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RESEARCH**

APPLICATION NUMBER:

208261Orig1s000

OTHER REVIEW(S)

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 # 208261
Product Name: Zepatier; elbasvir and grazoprevir fixed dose combination tablet

PMR/PMC Description: Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of elbasvir and grazoprevir in pediatric subjects 3 to 17 years of age with chronic hepatitis C infection

PMR/PMC Schedule Milestones:	Final Protocol Submission:	3/31/2016
	Study/Trial Completion:	12/31/2019
	Final Report Submission:	1/4/2021
	Other:	N/A

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 November 4, 2015. The PeRC agreed with the Division to grant a deferral for pediatric patients aged 3 through 17 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 goal of the deferred pediatric study is to evaluate the safety, efficacy (assessed as sustained virologic response), and pharmacokinetics of combination treatment with elbasvir and grazoprevir in children ages 3 years to 17 years of age with chronic hepatitis C infection. The Sponsor proposes a (b) (4) study: (b) (4) (b) (4). The Division is in general agreement with the Applicant's overall pediatric plan.

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.

A clinical trial is required to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of elbasvir and grazoprevir in pediatric subjects 3 to 17 years of age with chronic hepatitis C 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

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 # 208261
Product Name: Zepatier; elbasvir and grazoprevir fixed dose combination tablet

PMR/PMC Description: Collect and analyze long-term safety data from pediatric subjects 3 to 17 years of age enrolled in the pediatric elbasvir and grazoprevir safety, pharmacokinetic and efficacy study. Data should be collected for at least 3 years following the end of treatment in order to characterize the long-term safety of elbasvir and grazoprevir including growth assessment, sexual maturation and characterization of elbasvir and grazoprevir resistance associated substitutions in viral isolates from subjects failing therapy.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	3/31/2016
	Study/Trial Completion:	12/31/2022
	Final Report Submission:	07/20/2023
	Other:	N/A

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 in pediatric subjects treated in the elbasvir and grazoprevir safety, pharmacokinetic and efficacy study.

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 through 17 years of age. The study will collect and analyze long-term safety data for subjects enrolled in the pediatric elbasvir and grazoprevir safety, pharmacokinetic and efficacy study. Data should be collected for at least 3 years following the end of treatment in order to characterize the long-term safety of elbasvir and grazoprevir including growth assessment, sexual maturation and characterization of elbasvir and grazoprevir 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.

This study will collect long-term follow-up data from pediatric subjects ages 3 to 17 years of age with chronic hepatitis C infection who participated in the pediatric elbasvir and grazoprevir safety, pharmacokinetic and efficacy study. Data should be collected for at least 3 years following the end of treatment in order to characterize the long-term safety of elbasvir and grazoprevir including growth assessment, sexual maturation and characterization of elbasvir and grazoprevir 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

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 # 208261
Product Name: Zepatier

PMR/PMC Description: Conduct site-directed mutant phenotype analyses of elbasvir against HCV replicons carrying the following NS5A substitutions: K24R (GT1a), H54Y (GT4d), E62D (GT1a), D427N (GT1a). Please include cross-resistance analyses with approved NS5A inhibitors.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	03/31/2016
	Study/Trial Completion:	12/30/2016
	Final Report Submission:	01/27/2017
	Other:	MM/DD/YYYY

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

Additional treatment-emergent substitutions were identified from either cell culture selection studies or from virologic failures in the sponsor's clinical studies. The sponsor will need to phenotypically characterize these substitutions as well as determine the cross-resistance analyses with the approved drugs within the specific HCV direct-acting antiviral drug class.

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 impact of these substitutions on the antiviral activity of elbasvir needs to be evaluated to understand the possible impact of baseline polymorphisms on response to elbasvir/grazoprevir. Additionally, the impact of these substitutions on cross-resistance to approved NS5A inhibitors needs to be evaluated to inform retreatment options for subjects failing a elbasvir/grazoprevir regimen.

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.

Conduct site-directed mutant phenotype analyses of elbasvir against HCV replicons carrying the following NS5A substitutions: K24R (GT1a), H54Y (GT4d), E62D (GT1a), D427N (GT1a).
Include cross-resistance analyses with approved NS5A inhibitors.

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)
The impact of these substitutions on the antiviral activity of elbasvir needs to be evaluated to understand the possible impact of baseline polymorphisms on response to elbasvir/grazoprevir. Additionally, the impact of these substitutions on cross-resistance to approved NS3/4A or NS5A inhibitors need to be evaluated to inform retreatment options for subjects failing a elbasvir/grazoprevir regimen.

 - 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.*

(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 # 208261
Product Name: Zepatier

PMR/PMC Description: Conduct site-directed mutant phenotype analyses of grazoprevir against HCV replicons carrying the following NS3 substitutions: I48A/V (GT1a), T185S (GT1a/GT1b), E357G/K (GT1a). Please include cross-resistance analyses with approved NS3/4A inhibitors.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/31/2016</u>
	Study/Trial Completion:	<u>12/30/2016</u>
	Final Report Submission:	<u>01/27/2017</u>
	Other:	<u>MM/DD/YYYY</u>

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

Additional treatment-emergent substitutions were identified from either cell culture selection studies or from virologic failures in the sponsor's clinical studies. The sponsor will need to phenotypically characterize these substitutions as well as determine the cross-resistance analyses with the approved drugs within the specific HCV direct-acting antiviral drug class.

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 impact of these substitutions on the antiviral activity of grazoprevir needs to be evaluated to understand the possible impact of baseline polymorphisms on response to elbasvir/grazoprevir. Additionally, the impact of these substitutions on cross-resistance to approved NS3/4A inhibitors needs to be evaluated to inform retreatment options for subjects failing a elbasvir/grazoprevir regimen.

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.

Conduct site-directed mutant phenotype analyses of grazoprevir against HCV replicons carrying the following NS3 substitutions: I48A/V (GT1a), T185S (GT1a/GT1b), E357G/K (GT1a). Include cross-resistance analyses with approved NS3/4A inhibitors.

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)
The impact of these substitutions on the antiviral activity of grazoprevir needs to be evaluated to understand the possible impact of baseline polymorphisms on response to elbasvir/grazoprevir. Additionally, the impact of these substitutions on cross-resistance to approved NS3/4A or NS5A inhibitors need to be evaluated to inform retreatment options for subjects failing a elbasvir/grazoprevir regimen.

 - 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.*

(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 # 208261
Product Name: Zepatier

PMR/PMC Description: Conduct a trial in hepatitis C virus genotype 1a infected subjects with at least one baseline NS5A polymorphism at amino acid position 28, 30, 31, or 93 to evaluate if treatment with elbasvir/grazoprevir and ribavirin for at least 16 weeks reduces the rate of virologic failure and the rate of treatment-emergent drug resistant viral populations. The trial should have adequate representation of subjects with baseline NS5A polymorphisms that have been demonstrated to have the greatest impact on elbasvir/grazoprevir efficacy in clinical trials evaluating recommended regimens.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>07/31/2016</u>
	Study/Trial Completion:	<u>07/31/2018</u>
	Final Report Submission:	<u>12/31/2018</u>
	Other:	<u>MM/DD/YYYY</u>

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

Most HCV genotype 1a infected study subjects did not have baseline NS5A polymorphisms that substantially impacted efficacy of elbasvir/grazoprevir. However, a subset of genotype 1a infected subjects had baseline NS5A polymorphisms that reduced efficacy of elbasvir/grazoprevir when administered for 12 weeks. Available data indicate that 16 weeks of treatment with elbasvir/grazoprevir and the addition of ribavirin may overcome the effects of baseline NS5A polymorphisms, but confirmatory data are necessary. Waiting for these data would delay access to elbasvir/grazoprevir for the majority of patients who would benefit from it.

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 the trial is to establish whether treatment with elbasvir/grazoprevir and ribavirin for at least 16 weeks has adequate efficacy in HCV genotype 1a infected patients with at least one baseline NS5A polymorphism at amino acid position 28, 30, 31, or 93. Patients who are infected with GT1a virus with one or more NS5A polymorphisms at amino acid positions 28, 30, 31, or 93 have a lower rate of treatment success (defined as sustained virologic response) compared to patients who are infected with GT1a virus without NS5A polymorphisms at these positions. In addition, virologic failure is frequently associated with the accumulation of additional NS3 PI and/or NS5A resistance substitutions that may significantly impact future treatment options.

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.

A clinical trial with elbasvir/grazoprevir and ribavirin for at least 16 weeks in HCV genotype 1a infected subjects who have at least one baseline NS5A polymorphism at position 28, 30, 31, or 93. There should be adequate representation of subjects with baseline NS5A polymorphisms that have been demonstrated to have the greatest impact on elbasvir/grazoprevir efficacy and emergence of drug resistance in clinical trials evaluating recommended regimens.

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
 - 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.

(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 # 208261
Product Name: Zepatier

PMR/PMC Description: Evaluate the effect of SLCO1B1 genotype on grazoprevir pharmacokinetics (PK) and response to elbasvir/grazoprevir treatment in patients with chronic hepatitis C virus infection. To evaluate this effect, either conduct a prospective clinical trial with pharmacokinetic and pharmacodynamic endpoints or a retrospective analysis of previously conducted clinical trials with pharmacokinetic data for which stored biospecimens are available. The trial should be enriched or have sufficient numbers of subjects who are homozygous for reduced function alleles (i.e., N130D and V174A), respectively, to adequately assess whether there are differences in PK and treatment responses.

PMR/PMC Schedule Milestones: Final Protocol Submission: 05/30/2016
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 06/30/2017
Other: _____ MM/DD/YYYY

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

Grazoprevir is a substrate for OATP1B1, which is a liver uptake transporter. The gene encoding this transporter (SLCO1B1) is known to have polymorphisms that reduce transporter function. Decreased uptake of grazoprevir into the liver may lead to decreased efficacy of elbasvir/grazoprevir treatment. The subpopulation for which the homozygous alleles occur in is small; with an estimated occurrence rate in the U.S. of around 5%.

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.”

Grazoprevir is a substrate for OATP1B1, which is known to have two common polymorphisms that reduce transporter function. In vivo drug-drug interaction studies demonstrated that grazoprevir pharmacokinetics are significantly affected by OATP1B1 inhibition (atazanavir/ritonavir, lopinavir/ritonavir, cyclosporine), with 10- to 15-fold increases in the AUC of grazoprevir and 6- to 17-fold increases in the Cmax of grazoprevir. Given these changes in plasma concentrations, coadministration of elbasvir/grazoprevir with OATP1B inhibitors is contraindicated.

In addition, grazoprevir distributes into hepatic tissue where it exerts its antiviral activity. There may be reduced uptake of grazoprevir into the liver in patients with reduced OATP1B1 function. The potential for decreased efficacy of elbasvir/grazoprevir in this subpopulation has not been adequately evaluated. Therefore, this PMC aims to elucidate whether patients with significantly decreased OATP transporter function may experience a loss in response to elbasvir/grazoprevir 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.

To evaluate the effect of SLCO1B1 genotype on the pharmacokinetics of grazoprevir and clinical responses to elbasvir/grazoprevir treatment, either of the following studies may be performed:

- 1) Conduct a prospective clinical trial in patients with chronic hepatitis C virus infection (b) (4)
(b) (4)
- 2) Conduct a retrospective cohort study of existing data or data from ongoing or future clinical trials to evaluate differences in pharmacokinetics, SVR rates, and treatment emergent adverse events between different OATP1B1 genotype groups. (b) (4)
(b) (4)

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.*

(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 # 208261
Product Name: Zepatier

PMR/PMC Description: Submit the final report and datasets, including the SVR24 data, for Phase 3 Trial 068 (C-EDGE TE).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>02/29/2016</u>
	Other: _____	<u>MM/DD/YYYY</u>

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

Most subjects who achieve SVR12 have cleared HCV. However, a small percentage of subjects who achieve SVR experience late relapse. All subjects administered (b) (4) study drug will be followed (b) (4) to assess durability of SVR and the emergence and persistence of resistant viral variants. Subjects with a late relapse will be evaluated for reinfection. Waiting for these data would delay access to this drug for subjects who would benefit from it.

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 is to determine the extent of late relapse and distinguish late relapse from reinfection. Data (b) (4) will be submitted and reviewed to monitor the durability of virologic response of Zepatier. 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 trial used for registration of Zepatier.

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)

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

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.

(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 # 208261
Product Name: Zepatier

PMR/PMC Description: Submit the final report and datasets, including the SVR24 data, for Phase 2 Trial 048 (C-SALVAGE).

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 02/29/2016
Other: _____ MM/DD/YYYY

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

Most subjects who achieve SVR12 have cleared HCV. However, a small percentage of subjects who achieve SVR experience late relapse. All subjects administered (b) (4) study drug will be followed (b) (4) to assess durability of SVR and the emergence and persistence of resistant viral variants. Subjects with a late relapse will be evaluated for reinfection. Waiting for these data would delay access to this drug for subjects who would benefit from it.

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 is to determine the extent of late relapse and distinguish late relapse from reinfection. Data (b) (4) will be submitted and reviewed to monitor the durability of virologic response of Zepatier. 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

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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 trial used for registration of Zepatier.

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)

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

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?

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

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There is not enough existing information to assess these risks

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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 # 208261
Product Name: Zepatier

PMR/PMC Description: Submit the final report and datasets, including the SVR24 data, for Phase 3 Trial 061 (C-EDGE CO-INFECTION).

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 02/29/2016
Other: _____ MM/DD/YYYY

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

Most subjects who achieve SVR12 have cleared HCV. However, a small percentage of subjects who achieve SVR experience late relapse. All subjects administered (b) (4) study drug will be followed (b) (4) to assess durability of SVR and the emergence and persistence of resistant viral variants. Subjects with a late relapse will be evaluated for reinfection. Waiting for these data would delay access to this drug for subjects who would benefit from it.

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 is to determine the extent of late relapse and distinguish late relapse from reinfection. Data (b) (4) will be submitted and reviewed to monitor the durability of virologic response of Zepatier. 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

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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?

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Long-term follow-up data will be submitted from a primary clinical trial used for registration of Zepatier.

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)
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- 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)

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

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

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Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

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

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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

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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)

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

/s/

NINA MANI
01/27/2016

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: January 12, 2016
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: NDA 208261
Product Name and Strength: Zepatier
(elbasvir and grazoprevir) Tablets
50 mg and 100 mg
Submission Date: December 21, 2016
Applicant/Sponsor Name: Merck Sharp and Dohme Corp
OSE RCM #: 2015-1193
DMEPA Primary Reviewer: Mónica Calderón, PharmD, BCPS
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

Merck has submitted the revised container label and carton labeling (Appendix A) for Zepatier in response to recommendations we made during a previous label and labeling review.¹ Thus, the Division of Antiviral Products (DAVP) requested that we review the revised label and labeling to determine if it is acceptable from a medication error perspective.

2 CONCLUSION

The revised container label and carton labeling for Zepatier are acceptable from a medication error perspective. Merck provided the rationale for not adding the lot number and expiration date to the back outer panel of the blister sleeve (Appendix B) and we find their rationale reasonable. We have no further recommendations at this time.

¹ Calderon M. Label and Labeling Review for Zepatier (NDA 208261). 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); 2015 Dec 11. 32 p. OSE RCM No.: 2015-1193.

APPENDIX A. LABEL AND LABELING SUBMITTED ON DECEMBER 21, 2015

Dose Pak



Carton labeling



Outer Blister Sleeve

Appendix B

Merck's Response to FDA Comments of December 18, 2015

1. Proposed Container Label (blister sleeve of the dosepak)

a. The lot number and expiration date are required on the immediate container per 21CFR 201.10(i)(1) and 21 CFR 201.17, respectively. Add both to the back (outer) panel of the blister sleeve.

Merck response:

Merck believes that the current placement of lot number and expiration date (both on the exterior of the outer carton, and on the exteriors of the two individual dosepaks) is in compliance with the cited regulation. The blister sleeves, while appearing as separate artwork, will be assembled as part of each complete dosepak. Each dosepak is intended to be dispensed as one unit of packaging, to be drug listed with one NDC . The final complete dosepak serves as the immediate container.

Per 21 CFR 201.17, both the outer and immediate containers will contain an expiration date.

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

/s/

MONICA M CALDERON
01/12/2016

BRENDA V BORDERS-HEMPHILL
01/13/2016

**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: January 12, 2016

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: Morgan Walker, PharmD, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kemi Asante, PharmD, RAC
Patient Labeling Reviewer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): ZEPATIER (elbasvir and grazoprevir)

Dosage Form and Route: tablets, for oral use

Application Type/Number: 208261

Applicant: Merck Sharp & Dohme Corp.

1 INTRODUCTION

On May 28, 2015, Merck Sharp & Dohme Corp. submitted for the Agency's review a New Drug Application (NDA) 208261 for ZEPATIER (elbasvir and grazoprevir) tablets. The proposed indication is for the treatment of chronic hepatitis C genotypes (GT) 1, 4, or 6 infection in adults.

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 June 5, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ZEPATIER (elbasvir and grazoprevir) tablets.

2 MATERIAL REVIEWED

- Draft ZEPATIER (elbasvir and grazoprevir) PPI received on May 28, 2015, and received by DMPP and OPDP on December 30, 2015.
- Draft ZEPATIER (elbasvir and grazoprevir) Prescribing Information (PI) received on May 28, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 30, 2015.

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 PPI 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 PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI 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 PPI 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 PPI.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
01/12/2016

OLUWASEUN A ASANTE
01/12/2016

BARBARA A FULLER
01/12/2016

LASHAWN M GRIFFITHS
01/12/2016

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

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

Memorandum

Date: January 7, 2016

To: Nina Mani
Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Kemi Asante, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 208261
Zepatier (elbasvir and grazoprevir) tablets, for oral use

In response to DAVP's June 5, 2015 consult request, OPDP has reviewed the proposed package insert (PI), patient package insert (PPI) and carton/container labeling for Zepatier (elbasvir and grazoprevir) tablets for oral use.

Comments on the PI are provided below and are based on the review of the substantially complete version of the PI provided by DAVP via email on December 30, 2015.

We have no comments on the carton/container labeling accessed from the following EDR link provided by DAVP:

<\\CDSESUB1\evsprod\NDA208261\208261.enx>.

Please note that comments on the PPI will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at 301-796-7425 or Kemi.Asante@fda.hhs.gov.

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/s/

OLUWASEUN A ASANTE
01/07/2016

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: December 11, 2015
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: NDA 208261
Product Name and Strength: Zepatier
(elbasvir and grazoprevir) Tablets
50 mg /100 mg
Product Type: Multi-Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Merck Sharp and Dohme Corp
Submission Date: May 28, 2015
OSE RCM #: 2015-1193
DMEPA Primary Reviewer: Mónica Calderón, PharmD, BCPS
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD
DMEPA Associate Director: Irene Chan, PharmD, BCPS

1 REASON FOR REVIEW

Merck submitted a new drug application (NDA 208261) for the treatment of chronic hepatitis C (CHC) genotypes 1, 4, or 6 infection in adults. Thus, the Division of Antiviral Products (DAVP) requested DMEPA evaluate the Applicant's proposed labels and labeling and Patient Package Insert (PPI) labeling comprehension study results to identify areas of vulnerability that could lead to medication errors.

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
Previous DMEPA Reviews	B (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other – PPI Labeling Comprehension Study	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Merck is proposing a multi-ingredient tablet containing elbasvir 50 mg and grazoprevir 100 mg. The tablets will be packaged in a carton containing two (2) 14-count child-resistant dosepacks for a total of 28 tablets. This packaging configuration provides a 4-week supply of medication that supports the dosage and administration of this product, once daily.

Full Prescribing Information (FPI)- Dosage and Administration Section

We note the current FPI provides the recommended dosing for adult patients in the Dosage and Administration section. The instructions are clearly written and the dosing information contained within the table are clear. We have no risk mitigating recommendations at this time.

Patient Package Insert (PPI) Labeling Comprehension Study

Merck performed a labeling comprehension study to assess the readability and comprehension of the PPI for grazoprevir/elbasvir to optimize language, format, and presentation order for maximum consumer clarity and understanding.

Participants (n=60) representing a range of health literacy levels were given the PPI for review, followed by an “open book” untimed 18-question comprehension test, an “open book review” of comprehension test answers, and then were asked open-ended questions to assess their understanding of the medication, what it was for, how it should be taken, and important safety information and side effects with no access to the PPI.

Comprehension score was calculated as a percent of correct answers on the test, which consisted of a mix of multiple choice and true/false questions. The limited health literacy group scored an average of 91% and the adequate health literacy group scored an average of 97% on their reading comprehension test meeting Merck’s pre-set goal of 80%. Most respondents were able to recall key PPI information when given the closed book portion of the testing. However, Merck did not provide any data regarding study failures. On September 30, 2015, an information request was sent to Merck requesting information regarding errors or difficulties with comprehension seen in the PPI labeling comprehension study. In Merck’s response dated October 9, 2015, they note that there were no specific errors or difficulties with comprehension seen in the multiple-choice question portion. However, during the follow-up open-ended question portion when the PPI was removed, Merck noted difficulty among participants in the ability to accurately describe what to do if a subject missed a dose. As a result, Merck proposed changes to the PPI section “What if I forget to take TRADEMARK?”. Our review of this section of the PPI did not identify any areas vulnerable to confusion, and we recommend the Patient Labeling Team is consulted to evaluate the results of the labeling comprehension study and provide feedback for the proposed PPI. We defer to Patient Labeling Team for appropriate language. DMEPA notes that during the follow-up open-ended question portion, 12% of participants were unable to recall how often to take the medication. We reviewed the “How do I take TRADEMARK” section of the PPI and container label and carton labeling, assessed below, and determined that the dosage and administration is clearly presented for patients to refer to during administration. Given the lack of root cause information provided by Merck, we do not recommend any changes at this time, but will monitor postmarket for any confusion or medication errors regarding proper dosage of this product.

Container Label and Carton Labeling

Merck submitted container labels and carton labeling for a carton containing a dosepak which includes a blister sleeve for review. (b) (4)

The dosepak contains instructions highlighting the once daily dosage and administration of this medication. On October 16, 2015, an information request was sent to Merck (Appendix G), requesting formative or summative data from human factors studies that may have been conducted during the development of their packing configuration to support the safe and correct use of their product in this packaging. Merck noted they acquired data on comprehension of the packaging, (b) (4) According to Merck, all twenty-five subjects were given qualitative interviews, provided a sample package, and asked pre-defined questions with respect to use of the package and understanding the dosing instructions. We identified areas of improvement for the blister sleeve to help prevent

confusion about the frequency of administration (b) (4)
(b) (4). As the proposed blister card is currently presented, we are concerned (b) (4)

(b) (4). We also note that important and required information (e.g., lot number, expiration) is missing on the inner and outer portions of the blister sleeve of the dosepak. We provide recommendations in Section 4.1 to improve readability and include important information.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes the blister sleeve label of the dosepak, and carton labeling can be revised to improve clarity and readability as well as add important information. We recommend DAVP consults the Patient Labeling Team (PLT) to evaluate the PPI label comprehension study.

4.1 RECOMMENDATIONS FOR MERCK

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

Container Label

1) Proposed Container Label (blister sleeve of the dosepak)

- a. The lot number and expiration date are required on the immediate container per 21 CFR 201.10(i)(1) and 21 CFR 201.17, respectively. Add both to the back (outer) panel of the blister sleeve.
- b. On the outer blister sleeve, place the proprietary name, established name, strength, lot number, expiration date, and manufacturer so that the information appears on each segment panel, ensuring this important information is available in the event the sleeve is removed or torn at the fold. The strength should describe the milligram amount of drug per single unit so that there is no confusion as to how much product is contained in a single unit. We recommend the product strength appear as follows: 50 mg /100 mg per tablet.
- c. Ensure the directions to take one tablet daily are available on each segment panel in case the sleeve is removed or torn at the fold.
- d. On the inner blister sleeve (b) (4)
(b) (4) may cause confusion regarding the frequency of dosing. (b) (4)

(b) (4). We recommend you propose an alternate solution to address the risk for this type of medication error. Consider whether labeling (b) (4)
(b) (4) may help to mitigate the risk for this error. We recognize you conducted a packaging comprehension study; however, your response to the information request that described your testing suggests that this particular hazard was not investigated during your testing.

Carton Labeling

1) Proposed Carton Labeling

- a. Change the following statement (b) (4)
(b) (4) to read as follows: “This carton contains a total of 28 tablets packaged within 2 dose packs. Each dose pack contains 14 blister units with one-50mg/100 mg tablet per unit.”

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for elbasvir and grazoprevir that Merck submitted on May 28, 2015.

Table 2. Relevant Product Information for elbasvir and grazoprevir	
Active Ingredient	elbasvir and grazoprevir
Indication	Treatment of chronic hepatitis C (CHC) genotypes 1, 4, (b) (4) infection in adults.
Route of Administration	Oral
Dosage Form	Tablet
Strength	50 mg/100 mg
Dose and Frequency	One tablet once daily. Duration of therapy is based on the patient population and genotype in HCV mono-infected and HCV/HIV-1 co-infected patients with or without cirrhosis
How Supplied	tablets are packaged into a carton containing two (2) 14 count child-resistant dose packs for a total of 28 tablets
Storage	20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (between 59°F to 86°F)

APPENDIX F. LABELING COMPREHENSION STUDY - EXCERPTS FROM SUBMISSION

F.1 Study Design

The primary objective of the labeling comprehension study was to assess the readability and comprehension of patient labeling for elbasvir and grazoprevir to optimize language, format, and presentation order for maximum clarity and understanding.

F.2 Study Population

- 60 patient participants total interviewed by telephone or in-person
 - hepatitis C patients (n=40)
 - participants were recruited based on presence of related conditions (e.g. HIV and chronic kidney disease)
 - non-diagnosed general population (n=20)
- participants with limited health literacy (n=16)

Interview Demographics					
HCV Patients (n=40)			General Population (n=20)		
	In-Person Interviews	Telephone Interviews		In-Person Interviews	Telephone Interviews
HCV Only	0	12	Gen Pop Only	2	7
HCV + HIV	3	8	Gen Pop with CKD	1	3
HCV + CKD	0	5	Gen Pop with HIV	1	6
HCV + Cirrhosis	1	7			
HCV + HIV + Cirrhosis	0	2			
HCV + CKD + HIV	1	1			
Sub-Total	5	35		4	16
HCV Patient Total	40		Gen Pop Total	20	
Total Population	60				

Health Literacy Levels						
	HCV Patients (n=40)		General Population (n=20)		Total Limited	Total Adequate
	Limited	Adequate	Limited	Adequate		
In-Person Interviews	2	3	1	3	16	44
Telephone Interviews	6	29	7	9		
TOTAL	8	32	8	12	60	

- Measure of consumer's understanding of health information
 - Comprehension score of 80% or greater across all segments.

F.3 Design

In depth 40-60 minute interviews conducted between May and June of 2015. A mix of both in-person and phone/web-based interviews with 60 consumers.

Interview Flow

- Newest Vital Sign (NVS) Assessment – The NVS Health Literacy Exam was administered to consumers prior to the start of the interview.
- General Usage – Consumers were asked a general set of questions regarding patient labeling use, including when and if they read patient labeling information, their primary language, etc. In-person respondents completed a short questionnaire, whereas telephone respondents answered questions verbally.
- Review of Patient Labeling – Consumers read the patient labeling in its entirety at their own pace, which was timed to ensure it fell within the acceptable parameters of five minutes. On average, it took respondents 4.7 minutes to read the proposed labeling.
- Comprehension Test (Open Book Questions) – Patient labeling remained with the consumer. The untimed 18-question test consisted of a mix of multiple choice and true/false questions. Consumers were allowed to refer back to the patient labeling at any time to find the answers.
- Patient Labeling Deep Dive (Open Book Review) – Patient labeling was reviewed with consumers in detail to gain a greater depth of understanding of their comprehension. Specific attention was paid to questions answered incorrectly during the comprehension test. Consumers were asked to identify what they believed caused those questions to be answered incorrectly (e.g., they forgot the information, missed/skipped over the information, were confused by the information, misunderstood the information, etc.).
- Utilization and Recall (Closed Book Review) – Patient labeling was removed and consumers were then asked open-ended questions to assess their understanding of the medication, what it is for, how it should be taken, what important safety information they should tell their doctors, and possible side effects.
- Exit Survey – At the end of the interview, respondents identified if they are currently being treated for abusing drugs or alcohol, if they have ever been in jail, and if they are IV drug users. 7% of respondents across all segments (i.e., both limited and adequate health literacy, and both HCV patients and general population respondents) said they are being treated for abusing drugs or alcohol. 28% of respondents across all segments reported having been in jail. 5% of respondents across all segments indicated they are IV drug users.

F.4 Labeling Comprehension Results

Respondent comprehension across all categories exceeded this target, scoring an average of 96%. As shown in the table below, both limited and adequate health literacy groups had high comprehension scores (91% and 97%, respectively).

Reading Comprehension Test Score Average by Audience Group			
HCV Patients (n=40)	General Population (n=20)	Adequate Health Literacy (n=44)	Limited Health Literacy (n=16)
97%	93%	97%	91%

Reading Comprehension Test Score Average by Education Level					
Some High School (n=2)	Completed High School (n=8)	Some College (n=24)	Completed College (n=15)	Some Post Grad (n=1)	Completed Post Grad (n=10)
97%	92%	96%	95%	100%	97%

Reading Comprehension Test Score Average by Age				
Ages 18-34 (n=9)	Ages 34-44 (n=8)	Ages 45-54 (n=17)	Ages 55-64 (n=18)	Ages 65-75 (n=8)
94%	98%	95%	96%	96%

- Participant feedback was overall positive and the majority of participants liked the images included within the PPI and felt they enhanced comprehension of the PPI as a whole.

Applicant Conclusion

Most participants were able to recall key patient labeling information during the closed book review, confirming that most participants understood how often they should take elbasvir and grazoprevir in addition to what grazoprevir/elbasvir treats, common side effects, and what they should tell their doctor about before starting grazoprevir/elbasvir.

DMEPA Assessment

- Merck did not make any changes to the PPI after the labeling comprehension study as a result of the overall comprehension scores being at least 80% or greater across all segments.
- Merck did not provide any root cause information with regard to failures participants encountered during any particular portion of the interview and testing, limiting the ability to provide feedback on improvement to the PPI. Information on failures specific to administration of the medication also was not included.
- The labeling comprehension study did not evaluate the container label or carton labeling submitted by Merck for review.

F.4 Applicant Response to FDA Information Request regarding label comprehension study (October 9, 2015)

NDA 208,261: Merck Response to the FDA information request of September 30, 2015 regarding the Labeling Comprehension Study for Elbasvir/Grazoprevir (MK-5172A)

FDA Information Request:

To expedite our review of your labeling comprehension study, we request that you provide information regarding the errors or difficulties with comprehension seen in your labeling comprehension study, any follow up questions that were asked of study participants and their responses, your root cause analyses, discussion of effectiveness of existing mitigation, and your rationale for why additional mitigations are not necessary. Please submit your response by Friday, October 9, 2015.

Merck Response:

We appreciate the agency's thorough review of our labeling comprehension study and interest in the process for development and testing of patient labeling for new molecules. The engagement around patient labeling at this point in the review process creates opportunity for further discussion on this very important topic.

The label comprehension study was conducted in subjects with chronic HCV infection and subjects without HCV infection, representing a range of health literacy levels. Subjects without HCV were included to confirm that this information would be well-understood, even by those without prior knowledge of HCV or medications to treat HCV.

Subjects participated in qualitative interviews by reading the entire patient labeling and completed a multiple-choice, "open-book" comprehension questionnaire. The interviewer then reviewed the patient labeling with the participant in-depth to uncover areas of misunderstanding or confusion. The patient labeling was then removed (closed-book) and the participants were asked open-ended questions to assess their recall and understanding of the patient labeling. The testing was completed after Merck submitted its draft labeling with this NDA, and therefore the patient labeling that was tested was in all relevant respects identical to the draft patient labeling submitted with the NDA.

Merck's goal of achieving high comprehension was exceeded across all segments. Overall, respondents' comprehension was measured at 96% (91% for individuals presenting with limited health literacy, and 97% for those with adequate health literacy)—very high comprehension levels by any standard. Over a quarter of participants had limited health literacy. Previous research, conducted by (b) (4) and others in the context of Medication Guide comprehension, has demonstrated a strong differential in comprehension between individuals with adequate and limited health literacy levels.¹ The high comprehension level by both adequate and limited health literacy respondents in this testing reflects the new process that Merck has used, in partnership with health literacy experts, for the development of patient labeling for new molecules. This new process includes focus groups done by Dr. (b) (4) (b) (4) and her team (b) (4) and (b) (4) and his team (b) (4) with participants across a range of health literacy levels, to identify and correct areas of potential confusion (prior to comprehension testing). The process also includes significant, iterative input from these leaders in the field of health literacy.

There were no specific errors or difficulties with comprehension seen in the multiple-choice question portion of the labeling comprehension study. High levels of comprehension (87-100%) were demonstrated for each question.

After respondents completed the multiple-choice comprehension questions, and provided additional feedback on each section, the patient labeling was removed and follow up questions were asked "closed-book" of respondents. These questions focused on appropriate use, side effects, and dosing, and are standard questions in Merck's qualitative research process for patient labeling comprehension studies. Because this portion of the research asked open-ended questions, without multiple-choice responses, its focus was on the independent recall of the participants, rather than reading comprehension. Even with closed-book methodology, participants (including those with limited health literacy) had the following strong levels of recall:

- What does TRADEMARK treat?
 - All respondents (100%) correctly indicated chronic hepatitis C.
- What are some of the common side effects that might happen with you get TRADEMARK?
 - Most respondents (92%) recalled at least one side effect.
 - Many respondents (70%) recalled at least two side effects.

- What are some of the common side effects of TRADEMARK when used with ribavirin?
 - Most respondents (78%) recalled at least one side effect.
 - Most respondents (75%) recalled at least two side effects.
- What are the things you would need to tell your doctor about before starting TRADEMARK?
 - Most respondents (95%) recalled at least one thing they should tell their doctor.
 - Most respondents (85%) recalled at least two things they should tell their doctor.
- How often should you take TRADEMARK?
 - Most respondents (88%) recalled that one pill was to be taken once daily.

As described above, part of the qualitative testing involved an in-depth section-by-section review with participants to confirm comprehension of the information. Although nearly all respondents answered the following multiple-choice question correctly: "What should Katie do if she forgets to take TRADEMARK?" during the subsequent section-by-section review, many could not accurately describe what to do if a subject missed a dose. They expressed confusion about the specific timing. To address challenges with numeracy (the ability to understand, use, and evaluate numbers), Merck consulted again with (b) (4) and (b) (4) and their teams to streamline and simplify this text. As a result, we now propose the following change to improve the clarity of this section:

Tested (submitted) text:

What if I forget to take TRADEMARK?

(b) (4)

Proposed revisions:

What if I forget to take TRADEMARK?

(b) (4)



Merck will incorporate these revisions following receipt of specific feedback from the FDA on the patient labeling.

In summary, Merck believes that the content and format of this patient label is strongly supported by the clear comprehension of both adequate and limited health literacy respondents. Because of the iterative development and testing process, which included significant input from consumers (focus groups and comprehension testing) and continuous partnership with health literacy leaders, Merck believes that additional mitigation is not necessary.

KEY TO ANNOTATIONS

Ref. 5.4 = Literature References

(b) (4)



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 elbasvir and grazoprevir labels and labeling submitted by Merck on May 28, 2015 and September 3, 2015.

- Container label
- Carton labeling
- Patient Package Insert

G.2 Label and Labeling Images Proposed Inner Blister Sleeve



Outer Blister Sleeve



Dose Pak

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

(b) (4)

Carton Labeling

(b) (4)

G.3 Applicant Response to FDA Information Request regarding packaging (October 21, 2015)

NDA 208,261: Merck Response to the FDA Comments of October 16, 2015 on the Carton Labelling and Blister Packaging for the MK-5172A tablet

FDA comment:

We have identified some concerns with the carton labeling and blister packaging which may lead to confusion among patients in understanding the medication is to be taken once daily. Do you have any formative or summative data from human factors studies that you may have conducted during the development of your packaging configuration to support the safe and correct use of your product in this packaging?

Merck response:

Merck took a proactive approach to acquire data on comprehension of the packaging, including how to use the calendar feature. The objective of the research was to evaluate ease-of-use of a two-week "Dosepak" wallet including the labeling which holds the blisters. As part of this testing 25 of 25 (100%) of subjects correctly understood that medication was to be taken once daily.

- Twenty-five individual qualitative interviews were conducted with respondents ages 45-75, with greater than half over the age of 60. Respondents included males and females and several people with limited health literacy. The diversity of subjects helps to assure the understanding of a diverse patient population including those potentially at the greatest risk for confusion.
- Subjects were provided a sample package and were asked pre-defined questions with respect to use of the package and understanding of the dosing instructions.
- To mimic a real-life situation, subjects were not required to read the instructions on the package.
- When testing this package, every person correctly understood that one pill was to be taken every day (25 of 25 respondents).

Based on this assessment, Merck considers the very high rate of comprehension to indicate that the risk for misinterpretation of dosing instructions is low.

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/s/

MONICA M CALDERON
12/11/2015

BRENDA V BORDERS-HEMPHILL
12/11/2015

IRENE Z CHAN
12/12/2015

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: October 23, 2015

TO: Nina Mani, Ph.D., M.P.H., Regulatory Health Project Manager
Sarita Boyd, PharmD, Clinical Reviewer
Division of Anti-Viral Drug Products

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

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

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 208261

APPLICANT: Merck Sharp & Dohme Corp

DRUG: Zepatier (grazoprevir/elbasvir)
NME: Yes

THERAPEUTIC CLASSIFICATION: Priority review
INDICATION: Treatment of chronic hepatitis C genotype 1, 4, 5, or 6 virus infection in adults

CONSULTATION REQUEST DATE: June 18, 2016
DIVISION ACTION GOAL DATE: January 28, 2016
PDUFA DATE: January 28, 2016
INSPECTION SUMMARY DUE DATE: December 20, 2015

I. BACKGROUND:

The applicant is seeking approval of grazoprevir/elbasvir (GZR/EBR), a fixed dose combination of 100 mg of GZR and 50 mg of EBR. The recommended dose is 100 mg of MK-5172/ 50 mg of MK-7842 once daily administered orally with or without food; and the addition of RBV [REDACTED]^{(b)(4)} was recommended.

The Applicant sponsored two studies in support of the application: Study Protocols PN-5172-060 in treatment-naïve subjects with chronic HCV GT 1, GT 4, GT 5, and GT 6 infected subjects, and PN-5172-068 for treatment of the same genotypes but who have failed prior pegylated interferon and ribavirin.

1. **Study PN5172- 060-01:** “A Phase 3, Randomized, Clinical Trial to Study the Safety and Efficacy of the Combination Regimen of MK-5172/MK-8742 in Treatment-Naïve Subjects with Chronic HCV GT1, GT4, GT5, and GT6 Infection” and
2. **Study PN5172-068:** “A Phase 3, Randomized, Clinical Trial to Study the Safety and Efficacy of the Combination Regimen of MK-5172/MK-8742 in Subjects Who Have Failed Prior Treatment with Pegylated Interferon and Ribavirin (P/R) with Chronic HCV GT1, GT4, GT5, and GT6 Infection”

Protocol PN 5172- 060

The objectives of this study were: 1) to evaluate the efficacy of MK-5172 in combination with MK-7842 as assessed by the proportion of subjects in the immediate treatment arm achieving SVR 12 (Sustained Virologic Response, 12 weeks after the end of all study therapy), and 2) to evaluate the safety and tolerability of MK-5172 in combination with MK-7842 FDC as assessed by review of the accumulated safety data.

The secondary objectives of this study were: 1) to determine the proportion of subjects who attain SVR at 24 weeks after discontinuation of therapy, and 2) to evaluate the emergence of viral resistance associated variants (RAVs) to MK-5172 or MK-7842 when administered as part of a combination regimen.

This protocol was a randomized, parallel-group, placebo-controlled, multi-site, double-blind trial of 100 mg of MK-5172 in combination with 50 mg of MK-7842 in subjects with chronic Hepatitis C virus (HCV), genotype (GT) 1, 4, 5, or 6 infection who were treatment-naïve. It was conducted in conformance with Good Clinical Practices. A total of 400 HCV GT 1, 4, 5, and GT 6 infected subjects were studied with documented chronic genotypes listed above.

HCV study populations in PN5172- 060 were divided into 4 groups:

- Chronic HCV GT 1, 4, 5, and 6 infection
- Approximately 20% of subjects who were enrolled had evidence of compensated cirrhosis.
- Approximately 15% of subjects who were enrolled had HCV GT 4, 5, and 6.

- Treatment-naïve to all anti-HCV treatment including any Direct-Acting Antivirals (DAA)

Subjects in the immediate treatment group received MK-5172A 100 mg/50 mg (100 mg MK-5172 50 mg MK-7842 for 12 weeks with 24 weeks of follow-up after dosing is completed. Subjects in the deferred treatment group received Placebo for 12 weeks followed by 4 weeks of follow-up and then 12 weeks of open-label treatment with MK-5172A 100 mg/50 mg (100 mg MK-5172mg/50 mg MK-8742) with 24 weeks of follow-up after dosing is complete.

Protocol PN5172-068

The primary objectives of this study were: 1) to evaluate the efficacy of MK-5172 in combination with MK-8742 (+/- RBV) as assessed by the proportion of subjects achieving SVR 12 (Sustained Virologic Response 12 weeks after the end of therapy), defined as HCV RNA <LLOQ 12 weeks after the end of therapy, and 2) to evaluate the safety and tolerability of MK-5172 in combination with MK-7842.

The secondary and exploratory objectives were: 1) to determine the proportion of subjects achieving undetectable (TND) HCV RNA and HCV RNA <LLOQ at weeks 2, 4, 12, and follow-up at week 4 (SVR4), 2) to evaluate the emergence of viral resistance- associated variants to MK-5172 or MK-7842 +/- RBV when administered as part of a combination regimen.

This study was a randomized, parallel-group, multicenter, open-label trial of MK-5172 and MK-7842 in subjects with hepatitis C, with and without compensated cirrhosis who have failed prior treatment with pegylated interferon (peg-IFN) and ribavirin (RBV). This study was conducted in conformance with Good Clinical Practices. Approximately 400 subjects with HCV GT 1, 4, 5, or 6 were enrolled, with approximately 30% in each subgroup defined by genotype and prior treatment experience. Approximately 30% of subjects enrolled in each genotype by prior treatment status had compensated cirrhosis at screening and approximately 20% of the subjects were HIV co-infected. The number of subjects who were prior peg-IFN relapsers was capped at 20%. Study subjects received MK-5172A (fixed dose combination of 100 mg MK-5172 +50 mg MK-7842) QD for 12 or 16 weeks, with or without RBV with 24 weeks of follow-up after dosing was completed.

The duration of the study was 40 weeks. All subjects completed screening, on-treatment, and post-treatment assessments. Female subjects used adequate birth control. Subjects had taken no medication and did not have any medical conditions which were prohibited in the protocol.

The review division requested inspection of six clinical investigators because data from the studies are considered essential to the approval process. These sites were targeted for inspection due to 1) enrollment of a relatively large number of subjects with a treatment effect that was greater than average, and 2) the need to determine if sites conducted the trials ethically and were in compliance with GCP regulation and local requirements. It is for these reasons that it is critical that international sites were included in the inspection. As noted in the consult, specific reasons for site selection include:

Protocol PN 5172- 060: Dr. Di Martino's site was chosen because the site had the highest number of protocol deviations.

Protocol PN 5172- 068: Dr. Vierling’s site had an SAE altered to appear as if no SAE had occurred. In addition, there was a lack of oversight and issues with drug storage temperatures. Dr. Serfaty’s site was among the sites with higher number enrolled, and had a relatively high number of protocol deviations.

II. RESULTS (by protocol/site):

Name of CI, Location, and Site #	Protocol and # of Subjects Randomized	Inspection Dates	Final Classification
Vincent di Marino, M.D. Besancon, France 25030 Site #157	5172-060 Number of subjects: 8	9/7-9/2015	Pending (preliminary classification NAI)
Lawrence Serfaty, M.D. Paris, France 75012 Site #1672	5172-068 Number of subjects: 10	8/31- 9/3/2015	Pending (preliminary classification NAI)
Jonathan McConne, M.D. Alexandria, VA 22306 Site #399	5172-060 Number of subjects: 12	8/11-14/2015	Pending (preliminary classification NAI)
Reem Ghalib, M.D. Arlington, TX 76012 Site #390	5172-060 Number of subjects: 18 subjects	8/4-7/2015	NAI
Natarajan Ravendhran, M.D. Catonsville, MD 21228 Site #1429	5172-068 Number of subjects: 14	7/13-17/2015	Pending (preliminary classification VAI)
John Vierling, M.D. Houston, TX 77030 Site #1438	5172-068 Number of subjects 17	7/20-25/2015	Pending (preliminary classification NAI)

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data found 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. Vincent Di Martino, M.D.
Besancon, France 25030**

- a. What Was Inspected:** At this site, a total of 10 subjects were screened, two subjects were reported as screen failures, eight subjects were randomized into the study, and all eight subjects completed the study.

The medical records/source data for eight subjects were reviewed and compared to data listings. The review included drug accountability records, drug dispensing records, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for eight subjects were examined for eligibility criteria, protocol deviations, and prohibited medications and were compared to case report forms and data listings including primary efficacy endpoints and adverse events reporting. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Di Martino. Although no FDA 483 was issued to the clinical investigator, our FDA inspector discussed with the clinical investigator minor deficiencies in protocol compliance which did not affect subject safety or endpoint data. There were no unreported 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 at this site, and data generated by this site are considered reliable and appear acceptable in support of the pending applications.

**2. Lawrence Serfaty, M.D.
Paris, France 75012**

- a. What Was Inspected:** At this site a total of 12 subjects were screened, two subjects were reported as screen failures, 10 subjects were randomized into the study, and nine subjects completed the study.

The medical records/source documents for all subjects were reviewed. The medical records/source documents for enrolled subjects for certain visits were reviewed including drug accountability records, vital signs, IRB files, inclusion/exclusion criteria, prior and concomitant medications, and adverse events reporting. The field investigator compared the source documents/primary and secondary endpoints and adverse events reporting to the data listings for primary efficacy endpoints.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Serfaty. Our investigator presented and discussed the inspectional observation with the clinical investigator. The discussion included a minor protocol deviation related to informed consent issues. The revised informed consent included the requirement that the subjects must provide a urine sample. Due to a communication error, the revised consent was received by the site late. Once the site received the new version, the site obtained updated informed consent from all subjects.

In general, the medical records reviewed were found to be in order, organized, and the data verifiable. There was no evidence of under-reporting of adverse events to the sponsor or the agency. No major discrepancies were noted between source documents and data listings. Review of the Informed Consent Documents, for the majority of subjects records reviewed, verified that all subjects signed informed consent forms prior to enrollment. There were no known limitations to the inspection.

- c. Assessment of Data Integrity:** Although a minor protocol deviation was noted at this site, the finding appears to be isolated and unlikely to impact the outcome of the study or subject safety. The data in support of the clinical efficacy and safety at this site are considered reliable and may be used in support of the pending applications.

3. Jonathan McConne, M.D.
Alexandria, VA 22306

- a. What Was Inspected:** At this site, a total of 14 subjects were screened, two subjects were reported as screen failures, 12 subjects were randomized into the study, and 12 subjects completed the study.

The medical records/source data for 12 subjects were reviewed. The review included primary/secondary endpoints, drug accountability records, vital signs, IRB records, inclusion/exclusion criteria, and the use of concomitant medications and adverse events reporting. Source documents were compared to data listings for primary efficacy endpoints.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. McConne. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment. There were no discrepancies noted between source documents and data listings.

However, our ORA investigator discussed with the clinical investigator minor deficiencies such as abnormal ECG readings which were not included as part of the medical history. There were no known limitations to the inspection. There were no unreported 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 is considered reliable and may be used in support of the pending applications.

4. Reem Ghalib, M.D.
Arlington, TX 76012

- a. What Was Inspected:** At this site, 19 subjects were screened, two subjects were reported as screen failures, 18 subjects were enrolled, and all 18 subjects completed the study.

The medical records/source data for 11 subjects enrolled in the study were reviewed and compared to the data listings. The records for the 11 subjects compared source documents to electronic case report forms and to data listings including primary efficacy endpoints and adverse event reporting. In addition, the review included drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, and sponsor correspondence. .

- b. General Observations/Commentary:** Subject 435152 was hospitalized due to lower quadrant abdominal pain. A laparoscopic appendectomy was performed and was discharged from the hospital the same day. The subject expired one day later. The SAE was reported to the IRB. The causality was determined not to be related to study medication. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment. No discrepancies were found on examination of source data and data listings. At the conclusion of the inspection, no Form FDA 483 was issued to Dr.Ghalib. In general, the medical records were found to be in order, organized, and the data verifiable. There was 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 in support of the clinical efficacy and safety at Dr. Ghalib’s site is considered reliable and may be used in support of the pending application.

5. Natarajan Ravendhran, M.D.
Catonsville, MD 21228

- a. What was inspected:** At this site, a total of 14 subjects were screened, 14 subjects were randomized into the study, and 14 subjects completed the study treatment.

The medical records/source documents for 14 enrolled subjects were reviewed. The review included drug accountability records, vital signs, IRB files, primary efficacy endpoints, inclusion/exclusion criteria, study procedures, randomization, monitoring procedures, use of concomitant medications, and sponsor correspondence. Source documents were compared to CRFs and data listings, to include primary efficacy endpoints and adverse events.

- b. General Observations/Commentary:** At the conclusion of the inspection, a one-item Form FDA 483 with subsets was issued to Dr. Ravendhram. Our ORA investigator presented and discussed with the clinical investigator the enrollment of three subjects who did not satisfy the inclusion/exclusion criteria, and the failure to comply with IRB recommendations to re-consent all subjects with the most recently approved informed consent. The protocol violations included the following:

According to the protocol Section 5.1.3 “Subjects must be excluded from participating in the trial if the subject met exclusion criteria”. For example:

- Subject 689416 had cirrhosis but no liver imaging within 6 months of Day 1 showing evidence of hepatocellular carcinoma (HHCC). No imaging was done at screening.
- Subject 682080 had a history of malignancy less than or equal to 5 years prior to signing the informed consent document.

According to the protocol Section 5.1.2 “In order for subjects to be eligible for participation in this trial, the subject must have a previous HCV treatment status that is one of the following (documentation of mode of failure and duration of prior therapy as required”.

- Subject 682052 had no documentation showing previous treatment response or duration of prior therapy.

According to the protocol and federal regulations, subjects must sign an IRB approved informed consent document prior to enrollment. The IRB informed the clinical investigator that all subjects had to sign the revised informed consent document to remain in the study, and any new subjects enrolled were to sign the revised informed consent document.

- The ORA investigator found at least five subjects who did not sign the revised consent form in a timely manner (signed 2-4 weeks after the revised updated informed consent was approved). In addition, two subjects signed the informed consent document dated 5/9/2014 instead of the revised version dated 6/24/2014.

With the exceptions note above, 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. Review of the Informed Consent Documents for all subjects verified that all subjects signed informed consent forms prior to enrollment. Minor Exceptions for two subjects were noted as shown below. There were no known limitations to the inspection.

- c. Assessment of Data Integrity:** Other than the minor deviations noted at the above site, the study appears to have been conducted adequately, and the data generated in support of the clinical efficacy and safety at Dr. Ravendhram’s site is reliable and may be used in support of the pending applications. The review division may consider excluding the three subjects who failed inclusion/exclusion criteria from their final

analyses in their assessment of safety and efficacy in support of the pending application.

**6. John Vierling, M.D.
Houston, TX 77030**

- a. What was inspected:** At this site, a total of 21 subjects were screened, four subjects were reported as screen failures, 17 subjects were enrolled, and 17 subjects completed the study.

The complete medical records/source documents for 17 subjects were reviewed including drug accountability records, vital signs, IRB files, laboratory results, inclusion/exclusion criteria, use of concomitant medications, and adverse events reporting. Source documents for the majority of subjects were compared to case report forms and data listings and adverse events reporting.

- b. General Observations/Commentary:** Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment. The assignment included a complaint; however, the deviations listed in the complaint could not be substantiated. At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Vierling. In general, the medical records were legible, organized and the data verifiable. There was no evidence of under-reporting of adverse events. There was no known limitation to the inspection.
- c. Assessment of Data Integrity:** Overall the study appears to have been conducted adequately, and the data generated at this site in support of the clinical efficacy and safety is considered acceptable and may be used in support of the pending application.

IV. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Six clinical investigator sites were inspected in support of this application. The inspection of four clinical investigators listed above revealed no regulatory violations. The final classification for Dr. Ghalib site is No Action Indicated (NAI), and the pending classification for Drs. Martino, Serfaty, McConne and Vierling are No Action Indicated (NAI).

The pending classification for Dr. Ravendhran is Voluntary Action Indicated (VAI) resulting from instances of protocol deviation. For the pending classifications, a summary addendum will be generated if conclusions change upon receipt and review of the EIRs. Overall, while the above finding represent observed regulatory deficiency, the finding noted at Dr. Ravendhran is unlikely to have a significant impact on data acceptability. Other than this isolated observation at Dr. Ravendhran site, the remaining sites inspected appears to have been conducted adequately, and the data generated by the sites appear acceptable and may be used in support of the respective indication. The review division may consider conducting both intention to treat and per-protocol

analysis taking into account the three subjects who failed inclusion/exclusion criteria in their assessment of safety and efficacy in support of the pending application.

{See appended electronic signature page}

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/s/

ANTOINE N EL HAGE
10/28/2015

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10/28/2015

KASSA AYALEW
10/28/2015

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

NDA	208261
Generic Name	Grazoprevir/Elbasvir
Sponsor	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Indication	Treatment of chronic hepatitis C virus infection
Dosage Form	Tablet
Drug Class	Grazoprevir MK-5172 - NS3/4A protease inhibitor Elbasvir MK-8742 - Nonstructural protein 5A inhibitor
Therapeutic Dosing Regimen	Grazoprevir MK-5172 – 100 mg Elbasvir MK-8742 - 50 mg
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Well-tolerated up to the maximum tested single doses Grazoprevir MK-5172 – 1600 mg Elbasvir MK-8742 - 700 mg
Submission Number and Date	001 / 5/28/2015
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 of Grazoprevir MK-5172 1600 mg or Elbasvir MK-8742 700 mg was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between MK-5172 1600 mg and placebo and between MK-8742 700 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. Both of the largest lower bounds of the two-sided 90% CI in the Grazoprevir study and Elbasvir study for the $\Delta\Delta\text{QTcF}$ for moxifloxacin were greater than 5 ms, and the moxifloxacin profiles over time are adequately demonstrated (Figure 2 for Grazoprevir and Figure 3 for Elbasvir), indicating that assay sensitivity was established.

In MK-5172-049 study, a single-dose double-blind, placebo- and positive-controlled, 3-period crossover study, 41 healthy subjects received Grazoprevir MK-5172 1600 mg, placebo, and moxifloxacin 400 mg. In MK-8742-015 Part 2 study, a single-center, randomized, 3-period, 6-sequence, balanced study, 42 subjects received Elbasvir MK-8742 700 mg, placebo or 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 MK-5172 and MK-8742 and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Study	Treatment	Time (hour)	$\Delta\Delta QTcF$ (ms)	90% CI (ms)
Grazoprevir MK-5172	MK-5172 1600 mg	8	-0.3	(-2.5, 1.9)
	Moxifloxacin 400 mg*	3	14.6	(12.6, 16.5)
Elbasvir MK-8742 (Part 2)	MK-8742 700 mg	6	-0.1	(-3.3, 3.0)
	Moxifloxacin 400 mg*	1	8.6	(7.3, 9.9)

* Multiple endpoint adjustment was not applied. The largest lower bounds after Bonferroni adjustment for 4 time points are 11.9 ms and 6.8 ms for MK-5172-049 and MK-8742-015, respectively.

Grazoprevir MK-5172

The C_{max} achieved after a single dose of the MK-5172 1600 mg provides a 44-fold margin over the C_{max} previously achieved at the steady state with the 100-mg/day clinical dose. It is adequate to cover the predicted worst case scenario (e.g., elderly chirotic Asian female patient).

Elbasvir MK-8742

The supratherapeutic dose (700 mg) produces mean C_{max} which is 3.8-fold the mean steady state C_{max} at the therapeutic dose (50 mg/day). It is adequate to cover the predicted worst case scenario (e.g., Asian female with concomitant metadone).

2 PROPOSED LABEL

The following is the sponsor's proposed labeling language related to QT.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Thorough QT studies have been conducted for grazoprevir and elbasvir.

The effect of grazoprevir 1600 mg on QTc interval was evaluated in a randomized, single-dose, placebo- and active-controlled (moxifloxacin 400 mg) 3-period crossover thorough QT trial in 41 healthy subjects. At a concentration 40 times the therapeutic concentration, grazoprevir does not prolong QTc to any clinically relevant extent.

The effect of elbasvir 700 mg on QTc interval was evaluated in a randomized, single-dose, placebo- and active-controlled (moxifloxacin 400 mg) 3-period crossover thorough QT trial in 42 healthy subjects. At a concentration 3 to 4 times the therapeutic concentration, elbasvir does not prolong QTc to any clinically relevant extent.

The sponsor's labeling language is acceptable. We defer final labeling decisions to the Division.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Grazoprevir/elbasvir (MK-5172A) is a fixed-dose combination of two direct acting antiviral agents (DAAs) for the treatment of chronic hepatitis C virus (HCV) infection. Grazoprevir (GZR; MK-5172) is a novel, potent, reversibly binding P2-P4 quinoxaline macrocyclic inhibitor of the HCV non-structural (NS) 3/4A protease. NS3/4A-mediated cleavage of the polyprotein formed by translation of the HCV RNA genome is essential for HCV replication. Elbasvir (EBR; MK-8742) is a novel, potent, tetracyclic indole-based HCV inhibitor targeting the HCV NS5A protein. NS5A is a pleiotropic protein with important roles in both the replication and assembly of HCV virions.

3.2 MARKET APPROVAL STATUS

Grazoprevir MK-5172 and Elbasvir MK-8742 are not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Grazoprevir MK-8742

In accordance with ICH S7A and S7B, MK-8742 potential to effect cardiac repolarization and conduction was evaluated in both an *in vitro* electrophysiology study and *in vivo* conscious dog telemetry study. In the functional patch-clamp electrophysiology study, at a maximum testable concentration of 10 μ M (limited by solubility), MK-8742 caused a minimal decline in hERG current of 5.2%. This concentration is >106X the projected unbound C_{max} for efficacy in humans (unbound projected human C_{max} <0.1 nM). To evaluate the effect of MK-8742 on QT/QTc interval (a surrogate for assessment of ventricular repolarization), a conscious dog telemetry study was conducted in 4 male beagle dogs at single oral doses 0.5, 2, and 50 mg/kg. There were no changes in uncorrected QT or HR-corrected QT interval at any of the doses evaluated. There were no effects on PR and QRS intervals in this study either. Collectively, the results from the *in vitro* hERG current assessment and the conscious dog telemetry study demonstrate that MK-8742 does not delay ventricular repolarization (no effect on QT/QTc interval) or

significantly affect cardiac conduction (no effect on PR or QRS intervals) after single oral doses of 0.5, 2, and 50 mg/kg.

Elbasvir MK-5172

MK-5172 was evaluated for its potential effects on cardiovascular, neurological, and respiratory function in several experimental models.

MK-5172 inhibited hERG current with an IC₅₀ of 25 µM and had no effect on QTc interval in anesthetized dogs up to 2 mg/kg (plasma exposure of 74.4 µM represents 248-fold the expected highest clinical C_{max} of 0.3 µM) or conscious dogs up to 600 mg/kg (C_{max} plasma concentrations of 105 µM represents 350-fold the expected highest clinical C_{max} of 0.3 µM; see Study Day 1 TK parameters of the 1-month oral toxicology study in dogs, see Section 4.3.2.2.2). Based on test article-related increases in heart rate and coincident decreases in QT interval at 20 and 600 mg/kg and small decreases in PR interval at 600 mg/kg of MK-5172, the NOEL for cardiovascular function in the oral cardiovascular telemetry study was 5 mg/kg (projected C_{max} plasma concentration = 12 µM represents 40-fold the expected highest clinical C_{max} of 0.3 µM) (see Section 4.3.2.2.2). Based on the low amplitude of the increases in heart rate (up to 42 bpm), these changes are not considered adverse. There were no effects on respiratory function in dogs at single doses up to 600 mg/kg (NOEL ≥600 mg/kg).

3.4 PREVIOUS CLINICAL EXPERIENCE

Overall, 4143 persons have received at least one dose of GZR, EBR, or GZR with EBR.

There were very few deaths, SAEs or discontinuations; in particular, treatment-related events of significance were infrequent and demonstrated no consistent pattern. Common AEs of fatigue, headache, and nausea were unremarkable and occurred at a similar frequency on active and placebo treatments. RBV-containing regimens were associated with an expected increase in frequency of drug-related AEs of asthenia, anemia, pruritus, rash, and dyspnea. Tolerability did not differ substantially according to baseline factors such as age, gender, race/ethnicity, presence of cirrhosis, presence of HCV/HIV co-infection, or the presence of advanced CKD (Stage 4-5). Tolerability was not affected by treatment duration (12 vs 16 weeks). Late ALT/AST Elevation Events, a specific measure of GZR-related hepatic safety, occurred in a dose-related manner, and they occurred in <1% of subjects who received the proposed dose of GZR 100 mg. These events generally occurred at or after TW8, and were transient, with most resolving while continuing treatment and the remaining events resolving after discontinuation of treatment. These events were not of clinical concern in that they were overwhelmingly not accompanied by abnormalities of other tests of hepatic function, or by liver-related symptoms. The risk of Late ALT/AST Elevation Events was increased moderately by intrinsic and extrinsic factors that increase GZR pharmacokinetics (<2% rate predicted for any separate factor, 3.8% rate predicted for very rare combinations of intrinsic and extrinsic factors). GZR exposure is expected to be increased by >12-fold (with geometric mean ratio [90% CIs] of 11.68 [6.10, 22.35] in patients with Child-Pugh C cirrhosis. The risk of Late ALT/AST

Elevation Events is predicted to be >5% in this population, especially in the context of the underlying advanced liver disease. Labeling will address specific patient populations and DDIs that are pertinent to the risk of Late ALT/AST Elevation Events. Increase in ALT is the most specific hepatic laboratory parameter for assessing hepatic safety of GZR with EBR. Periodic monitoring of ALT is recommended in the proposed label.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of Grazoprevir/Elbasvir's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocols prior to conducting Grazoprevir MK-5172 under IND 110261 and Elbasvir MK-8742 under IND 114298. The sponsor submitted the study reports MK-5172-049 and MK-8742-015 for study drug of Grazoprevir MK-5172 and Elbasvir MK-8742, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

Grazoprevir MK-5172:

A Single Dose Study to Assess the Effect of MK-5172 on the QTc Interval of Healthy Adult Subjects

Elbasvir MK-8742:

A Single Dose Trial to Assess the Effect of MK-8742 on QTc Interval in Healthy Adult Volunteers

4.2.2 Protocol Number

MK-5172-049

MK-8742-015

4.2.3 Study Dates

Grazoprevir MK-5172:

Trial initiation date: 17-Dec-2013

Trial completion date: 25-Feb-2013

Elbasvir MK-8742

15-Oct-2013 to 06-Feb-2014

Planned duration of Part 1: 11 weeks

Planned duration of Part 2: 9 weeks

4.2.4 Objectives

Grazoprevir MK-5172:

Primary: To evaluate effects of a single suprathapeutic oral dose of MK-5172 on corrected QT interval (QTc).

Secondary: To demonstrate sensitivity of this QTc assay using moxifloxacin as a positive control.

Elbasvir MK-8742

Primary objectives:

Part 1: To identify a dose of the preliminary market formulation (PMF) of MK-8742 that can achieve a safe and well tolerated maximum observed concentration (C_{max}) at least 5 X higher than the C_{max} associated with the clinical dose of MK-8742.

Part 2: To evaluate effects of a supra-therapeutic dose of MK-8742 on the (QT corrected by heartrate) QTc interval.

Secondary Objectives:

Part 1: To evaluate the safety and tolerability of MK-8742 after administration of single supra-therapeutic oral dose to healthy young adult subjects.

Part 2: To demonstrate sensitivity of this QTc assay using moxifloxacin as a positive control.

4.2.5 Study Description

4.2.5.1 Design

Grazoprevir MK-5172

This was a single-dose, double-blind (with respect to MK-5172 only), randomized, placebo- and active-controlled, 3-period, balanced crossover study to assess the effect of MK-5172 on the QTc interval.

Elbasvir MK-8742

Part 1:

Part 1 was a single-center, double-blind, randomized, placebo-controlled, 3-period (Periods 1 to 3) fixed-sequence, single rising dose trial in healthy male and female subjects. This part of the trial was designed to establish the supra-therapeutic MK-8742 dose to be used in Part 2. Eight (8) healthy male and female subjects received MK-8742 or placebo (6:2 ratio). Periods 1 and 2 were separated by a washout period of at least 7 days, while Periods 2 and 3 were separated by 14 to 21 days.

Part 2:

Part 2 was a single-center, randomized, 3-period, 6-sequence, balanced crossover trial in healthy male and female subjects. Forty-two (42) healthy male and female subjects

received MK-8742, placebo or moxifloxacin in a randomized sequence in a crossover design. Treatments were separated by a washout period of at least 7 days.

4.2.5.2 Blinding

MK-5172 and MK-8742

Moxifloxacin was administered in an open-label fashion.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Grazoprevir MK-5172

- 1600 mg MK-5172 - A single oral suprathapeutic dose of 1600 mg MK-5172 (16 x 100 mg tablet) on Day 1 following an overnight fast.
- 400 mg Moxifloxacin - A single oral dose of 400 mg moxifloxacin (1 x 400 mg tablet) on Day 1 following an overnight fast.
- Placebo - A single oral dose of MK-5172 matching placebo (16 x 100 mg matching placebo tablet) on Day 1 following an overnight fast.

Elbasvir MK-8742:

Part 1: 3-period fixed-sequence

- Period 1: 200 mg oral MK-8742 (N=6) or placebo (N=2)
- Period 2: 400 mg oral MK-8742 (N=6) or placebo (N=2)
- Period 3: 800 mg oral MK-8742 (N=6) or placebo (N=2)

Part 2: 3-period balanced crossover

- Treatment A: Supra-therapeutic oral MK-8742 dose (700 mg MK-8742 as determined in Part 1) (N = 39)
- Treatment B: 400 mg oral moxifloxacin (N=38)
- Treatment C: Placebo for oral MK-8742 (N=41)

4.2.6.2 Sponsor's Justification for Doses

Grazoprevir MK-5172

A single dose of 1600 mg MK-5172 in healthy subjects was selected as the suprathapeutic dose for the MK-5172 QTc study to achieve exposures that provide ample exposure margins to the projected peak exposure associated with 100 mg (the highest clinical dose) of MK-5172 in HCV-infected patients. This dose was determined using the highest individual geometric mean (GM) C₂ values (GM of steady state measurements pooled from Day 7 to the end of trial for each individual subject) from non-cirrhotic HCV-infected patients in the Phase II PN003 study as the reference. The

GM C₂ values for the 100 mg dose of MK-5172 rather than the C_{max} values from PN003 were used to determine the suprathreshold dose for this QTc study, because only C₂ pharmacokinetic samples were collected in Phase II studies as a surrogate for C_{max} (T_{max} ~3 hours). In addition, the highest individual GM C₂ value was chosen as the reference rather than the mean C₂ value in order to provide coverage for the potential worst case scenario due to the high pharmacokinetic variability of MK-5172. The highest individual GM C₂ following a 100 mg dose in non-cirrhotic HCV-infected patients was 1.38 μM. In addition, this value is higher than the upper 95% CI for populations who have higher than average concentrations of MK-5172, such as in subjects with moderate hepatic insufficiency and in healthy Japanese and Chinese subjects following once daily (QD) administration of 100 mg MK-5172.

Elbasvir MK-8742

The maximum anticipated clinical dose of MK-8742 used in the treatment of HCV infection is 50 mg. The geometric mean C_{max} following a single 50 mg dose of MK-8742 fit-for-purpose (FFP) formulation in male subjects was 104 nM, whereas the highest achievable geometric mean C_{max} with the initial FFP formulation was achieved at 200 mg MK-8742 and was only 340 nM. Doses higher than 200 mg using the 100 mg potency MK-8742 (b)(4) did not lead to increases in C_{max}. The single dose ranging part of the current trial (i.e., Part 1) attempted to achieve 5 to 10-fold C_{max} by using a new formulation of MK-8742, which was designed to reduce the limitations of solubility and dissolution on the absorption of MK-8742 seen with the 100 mg potency FFP formulation of MK-8742. Based on the single-dose C_{max}-dose relationship established using data from the FIH study, the estimated C_{max} values at the doses of 200, 400 and 800 mg of the MK-8742 PMF were 356 nM, 650 nM, and 1194 nM, respectively. These exposures were acceptable in terms of pre-clinical safety experience as the top dose of 1000 mg/kg/day in the 5-week results of the dog toxicity study resulted in an arithmetic mean C_{max} of 1.74 μM. Subsequent to the determination of a suitable supra-therapeutic dose in Part 1, the definitive QTc trial was performed in Part 2.

Safety, tolerability, and pharmacokinetic data from Part 1 supported a dose of 700 mg for Part 2. The 800 mg dose assessed in Part 1 exceeded the desired C_{max} target and was a dose which could have been used in Part 2; however, a dose of 700 mg was also projected to achieve the desired C_{max} target and additionally decrease pill burden from 16 tablets (for an 800 mg dose) to 14 tablets (for a 700 mg dose) which was considered to be better tolerated for oral administration.

Reviewer's Comment: Applicant's approach is reasonable.

Grazoprevir MK-5172

The C_{max} achieved after a single dose of the MK-5172 1600 mg provides a 44-fold margin over the C_{max} previously achieved at the steady state with the 100-mg/day clinical dose. It

is adequate to cover the predicted worst case scenario (e.g., elderly chirotic Asian female patient).

Elbasvir MK-8742

The suprathreshold dose (700 mg) produces mean C_{max} which is 3.8-fold the mean steady state C_{max} at the therapeutic dose (50 mg/day). It is adequate to cover the predicted worst case scenario (e.g., Asian female with concomitant metadone).

4.2.6.3 Instructions with Regard to Meals

MK-5172 and MK-8742

Subjects were administered the trial drug in the fasted state.

Reviewer's Comment: In the proposed label, drug will be taken with or without food.

The AUC and C_{max} of MK-5172 increased by 1.5-fold and ~2.8-fold after a high-fat meal, respectively. The C_{max} achieved in this study after a single dose of the MK-5172 1600 mg provides a 44-fold margin over the C_{max} previously achieved at the steady state with the 100 mg/day clinical dose. It is adequate to cover the food effect on MK-5172 absorption.

MK-8742 AUC and C_{max} is 11% and 15% lower due to a fat meal. Applicant's instructions with regards to meals is therefore appropriate.

4.2.6.4 ECG and PK Assessments

Grazoprevir MK-5172

Holter monitor data on Day 1 at -0.333, -0.167, and 0 hours predose, and at 0.5, 1, 1.5, 2, 3, 4, 5.5, 6, 8, and 24 hours postdose, within a 5-minute time window around the scheduled time points outlined in the study.

Blood samples were collected and processed for the analysis of MK-5172 in plasma at the following scheduled time points relative to the time of study treatments: Hours 0, 0.5, 1, 1.5, 2, 3, 4, 5.5, 6, 8, 12, 16, and 24.

Elbasvir MK-8742

In order to assess QT prolongation in response to each of the study treatments, quintuplicate 10-second, 12-lead ECG recordings were extracted from the Holter monitor data on Day 1 at -0.333, -0.167, and 0 hours predose, and at 0.5, 1, 1.5, 2, 3, 4, 5.5, 6, 8, and 24 hours postdose, within a 5-minute time window around the scheduled time points outlined in the study.

Blood samples were collected and processed for the analysis of MK-5172 in plasma at the following scheduled time points relative to the time of study treatments: Hours 0, 0.5, 1, 1.5, 2, 3, 4, 5.5, 6, 8, 12, 16, and 24.

Reviewer's Comment: Applicant's approach is appropriate.

4.2.6.5 Baseline

MK-5172 and MK-8742

Sponsor used the average of predose on Day 1 at -0.333, -0.167, and 0 hours as baseline values.

4.2.7 ECG Collection

MK-5172 and MK-8742

Intensive 12-Lead Holter monitoring will be 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

Grazoprevir MK-5172

Forty-one (41) healthy adult male and female subjects were enrolled and 39 subjects completed the study. One (1) subject was discontinued from the study by the Investigator due to adverse experiences following Period 1 dosing (1600 mg MK-5172). One (1) subject was lost to follow-up after failing to return to sign the updated informed consent form. The subject completed all other study procedures.

Elbasvir MK-8742

Part 1

Nine (9) of the 11 enrolled subjects received trial drug administration and 8 subjects completed the trial. Two (2) subjects were withdrawn from the trial before any trial drug was administered, due to mild non-serious AEs. One (1) subject was discontinued from the trial due to loss to follow-up.

Part 2

All 42 enrolled subjects received the trial drug and 36 subjects completed the trial. Six (6) subjects were withdrawn from the trial. One (1) subject was withdrawn due to the subject's own request, 2 subjects were withdrawn due to protocol violation, and 3 subjects were withdrawn due to inability to comply with trial timelines and procedures.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

Grazoprevir MK-5172

The primary endpoint was time-averaged, baseline-adjusted, placebo-corrected analysis in QTcF of MK-5172 1600 mg. The results presented in Table 3. The sponsor used a repeated measures mixed model and the model included period, treatment, time, and treatment-by-time interaction as fixed effects, and a double compound symmetry

covariance structure was assumed. The within-subject correlation across periods was modeled by specifying subject as a random effect. The within-subject correlation across time points within a period was modeled by specifying the subject by period interaction as the repeated measure with residual compound symmetry. The sponsor concluded that MK-5172 did not prolong the QTc interval as the upper bounds of the 2-sided 90% CIs for the mean differences between MK-5172 and placebo were below 10 ms at all times point after dosing.

Table 2: Sponsor's Mixed-Model Analysis of Δ QTcF and $\Delta\Delta$ QTcF for MK-5172 1600 mg and Moxifloxacin 400 mg

Treatment	Hour	N	QTcF (msec)		Change From Baseline		Difference From Placebo			
			Mean [†]	95% CI [†]	LSMean [‡]	95% CI [‡]	LSMean [‡]	90% CI [‡]	P-value [§]	
Placebo	Predose	40	410.27	(403.88, 416.66)	--	--	--	--	.	
	0.5 hour	40	409.06	(403.09, 415.03)	-1.22	(-3.14, 0.69)	--	--	.	
	1 hour	40	409.09	(402.94, 415.24)	-1.19	(-3.11, 0.72)	--	--	.	
	1.5 hour	40	410.20	(403.86, 416.54)	-0.08	(-2.00, 1.83)	--	--	.	
	2 hour	40	409.65	(403.61, 415.69)	-0.63	(-2.55, 1.28)	--	--	.	
	3 hour	40	410.49	(404.01, 416.96)	2	(-1.71, 2.12)	--	--	.	
	4 hour	40	409.72	(403.42, 416.02)	-0.56	(-2.48, 1.35)	--	--	.	
	5.5 hour	40	407.85	(402.52, 413.18)	-2.43	(-4.35, -0.52)	--	--	.	
	6 hour	40	405.68	(400.21, 411.15)	-4.60	(-6.52, -2.69)	--	--	.	
	8 hour	40	403.00	(397.63, 408.36)	-7.29	(-9.20, -5.37)	--	--	.	
	24 hour	40	405.48	(399.15, 411.81)	-4.80	(-6.72, -2.89)	--	--	.	
	Predose	41	410.67	(405.12, 416.22)	--	--	--	--	.	
1600 mg MK-5172	0.5 hour	41	408.01	(402.80, 413.22)	-2.67	(-4.57, -0.78)	-1.45	(-3.50, 0.60)	.	
	1 hour	41	407.44	(402.01, 412.86)	-3.24	(-5.14, -1.35)	-2.05	(-4.10, -0.00)	.	
	1.5 hour	41	406.80	(401.04, 412.55)	-3.89	(-5.78, -1.99)	-3.80	(-5.85, -1.75)	.	
	2 hour	41	406.42	(401.04, 411.80)	-4.26	(-6.16, -2.37)	-3.63	(-5.68, -1.58)	.	
	3 hour	41	404.76	(398.92, 410.59)	-5.93	(-7.82, -4.03)	-6.13	(-8.18, -4.08)	.	
	4 hour	40	404.91	(399.06, 410.75)	-5.89	(-7.80, -3.98)	-5.33	(-7.39, -3.27)	.	
	5.5 hour	40	404.48	(399.78, 409.17)	-6.32	(-8.23, -4.41)	-3.89	(-5.95, -1.83)	.	
	6 hour	40	404.85	(399.99, 409.71)	-5.95	(-7.86, -4.04)	-1.35	(-3.40, 0.71)	.	
	8 hour	40	403.03	(398.53, 407.53)	-7.77	(-9.68, -5.86)	-0.48	(-2.54, 1.58)	.	
	24 hour	39	405.53	(399.87, 411.19)	-5.38	(-7.31, -3.46)	-0.58	(-2.65, 1.49)	.	
	Moxifloxacin	Predose	40	408.72	(403.09, 414.35)	--	-- (4.19, 8.03)	--	-- (5.27, 9.39)	.
		0.5 hour	40	414.85	(409.79, 419.90)	6.11	(9.70, 13.53)	7.33	(10.75, 14.87)	<.0001
1 hour		40	420.35	(414.81, 425.89)	11.62	(10.82, 14.66)	12.81	(10.76, 14.88)	<.0001	
1.5 hour		40	421.48	(415.61, 427.34)	12.74	(11.68, 15.51)	12.82	(12.17, 16.29)	<.0001	
2 hour		40	422.33	(416.40, 428.26)	13.60	(12.81, 16.65)	14.23	(12.47, 16.59)	<.0001	
3 hour		40	423.47	(417.17, 429.76)	14.73	(11.15, 14.98)	14.53	(11.57, 15.69)	<.0001	
4 hour		40	421.80	(415.73, 427.87)	13.07	(4.01, 7.85)	13.63	(6.30, 10.42)	.	
5.5 hour		40	414.67	(409.49, 419.84)	5.93	(3.22, 7.06)	8.36	(7.68, 11.8)	.	
6 hour		40	413.88	(409.11, 418.64)	5.14	(0.66, 4.50)	9.74	(7.81, 11.93)	.	
8 hour		40	411.31	(406.17, 416.46)	2.58	(-2.01, 1.82)	9.87	(2.65, 6.77)	.	
24 hour		40	408.64	(402.68, 414.60)	-0.09		4.71		.	

1600 mg MK-5172: A single suprathreshold dose of 1600 mg MK-5172 (16 x 100 mg tablet) on Day 1.
Moxifloxacin: A single oral dose of 400 mg moxifloxacin (1 x 400 mg tablet) on Day 1.
Placebo: A single oral dose MK-5172 matching placebo (16 x 100 mg matching placebo tablet) on Day 1.
[†]Arithmetic mean and non-model based 95% confidence interval.
[‡]Least-squares mean and confidence interval reported from the linear mixed-effects model.
LSMean = Least-squares means; CI = Confidence interval
[§]1-sided p-values regarding the null hypothesis that difference = 5 msec and alternative hypothesis that difference > 5 msec.
^{||}Baseline is the average of predose measurements taken at -0.333, -0.167, and prior to dosing in each period.
Subject AN 0014's 12-Lead ECG recordings were not collected at the 24-hour time point after receiving 1600 mg MK-5172.
Subject AN 0034 discontinued from the study following Hour 3 Period 1. The subject only received 1600 mg MK-5172.

Elbasvir MK-8742

Part 2

The primary endpoint was time-averaged, baseline-adjusted, placebo-corrected analysis in QTcF of MK-8742 700 mg. The results presented in Table 3. The sponsor used a repeated measures mixed model. The model included fixed factors period, treatment, time, and treatment-by-time interaction, and a heterogenous compound symmetry covariance structure was assumed. The within-subject correlation across periods was

modeled by specifying subject as a random effect. The within-subject correlation across time points within a period was modeled by specifying the subject by period interaction as the repeated measure with residual compound symmetry. The sponsor concluded that MK-8742 did not have a prolongation effect on QTcF as the upper bounds of the 2-sided 90% CIs for the mean differences between MK-8742 and placebo were below 10 ms at all times point after dosing.

Table 3: Sponsor’s Mixed-Model Analysis of Δ QTcF and $\Delta\Delta$ QTcF for MK-5172 700 mg and Moxifloxacin 400 mg (Part 2)

Treatment	Time (h)	N ^a	QTcF Value (msec)		Change from Baseline (msec)		Difference from Placebo (msec)	
			LSMean	95% CI	LSMean	95% CI	LSMean Difference	90% CI
700 mg MK-8742	0.5	39	402	(397, 407)	-2.69	(-4.41, -0.976)	-0.465	(-2.38, 1.45)
	1	39	403	(398, 408)	-1.43	(-3.15, 0.280)	0.791	(-1.12, 2.71)
	1.5	39	403	(398, 408)	-1.92	(-3.64, -0.207)	0.856	(-1.06, 2.78)
	2	39	403	(398, 408)	-1.74	(-3.46, -0.0275)	0.00930	(-1.91, 1.93)
	3	39	404	(399, 409)	-1.00	(-2.72, 0.716)	-0.0103	(-1.93, 1.91)
	4	39	404	(399, 409)	-0.336	(-2.05, 1.38)	-0.185	(-2.10, 1.73)
	6	39	394	(389, 399)	-10.8	(-12.5, -9.13)	-0.183	(-2.11, 1.75)
	8	39	397	(392, 402)	-7.90	(-9.61, -6.18)	-0.513	(-2.43, 1.41)
	12	39	398	(393, 403)	-6.92	(-8.64, -5.20)	-0.407	(-2.32, 1.51)
	16	39	404	(399, 409)	-0.874	(-2.59, 0.844)	-0.487	(-2.40, 1.43)
24	39	402	(397, 407)	-2.97	(-4.69, -1.25)	0.410	(-1.50, 2.33)	
400 mg Moxifloxacin	0.5	38	406	(401, 411)	-0.0220	(-1.76, 1.72)	2.21	(0.273, 4.14)
	1	38	413	(407, 418)	6.35	(4.60, 8.09)	8.58	(6.64, 10.5)
	1.5	38	411	(406, 416)	4.74	(3.00, 6.48)	7.52	(5.59, 9.46)
	2	38	413	(408, 418)	6.82	(5.08, 8.56)	8.58	(6.64, 10.5)
	3	38	414	(409, 419)	7.61	(5.87, 9.35)	8.60	(6.67, 10.5)
	4	38	414	(409, 419)	7.85	(6.10, 9.59)	8.00	(6.06, 9.93)
	6	38	403	(398, 408)	-3.33	(-5.08, -1.59)	7.33	(5.38, 9.27)
	8	38	405	(400, 410)	-1.31	(-3.05, 0.431)	6.08	(4.14, 8.01)
	12	38	404	(399, 409)	-2.39	(-4.13, -0.648)	4.13	(2.19, 6.06)
	16	38	409	(404, 414)	2.87	(1.13, 4.61)	3.26	(1.33, 5.19)
24	37	406	(401, 411)	-0.0287	(-1.78, 1.73)	3.36	(1.41, 5.30)	

Reviewer’s Comments: We will provide our independent analysis result in Section 5.2. Our $\Delta\Delta$ QTcF results are similar as those reported by the sponsor.

4.2.8.2.2 Assay Sensitivity

Grazoprevir MK-5172

The sponsor concluded that the positive control, moxifloxacin, produced mean differences from placebo (moxifloxacin-placebo) in QTcF change from baseline at 1, 2, 3, and 4 hours postdose that were all greater than 10 ms, with all p-values < 0.0001 and with lower 90% CIs ranging from 10.75 - 12.47 ms, all greater than the pre-specified 5 ms. Therefore, the secondary hypothesis that administration of moxifloxacin is associated with an increase in QTc interval was supported.

Elbasvir MK-8742

Part 2

The sponsor concluded that a single 400-mg dose of moxifloxacin is associated with an increase in the QTc interval. The true mean difference (moxifloxacin-placebo) in QTc

change from baseline is greater than 5 msec over the first 4 hours post-dose, demonstrating assay sensitivity.

4.2.8.2.3 Categorical Analysis

Grazoprevir MK-5172

Categorical analysis was used to summarize in the categories of QTc \leq 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and $>$ 500 ms, and changes from baseline QTc \leq 30 ms, between 30 and 60 ms, and $>$ 60 ms. No subject's absolute QTc was $>$ 480 ms. No subject's Δ QTc was $>$ 30 ms.

Elbasvir MK-8742

Part 2

None of the subjects had average QTcF readings of $>$ 450 ms, and all subjects had a QTcF change from baseline of \leq 30 ms at all treatments at all time points.

4.2.8.3 Safety Analysis

Grazoprevir MK-5172

Overall, 22 (54%) subjects reported a total of 55 adverse experiences that were of mild or moderate intensity, with the most commonly reported being headache (11 subjects, 27%), diarrhea (8 subjects, 20%), and nausea (7 subjects, 17%). All other postdose adverse experiences were reported by \leq 2 (4.9%) subjects each. One (1) subject reported 1 predose adverse experience.

Twenty-seven (27) adverse experiences were considered drug-related (18 during 1600 mg MK-5172, 3 during moxifloxacin, and 6 during placebo) with the most common drug related adverse experiences being diarrhea (20%), nausea (15%), and headache (9.8%). All other drug-related adverse experiences were reported by \leq 2 (4.9%) subjects each. One (1) subject was considered as not completing the study as the subject did not return to sign the updated informed consent form (ICF) and was also considered lost to follow-up; however, the subject completed all other study procedures. One (1) subject was discontinued by the Investigators due to adverse experiences following the dosing of 1600 mg MK-1572 in Period 1. The first adverse experience (syncope) in the series of adverse experiences for the subject at that time (forehead laceration, forehead contusion, and tongue wound experienced during the syncope event) was considered by the investigator as related to study treatment and possibly due to vasovagal reaction following blood draw.

All adverse experiences reported during the study resolved by the end of the study with the exception of 1 adverse experience of upper respiratory tract infection and 1 adverse experience of urinary tract infection considered not related to study drug for which outcomes were unknown. These subjects completed all scheduled study visits and procedures; however, attempts to contact them for follow-up after the study for further information was unsuccessful resulting in an outcome of unknown. There were no serious adverse experiences; events of clinical interest (ECIs), or other adverse experiences of

special interest; vital sign adverse experiences, safety ECG adverse experiences, pregnancies; or deaths reported during the study.

No clinically meaningful relationships were observed for differences between clinical laboratory values or vital signs as a function of treatment.

Elbasvir MK-8742

Part 1

No deaths, SAEs, severe TEAEs, events of clinical interest, or pregnancies were reported. Adverse events leading to discontinuation were reported for 2 subjects. These AEs leading to discontinuation occurred before any treatment was administered. In total, 12 TEAEs were reported for 5 (83.3%) subjects after 800 mg MK-8742 administration, 2 TEAEs were reported for 1 (16.7%) subject after 400 mg MK-8742 treatment and 1 TEAE was reported for 1 (16.7%) subject after 200 mg MK-8742 administration. All of these reported TEAEs were mild in intensity. All TEAEs reported after 400 mg (nausea and headache) and 800 mg (abdominal discomfort, diarrhea, nausea, vomiting, headache and pruritus) MK-8742 administration, were considered related to the trial drug. No TEAEs were reported for subjects after placebo treatment. The SOC with the most reported TEAEs was gastrointestinal disorders with incidences reported in 4 (66.7%) subjects after 800 mg MK-8742 treatment and in 1 (16.7%) subject after 400 mg MK-8742 treatment. Nausea was the highest reported TEAE in this class with all subjects with gastrointestinal disorders being affected. The most commonly reported TEAEs (reported in ≥ 2 subjects) were nausea (4), headache (4), and vomiting (2). All AEs were limited in duration.

Part 2

No deaths, SAEs, severe TEAEs, events of clinical interest, or pregnancies were reported, no subjects were discontinued from the trial due to safety reasons and all AEs were limited in duration. In total, 10 TEAEs were reported for 8 (20.5%) subjects after 700 mg MK-8742 administration, 8 TEAEs reported for 6 (14.6%) subjects after placebo administration and 4 TEAEs reported for 3 (7.9%) subjects after 400 mg moxifloxacin administration. The majority of the TEAEs were considered not related to the trial drug, except for 2 incidences of nausea, 1 incidence of vomiting, 1 incidence of dizziness, 3 incidences of headache. The majority of TEAEs were mild in intensity, with 4 TEAEs following placebo treatment and 1 TEAE following 400 mg moxifloxacin, considered moderate in intensity. No severe TEAEs were reported. The SOC with the most reported TEAEs was gastrointestinal disorders with incidences reported in 2 (5.1%) subjects after 700 mg MK-8742 treatment, 1 (2.6%) subject after 400 mg moxifloxacin treatment and 1 (2.4%) subject after placebo treatment. The most commonly reported TEAEs (reported in ≥ 2 subjects) were headache (3), dysmenorrhea (2), nausea (2), and vomiting (2).

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Grazoprevir MK-5172

The geometric mean (GCV%) C_{max} 14.1 μM (52.6%). Geometric mean (GCV%) AUC_{0-24hr} was 77.0 hr* μM (78.1 %) for the 1600 mg mg dose level. The median T_{max} was 4.08 hours (range 2.08 to 12.0 hours).

The C_{max} achieved after a single dose of the MK-5172 1600 mg provides a 44-fold margin over the C_{max} previously achieved at the steady state with the 100 mg/day clinical dose (0.32 μM) (*Summary of clinical pharmacology studies, Table 2.7.2: 8*).

Elbasvir MK-8742

During Part 2 of the trial, 700 mg MK-8742 was administered as a single dose. The geometric mean (GCV%) C_{max} was 567 nM (38.5%). Geometric mean (GCV%) AUC_{0-24hr} was 6200 hr*nM (40.1%). The median T_{max} was 4.1 hours (range 3.0 to 8.0 hours). The geometric mean following a 700 mg single dose of MK-8742 was greater than 3.78 times the geometric mean C_{max} at the steady state with the 50 mg/day clinical dose (150 nM) (*Summary of clinical pharmacology studies, Table 2.7.2: 9*)

4.2.8.4.2 Exposure-Response Analysis

Grazoprevir MK-5172

The applicant did not conduct a formal exposure response analysis.

Elbasvir MK-8742

The applicant did not conduct an exposure response analysis because no QTc signal was observed.

Reviewer's Analysis: A plot of $\Delta\Delta QTcF$ vs. drug concentrations is presented in Figure 5.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the rrection. For study MK-5172-049, it appears that QTcP (Population-corrected QTc) is better than QTcF and QTcF (see Table 4). For Study MK-8742-015, QTcF is better than QTcB (see Table 5). To be consistent with the sponsor's analyses, this reviewer used QTcF as primary statistical analysis.

Table 4: Average of Sum of Squared Slopes for Different QT-RR Correction Methods (MK-5172-049)

Treatment Group	QTcB		QTcF		QTcP	
	N	MSSS	N	MSSS	N	MSSS
Placebo	40	0.00477	40	0.00207	40	0.00167
Moxifloxacin 400 mg	40	0.00298	40	0.00347	40	0.00231
MK-5172 1600 mg	40	0.00707	40	0.00377	40	0.00353
All	41	0.00466	41	0.00230	41	0.00181

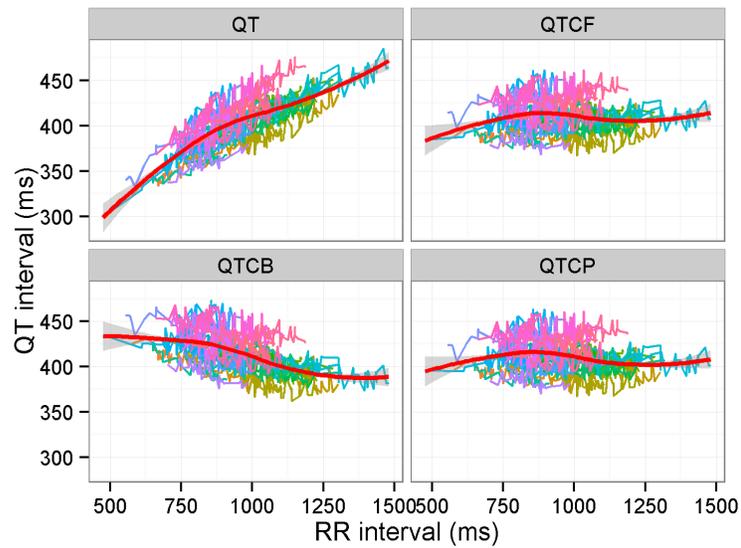
Table 5: Average of Sum of Squared Slopes for Different QT-RR Correction Methods (MK-8742-015)

Treatment Group	QTcB		QTcF	
	N	MSSS	N	MSSS
Placebo	40	0.00355	40	0.00216
400 mg Moxifloxacin	38	0.00365	38	0.00292
700 mg MK-8742	39	0.00470	39	0.00279
All	42	0.00457	42	0.00161

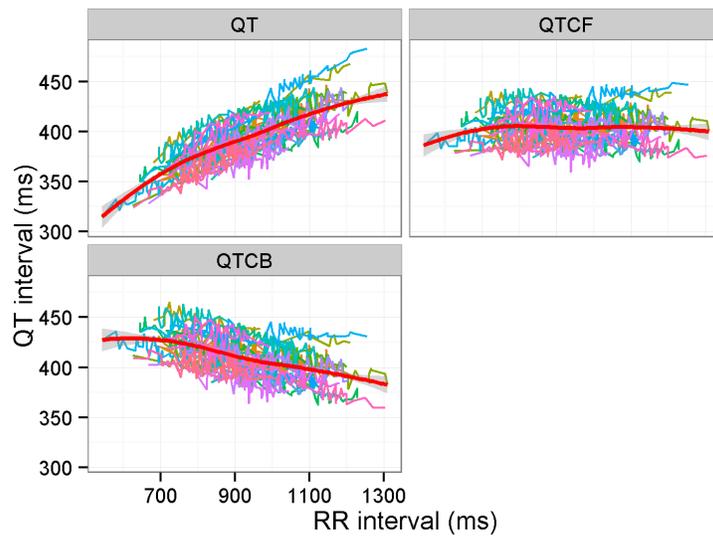
The relationship between different correction methods and RR is presented in Figure 1.

Figure 1: QT, QTcB, QTcF, and QTcP vs. RR (Each Subject's Data Points are Connected with a Line)

A) Grazoprevir MK-5172



B) Elbasvir MK-8742



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analyses for Grazoprevir MK-5172 and Elbasvir MK-8742

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 6 and Table 7. The largest upper bounds of the 2-sided 90% CI for the mean differences between MK-5172 1600-mg and placebo, and between MK-8742 700-mg and placebo are 1.9 ms and 3.0 ms, respectively.

Table 6: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Grazoprevir MK-5172 1600 mg and Moxifloxacin 400 mg

	Treatment Group									
	Placebo	MK-5172 1600 mg				Moxifloxacin 400 mg				
	Δ QTcF	Δ QTcF		$\Delta\Delta$ QTcF		Δ QTcF		$\Delta\Delta$ QTcF		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	Adj. 90% CI
0.5	-1.2	40	-2.3	-1.1	(-2.9, 0.7)	40	6.0	7.2	(5.3, 9.0)	(4.7, 9.6)
1	-1.2	40	-3.1	-2.0	(-3.6, -0.4)	40	11.6	12.7	(11.1, 14.3)	(10.5, 14.9)
1.5	-0.1	40	-3.9	-3.9	(-5.5, -2.2)	40	12.7	12.8	(11.1, 14.5)	(10.5, 15.1)
2	-0.6	40	-4.2	-3.6	(-5.4, -1.8)	40	13.6	14.2	(12.4, 15.9)	(11.7, 16.6)
3	0.2	40	-5.8	-6.0	(-8.0, -4.1)	40	14.8	14.6	(12.6, 16.5)	(11.9, 17.2)
4	-0.5	40	-5.8	-5.3	(-7.5, -3.1)	40	13.0	13.6	(11.4, 15.8)	(10.6, 16.6)
5.5	-2.3	40	-6.1	-3.7	(-6.3, -1.2)	40	5.7	8.0	(5.5, 10.6)	(4.5, 11.5)
6	-4.5	40	-5.7	-1.2	(-3.8, 1.5)	40	4.9	9.4	(6.7, 12.0)	(5.7, 13.0)
8	-7.2	40	-7.5	-0.3	(-2.5, 1.9)	40	2.3	9.5	(7.3, 11.7)	(6.5, 12.6)
24	-4.8	39	-5.3	-0.5	(-2.9, 1.9)	40	-0.2	4.6	(2.2, 7.0)	(1.3, 7.9)

* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

Table 7: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Elbasvir MK-8742 700 mg and Moxifloxacin 400 mg

		Treatment Group								
		400 mg Moxifloxacin					700 mg MK-8742			
		Δ QTcF		$\Delta\Delta$ QTcF			Δ QTcF		$\Delta\Delta$ QTcF	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	*Adj 90% CI	N	LS Mean	LS Mean	90% CI
0.5	-2.2	38	0.1	2.4	(1.1, 3.7)	(0.6, 4.2)	39	-2.6	-0.4	(-2.2, 1.4)
1	-2.2	38	6.4	8.6	(7.3, 9.9)	(6.8, 10.4)	39	-1.4	0.8	(-1.0, 2.6)
1.5	-2.7	38	4.8	7.4	(6.1, 8.8)	(5.6, 9.3)	39	-1.9	0.8	(-1.0, 2.6)
2	-1.8	38	6.8	8.6	(7.0, 10.2)	(6.4, 10.8)	39	-1.7	0.1	(-2.1, 2.3)
3	-0.9	38	7.6	8.5	(6.8, 10.3)	(6.2, 10.9)	39	-0.9	-0.0	(-2.4, 2.3)
4	-0.2	38	7.9	8.1	(6.3, 10.0)	(5.6, 10.7)	39	-0.2	0.0	(-2.5, 2.5)
6	-10.7	38	-3.4	7.3	(5.0, 9.6)	(4.1, 10.4)	39	-10.8	-0.1	(-3.3, 3.0)
8	-7.3	38	-1.3	6.1	(4.0, 8.1)	(3.3, 8.9)	39	-8.0	-0.6	(-3.4, 2.2)
12	-6.8	38	-2.4	4.4	(2.1, 6.7)	(1.3, 7.5)	39	-6.9	-0.1	(-3.2, 2.9)
16	-0.2	38	2.8	3.0	(0.6, 5.4)	(-0.3, 6.3)	39	-0.9	-0.7	(-4.0, 2.6)
24	-3.5	37	-0.1	3.4	(1.3, 5.5)	(0.5, 6.2)	39	-3.0	0.5	(-2.3, 3.3)

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 6 and Table 7. The largest unadjusted 90% lower confidence intervals are 12.6 ms and 7.3 ms for MK-5172 and MK-8742, respectively. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval are 11.9 ms and 6.8 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected.

5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

The following figures display the time profile of $\Delta\Delta$ QTcF for different treatment groups of MK-7172 and MK-8742.

Figure 2 : Mean and 90% CI $\Delta\Delta$ QTcF Time Course (Grazoprevir MK-5172)

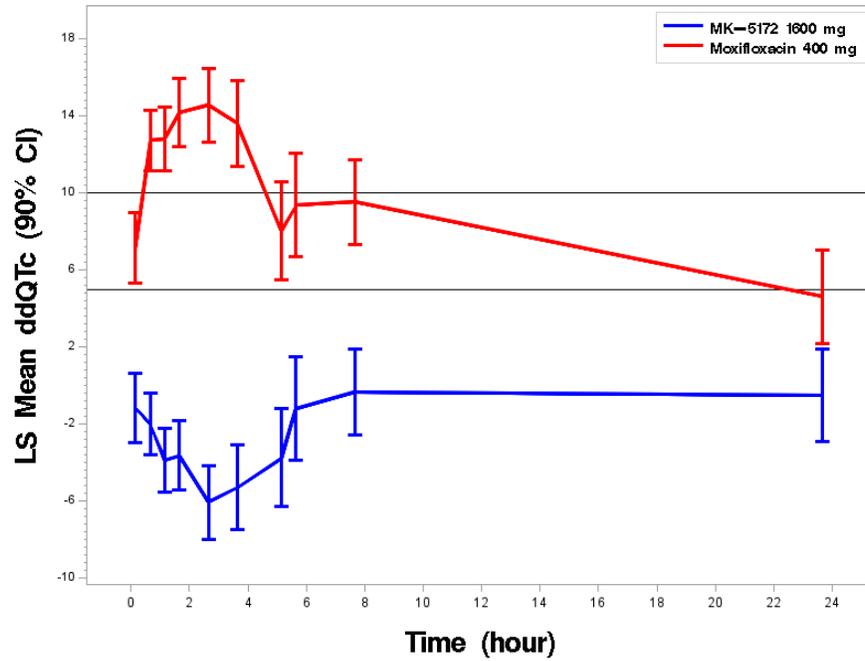
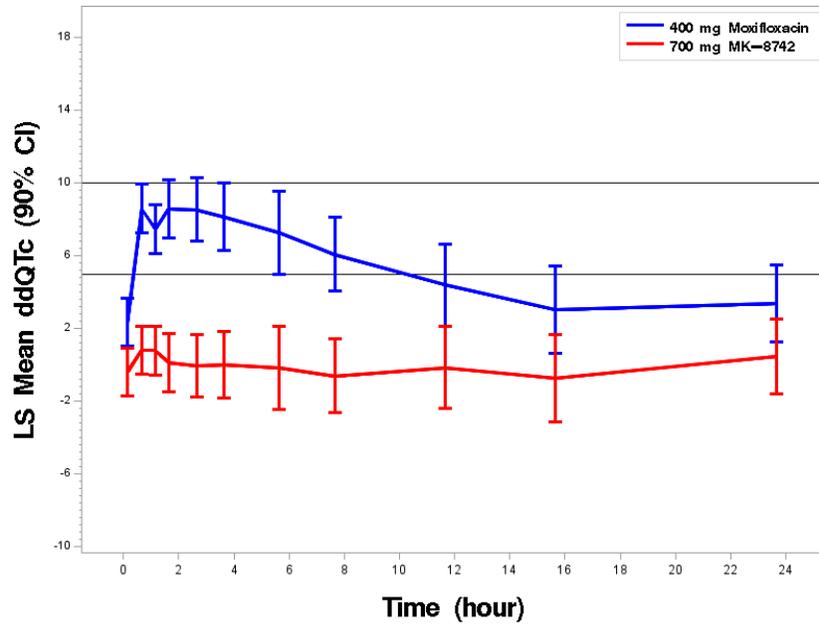


Figure 3: Mean and 90% CI $\Delta\Delta$ QTcF Time Course (Elbasvir MK-8742)



5.2.1.4 Categorical Analysis

Table 8 and Table 9 list the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms. No subject's QTcF was above 480 ms for MK-5172 group. No subject's QTcF was above 450 ms for MK-8742 group.

Table 8: Categorical Analysis for QTcF (Grazoprevir MK-5172)

Treatment Group	Total N	Value \leq 450 ms	450 ms $<$ Value \leq 480 ms	480 ms $<$ Value \leq 500 ms	Value $>$ 500 ms
MK-5172 1600 mg	40	39 (97.5%)	1 (2.5%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	40	35 (87.5%)	5 (12.5%)	0 (0.0%)	0 (0.0%)
Placebo	40	39 (97.5%)	1 (2.5%)	0 (0.0%)	0 (0.0%)

Table 9: Categorical Analysis for QTcF (Elbasvir MK-8742)

Treatment Group	Total N	Value \leq 450 ms	450 ms $<$ Value \leq 480 ms	480 ms $<$ Value \leq 500 ms	Value $>$ 500 ms
400 mg Moxifloxacin	38	38 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
700 mg MK-8742	39	39 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Placebo	40	40 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 10 and Table 11 list changes from baseline QTc ≤ 30 ms, between 30 and 60 ms, between 60 ms and 90, and >90 ms. No subject's change from baseline was above 30 ms for MK-5172 and MK-8742 treatment groups.

Table 10: Categorical Analysis of Δ QTcF (Grazoprevir MK-5172)

Treatment Group	Total N	Value \leq 30 ms	30 ms $<$ Value \leq 60 ms	60 ms $<$ Value \leq 90 ms	Value $>$ 90 ms
MK-5172 1600 mg	40	40 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	40	40 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Placebo	40	40 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 11: Categorical Analysis of Δ QTcF (Elbasvir MK-8742)

Treatment Group	Total N	Value \leq 30 ms	30 ms<Value \leq 60 ms	60 ms<Value \leq 90 ms	Value>90 ms
400 mg Moxifloxacin	38	38 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
700 mg MK-8742	39	39 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Placebo	39	39 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the Δ HR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 12 and Table 13. The largest upper bounds of the 2-sided 90% CI for the mean differences between MK-5172 1600 mg and placebo, and between MK-8741 700 mg and placebo are 3.5 bpm and 4.4 bpm, respectively. Table 14 and Table 15 present the categorical analysis for MK-5172 and MK-8742, respectively. There is one subject who experienced HR interval greater than 100 bpm in MK-5172 and MK-8742 group.

Table 12: Analysis Results of Δ HR and $\Delta\Delta$ HR for Grazoprevir MK-5172 1600 mg and Moxifloxacin 400 mg

Time (h)	Treatment Group								
	MK-5172 1600 mg					Moxifloxacin 400 mg			
	Δ HR	Δ HR		$\Delta\Delta$ HR		Δ HR	$\Delta\Delta$ HR		
LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	
0.5	0.9	40	0.1	-0.8	(-2.0, 0.4)	40	1.4	0.5	(-0.8, 1.7)
1	0.2	40	0.8	0.6	(-0.8, 2.1)	40	1.8	1.6	(0.2, 3.1)
1.5	-0.5	40	0.2	0.7	(-0.6, 2.1)	40	0.6	1.1	(-0.3, 2.4)
2	-0.1	40	0.6	0.7	(-0.7, 2.1)	40	-0.1	-0.0	(-1.4, 1.4)
3	-0.4	40	1.4	1.8	(0.1, 3.5)	40	-0.2	0.2	(-1.5, 1.9)
4	1.5	40	2.5	1.0	(-1.0, 2.9)	40	1.5	-0.0	(-1.9, 1.9)
5.5	9.6	40	7.4	-2.2	(-4.5, 0.1)	40	8.5	-1.1	(-3.4, 1.2)
6	8.0	40	7.4	-0.5	(-2.7, 1.6)	40	9.1	1.1	(-1.0, 3.3)
8	5.8	40	5.6	-0.2	(-2.9, 2.5)	40	6.3	0.6	(-2.1, 3.2)
24	1.8	39	1.1	-0.7	(-2.6, 1.1)	40	2.4	0.6	(-1.2, 2.4)

Table 13: Analysis Results of Δ HR and $\Delta\Delta$ HR for Elbasvir MK-8742 700 mg and Moxifloxacin 400 mg

	Treatment Group								
	Placebo	400 mg Moxifloxacin				700 mg MK-8742			
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	-1.0	38	1.8	2.8	(1.1, 4.6)	39	-0.6	0.4	(-1.3, 2.2)
1	-2.1	38	1.2	3.4	(1.6, 5.2)	39	0.5	2.6	(0.8, 4.4)
1.5	-0.9	38	2.7	3.7	(1.8, 5.6)	39	-0.2	0.8	(-1.1, 2.7)
2	-1.9	38	0.6	2.5	(0.9, 4.1)	39	-0.6	1.3	(-0.3, 2.9)
3	-1.7	38	1.5	3.2	(1.4, 5.0)	39	0.4	2.1	(0.3, 3.9)
4	-0.6	38	2.0	2.6	(1.0, 4.2)	39	0.4	1.0	(-0.6, 2.6)
6	5.4	38	6.9	1.5	(-0.5, 3.6)	39	4.8	-0.6	(-2.7, 1.5)
8	1.3	38	3.8	2.6	(0.6, 4.5)	39	1.6	0.3	(-1.6, 2.3)
12	7.2	38	9.1	2.0	(-0.5, 4.4)	39	7.1	-0.1	(-2.6, 2.4)
16	2.1	38	4.5	2.4	(0.4, 4.5)	39	3.5	1.5	(-0.6, 3.5)
24	2.2	37	3.0	0.9	(-0.9, 2.6)	39	2.1	-0.1	(-1.8, 1.6)

Table 14: Categorical Analysis for HR (Grazoprevir MK-5172)

Treatment Group	Total N	HR \leq 100 bpm	HR $>$ 100 bpm
MK-5172 1600 mg	40	39 (97.5%)	1 (2.5%)
Moxifloxacin 400 mg	40	39 (97.5%)	1 (2.5%)
Placebo	40	40 (100%)	0 (0.0%)

Table 15: Categorical Analysis for HR (Elbasvir MK-8742)

Treatment Group	Total N	HR \leq 100 bpm	HR $>$ 100 bpm
400 mg Moxifloxacin	38	37 (97.4%)	1 (2.6%)
700 mg MK-8742	39	38 (97.4%)	1 (2.6%)
Placebo	40	40 (100%)	0 (0.0%)

4.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the Δ PR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 16 and Table 17. The largest upper bounds of the 2-sided 90% CI for the mean differences between MK-5172 1600 mg and placebo, and between MK-8741 700-mg and placebo are 4.5 ms and 4.7 ms, respectively.

Table 18

Table 18 and Table 19 present the categorical analyses for MK-5172 and MK-8742, respectively. One subject in MK-5172 and two subjects in MK-8742 experienced PR interval greater than 200 ms.

Table 16: Analysis Results of Δ PR and $\Delta\Delta$ PR for Grazoprevir MK-5172 1600 mg and Moxifloxacin 400 mg

	Treatment Group								
	MK-5172 1600 mg					Moxifloxacin 400 mg			
	Δ PR	Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	-0.2	40	0.0	0.2	(-1.9, 2.3)	40	1.0	1.2	(-0.9, 3.3)
1	-0.5	40	-2.2	-1.7	(-4.0, 0.6)	40	0.7	1.2	(-1.2, 3.5)
1.5	-0.1	40	-0.6	-0.5	(-2.8, 1.8)	40	0.4	0.5	(-1.8, 2.8)
2	-1.1	40	-0.0	1.1	(-1.0, 3.2)	40	-0.3	0.8	(-1.3, 2.9)
3	-0.9	40	-0.9	0.0	(-2.4, 2.4)	40	-0.9	0.0	(-2.4, 2.4)
4	-2.6	40	-0.9	1.7	(-1.0, 4.5)	40	-1.3	1.3	(-1.4, 4.1)
5.5	-4.7	40	-5.4	-0.7	(-3.9, 2.5)	40	-6.2	-1.5	(-4.7, 1.7)
6	-4.4	40	-5.4	-1.0	(-4.0, 2.1)	40	-7.1	-2.7	(-5.7, 0.3)
8	-5.9	40	-5.0	0.9	(-2.5, 4.2)	40	-6.9	-1.0	(-4.4, 2.4)
24	2.2	39	0.0	-2.2	(-5.3, 0.8)	40	0.6	-1.7	(-4.7, 1.3)

Table 17: Analysis Results of Δ PR and $\Delta\Delta$ PR for Elbasvir MK-8742 700 mg and Moxifloxacin 400 mg

Time (h)	Treatment Group								
	400 mg Moxifloxacin					700 mg MK-8742			
	Δ PR	Δ PR		$\Delta\Delta$ PR		Δ PR	$\Delta\Delta$ PR		
LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	
0.5	0.6	38	-1.3	-1.9	(-3.5, -0.3)	39	-0.4	-0.9	(-2.5, 0.7)
1	-0.4	38	-2.4	-2.0	(-4.3, 0.3)	39	0.2	0.6	(-1.7, 2.9)
1.5	1.5	38	-1.5	-2.9	(-5.1, -0.8)	39	-1.0	-2.5	(-4.6, -0.4)
2	-0.6	38	-1.4	-0.7	(-3.0, 1.5)	39	1.0	1.6	(-0.6, 3.8)
3	-1.5	38	-4.2	-2.7	(-5.2, -0.2)	39	-1.2	0.3	(-2.1, 2.8)
4	-2.1	38	-4.0	-1.9	(-4.4, 0.6)	39	-1.7	0.4	(-2.1, 2.9)
6	-3.8	38	-6.5	-2.7	(-5.3, 0.0)	39	-2.3	1.5	(-1.2, 4.1)
8	-5.0	38	-5.4	-0.4	(-3.1, 2.2)	39	-3.5	1.5	(-1.2, 4.1)
12	-3.7	38	-4.5	-0.8	(-3.9, 2.3)	39	-2.1	1.6	(-1.5, 4.7)
16	-0.9	38	-1.9	-1.0	(-3.8, 1.7)	39	-0.2	0.7	(-2.1, 3.4)
24	-2.0	37	-0.1	1.9	(-0.4, 4.1)	39	-2.4	-0.4	(-2.6, 1.8)

Table 18: Categorical Analysis for PR (Grazoprevir MK-5172)

Treatment Group	Total N	PR \leq 200 ms	PR $>$ 200 ms
MK-5172 1600 mg	40	39 (97.5%)	1 (2.5%)
Moxifloxacin 400 mg	40	37 (92.5%)	3 (7.5%)
Placebo	40	38 (95.0%)	2 (5.0%)

Table 19: Categorical Analysis for PR (Elbasvir MK-8742)

Treatment Group	Total N	PR \leq 200 ms	PR $>$ 200 ms
400 mg Moxifloxacin	38	37 (97.4%)	1 (2.6%)
700 mg MK-8742	39	37 (94.9%)	2 (5.1%)
Placebo	40	38 (95.0%)	2 (5.0%)

5.2.3 QRS Analysis

The statistical reviewer used mixed model to analyze the Δ QRS effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 20 and Table 22. The largest upper bounds of the 2-sided 90% CI for the mean differences between MK-5172 1600 mg and placebo, and between MK-8742 700-mg and placebo are 1.0 ms and 1.6 mg, respectively. Table 22 and Table 23 present the categorical analysis for MK-5172 and MK-8742, respectively. No subject experienced QRS interval greater than 110 ms is in MK5172 or MK-8742 group.

Table 20: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Grazoprevir MK-5172 1600 mg and Moxifloxacin 400 mg

	Treatment Group								
	Placebo	MK-5172 1600 mg				Moxifloxacin 400 mg			
	Δ QRS	Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	0.1	40	0.2	0.1	(-0.5, 0.6)	40	0.2	0.1	(-0.4, 0.6)
1	0.1	40	-0.3	-0.4	(-0.9, 0.1)	40	0.0	-0.1	(-0.6, 0.5)
1.5	-0.5	40	-0.1	0.5	(-0.0, 0.9)	40	0.1	0.6	(0.2, 1.1)
2	-0.2	40	0.3	0.4	(-0.1, 1.0)	40	0.2	0.4	(-0.2, 1.0)
3	0.0	40	-0.0	-0.1	(-0.6, 0.5)	40	0.3	0.2	(-0.4, 0.8)
4	-0.2	40	-0.4	-0.2	(-0.8, 0.4)	40	-0.3	-0.0	(-0.6, 0.5)
5.5	1.5	40	0.3	-1.2	(-2.4, 0.0)	40	0.8	-0.7	(-1.9, 0.5)
6	0.7	40	0.1	-0.6	(-1.6, 0.5)	40	0.4	-0.3	(-1.3, 0.8)
8	0.2	40	0.1	-0.1	(-1.1, 1.0)	40	-0.4	-0.6	(-1.6, 0.4)
24	-0.5	39	-0.5	0.1	(-0.4, 0.5)	40	-0.3	0.2	(-0.2, 0.7)

Table 21: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Elbasvir MK-8742 700 mg and Moxifloxacin 400 mg

	Treatment Group								
	Placebo	400 mg Moxifloxacin				700 mg MK-8742			
	Δ QRS	Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	0.3	38	-0.5	-0.8	(-1.6, -0.0)	39	0.2	-0.1	(-0.9, 0.7)
1	0.3	38	-0.2	-0.5	(-1.3, 0.3)	39	-0.1	-0.4	(-1.2, 0.3)
1.5	-0.4	38	-0.4	0.0	(-1.0, 1.0)	39	-0.1	0.3	(-0.7, 1.4)
2	-0.1	38	-0.1	0.0	(-0.7, 0.8)	39	-0.1	0.1	(-0.7, 0.8)
3	-0.2	38	-0.2	-0.0	(-0.9, 0.9)	39	-0.3	-0.1	(-0.9, 0.8)
4	0.7	38	-0.4	-1.1	(-2.0, -0.3)	39	-0.4	-1.1	(-1.9, -0.2)
6	0.5	38	-0.2	-0.6	(-1.7, 0.5)	39	0.3	-0.2	(-1.3, 0.9)
8	-0.1	38	-1.1	-1.0	(-2.1, 0.1)	39	-0.3	-0.2	(-1.3, 0.8)
12	1.4	38	0.9	-0.5	(-1.4, 0.5)	39	2.0	0.7	(-0.3, 1.6)
16	0.9	38	0.2	-0.7	(-1.8, 0.3)	39	1.2	0.3	(-0.7, 1.3)
24	0.1	37	0.1	-0.0	(-1.1, 1.0)	39	0.1	0.0	(-1.0, 1.0)

Table 22: Categorical Analysis for QRS (Grazoprevir MK-5172)

Treatment Group	Total N	QRS \leq 110 ms	QRS $>$ 110 ms
MK-5172 1600 mg	40	40 (100%)	0 (0.0%)
Moxifloxacin 400 mg	40	40 (100%)	0 (0.0%)
Placebo	40	40 (100%)	0 (0.0%)

Table 23: Categorical Analysis for QRS (Elbasvir MK-8742)

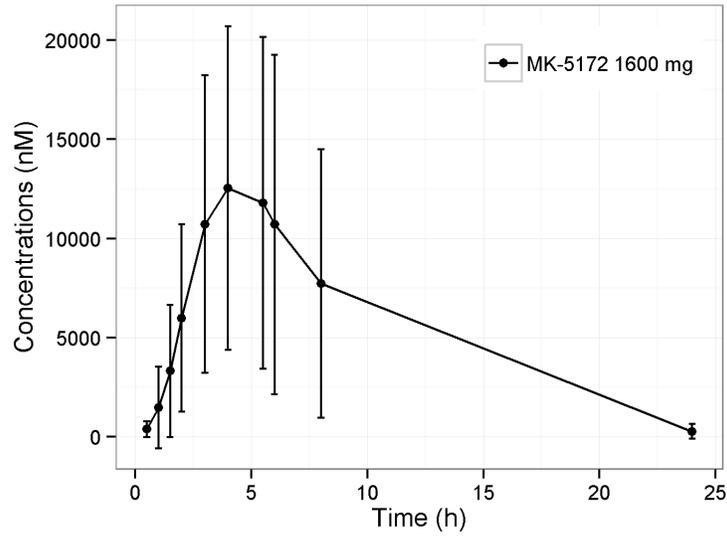
Treatment Group	Total N	QRS \leq 110 ms	QRS $>$ 110 ms
400 mg Moxifloxacin	38	38 (100%)	0 (0.0%)
700 mg MK-8742	39	39 (100%)	0 (0.0%)
Placebo	40	40 (100%)	0 (0.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile is illustrated in Figure 4.

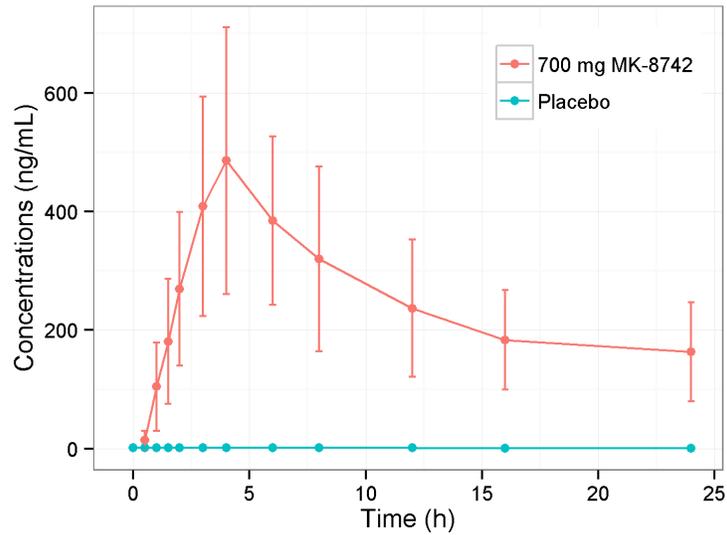
Figure 4: Mean \pm SD Concentration-Time Profiles for A) MK-5172 and B) MK-8742

A) Grazoprevir MK-5172



Data source: *qtpk dataset*

B) Elbasvir MK-8742



Note: *A number of subjects administered placebo had small but measurable plasma concentrations of MK-8742*

Data source: *qtpk dataset*

The relationship between ΔQTcF and MK-5172 exposure was analyzed using a linear mixed effects model, with the general form:

$$\Delta\text{QTcF} = \mu_l + p_t + qC_{lkt} + W_k + D_k + \varepsilon_{lkt}$$

μ_l = Fixed effect, treatment specific (l) intercept (active, placebo)

p_t = Fixed effect, time (t) specific intercept (as factor)

q = Fixed effect, slope parameter

C_{lkt} = Independent variable, Concentration for time point (t), treatment (l), and subject (k)

W_k = Random effect, random subject level (k) effect on intercept (μ)

D_k = Random effect, random subject level (k) effect on slope (q)

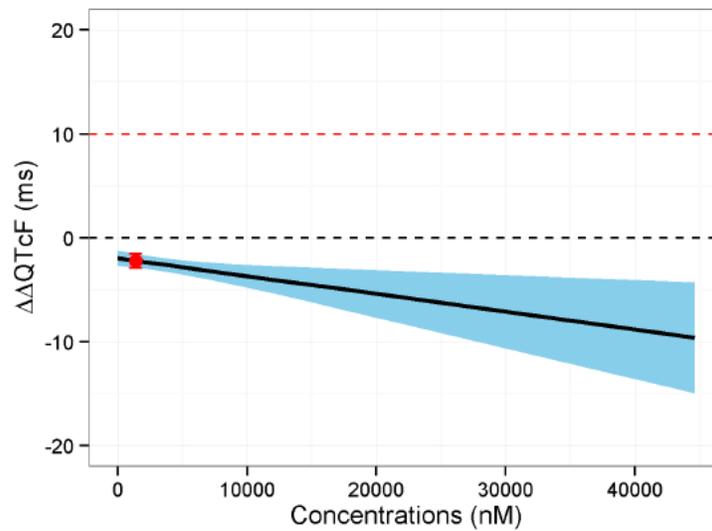
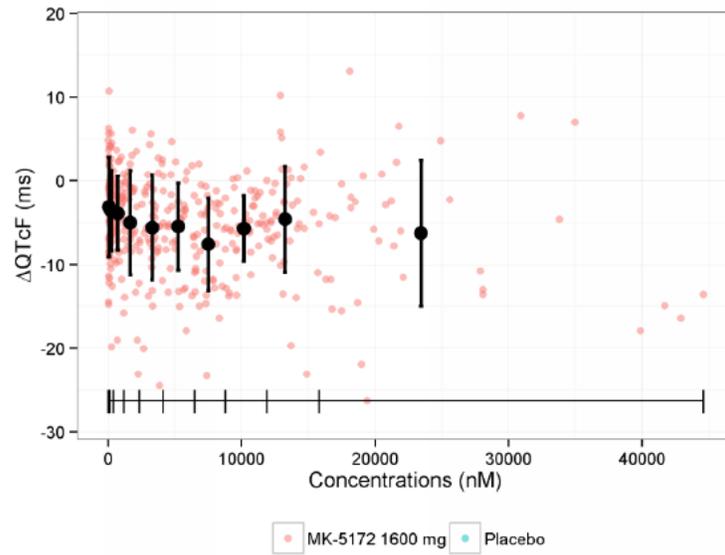
ε_{lkt} = Random effect, residual error for time point (t), treatment (l), and subject (k)

Baseline and placebo adjusted QTcF ($\Delta\Delta\text{QTcF}$) was estimated by contrasting placebo effect at concentration zero with the estimate of baseline adjusted QTcF at various concentrations. The relationship between $\Delta\Delta\text{QTcF}$ and MK-5172 concentrations is visualized in Figure 5. A negative statistically significant ($p= 0.022$) relationship between MK-5172 and $\Delta\Delta\text{QTcF}$ has been shown (the slope of $-171 \text{ ms} \cdot \text{nM}$ with a 95% confidence interval of -317 to $-25 \text{ ms} \cdot \text{nM}$).

The relationship between MK-8742 and ΔQTcF is illustrated in Figure 5. No significant exposure response relationship was detected.

Figure 5: $\Delta\Delta$ QTcF vs. A) MK-5172 and B) MK-8742 Concentrations

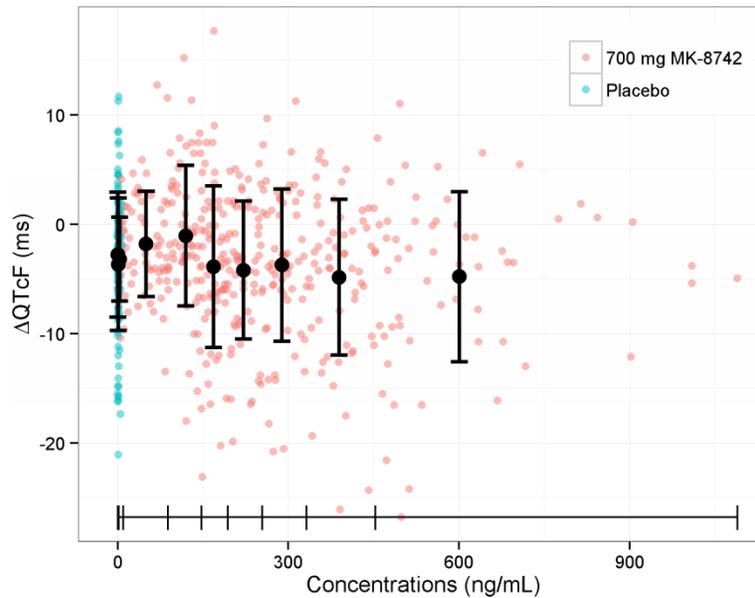
A) Grazoprevir MK-5172



Note: The solid black line and the shaded blue area describe the linear relationship between MK-5172 concentration and $\Delta\Delta$ QTcF. The shaded area represents the 90% CI of that relationship. The red circle and lines show the estimated effect on $\Delta\Delta$ QTcF at the maximum concentration at steady state following the therapeutic dosing regimen of MK-5172

Data source: qtpk dataset

B) Elbasvir MK-8742



5.4 CLINICAL ASSESSMENTS

5.4.1 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.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There were no clinically relevant effects on PR and QRS for both studies.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Grazoprevir (GZR, MK-5172) Clinical Pharmacology

Therapeutic dose	100 mg once daily
Maximum tolerated dose	Safe and well-tolerated up to the maximum doses tested

Principal adverse events	Adverse Events: AST/ALT elevation, headaches, dizziness, fatigue, dry mouth	
Maximum dose tested	Single Dose	1600 mg in healthy subjects (P049)
	Multiple Dose	1000 mg QD in healthy subjects (P001) 800 mg QD in HCV patients (P004, P003)
Exposures Achieved at Maximum Tested Dose	Single Dose	1600 mg in healthy subjects (P049): Geometric Mean (GM %CV): AUC0-24 – 77.0 $\mu\text{M}\cdot\text{hr}$ (78.1%), Cmax – 14.1 μM (52.6%)
	Multiple Dose	1000 mg QD in healthy subjects (P001): Geometric Mean (GM %CV) - AUC0-24 33.6 $\mu\text{M}\cdot\text{hr}$ (76.5%), Cmax 8.14 μM (63.8%) 800 mg QD in HCV patients (P004): Geometric Mean (GM %CV) AUC0-24 – 74.8 $\mu\text{M}\cdot\text{hr}$ (57.5%), Cmax – 11.5 μM (45.5%)
Range of linear PK	Nonlinear 50-1600 mg SD in healthy subjects (P001) Nonlinear 100-1000 mg QD in healthy subjects (P001) Nonlinear 10-800 mg QD in HCV-infected patients (P004, Ph2/3)	
Accumulation at steady state	2-fold accumulation at steady-state for 100 mg QD in HCV-infected patients (population PK model estimated)	
Metabolites	No circulating metabolites detected	
Absorption	Absolute/Relative Bioavailability	10-40% at 25-200 mg
	Tmax	3.0 hours (2.0 - 4.0 hours) for 100 mg QD in HCV-infected patients
Distribution	Vd/F or Vd	Vd: 1400-3600 L in healthy subjects Vd/F: ~1250 L (IIV = 69%): Population-PK model estimated for 100 mg QD in HCV-infected patients

	% bound	98.8%
Elimination	Route	Feces: 110% of dose (full recovery within limits of assay variability) Urine: <1% of dose (P007)
	Terminal t _{1/2}	GM (GM %CV): 31 hours (34%) 100 mg QD in HCV infected patients
	CL/F or CL	CL: 20-40 L/hr in healthy subjects CL/F: ~85 L/hour (IIV = 42%): Population-PK model estimated for 100 mg QD in HCV-infected patients
Intrinsic Factors	Age	P014: ≥65 years of age AUC GMR [90% CI] of 2.18 [1.01, 4.71] relative to 18-45 years Population PK: 72% higher AUC in 67-year-old subjects compared to 31-year-old subjects.
	Sex	P014: elderly females AUC GMR [90% CI] of 1.76 [0.82, 3.81] relative to elderly males Population PK: 30% higher AUC in females compared to males
	Race	P009: healthy Japanese AUC GMR [90% CI] of 2.88 [2.01, 4.12]) compared to Caucasian P042: healthy Chinese AUC GMR [90% CI] of 1.80 [1.20, 2.71] compared to Caucasian (100 mg) Population PK: 50% higher AUC in Asians compared to Caucasians; comparable AUC between Caucasians and Black/African Americans; 20% higher AUC in Hispanics compared to non-Hispanics

	Hepatic Impairment	P013 (non-HCV-infected subjects with hepatic impairment): 70% higher AUC in Child-Pugh A subjects, 5-fold increase in AUC in Child-Pugh B subjects, 12-fold increase in AUC in Child-Pugh C subjects compared to healthy matched controls
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		Population PK of HCV-infected patients: 65% higher AUC in Child- Pugh A patients with compensated cirrhosis and 5-fold increase in AUC in Child-Pugh B patients compared to non- cirrhotic subjects.
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	Renal Impairment	<p>P050 (non-HCV-infected subjects with renal impairment): 65% higher AUC in subjects with severe renal impairment who are not on dialysis and comparable in subjects with severe renal impairment who are dialysis-dependent relative to non-HCV-infected subjects with normal renal function. GZR is highly bound to plasma protein. GZR is not removed by hemodialysis. Less than 0.5% of GZR was recovered in dialysate over a 4-hour dialysis session</p> <p>Population PK of HCV-infected patients: 10% higher GZR AUC in dialysis-dependent subjects and 40% higher GZR AUC in non-dialysis-dependent subjects with severe renal impairment compared to GZR AUC in subjects without severe renal impairment</p>
Extrinsic Factors	Drug interactions	See Tables 1 & 2 below
	Food Effects	P069: ~1.5-fold increase in AUC and ~2.8-fold increase in Cmax (high-fat meal)
Expected High Clinical Exposure Scenario	<p>Combinations of factors that could increase GZR exposures were considered using the population pharmacokinetic models. Considering the intrinsic factor effects as summarized above, the highest GZR exposures are likely to occur in Asian, female patients with cirrhosis. The magnitude of increase for this population compared to white, male patients with no cirrhosis was estimated from the population pharmacokinetic model to be ~3.6-fold (GMR [90% CI] of 3.63 [3.16, 4.17]). Adding in additional effects of low weight (e.g., 53 kg) and increased age (e.g., 67 years) gave an estimated fold increase in GZR of 4.37 [3.91, 4.89]. This estimate should be considered with caution, as there were only two Asian females with cirrhosis who had body</p>	

APPEARS THIS WAY ON ORIGINAL

weight <53 kg and age \geq 65 years in the dataset. Regardless, the estimated ~4.4-fold increase in GZR exposure in an elderly, low-weight, cirrhotic, Asian, female patient (corresponding to a steady state AUC₀₋₂₄ of ~7 $\mu\text{M}\cdot\text{hr}$ and C_{max} of ~1 μM) is within the clinical comparability bounds for GZR.

In addition, if extrinsic factor effects as summarized below were also to be considered in patients who have a combination of intrinsic factors, the use of moderate or strong inhibitors of CYP3A/P-gp may further increase GZR AUC. Based on analysis from the population pharmacokinetic model, the additional effect of moderate inhibitors of CYP3A/P-gp is estimated to result in a 32% increase in GZR AUC in HCV-infected patients who used moderate CYP3A/P-gp inhibitors in the Phase 2 and 3 studies. The effect of strong inhibitors of CYP3A/P-gp may be larger given the 3-fold increase in GZR AUC that was observed in healthy subjects following coadministration with ketoconazole (5172-P001). There was insufficient use of strong inhibitors of CYP3A/P-gp in the Phase 2 and 3 studies to estimate the effect on GZR AUC in an HCV-infected patient population using the population pharmacokinetic model. Although the combination of all the intrinsic and extrinsic factor effects that could increase GZR exposure was not observed in the clinical database, it is possible that a patient with all of the intrinsic factor effects described above who also uses a strong inhibitor of CYP3A/P-gp may have a ~10-fold increase compared to the reference population used for the analysis of the relationship between GZR exposure and Late ALT/AST Elevation Events (corresponding to a steady state AUC₀₋₂₄ of ~18 $\mu\text{M}\cdot\text{hr}$ and C_{max} of ~1 μM).

In 5172-P049, the thorough QT study, the dose of 1600 mg of GZR resulted in a geometric mean AUC₀₋₂₄ (77.0 $\mu\text{M}\cdot\text{hr}$) and C_{max} (14.1 μM) that provided adequate margins to the corresponding steady-state AUC₀₋₂₄ and C_{max} of GZR following administration of 100 mg QD of GZR to elderly, low-weight, cirrhotic, Asian, female patients with or without receiving concomitant CYP3A inhibitors.

Highlights of Elbasvir (EBR, MK-8742) Clinical Pharmacology

Therapeutic dose	50 mg once daily	
Maximum tolerated dose	700 mg single dose administered alone	
Principal adverse events	<p>The most common AEs were headache, nausea and fatigue.</p> <p>Due to AEs of abdominal discomfort, diarrhea, nausea, vomiting, headache and pruritus, the 800 mg dose was not well tolerated, whereas a 700 mg dose was well tolerated.</p>	
Maximum dose tested	Single Dose	800 mg SD administered alone to healthy subjects (8742-P015)
	Multiple Dose	<p>200 mg QD administered alone to healthy subjects (8742-P001)</p> <p>100 mg QD administered alone to HCV-infected patients (8742-P002)</p>
Exposures Achieved at Maximum Tested Dose	Single Dose	<p>800 mg SD administered alone (8742-P015)</p> <p>Geometric Mean (%GCV): AUC₀₋₂₄: 8.41 $\mu\text{M}\cdot\text{hr}$ (25.6); C_{max} 0.666 μM (30.7)</p>
	Multiple Dose	<p>200 mg QD administered alone to healthy subjects (8742-P001)</p> <p>Geometric Mean (%GCV) AUC₀₋₂₄: 3.54 $\mu\text{M}\cdot\text{hr}$ (73.3); C_{max}: 0.281 μM (71.5)</p> <p>100 mg QD administered alone to HCV-infected patients (8742-P002)</p> <p>Geometric Mean (%GCV) AUC₀₋₂₄: 2.08 $\mu\text{M}\cdot\text{hr}$ (39.5); C_{max}: 0.170 μM (43.6)</p>
Range of linear PK	<p>Approximately linear 5-100 mg SD in healthy subjects (8742-P001)</p> <p>Approximately linear 10-100 mg QD in healthy subjects (8742-P001)</p> <p>Approximately linear 5-50 mg QD in HCV patients (8742-P002)</p>	
Accumulation at steady state	<p>50 mg QD x 5 in HCV-infected patients (8742-P002)</p> <p>Geometric Mean (%GCV): AUC₀₋₂₄ 1.89 (98.1)</p>	
Metabolites	No circulating metabolites were detected.	

Absorption	Absolute/Relative Bioavailability	Evaluated in an ongoing clinical study; results not included in the submitted dossier. Fraction absorbed estimated based on PBPK modeling is ~0.4
	Tmax	3.01 hours (2.93 - 6.03 hours) at 50 mg in combination with 100 mg grazoprevir in HCV-infected patients (5172-P059)
Distribution	Vd/F or Vd	Vd/F in healthy subjects: geometric mean (%GCV) ~700 L (~28) (50 mg SD, 8742-P001) Vd/F in HCV-infected patients: ~680 L (IIV ~26%) (50 mg QD population-PK model estimated)
	% bound	>99.9%
Elimination	Route	Feces: 94.1% as both parent and oxidative metabolites Urine: 0.2% (8742-P014)
	Terminal t _{1/2}	Geometric mean (%GCV) ~24 hours (24) at 50 mg QD in HCV-infected patients (8742-P002)
	CL/F or CL	CL/F: geometric mean (%GCV) 32.4 L/hr (37) in healthy subjects at 50 mg SD (8742-P001) CL/F: ~30 L/hr (IIV=13.4%) (50 mg QD population-PK model estimated)
Intrinsic Factors	Age	P004: ≥65 years of age AUC GMR [90% CI] of 1.02 [0.69, 1.53] relative to 18-45 years Population PK: 14% higher AUC in 68-year-old subjects compared to 32-year-old subjects.
	Sex	P004: elderly females AUC GMR [90% CI] of 1.67 [1.12, 2.48] relative to elderly males Population PK: 50% higher AUC in females compared to males
	Race	7009-P050: healthy Japanese AUC GMR [90% CI] of 1.44 [0.96, 2.15] compared to Caucasian Population PK: 15% higher AUC in

		Asians compared to Caucasians; comparable AUC between Caucasians and Black/African Americans; 10% higher AUC in Hispanics compared to non-Hispanics
	Hepatic Impairment	<p>P009 (non-HCV-infected subjects with hepatic impairment): 40% decreased AUC in Child-Pugh A subjects, 28% decreased AUC in Child-Pugh B subjects, 12% decreased AUC in Child-Pugh C subjects compared to healthy matched controls.</p> <p>Population PK of HCV-infected patients: comparable AUC in Child-Pugh A and B patients compared to non-cirrhotic subjects</p>
	Renal Impairment	<p>5172-P050 (non-HCV-infected subjects with renal impairment): 86% higher EBR AUC in subjects with severe renal impairment who are not on dialysis and comparable in subjects with severe renal impairment who are dialysis-dependent relative to non-HCV-infected subjects with normal renal function. EBR is highly bound to plasma protein. EBR is not removed by hemodialysis. Concentrations of EBR were not quantifiable in the dialysate samples.</p> <p>Population PK of HCV-infected patients: 25% higher EBR AUC in dialysis-dependent subjects and 46% higher EBR AUC in non-dialysis-dependent subjects with severe renal impairment compared to EBR AUC in subjects without severe renal impairment.</p>
Extrinsic Factors	Drug interactions	See Tables 1 and 2 below
	Food Effects	~11% decrease in AUC and ~15% decrease in C _{max} (50 mg SD in combination with 100 mg grazoprevir in a fixed-dose combination tablet in healthy subject, high-fat meal) (P069)

<p>Expected High Clinical Exposure Scenario</p>	<p>The highest EBR exposures are likely to occur in Asian females with severe renal impairment with an estimated increase for this population compared to white, male patients with no renal impairment from the population pharmacokinetic model of 1.96 [1.85, 2.08], which corresponds to a steady-state AUC₀₋₂₄ of 3.69 $\mu\text{M}\cdot\text{hr}$ and C_{max} of 0.211 μM in this population. Coadministration of methadone may further increase EBR exposure by 30%, resulting in a steady-state AUC₀₋₂₄ of 4.74 $\mu\text{M}\cdot\text{hr}$ and C_{max} of 0.255 μM.</p> <p>In 8742-P015, the thorough QT study, the dose of 700 mg of EBR resulted in a geometric mean AUC₀₋₂₄ (6.20 $\mu\text{M}\cdot\text{hr}$) and C_{max} (0.567 nM) that provided adequate margins to the AUC₀₋₂₄ and C_{max} in an Asian female with severe renal impairment and with or without concomitant methadone coadministration.</p>
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MOH JEE NG
09/21/2015

QIANYU DANG
09/21/2015

DINKO REKIC
09/21/2015

JIANG LIU
09/21/2015

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09/22/2015

**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 208261

Application Type: New NDA

Name of Drug/Dosage Form: [TRADENAME] (grazoprevir/elbasvir) Tablet

Applicant: Merck Sharp & Dohme Corp.

Receipt Date: May 28, 2015

Goal Date: January 28, 2016

1. Regulatory History and Applicant's Main Proposals

Merck Sharp & Dohme Corp. (Merck) submitted a new drug application (NDA) for the fixed dose combination (FDC) tablet of grazoprevir (100 mg), a hepatitis C virus (HCV) NS3/4A protease inhibitor, and elbasvir (50 mg), an HCV NS5A inhibitor. Merck proposed the following indication "TRADEMARK™ is indicated for the treatment of chronic hepatitis C (CHC) genotypes 1, 4, or 6 infection in adults."

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

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by August 31, 2015. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

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:

- YES** 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:

- 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:

- YES** 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:

- YES** 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:

- 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

Selected Requirements of Prescribing Information

• 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:

Initial U.S. Approval in Highlights

- N/A** 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:

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.

Selected Requirements of Prescribing Information

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:

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

Selected Requirements of Prescribing Information

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:

Selected Requirements of Prescribing Information

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:
- NO** 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: *In section 14, subsection 14.3 the preposition "Without" should be in lower case.*
- 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:

Selected Requirements of Prescribing Information

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: *The TOC listed above has not been updated to reflect the new titles that should be included under section 8, however, the sponsor's TOC is accurate.*

- YES** 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)*]”.

Selected Requirements of Prescribing Information

Comment:

- 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:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 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:

- YES** 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:

Selected Requirements of Prescribing 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*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

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

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*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/

NINA MANI
07/20/2015

KAREN D WINESTOCK
07/21/2015

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 # 208261 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Established/Proper Name: grazoprevir/elbasvir Dosage Form: Tablet Strengths: 100 mg/50 mg		
Applicant: Merck Sharp & Dohme Corp. Agent for Applicant (if applicable):		
Date of Application: May 28, 2015 Date of Receipt: May 28, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: January 28, 2016		Action Goal Date (if different):
Filing Date: July 27, 2015		Date of Filing Meeting: July 1, 2015
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): [TRADENAME] is indicated for the treatment of chronic hepatitis C (CHC) genotypes 1, 4, or 6 infection in adults		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
The application will be a priority review if:	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> No	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

<input type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s):

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>	N/A	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>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.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>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.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:							
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				<input type="checkbox"/>	<input type="checkbox"/>		
• 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)].				<input type="checkbox"/>	<input type="checkbox"/>		
• 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)]?				<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted 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 for advice.</i>							
• Is there unexpired exclusivity on another listed drug product containing the same 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				<input type="checkbox"/>	<input type="checkbox"/>		
If yes , please list below:							
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration				
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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.</i>							
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	<input type="checkbox"/>	<input checked="" type="checkbox"/>					
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)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>				
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>							
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				
If yes , # years requested: 5							
<i>Note: An applicant can receive exclusivity without requesting it;</i>							

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>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.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> 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).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>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 (3397/3792), 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.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>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...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>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)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		PeRC date: November 4, 2015

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

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<i>(including new fixed combinations), 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.</i>				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input checked="" type="checkbox"/> Other (specify) Blister and Dosepak			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	PI is in PLLR format.
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR 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? <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	May 5, 2015
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	May 5, 2015
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	May 5, 2015
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

5

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent :QT IRT and PMHS: IRT-QT: April 22, 2015</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	PMHS will be consulted later in the review cycle.
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): May 20, 2014 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		At sponsor's request the May 22, 2014 meeting was cancelled because sponsor indicated that the FDA's responses in the Preliminary comments sent on May 20, 2014 were clear.
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): February 20, 2015 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Converted to T-con at sponsor's request
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 1, 2015

BACKGROUND:

Merck Sharp & Dohme Corp. (Merck) submitted a new drug application (NDA) for the fixed dose combination (FDC) of grazoprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and elbasvir, an HCV NS5A inhibitor. The application contains studies to support an indication for treatment of chronic hepatitis C (CHC) genotypes 1, 4, or 6 infection in adults.

The FDC of grazoprevir/elbasvir was granted Breakthrough Designation for the treatment of chronic hepatitis C virus (HCV) infection in April 2015 for:

- genotype 4 subjects, and
- genotype 1 infection in patients with end stage renal disease on hemodialysis

Both components of the FDC, grazoprevir and elbasvir are new molecular entities, and the application is subject to “The Program” under PDUFA V.

The application was received on May 28, 2015 and has received priority review under PDUFA V (8 month review). PDUFA goal date is January 28, 2016.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Nina Mani	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Adam Sherwat		Y
Division Director/Deputy	Debra Birnkrant		Y
	Jeffrey Murray		N
Office Director/Deputy	Edward Cox		Y
	John Farley		Y
Clinical	Reviewer:	Sarita Boyd Prabha Viswanathan	Y Y
	TL:	Adam Sherwat	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		

OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Su-Young Choi	Y
	TL:	Shirley Seo	Y
• Genomics	Reviewer:	Jeffrey Kraft	N
• Pharmacometrics	Reviewer:	Luning (Ada) Zhuang	Y
	TL:	Jeff Florian	N
Biostatistics	Reviewer:	Laree Tracy	Y
	TL:	Guoxing (Greg) Soon	N

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Christopher Ellis	Y
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Steve Miller	Y
	RBPM:	Bamidele (Florence) Aisida	Y
• Drug Substance- grazoprevir	Reviewer:	Monica Cooper	Y
• Drug Substance- elbasvir	Reviewer:	Sharon Kelly	N
• Drug Product	Reviewer:	George Lunn	Y
• DP Process (and Microbiology)	Reviewer:	Ying Wang	N
• Microbiology	Reviewer:		
• Manufacturing Facility	Reviewer:	Denise DiGiulio	N
• Biopharmaceutics	Reviewer:	Jing Li	Y
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	EA Reviewer:	Jim Laurenson	N
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Morgan Walker	N
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Kemi Asante	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Monica Calderon	N
	TL:	Vicky Borders-Hemphill	N
OSE/DRISK (REMS)	Reviewer:	Jasminder Kumar	N
	TL:	Jamie Wilkins Parker	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Antoine el Hage	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
<ul style="list-style-type: none"> Discipline <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:		
	TL:		
Other attendees	DPV: Mihaela Jason		N
	TL: Kelly Cao		N
	DEPI: James Trinidad		N
	TL: Elizabeth Mahoney		N
	OSE RPM: Danyal Chaudhry Deputy Director, Safety, DAVP: Poonam Mishra		Y
	Acting ADRA, DAVP: Katherine Schumann		Y
	ADL, DAVP: Stacey Min		Y
	RPM, DAVP: Christian Yoder		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues: <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

If no, explain:	
<ul style="list-style-type: none">• Electronic Submission comments List comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments

<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <i>Sites have been selected and inspections have been assigned.</i> If no, explain: 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>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</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: The components of this drug combination are not the first in their respective classes.
<ul style="list-style-type: none"> • 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p> <ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: <i>P/T will work on the PLLR before consulting with PMHS. They will also analyze the testicular toxicity observed in dogs, which is a class effect observed with other HCV PIs, simeprevir, boceprevir and telaprevir. Since human exposure to the drugs is less than 24 weeks, sponsor did not conduct carcinogenicity studies with DAVP concurrence.</i></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: <i>10 facilities are involved in the manufacture of the drug substances. Three of them are known to be acceptable; two in Oregon are on the inspection list, and a determination is being made regarding inspection of foreign sites.</i></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>New Molecular Entity (NDAs only)</u></p> <ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments: OPQ is deciding on the sites that need to be inspected.</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> 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? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	<ol style="list-style-type: none"> Labeling comprehension study report- June 25, 2015 Hepatic safety assessment (At pre-NDA Meeting it was agreed that sponsor could submit within 60 days of NDA submission)- Expected July 28, 2015
<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none">• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none">• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Office: TBD; DAVP Deputy Division Director: Jeffrey Murray	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): September 10, 2015	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTION ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	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.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

Version: 5/27/2015

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

/s/

NINA MANI
07/20/2015

KAREN D WINESTOCK
07/21/2015