administered drug over DAA alone.

Figure 1. Interactions with DAAs as Inhibitors of Metabolic Enzymes and Transporters (LSM and 90% CI)

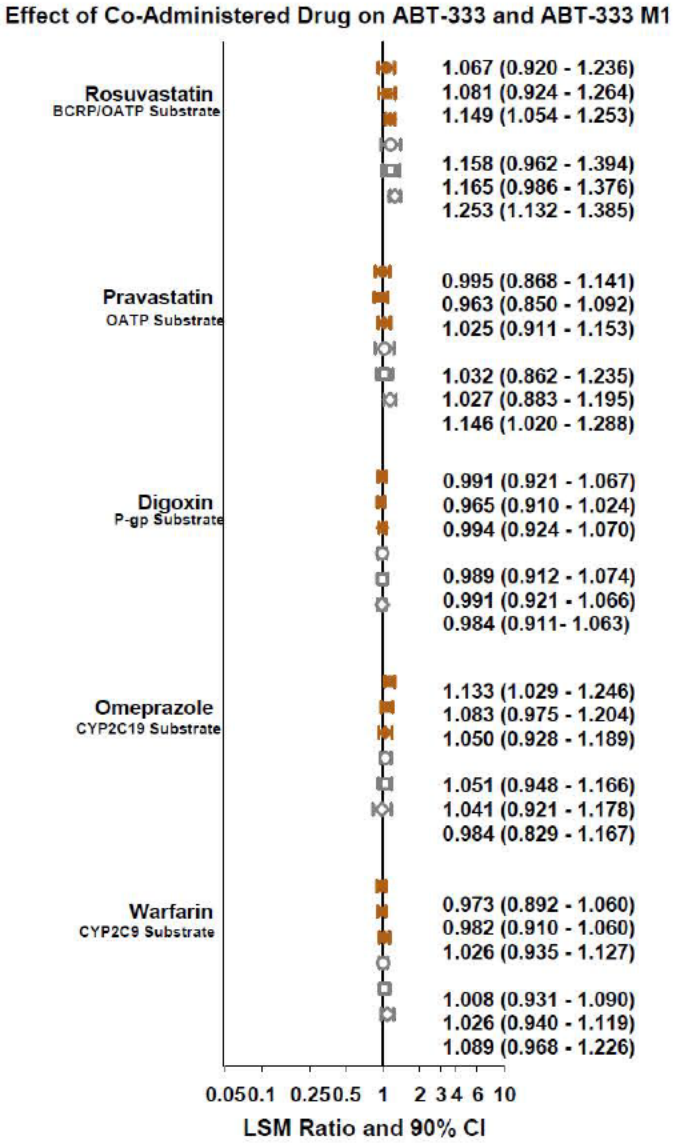


Circle = C_{max}; square = AUC; diamond = C_{trough}.

Solid symbol = ABT-267 or ABT-450; open symbol = ritonavir.

LSM ratio and 90% CI are for DAA + co-administered drug over DAA alone.

Figure 2. **Interactions with DAAs as Inhibitors of Metabolic Enzymes and Transporters (LSM and 90% CI) (Continued)**

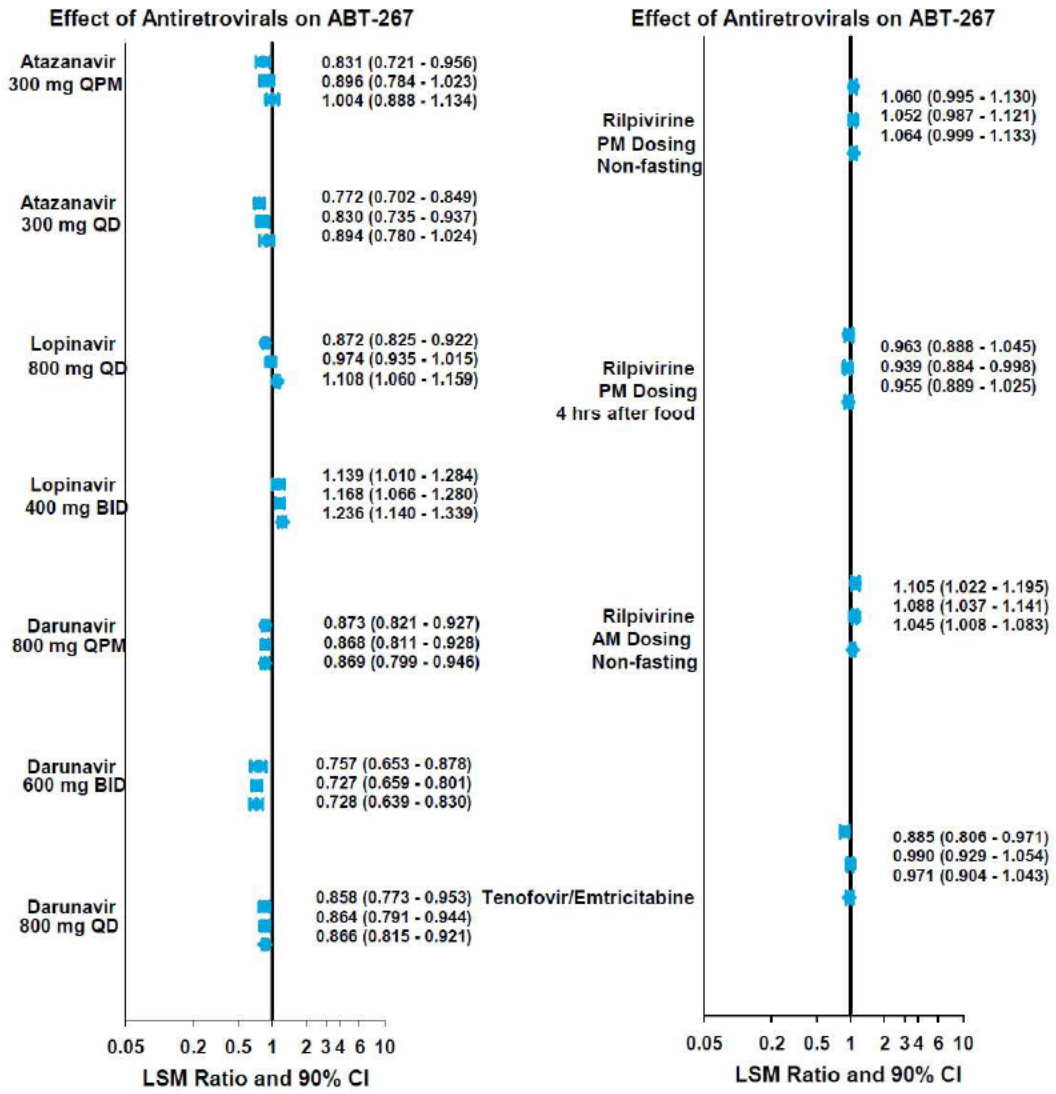


Circle = C_{max}; square = AUC; diamond = C_{trough}.

Solid symbol = ABT-333; open symbol = ABT-333 M1.

LSM ratio and 90% CI are for DAA + co-administered drug over DAA alone.

Figure 3. **Effect of Antiretroviral Agents on C_{max}, AUC and C_{trough} of DAAs and Ritonavir (LSM and 90% CI)**



Circle = C_{max}; square = AUC; diamond = C_{trough}.

LSM ratio and 90% CI are for DAA + co-administered drug over DAA alone.

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

/s/

MOH JEE NG
07/22/2014

QIANYU DANG
07/22/2014

XIAOFENG WANG
07/22/2014

JIANG LIU
07/22/2014

MICHAEL Y LI
07/22/2014

NORMAN L STOCKBRIDGE
07/23/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application:	NDA 206619
Application Type:	New NDA
Name of Drug/Dosage Form:	Viekira Pak (proposed) ombitasvir/ABT-450/ritonavir tablets copackaged with dasabuvir tablets
Applicant:	AbbVie Inc.
Receipt Date:	April 21, 2014
Goal Date:	December 21, 2014 (by Friday, December 19, 2014)

1. Regulatory History and Applicant's Main Proposals

This original NDA is for the NMEs ombitasvir (ABT-267, NS5A inhibitor), ABT-450 (INN pending, NS3/4A protease inhibitor) and dasabuvir (ABT-333, non-nucleoside NS5B polymerase inhibitor). Ombitasvir, ABT-450 and ritonavir are co-formulated into one tablet, co-packaged with a second tablet containing dasabuvir. The proposed indication for this drug product is the treatment of chronic hepatitis C virus genotype 1 infection. The regimen may be dosed with or without ribavirin.

The combination of ombitasvir/ABT-450/ritonavir and dasabuvir was granted Breakthrough Therapy Designation on May 1, 2013.

This NDA is being reviewed on a Priority clock, as part of "The Program" under PDUFA V.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

1. 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). The applicant will be instructed not to included bolded subheadings in the FPI (refer to Section 13 NONCLINICAL TOXICOLOGY and Section 17 PATIENT COUNSELING INFORMATION).

2. Once a non-proprietary name for ABT-450 is adopted, the applicant should re-submit all labeling with updated nomenclature. This was already communicated to the applicant and captured in the May 16, 2014 Type A meeting minutes under NDA 206619 and will be reiterated in the filing communication.

3. The presentation of the product title will be discussed with ONDQA and DMEPA during the review cycle.

4. In the HIGHLIGHTS, the CONTRAINDICATIONS section does not include a reference to the ribavirin PI for contraindications other than pregnancy, although this is included in the FPI CONTRAINDICATIONS section. This will be discussed with the team during review of labeling.

All SRPI format deficiencies of the PI and some of the additional labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by July 18, 2014. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

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

Comment:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *The applicant has requested a waiver of the one-half page length requirement in the NDA (refer to section 1.12.5). The CDTL will be notified.*

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

NO 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *Applicant will be instructed to extend horizontal lines over the entire width of the columns in the HL.*

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *Applicant will be instructed to remove white space between HL heading and HL limitation statement. Applicant will be informed that white space may be added between the limitation statement and the product title. Applicant will be instructed to add white space before each major heading, as some headings are not preceded by white space (Indications and Usage, Dosage and Administration, Drug Interactions).*

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

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

The applicant will be asked to insert a comma after the parentheses and before "for oral use."

Note that other co-packaged products have presented the product title as follows (as the dosage form is not technically part of the nonproprietary name): MYDRUG (drugozide and drugolide) tablets, for oral use. However, because DMEPA and ONDQA previously requested the use of the word "copackaged" in the product title, it may not be advisable to move the word "tablets" outside of the parentheses. ONDQA and DMEPA will be consulted.

Initial U.S. Approval in Highlights

Selected Requirements of Prescribing Information

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *The year has been left blank. Applicant will be asked to update it towards the end of the review cycle.*

Boxed Warning (BW) in Highlights

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

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment: *Will consult the review team to see if the company needs to specify which drug component of the regimen corresponds to which pharmacologic class, or if the way it is currently worded is sufficient.*

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment: *Revision date will be updated prior to action.*

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

NO 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment: *Cross-reference in Section 1 INDICATIONS and USAGE of the FPI references a table.*

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES

Selected Requirements of Prescribing Information

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

    Comment:

NO 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

    Comment: *It is not clear whether the Patient Information is a stand-alone document or not. The applicant will be instructed as follows: If the FDA-approved patient lableign 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.*

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

KATHERINE SCHUMANN
06/16/2014

ELIZABETH G THOMPSON
06/16/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 206619 BLA#	NDA Supplement # BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Viekira Pak (proposed) Established/Proper Name: ombitasvir/ABT-450/ritonavir copackaged with dasabuvir Dosage Form: tablets, co-packaged for oral use Strengths: ombitasvir/ABT-450/ritonavir (12.5 mg/75 mg/50 mg) and dasabuvir (250 mg)		
Applicant: AbbVie Inc. Agent for Applicant (if applicable):		
Date of Application: April 21, 2014 Date of Receipt: April 21, 2014 Date clock started after UN:		
PDUFA Goal Date: December 21, 2014	Action Goal Date (if different): December 19, 2014	
Filing Date: June 20, 2014	Date of Filing Meeting: May 22, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1, 4		
Proposed indication(s)/Proposed change(s): treatment of genotype 1 chronic hepatitis C virus infection, including patients with cirrhosis		

Type of Original NDA: AND (if applicable)	☒ 505(b)(1) ☐ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted ☐ Pediatric Rare Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☒ Fast Track Designation ☒ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☒ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): IND 103,526 / IND 108,434 / IND 101,636

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		Note that the proprietary name is under review and the established/proper name for ABT-450 is still pending. DARRTS will be updated during the review as appropriate.
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**

Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		The user fee cover sheet was provided prior to first rolling submission component dated 1/15/2014.

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐	☐	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐	☐	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	☐	☐	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐	☐	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric

exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.				
Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☐	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	This NDA contains 3 active moieties that have never been approved, but one (ritonavir) that was previously approved. CDER's policy on 5-year NCE exclusivity is currently under review. Should the draft guidance "New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products" be finalized prior to approval, this drug product could be eligible for 5-year exclusivity.
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological*	☐	☐	☐	

reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	
Forms and Certifications				

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		Application is correctly coded with Form 3674 in DARRTS
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification	**YES**	**NO**	**NA**	**Comment**

(NDAs/NDA efficacy supplements only)				
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff: N/A* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☒	☐	☐	At the pre-NDA meeting, it was agreed that the drug product contained in this submission does not pose a potential for abuse and would not be considered for DEA scheduling.
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☒	☐	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☒	☐	☐	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☒	☒	☐	See "Request for Waiver of Pediatric Studies" page 2. Certification was not included for the deferral and will be requested.
BPCA (NDAs/NDA efficacy supplements only):	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	Application is appropriately coded.
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	PPI (plus PI) consulted to patient labeling (DMPP).
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** *OSE consult (see comments): 5/1/2014* *QT IRT consult for study report: 5/20/14*	☒	☐	☐	OSE consulted regarding pharmacovigilance plan and human use factors report (5/01/2014).
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** October 1, 2012 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** January 29, 2014 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ABT-450 rat and mouse carcinogenicity, September 8, 2010 ABT-267 rat and mouse carcinogenicity, December 8, 2011 ABT-333 rat and mouse carcinogenicity, June 8, 2011 ***If yes, distribute letter and/or relevant minutes before filing meeting***	☒	☐		Carcinogenicity SPAs only, no meetings held.

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 22, 2014

BLA/NDA/Supp #: 206619

PROPRIETARY NAME: Viekira Pak

ESTABLISHED/PROPER NAME: ombitasvir/ABT-450/ritonavir copackaged with dasabuvir

DOSAGE FORM/STRENGTH: ombitasvir/ABT-450/ritonavir (12.5 mg/75 mg/50 mg) tablets copackaged with dasabuvir (250 mg) tablets

APPLICANT: AbbVie Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of genotype 1 chronic hepatitis C virus infection

BACKGROUND:

This original NDA is for the NMEs ombitasvir (ABT-267, NS5A inhibitor), ABT-450 (INN pending, NS3/4A protease inhibitor) and dasabuvir (ABT-333, non-nucleoside NS5B-palm polymerase inhibitor). Ombitasvir and ABT-450 are co-formulated with ritonavir into one tablet, to be co-administered with a second tablet containing dasabuvir. The proposed indication for this drug product is the treatment of chronic hepatitis C virus genotype 1 infection. The regimen may be dosed with or without ribavirin.

The combination of ombitasvir/ABT-450/ritonavir and dasabuvir was granted Breakthrough Therapy Designation on May 1, 2013. Each individual component had previously been granted Fast Track status, as well. As part of these programs, the Division agreed to accept the NDA for rolling review. The first component was received on January 15, 2014, and the final component (triggering the review clock) was received April 21, 2014.

This NDA will be reviewed under a Priority clock, as part of "The Program" under PDUFA V. A pre-NDA meeting was held on January 29, 2014, during which the contents of a complete application were discussed.

These drugs were previously reviewed under IND 103526 (ABT-450 individual drug and the 3-drug combination), IND 108434 (ombitasvir [ABT-267]) and IND 101636 (dasabuvir [ABT-333]]).

REVIEW TEAM:

Discipline/Organization	Names	Present at filing meeting? (Y or N)

Regulatory Project Management	RPM:	Katherine Schumann	Yes
	CPMS/TL:	Elizabeth Thompson	Yes
Cross-Discipline Team Leader (CDTL)	Linda Lewis		Yes
Clinical	Reviewer:	Russell Fleischer	Yes
	TL:	Linda Lewis	Yes
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Pat Harrington	Yes
	TL:	Jules O'Rear	Yes

Clinical Pharmacology	Reviewer:	Vikram Arya	Yes
	TL:	Islam Younis	Yes
Biostatistics	Reviewer:	Joy Mele	Yes
	TL:	Greg Soon	Yes
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Mark Seaton	Yes
	TL:	Hanan Ghantous	Yes
Statistics (carcinogenicity)	Reviewer:	Steven Thomson	No
	TL:	Karl Lin	No
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Caroline Strasinger Milton Sloan Maotang Zhou	Yes
	TL:	Steve Miller	Yes
Quality Microbiology *(for sterile products)*	Reviewer:	Erika Pfeiler Note: review is completed, application is acceptable	No
	TL:	Stephen E Langille	No
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Krishna Ghosh	Yes
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Monica Calderon	Yes
	TL:	Irene Chan	Yes
OSE/DRISK (REMS) *Note: Primary reviewer will be changed per 6/11/14 email from DRISK.*	Reviewer:	George Neyarapally	No
	TL:	Jamie Wilkins Parker	No
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Antoine El-Hage	No
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Division of Pharmacovigilance (OSE): Reviewer: Mihaela Jason TL: Kelly Cao Pharmacometrics (OCP): Reviewer: Dhananjay Marathe TL: Jeffry Florian Patient Labeling (DMPP): Reviewer: Sharon Mills TL: Barbara Fuller Biopharmaceutics: Reviewer: Elsbeth Chikhale TL: Angelica Dorantes		Yes (pharmaco-metrics and biopharm)
Other attendees	Ed Cox, Director, OAP Jeffrey Murray, Deputy Director, DAVP Debra Birnkrant, Director, DAVP		

FILING MEETING DISCUSSION:

GENERAL	
• 505(b)(2) filing issues:	☒ Not Applicable
○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☐ YES ☐ NO
Describe the scientific bridge (e.g., BA/BE studies):	
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: No comments	☐ Not Applicable

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: The application ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: The components of this application are not first in their class and the application does not raise significant safety or efficacy issues.
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: Review issues for 74-day letter regarding cross-referencing of ritonavir information and packaging.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	☐ Not Applicable ☐ YES ☐ NO

Comments: Quality microbiology review is completed, application found acceptable. Not a sterile product, so validation of sterilization is not applicable.	
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☒ YES ☐ NO Note: During the pre-NDA meeting, DAVP asked the applicant to follow up with a proposal for possible submission of transplant and co-infection data. Agreement was made following the pre-submission meeting regarding submission of the transplant report within 30 days after receipt of the original application. ☒ YES ☐ NO

• What late submission components, if any, arrived after 30 days?	Agreed-upon transplant report submitted on May 21, 2014.
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Ed Cox, MD, MPH

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): July 7, 2014

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

Filing Date: June 20, 2014
74-Day Letter Date: June 27, 2014
Mid-Cycle Meeting: July 7, 2014
Mid-Cycle Communication: July 14, 2014
Primary Reviews Due: September 21, 2014
Labeling & PMR/PMC Discussions Due: September 30, 2014
Late Cycle Package Due: October 9, 2014
Late Cycle Meeting: October 20, 2014
Wrap-Up Meeting: November 13, 2014
CDTL Review Due: November 24, 2014
PDUFA Goal Date: December 21, 2014 (by Friday, December 19, 2014)

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing.

	Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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
06/16/2014

ELIZABETH G THOMPSON
06/16/2014