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RESEARCH**

APPLICATION NUMBER:

206843Orig1s000

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/BLA # 206843
Product Name: Daclatasvir

PMR/PMC Description: Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of daclatasvir in combination with other direct acting antivirals in pediatric subjects 3 through 17 years of age with chronic hepatitis C.

PMR/PMC Schedule Milestones: Final Protocol Submission: 10/31/2019
Study/Trial Completion: 07/31/2023
Final Report Submission: 12/31/2023
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

Adult studies are completed and ready for approval. The review team met with the Pediatric Review Committee (PeRC) on June 3, 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 study is a deferred pediatric trial under PREA to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of daclatasvir in combination with other direct acting antivirals for the treatment of chronic hepatitis C virus (HCV) infection in pediatric subjects 3 through 17 years of age. 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.

Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of daclatasvir in combination with other direct acting antivirals in pediatric subjects 3 through 17 years of age with chronic hepatitis C.

Required

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

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

- Other
-

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

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

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

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

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

PMR/PMC Development Coordinator:

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

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/s/

SOHAIL MOSADDEGH
07/23/2015

PMR/PMC Development Template

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

NDA/BLA # 206843: Daclatasvir

Product Name:

PMR/PMC Description: Characterize the long-term (≥ 1 year) persistence of treatment-emergent, daclatasvir resistance-associated substitutions in HCV genotype 3 infected subjects.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>N/A</u>
	Study/Trial Completion:	<u>09/30/2017</u>
	Final Report Submission:	<u>09/30/2018</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

Chronic HCV infection is a serious and life-threatening disease. NDA 206843 for daclatasvir will likely be approved and indicated for use in combination with sofosbuvir (an approved drug) for patients with chronic HCV genotype 3 infection. During the NDA review it was found that failure to achieve the primary efficacy endpoint (sustained virologic response [SVR]) with daclatasvir/sofosbuvir treatment was associated with the emergence of daclatasvir-resistant HCV populations, which are cross-resistant to other drugs in the same class (NS5A inhibitors) and may limit re-treatment options. The intention of this PMR is to assess the long-term persistence of daclatasvir-resistant HCV genotype 3 populations following treatment failure. It is not feasible to conduct this long-term study pre-approval, as it would limit the availability of an important treatment option for HCV genotype 3 infected patients.

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.”

Failure of patients to achieve SVR with daclatasvir/sofosbuvir treatment is associated with the emergence of daclatasvir-resistant HCV populations, which are cross-resistant to other drugs in the same class (NS5A inhibitors) and may limit re-treatment options. The intention of this PMR is to assess the long-term persistence of daclatasvir-resistant HCV genotype 3 populations following treatment failure. These data will help guide re-treatment approaches for HCV genotype 3 infected patients who fail treatment with daclatasvir/sofosbuvir.

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.

We recommend the sponsor conducts an observational study to characterize the long-term persistence (≥ 1 year, if feasible prior to receiving re-treatment) of daclatasvir resistance-associated substitutions in HCV genotype 3 infected subjects who failed treatment with daclatasvir-containing treatment 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

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)
Observational clinical study to assess persistence of drug-resistant virus
-

Agreed upon:

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

-
- Other
-

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

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

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

PMR/PMC Development Coordinator:

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

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/s/

SOHAIL MOSADDEGH
07/23/2015

PMR/PMC Development Template

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

NDA/BLA # 206843: Daclatasvir

Product Name:

PMR/PMC Description: To evaluate the potential mechanism of both pharmacodynamic and pharmacokinetic interactions between amiodarone and HCV direct acting antivirals (DAAs), including daclatasvir (DCV) using a multielectrode array electrophysiology study in human stem-cell derived cardiomyocytes.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	N/A- study is ongoing
	Study/Trial Completion:	<u>12/31/2015</u>
	Final Report Submission:	<u>02/01/2016</u>
	Other: N/A	<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

With approval, the Warnings and Precautions section of the package insert for daclatasvir will include a recently identified drug-drug interaction (DDI) describing the risk of severe, life-threatening bradycardia associated with use of amiodarone co-administered with sofosbuvir in combination with another HCV direct acting antiviral, including DCV. This DDI was not identified in the DCV clinical trials (where amiodarone use was prohibited) but was observed in a large European expanded access program where DCV was used in combination with sofosbuvir (SOF) with and without ribavirin and use of amiodarone was allowed. The safety signal was identified and reported during the current review cycle due to ongoing safety assessment of the expanded access program. The patient population in the expanded access program represents those with more advanced liver disease and complex comorbid conditions requiring multiple concomitant medications compared to the clinical trials population.

Of note, the safety events presented in the DCV NDA resubmission were a subset of the overall nine cases identified in an EMA report and in FDA postmarketing reports that led to FDA's Drug Safety Communication, Gilead's Dear Healthcare Provider letter and revisions to the SOF, SOF/LDV and SMV label to include Warnings and Precautions. Consequently, the DCV label will include the same Warnings and Precautions.

Given the exploratory nature of the ongoing in vitro study, there is no protocol. Design of the study may be changed based on experimental outcomes and as other information becomes available after study initiation.

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.”

A drug-drug interaction leading to the serious risk of severe, life-threatening bradycardia has been associated with the combination of SOF with another DAA, including DCV, and concomitant use of amiodarone. Without use of amiodarone, no cardiac safety signals have been identified for DCV/SOF.

The goal of this PMR is to further evaluate the potential mechanism of the pharmacodynamic and pharmacokinetic interactions between amiodarone and other HCV DAAs, including DCV. This study will evaluate the effect of amiodarone and HCV DAAs (sofosbuvir, daclatasvir and ledipasvir) alone or in combination, on spontaneous beat rate (a surrogate for heart rate) using human stem-cell derived cardiomyocytes and multi-electrode array electrophysiology.

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 in vitro study will evaluate the effect of amiodarone and HCV DAAs (sofosbuvir, daclatasvir and ledipasvir) alone or in combination, on spontaneous beat rate (a surrogate for heart rate) using human stem-cell derived cardiomyocytes and multi-electrode array electrophysiology.

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)
In vitro multielectrode array electrophysiology study in human stem-cell derived cardiomyocytes

Agreed upon:

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

- Other

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

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

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

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

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

PMR/PMC Development Coordinator:

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

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SOHAIL MOSADDEGH
07/23/2015

PMR/PMC Development Template

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

NDA/BLA # 206843: Daclatasvir
Product Name: _____

PMR/PMC Description: To evaluate the effect of individual direct acting antivirals ((b) (4) daclatasvir (b) (4)) on the plasma protein binding of amiodarone using the TRANSIL high sensitivity binding assay to help elucidate the potential mechanism of an interaction between amiodarone and HCV direct acting antivirals.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	N/A- Study is ongoing
	Study/Trial Completion:	12/31/2015
	Final Report Submission:	02/01/2016
	Other: N/A	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

With approval, the Warnings and Precautions section of the package insert for daclatasvir will include a recently identified drug-drug interaction (DDI) describing the risk of severe, life-threatening bradycardia associated with use of amiodarone co-administered with sofosbuvir in combination with another HCV direct acting antiviral, including DCV. This DDI was not identified in the DCV clinical trials (where amiodarone use was prohibited) but was observed in a large European expanded access program where DCV was used in combination with sofosbuvir (SOF) with and without ribavirin and use of amiodarone was allowed. The safety signal was identified and reported during the current review cycle due to ongoing safety assessment of the expanded access program. The patient population in the expanded access program represents those with more advanced liver disease and complex comorbid conditions requiring multiple concomitant medications compared to the clinical trials population.

Of note, the safety events presented in the DCV NDA resubmission were a subset of the overall nine cases identified in an EMA report and in FDA postmarketing reports that led to FDA's Drug Safety Communication, Gilead's Dear Healthcare Provider letter and revisions to the SOF, SOF/LDV and SMV label to include Warnings and Precautions. Consequently, the DCV label will include the same Warnings and Precautions.

Given the exploratory nature of the ongoing in vitro study, there is no protocol. Design of the study may be changed based on experimental outcomes and as other information becomes available after study initiation.

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.”

A drug-drug interaction leading to the serious risk of severe, life-threatening bradycardia has been associated with the combination of SOF with another DAA, including DCV, and concomitant use of amiodarone. Without use of amiodarone, no cardiac safety signals have been identified for DCV/SOF.

The goal of this PMR is to further evaluate the potential mechanism of the pharmacodynamic and pharmacokinetic interactions between amiodarone and other HCV DAAs, including DCV. This study will evaluate plasma protein binding displacement using the TRANSIL high sensitivity binding assay to evaluate the effect of individual DAAs ((b)(4) daclatasvir, (b)(4)) on free fraction of amiodarone in human plasma.

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.

An in vitro study to explore the potential for plasma protein binding displacement using the TRANSIL high sensitivity binding assay. The TRANSIL assay is being explored to evaluate the effect of individual DAA ((b)(4) daclatasvir, (b)(4)) on free fraction of amiodarone in human plasma. As noted by the sponsor, “However, while there has been significant testing of the TRANSIL high sensitivity binding assay by the manufacturers to determine the quality of the results, there is very little experience in testing drug combinations with this experimental approach”.

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)
In vitro study to explore the potential for plasma protein binding displacement using the TRANSIL high sensitivity binding assay.

Agreed upon:

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

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

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

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

PMR/PMC Development Coordinator:

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

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/s/

SOHAIL MOSADDEGH
07/23/2015

PMR/PMC Development Template

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

NDA/BLA # 206843: Daclatasvir

Product Name:

PMR/PMC Description: Conduct a trial in hepatitis C virus genotype 3 infected subjects with cirrhosis treated with daclatasvir plus sofosbuvir to determine if a longer duration of treatment or the addition of ribavirin reduces the rate of virologic failure and the rate of treatment-emergent drug resistant viral populations.

PMR/PMC Schedule Milestones: Final Protocol Submission: 12/31/2015
Study/Trial Completion: 05/31/2017
Final Report Submission: 11/30/2017
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 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

Chronic HCV infection is a serious and life-threatening disease. NDA 206843 for daclatasvir will likely be approved and indicated for use in combination with sofosbuvir (an approved drug) for patients with chronic HCV genotype 3 infection. Efficacy data supporting this indication are primarily from clinical trial AI444218 (ALLY-3), which studied daclatasvir plus sofosbuvir for 12 weeks in HCV genotype 3 infected subjects with or without cirrhosis. The natural history of chronic HCV infection involves progression to cirrhosis, hepatocellular carcinoma, liver failure, and death. The consequences of treatment failure in patients with cirrhosis include risk of progressing to hepatic decompensation. During the NDA review it was found that efficacy (i.e., sustained virologic response [SVR] rate) was lower and virologic failure was more common in subjects with cirrhosis compared to those without cirrhosis (virologic failure rates of 38% and 4%, respectively), and virologic failure was associated with the emergence of daclatasvir-resistant HCV populations, which are cross-resistant to other drugs in the same class (NS5A inhibitors) and limit re-treatment options. Therefore, it is important that treatment with daclatasvir and sofosbuvir is optimized to limit the rate of virologic failure and treatment-emergent drug resistance. Ribavirin is contraindicated or poorly tolerated in some populations, such as patients with bleeding disorders, hence a ribavirin-free treatment option will address an unmet need in certain subgroups.

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.”

As noted above, in the ALLY-3 trial approximately 38% of HCV genotype 3 infected subjects with cirrhosis (compared to ~4% of subjects without cirrhosis) experienced virologic failure with daclatasvir plus sofosbuvir for 12 weeks. Drug resistance is a concern of virologic failure, as virologic failure was associated with the emergence of HCV populations carrying an NS5A Y93H coding substitution (and possibly other resistance-associated substitutions) that confers viral resistance to daclatasvir, and confers cross-resistance to other NS5A inhibitors, limiting potential re-treatment options. As further evidence of the potential clinical consequence of virologic failure and HCV-Y93H emergence, efficacy was shown to be reduced in subjects with daclatasvir plus sofosbuvir in ALLY-3 who had a natural HCV NS5A Y93H polymorphism detected at baseline: SVR rates were ~30-40% lower in cirrhotic and non-cirrhotic subjects with the Y93H polymorphism compared to those without the Y93H polymorphism.

It is important that treatment with daclatasvir and sofosbuvir is optimized in the cirrhotic population to reduce the rate of virologic failure and treatment-emergent drug resistance. It has been shown with other HCV combination antiviral therapies and patient populations that a longer treatment duration, with or without the addition of the FDA-approved drug ribavirin, can improve efficacy and reduce the rate of virologic failure, which in turn reduces the rate of drug resistance emergence in the treated population. We recommend the sponsor conducts a trial to determine if one or more of these approaches improves the efficacy of the daclatasvir plus sofosbuvir regimen in HCV genotype 3 infected patients with cirrhosis.

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

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

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

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

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

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

We recommend a historically controlled trial in which HCV genotype 3 infected subjects with cirrhosis are randomized to receive (A) 12 weeks of daclatasvir and sofosbuvir plus ribavirin, (B) 24 weeks of daclatasvir and sofosbuvir, or (C) 24 weeks of daclatasvir and sofosbuvir plus ribavirin. SVR rates from these arms can be compared to those from HCV genotype 3 infected subjects with cirrhosis treated with 12 weeks of daclatasvir and sofosbuvir (no ribavirin) in ALLY-3, as the historical control. A historically controlled trial is acceptable as one or more of the three experimental approaches described above is expected to reduce the rate of virologic failure and drug resistance emergence in this population, as observed with other HCV antiviral treatments.

Required

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

Continuation of Question 4

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

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

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

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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

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

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

PMR/PMC Development Coordinator:

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

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/s/

SOHAIL MOSADDEGH
07/23/2015

**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: June 26, 2015

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
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): DAKLINZA (daclatasvir)

Dosage Form and Route: tablet, for oral use

Application Type/Number: NDA 206843

Applicant: Bristol-Myers Squibb

1 INTRODUCTION

On February 13, 2015, Bristol-Myers Squibb submitted for the Agency's review a resubmission of New Drug Application (NDA) 206843 for DAKLINZA (daclatasvir) tablet. This resubmission is in response to the Complete Response letter issued by the Agency on November 25, 2014. The proposed indication for DAKLINZA is for use with sofosbuvir for the treatment of patients with genotype 3 chronic hepatitis C virus (HCV) infection.

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 March 4, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for DAKLINZA (daclatasvir) tablet.

2 MATERIAL REVIEWED

- Draft DAKLINZA (daclatasvir) PPI received on February 13, 2015, and received by DMPP and OPDP on June 18, 2015.
- Draft DAKLINZA (daclatasvir) Prescribing Information (PI) received on February 13, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 18, 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
06/26/2015

OLUWASEUN A ASANTE
06/26/2015

BARBARA A FULLER
06/26/2015

LASHAWN M GRIFFITHS
06/29/2015

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

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

Memorandum

Date: June 26, 2015

To: Sohail Mosaddegh
Regulatory Project Manager
Division of Antiviral Products (DAVP)

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

Subject: NDA 206843
Daklinza (daclatasvir) tablets, for oral use

In response to DAVP's March 4, 2015 consult request, OPDP has reviewed the proposed package insert (PI), patient package insert (PPI) and carton/container labeling for Daklinza (daclatasvir) 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 accessed from the following link provided by DAVP via email on June 18, 2015: <http://sharepoint.fda.gov/orgs/CDER-OAP-DAVP/davpactiveprojecsts/Shared%20Documents/Mosaddegh,%20Sohail/pi-ppi-206843.docx>

We have no comments on the carton/container labeling at this time.

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
06/26/2015

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: June 2, 2015

TO: Sohail Mosaddegh, PharmD, Regulatory Health Project Manager
Wendy Carter, D.O., Medical Officer
Division of Antiviral 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., MPH
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206843

APPLICANT: Bristol Myers Squibb Co.

DRUG: Daclatasvir/Sofosbuvir

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority review

INDICATION: Treatment of chronic genotype HCV-infection in adults, (b) (4)

CONSULTATION REQUEST DATE: March 23, 2015

DIVISION ACTION GOAL DATE: July 30, 2015

PDUFA DATE: August 13, 2015

INSPECTION SUMMARY DUE DATE: July 15, 2015

I. BACKGROUND:

The Applicant conducted one pivotal trial in support of approval of a combination of daclatasvir and sofosbuvir regimen because of a need for new compounds that may overcome the disadvantages of current HCV therapy. Both sofosbuvir and daclatasvir (SOF and DCV) are designed as NMEs and are currently being reviewed in support of an application for HCV (b) (4) subjects.

The Applicant sponsored Protocol A1444218 entitled “A Phase 3 Evaluation of Daclatasvir and Sofosbuvir in Treatment-Naïve and Treatment Experienced Subjects with Genotype 3 Chronic Hepatitis C Infection” to support the pending application.

The objective of this study was to estimate the sustained virologic response rate at follow-up Weeks 12 (SVR12); hepatitis C virus (HCV) ribonucleic acid (RNA less than the lower limit of quantitation. Clinical success was defined as target detected or target not detected at follow-up Week 12 in treatment-naïve and experienced subjects treated with 12 weeks of daclatasvir (DCV/sofosbuvir (SOF)) therapy.

The secondary objectives of this study were: 1) to assess safety, as measured by the frequency of serious adverse events (SAEs), discontinuation due to AEs, AEs, and abnormalities observed from clinical laboratory tests, and 2) to assess the proportion of subjects with HCV RNA below the lower limit of quantification (LLOQ: 15 IU/mL), Target detected (TD) or target not detected (TND), at weeks 1, 2, 4, 6, 8, 10, and 12; Weeks 4 and 12; end of treatment (EOT) or post-treatment week 12.

This study was an open-label, two cohort trial evaluating the combination therapy of DCV and SOF for 12 weeks duration in GT-3 subjects. The planned number of subjects to be treated was 150: 100 treatment-naïve and 50 treatment-experienced. The main criteria for inclusion:

- HCV treatment naïve: no previous exposure to an interferon (IFN formulation or RBV) or other HCV-specific direct acting antivirals (DAAs).
- HCV treatment experienced: previous treatment with either: 1) IFN +RBV, 2) SOF/RBV.

Subjects with compensated cirrhosis were allowed (up to 50% of subjects in each group). Subjects received 60 mg DCV QD+ 400 SOF QD administered for 12 weeks.

The Division of Antiviral Products (DAVP) requested inspections of the following clinical investigator sites due to high subject enrollment.

II. RESULTS (by protocol/site):

Name of CI, Location, and Site #	Protocol and # of Subjects Randomized	Inspection Dates	Final Classification
Godson I. Oguchi, M.D 665 Peachwood Dr. Deland, FL 32720 Site #0008	Protocol A1444218 Number of subjects: 7	5/19-22/2015	Pending (preliminary classification NAI)
James N. Cooper, M.D. 3300 Gallows Rd. Falls Church, VA 22042 Site# 0019	Protocol A1444218 Number of subjects: 12	5/11-15/2015	Pending (preliminary classification NAI)
Paul Thuluvath, M.D 301 St. Paul Place Baltimore, MD 21202 Site #0011	Protocol A1444218 Number of subjects: 7	4/24-28/2015	Pending (preliminary classification NAI)

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; the Establishment Inspectional Report (EIR) has not been received from the field and complete review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

**1. Godson Ogucji, M.D.
Deland, FL 32720**

- a. What Was Inspected:** At this site, a total of seven subjects were screened, one subject was reported as screen a failure, six subjects were randomized into the study, and five subjects completed the study. One subject was discontinued due to an adverse event (pregnancy). Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for 6 subjects were reviewed and compared to data listings. The review included drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for all subjects were compared to case report forms and data listings

including for primary efficacy endpoints and adverse events listings. No deficiencies were noted.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Oguchi. However, the field investigator noted that at least two subjects were enrolled on the same day, but did not receive a liver biopsy prior to day 1. The subjects had conflicting APRI/Fibro Test Scores giving them a liver cirrhosis status of intermediate and thus required a fresh biopsy to confirm status. This error was caught and the subjects received biopsy at the appropriate time.

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

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

**2. James N. Cooper, M.D.
Falls Church, VA 22042**

- 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 10 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for six subjects were reviewed and compared to data listings. The review included drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for all subjects were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings. No deficiencies were noted.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Cooper. However, our field investigator noted at least two subjects experienced bradycardia at Week 12. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

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

**3. Paul Thuluvath, M.D.
Baltimore, MD 21202**

- a. What Was Inspected:** At this site, a total of 7 subjects were screened, two subjects were reported as screen failures, 5 subjects were randomized into the study, and all 5 subjects completed treatment. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for 5 subjects were reviewed for primary/secondary endpoints, including drug accountability records, vital signs, IRB records, prior and current medications, and inclusion/exclusion criteria. Source documents for all subjects were compared to data listings for primary efficacy endpoints and adverse events listing. There was no evidence of under-reporting of adverse events at this site.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr.Thuluvath. The medical records reviewed were verifiable based on the information available at the site. There were no known limitations to the inspection. There were no deaths and no evidence of under-reporting of adverse events at this site.
- c. Assessment of Data Integrity:** Overall, the data submitted in support of the clinical efficacy and safety from this site is considered reliable and may be used in support of the pending applications.

**III.OVERALL ASSESSMENT OF FINDINGS AND GENERAL
RECOMMENDATIONS**

Three clinical investigator sites were inspected in support of this application. The inspection of the three clinical investigators listed above revealed no regulatory violations. The pending classification for Drs. Oguchi, Cooper, and Thuluvath sites are No Action Indicated (NAI). For the pending classifications, a summary addendum will be generated if conclusions change upon receipt and review of the EIRs. Overall, the data submitted from these three sites are considered acceptable and may be used in support of the pending application.

{See appended electronic signature page}

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

Susan Thompson, M.D.
Team Leader
Good clinical Practice Assessment branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations.

CONCURRENCE:

{See appended electronic signature page}

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

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/s/

ANTOINE N EL HAGE
06/03/2015

SUSAN D THOMPSON
06/03/2015

KASSA AYALEW
06/05/2015

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: May 21, 2015
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: NDA 206843
Product Name and Strength: Daklinza (daclatasvir) Tablets, 30 mg and 60 mg
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Bristol-Myers Squibb
Submission Date: February 13, 2015
OSE RCM #: 2014-672
DMEPA Primary Reviewer: Mónica Calderón, PharmD, BCPS
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

Bristol-Myers Squibb (BMS) resubmitted NDA 206843 for the treatment of chronic Hepatitis C after receiving a Complete Response (CR) on November 25, 2014. Thus, the Division of Antiviral Products (DAVP) requested DMEPA evaluate the BMS's proposed container labels and full prescribing information (FPI) for 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.

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

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

BMS is proposing multiple strength (30 mg and 60 mg), single ingredient tablets. The daily dose is 60 mg; however, a 30 mg tablet is intended to be utilized for dose increase or reduction during concomitant therapy with a strong cytochrome P450 enzyme 3A4 inducer or inhibitor, respectively. The product will be packaged in 28-count bottles, which is supported by the dosage and administration of this product. DMEPA performed a risk assessment of the proposed container label, Patient Package Insert, and FPI and notes the strengths are clearly differentiated and the Dosage and Administration section is clearly stated, respectively.

In a previous review¹, DMEPA recommended the following statement, [REDACTED] (b) (4)
[REDACTED] ." be added to the Patient Package Insert for [REDACTED] (b) (4)
[REDACTED] . In an email dated March 17, 2015, the Medical Officer (MO) in DAVP determined that the statement be removed from the FPI due the absence of data or formulation concerns. We defer to DAVP regarding removal of this general

¹ Calderon M. Label and Labeling Review for Daklinza (NDA 206842). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 June 29. 32 p. OSE RCM No.: 2014-672.

statement. However, there is a statement in Section 2.2 (Dose Modification) of the FPI, (b) (4)

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes BMS's proposed 30 mg container label is acceptable. However, for consistency with the information in the PI, we recommend that (b) (4) be added to the container label. We defer to DAVP regarding removal of the general statement (b) (4) of the FPI. We provide recommended changes to Section 2.2 (Dose Modification) of the FPI and to the Patient Package Insert (b) (4)

We advise the recommendations below are implemented prior to approval of this application.

(b) (4)

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APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Daklinza that Bristol-Myers Squibb submitted on February 13, 2015.

Table 2. Relevant Product Information for Daklinza	
Active Ingredient	daclatasvir
Indication	In combination with other agents for the treatment of chronic hepatitis C infection.
Route of Administration	Oral
Dosage Form	Tablet
Strength	30 mg and 60 mg
Dose and Frequency	60 mg once daily
How Supplied	Bottles of 28 tablets
Storage	25°C (77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F)

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/s/

MONICA M CALDERON
05/21/2015

BRENDA V BORDERS-HEMPHILL
05/21/2015



Shari L. Targum, M.D., M.P.H.
Division of Cardiovascular and Renal Products

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tel (301) 796-1151

Memorandum

DATE: May 12, 2015

FROM: Shari L. Targum, M.D., M.P.H., Clinical Team Leader
Division of Cardiovascular and Renal Products

THROUGH: Norman Stockbridge, M.D., Ph.D., Director
Division of Cardiovascular and Renal Products

TO: Wendy Carter, D.O., Medical Officer
Division of Antiviral Products

Kimberly Struble, Pharm.D., Clinical Team Leader
Division of Antiviral Products

SUBJECT: NDA 206843 (IND 79599)

NAME OF PRODUCT: Daclatasvir

TRADE NAME: Daklinza

FORMULATION: oral tablet

RELATED APPLICATIONS: N/A

PROPOSED INDICATION: Treatment of hepatitis C

SPONSOR: Bristol Myers Squibb

DOCUMENTS AVAILABLE FOR REVIEW: 4/9/2015 submission (response to Agency information request); electronic document room

DATE CONSULT RECEIVED: 4/17/2015

REQUESTED COMPLETION DATE: 5/14/2015

DATE CONSULT COMPLETED: 5/12/2015

REASON FOR CONSULTATION:

The original NDA for daclatasvir (DCV) was submitted on March 31, 2014 by the applicant along with NDA 206844 for asunaprevir (ASV), as the two products had been studied together in clinical trials. On October 5, 2014, the applicant withdrew NDA 206844 for ASV. The DCV application received a Complete Response action, since the original NDA did not contain sufficient evidence of the efficacy and safety of DCV with ASV for the proposed indication.

On February 13, 2015, the applicant resubmitted the NDA for DCV and has responded to inquiries from the review division related to cardiac issues identified with sofosbuvir (SOF) in combination with other direct acting antivirals.

We have been asked to review the sponsor's resubmission, including an EMA report, ECGs from patients with potential amiodarone drug-drug interactions with DCV/SOF, and evaluation of phase 3 data for subjects who were taking calcium channel blockers and/or beta blockers while on DCV/SOF.

Specific requests from the Division of Antiviral Products (DAVP), with responses from the Division of Cardiovascular and Renal Products, are listed below.

BACKGROUND:

Sofosbuvir (SOF, brand name Sovaldi) is a hepatitis C virus (HCV) analog NS5B polymerase inhibitor approved in a once-daily dose of 400 mg for the treatment of chronic hepatitis C. SOF is commonly administered with other HCV drugs.

Daclatasvir (DCV) is an NS5A polymerase inhibitor used in combination with other antiviral agents for the treatment of chronic hepatitis C. DCV is currently approved in several countries (Japan, European Union, Brazil) and has been studied in 90 clinical trials in multiple regimens; the overall exposure has been estimated at approximately 7,900 in clinical trials, 5,500 in the Early Access Program, and 14,813 in the post-marketing setting. The proposed dosage is 60 mg once daily, with dose adjustments to 30 or 90 mg once daily when co-administered with certain interacting drugs.

Preclinical cardiac safety evaluation of daclatasvir revealed the following:

- Daclatasvir (IC₅₀ 29 μM) exhibited weak inhibition of hERG/I_{kr}, and sodium and L-type calcium currents (> 214x RHD free [unbound] C_{max}) but no effects on any Purkinje fiber action potential parameters.
- In anesthetized rabbits given 30 mg/kg intravenously (C_p = 159 μg/mL, 92x RHD C_{max}), QRS, PR, AH and HV intervals were moderately increased.
 - DCV also produced a small increase (7%) in mean arterial blood pressure.
 - The NOEL was 10 mg/kg (C_p = 72.9 μg/mL, 42x RHD C_{max}).
- In telemetered dogs, a single dose of 100 mg/kg (C_p = 10.9 μg/mL) induced reversible increases in systemic pressures and small decreases in an index of cardiac contractility, whereas 15 mg/kg (2.2x RHD C_{max}) was the NOEL.
- There were no cardiovascular system effects identified in repeat-dose single-agent (≤ 9 months) or combination (≤ 3 months) toxicity studies in rats, dogs, or monkeys at the highest doses tested.

A thorough QT (TQT) study for daclatasvir was negative at the suprathreshold dose (180 mg), selected to target concentrations 2.5-fold what is obtained at the highest therapeutic dose (60 mg). In their review of the TQT study, the interdisciplinary review team noted that “no clinically relevant effect on vital signs, ECGs, physical examinations, clinical laboratory values, or adverse event profiles have been noted.”

Specifically, no clinically relevant effect on heart rate, PR or QRS was observed at the suprathreshold dose.

Exposure data are shown in the table below:

Table 1.1.1-1: Summary of Subjects Treated with DCV at the Recommended Dose of 60 mg QD for 12 Weeks or Longer

Regimen	Study	Duration	Number Included in DCV SCS and DCV SUR	Number Included in this ALLY-3 SCS
Completed Studies				
DCV/SOF	ALLY-3 (AI444218) ¹	12 weeks	0	152
	AI444040 ^{2,3}	12 weeks 24 weeks	41 80	41 80
DCV/SOF/RBV	AI444040 ^{2,3}	12 weeks	41	41
		24 weeks	49	49
Total		12 to 24 weeks	211	363
DCV (60 mg QD) + pegIFN/RBV	AI444014 ^{9,10}	48 weeks	12	12
	AI444010 ⁷	12 or 24 weeks	158	158
	AI444011 ⁸	24 weeks	199	199
	AI444021 ¹¹	24 weeks	19	19
	AI444022 ¹²	24 weeks	17	17
	AI444031 ¹³	12 or 16 weeks	100	100
Total		12 weeks or longer	505	505
Total Safety Database for DCV (Completed Studies) for ALLY-3 SCS				868
Ongoing Studies				
DCV/SOF	ALLY-2 (AI444216)	12 weeks	0	203
DCV/SOF/RBV	ALLY-1 (AI444215)	12 weeks	0	113
TOTAL		12 weeks	0	316

Abbreviations: DCV, daclatasvir; QD, once daily; RBV, ribavirin; SCS, Summary of Clinical Safety; SOF, sofosbuvir; SUR, Safety Update Report.

Source: DCV SCS,⁵ DCV SUR⁶

A brief review of the integrated summary of safety (NDA resubmission, 2/13/2015) did not reveal a cardiac safety signal in the available data. There were no deaths in the DCV/SOF ± RBV regimen. No signals for bradycardia, dizziness, syncope, or dyspnea were seen in the DCV/SOF group (total AI444040 and AI444218 population N=273).

Cardiac disorders and/or chest pain were reported in 1.9%, or 7/363 subjects treated with DCV/SOF ± RBV. Subjects treated with RBV (DCV/SOF/RBV in study AI444040) had a higher proportion of cardiac disorders and/or chest pain than those treated without RBV (DCV/SOF only, in AI444218 and AI444040): 5.6% (5/90) vs. 0.7% (2/273). No event led to study discontinuation.

A cumulative review of clinical trial reports of cardiac adverse events, performed on April 15, 2014, included 4 cases of relevance with the following events: cardiac failure (1), cardiac failure congestive (3), cardiomyopathy (1) and systolic dysfunction (1). Based on these events, the incidence rate for heart failure was 1.9 per 1000 person-year, and for myocardial disorder 0.95 per 1000 person-years.

According to the sponsor, the literature-based rate for congestive heart failure is 38.4 +/- 15.0 per 1000 patient-years for chronic hepatitis C patients and 8.9 +/- 2.0 per 1000 patient-years for controls (Younossi 2013).

A cumulative search was also conducted to identify all adverse events received for daclatasvir, including the terms “Cardiac Failure” or “Cardiomyopathy,” and including serious interventional clinical trial reports and all serious and non-serious spontaneous, EAP and literature adverse events. This search identified 39 reports of cardiac failure or cardiomyopathy-related events associated with daclatasvir. Of these 39 cases, 13 were excluded as the treatment regimen included an investigational drug no longer in development (BMS-986094) due to known cardiotoxicity.

Of the 26 remaining cases, all were serious: 2 were reported from interventional clinical trials, 17 from the daclatasvir EAP (including 7 from the French cohort ATU), 2 from the German Registry of HCV, and 5 were spontaneous reports (4 from Japan, 1 from France). The cases comprised 20 males and 6 females, ranging in age from 50 to 79 years (median 64 years). The time to onset (provided in 17 cases) ranged from 9 to 185 days (median 51 days) after initiation of daclatasvir combination therapy. Of the 26 cases, 7 had a fatal outcome.

Of the 18 reports with the Preferred Terms “cardiac failure” or “cardiac failure congestive,” 10 patients received DCV/SOF with (4) or without (6) RBV. Five patients received DCV/ASV with (2) or without (3) pegIFN/RBV. One patient received DCV/pegIFN/RBV.

There were 4 reports of pulmonary edema (2 of these with a fatal outcome). The 2 cases with a fatal outcome were enrolled to receive DCV/SOF in the Early Access Program; both cases had cirrhotic decompensation, renal dysfunction, and current or recent sepsis associated with the pulmonary edema.

The cases with fatal outcome are briefly discussed below:

1. 52 year-old Caucasian male smoker with HIV/HCV, receiving DCV/pegIFN/RBV, hospitalized with pancytopenia (hemoglobin 6.2 g/dL), elevated bilirubin (3 mg/dL) and increasing troponin levels, experienced congestive heart failure and died 4 days later.
2. 50 year-old male with HIV/HCV, liver transplantation, portal shunt, hepatic cirrhosis, ascites, hepatorenal syndrome, and pancytopenia treated with DCV/SOV/RBV, hospitalized with sepsis (due to pancytopenia from immunosuppressant therapy); biventricular output was reported to be severely depressed and patient died due to acute biventricular failure.
3. 60 year-old Caucasian male receiving DCV/SOF hospitalized with malignant pleural effusion due to known hepatocellular carcinoma and tachycardia; developed cardiopulmonary failure, received palliative care and expired.
4. 68 year-old Caucasian female receiving DCV/SOF, with history of poorly controlled hypertension and atrial fibrillation, experienced “hypertensive peak” and tachycardia, resulting in cardiac failure and hemorrhagic stroke with fatal outcome.
5. 77 year-old Asian female receiving DCV/ASV found dead at home; death attributed to cardiac failure, no further details provided. (*Reviewer comment: Likely ischemic or arrhythmic event; sudden death can occur spontaneously in this age group and there is no evidence to suggest congestive heart failure or cardiomyopathy. No information on length of DCV treatment.*)
6. 68 year-old female receiving DCV/SOF with history of hypertension, aortic stenosis, cirrhosis and chronic alcohol use experienced hepatic encephalopathy, sepsis, acute renal insufficiency, hepatorenal syndrome and pulmonary edema. During the hospitalization, metastatic breast cancer was diagnosed and she received palliative care until her death; cause of death was end-stage cirrhosis.
7. 68 year-old male receiving DCV/SOF was hospitalized 20 days prior to the onset of pulmonary edema with pulmonic (*Reviewer comment: pleural?*) effusion, ascitic decompensation, portal and

splenic thrombosis, renal dysfunction, and pulmonary and urinary infections: subsequent pulmonary edema was attributed to persistent effects of these prior events.

The case narratives for subjects/patients with heart failure and/or cardiomyopathy were also reviewed (Appendices 1 and 2) and do not change this reviewer's conclusions.

Comments: The sponsor has cited a report (Younossi et al¹) of an association of chronic hepatitis C and congestive heart failure; if true, one would expect a higher incidence of congestive heart failure occurring spontaneously with HCV, making it more difficult to interpret these individual cases.

However, even without such an association, it would be difficult to ascribe causality for the following reasons:

- 1. Case definition: Several cases, such as case #5 and 7 (fatal cases, above), do not contain enough information to ascertain whether the classification for cardiomyopathy or congestive heart failure is appropriate. Edema, ascites and fluid retention, observed in right-sided heart failure, can also occur in cirrhosis.*
- 2. These cases occurred in a middle aged and elderly population. The incidence of risk factors for atherosclerosis and ischemic heart disease (which could manifest as cardiomyopathy or congestive heart failure) increases with age. Since cases of ischemic cardiomyopathy or congestive heart failure can occur spontaneously in this age group, it is difficult to interpret individual cases.*
- 3. Confounding: Most of these cases report subjects with co-morbid conditions that can cause or exacerbate heart failure. Examples include anemia (case #1), tachycardia (case #3), and aortic stenosis/alcohol/sepsis (case #6). HIV is also a recognized cause of cardiomyopathy (cases #1 and 2).² Moreover, one cannot exclude confounding from concomitant medications.*

The sponsor was also asked to provide subgroup analyses from the ALLY program (3 independent studies, ALLY-1, -2, -3), designed to assess the safety and efficacy of DCV/SOF in patient populations of high unmet medical need. The program included a total of 468 treated patients, with mean age approximately 52 to 59 years, 75% male, 50% with history of at least one baseline cardiac condition across the studies; 15% (71/468) of subjects were on a stable beta blocker regimen and 10% (47/468) were on a stable calcium channel blocker regimen.

¹ Younossi hypothesized that since chronic hepatitis C infection is associated with insulin resistance and type 2 diabetes, chronic hepatitis C infection would also increase the risk of cardiovascular disease. Using retrospective National health and Nutrition Examination Surveys (NHANES) collected between 1999 and 2010, the authors found an association with type 2 diabetes, hypertension and congestive heart failure.

² Barbaro G. Cardiovascular manifestations of HIV infection. *Circulation* 2002; 106: 1420-1425.

Table -A: Subjects Receiving Stable Regimen of Beta Blockers or Calcium Channel Blockers Throughout the Treatment Period within the ALLY Program

Cardiac Medication	Number of Subjects (%)				
	ALLY-1		ALLY-2 (N=203)	ALLY-3 (N=152)	Total (N = 468)
	Cirrhotic Cohort (N = 60)	Post-transplant Cohort (N = 53)			
BB	25 (41.7)	13 (24.5)	21 (10.3)	12 (7.9)	71 (15.2)
CCB	2 (3.3)	14 (26.4)	17 (8.4)	14 (9.2)	47 (10.0)

Source: Supplemental Tables 1, 2, 3, 4, 5, 6, and 19

Subjects receiving both a beta blocker and a calcium channel blocker during the treatment phase are accounted for among each of the medication classes.

CCB = calcium channel blocker; BB = beta blocker

Table -B: Mean Change in Heart Rate from Baseline in Subjects Receiving Stable Regimen of Beta Blockers or Calcium Channel Blockers Throughout the Treatment Period within the ALLY Program

Mean Heart Rate (bpm)	ALLY-1				ALLY-2 (N = 203)		ALLY-3 (N = 152)	
	Cirrhrotic Cohort (N = 60)		Post-transplant Cohort (N = 53)		BB (n = 21)	CCB (n = 17)	BB (n = 12)	CCB (n = 14)
	BB (n = 25)	CCB (n = 2)	BB (n = 13)	CCB (n = 14)				
Week 8 or 12 ^a	65.2 ^b	78.0 ^c	64.8	71.5	66.6	74.1	66.3	72.1
Change from Baseline	-1.3 ^b	5.0 ^c	1.2	1.0	-3.0	-2.1	-2.3	-2.2

Source: Supplemental Tables 1, 2, 3, 4, 5, and 6

^a Represents Week 12 data for ALLY-1/ALLY-3 and Week 8 results in the ALLY-2 study in order to capture last available heart rate values from all subjects with baseline results

^b Week 12 mean heart rate and change from baseline includes 23 subjects (i.e., n = 23)

^c Week 12 mean heart rate and change from baseline includes 1 subject (i.e., n=1)

Subjects receiving both a beta blocker and a calcium channel blocker during the treatment phase are accounted for among each of the medication classes.

bpm = beats per minute; CCB = calcium channel blocker; BB = beta blocker

Based on a review of vital sign listings, an estimated 1/3 of subjects on a stable beta blocker and/or calcium channel blocker had at least 1 recorded heart rate < 60 bpm while on study therapy; these rates were comparable across the ALLY studies and comparable with the proportion of subjects who were not receiving one of these concomitant medications.

The sponsor received and reviewed ECGs for 4 of the 5 patients with potential amiodarone drug-drug interactions with DCV/SOF.

Patient #21349394: The sponsor provided a single ECG on 12 July 2014, two days after the rechallenge of DCV/SOF (10 July 2014) which was associated with a two hour episode of bradycardia. This reviewer concurs with the sponsor's interpretation of sinus rhythm at 60 bpm with left axis deviation. There is early QRS transition and nonspecific repolarization changes. This reviewer does not see evidence of sinus arrest on the tracing (which was not performed during the bradycardic episode).

Patient #2152184: This reviewer concurs with the sponsor. Rather than third degree AV block, the tracing shows sinus arrest and junctional bradycardia ~ 20 bpm (rather than 3rd degree AV block as reported in the narrative). This patient nonetheless experienced symptomatic bradycardia requiring interventions.

Patient #20786414: As the sponsor has noted, the ECGs show a right bundle branch block with rightward axis. Several pauses over 2.5 seconds are noted. The tracings (16 May 2015 at 17:36) appears to show premature supraventricular beats preceding pauses, with a delay in recovery. The tracings are consistent with junctional (or supraventricular bigeminy).

BMS-2015-003146: spontaneous report, France: 61 year-old female with history of atrial fibrillation, hypertension, dyslipidemia, acute coronary syndrome and ischemic stroke, on baseline amiodarone and atenolol, experienced cardiopulmonary arrest 30 minutes after the first dose of DCV/SOF. Epinephrine was administered by first responders, with "recovery of sinus rhythm at 30 bpm." The patient was hospitalized and DCV, SOF and amiodarone were discontinued. The only two available ECGs were prior to anti-HCV therapy and thus do not capture the event. Both tracings show sinus bradycardia ~ 50 bpm, normal PR interval, QRS axis and interval, prolonged QT with prominent U wave. This reviewer concurs with the sponsor.

Specific requests from DAVP:

1. The EMA report is provided for more detailed background and BMS' assessment of the observed cardiac safety issues in relation to DCV. For this document, please provide:
 - a. Any comments or findings that you find inconsistent with your prior evaluation and assessment of the SOF + DAA information.

Response: At least one ECG provided by the sponsor was interpreted as "3rd degree AV block" and instead appears to be sinus arrest with junctional bradycardia. We agree with some but not all of the applicant's interpretations of the tracings. We agree that some of the cardiac rhythm abnormalities are consistent with amiodarone's effect, but cannot further explain the temporal relationship between SOF/DCV administration and this effect. Thus, our position has not changed regarding conclusions and recommendations.

- b. Your overall assessment of DCV in combination with SOF in relation to cardiac dysrhythmias.

Response: Based on its preclinical profile and thorough QT study, there does not appear to be a pro-arrhythmic risk with DCV alone. The available clinical data do not suggest a risk of cardiac dysrhythmias or symptomatic bradycardias with DCV/SOF in the absence of background amiodarone therapy.

2. For the documents: DCV_Response to FDA_RFI17Mar2015_Q1 (ECG recordings) and Response_To_RFI_17Mar2015_Q3-Q4 (Eval of CCB and BB) please respond to the following questions:
 - a. Please provide your assessment of the ECG findings and determine if any additional information or follow up is necessary for these cases or overall.

Response: The sponsor provided ECG recordings and re-analyses for four patients who developed cardiac events with DCV/SOF against a background of amiodarone. In two cases, the ECGs did not capture the events. Several patients appeared to have baseline conduction system abnormalities (e.g., right bundle branch block, prolonged QT).

Most of the cases occurred in middle-aged and elderly patients against a background of amiodarone therapy. The clinical pharmacologists and pharmacologists should provide input regarding relevant drug-drug interactions with amiodarone. We do not think that additional clinical information or follow up will be informative.

- b. Please provide your assessment of the evaluation of concomitant use of CCB and BB and determine if additional analyses or information is warranted.

Response: Subgroup analyses of the ALLY program do not suggest a risk of symptomatic bradycardia or high-grade AV block with the concomitant use of CCB and BB and DCV/SOF and no additional analysis or information is warranted.

- c. Please provide your overall assessment of DCV in combination with SOF in relation to cardiac dysrhythmias.

Response: Based on the available information, there does not appear to be a signal for cardiac dysrhythmias for DCV/SOF use in the absence of amiodarone therapy.

Thank you. If you have any further questions please feel free to contact us.

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

/s/

SHARI L TARGUM
05/12/2015

NORMAN L STOCKBRIDGE
05/12/2015

Hepatology Consultation

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY

DATE: 17 November 2014

FROM: John R. Senior, M.D.
Associate Director for Science (Hepatology)
Office of Pharmacovigilance and Epidemiology (OPE)
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TO: Debra Birnkrant, M.D., Director, Division of Anti-Viral Products (DAVP)
Jeff Murray, M.D., Deputy Director for Safety, DAVP
Kimberly Struble, M.D., Clinical Team Leader, DAVP
Wendy Carter, D.O., Clinical Reviewer, DAVP

VIA: Solomon Iyasu, M.D., Director, OPE

SUBJECT: Hepatic adverse effects of combined asunaprevir and daclatasvir treatment in patients with chronic hepatitis C

Documents reviewed initially:

- 1) Consultation request from DAVP dated 7 August 2014 asking for review of findings related to liver toxicity, desired response date 29 August 2014;
- 2) Backgrounder document, 6 August, 132 pages;
- 3) Data from Studies 26, 28, and 29 for DUAL and QUAD treatments;
- 4) Clinical review, submitted to DARRTS 29 August, 181 pages

It was immediately evident that it would not be possible for me to respond to this request within 22 days, especially since I was already working on several other consultations with due dates of requested responses of 8, 15, 20, 25 and 27 August, and so was not able even to start review of this request until 27 August. The sponsor, Bristol-Myers Squibb, had submitted separate NDAs 206843 and 206844 for two drugs, daclatasvir and asunaprevir on 31 March 2014, although both agents in combination had been studied in the main clinical trials. It was also evident that major modifications would have to be made to our eDISH program (for evaluation of Drug-Induced Serious Hepatotoxicity), to include serial data for the serum viral load by RNA assays, and very unlikely that it could be done before the discussion scheduled for 10 September (in preparation for a scheduled late-cycle meeting with the sponsor and consultants on 22 September), especially since Dr. Guo went on a month-long visit to China. It was also planned to schedule an Advisory Committee meeting for Monday, 17 November 2014. In preparing her excellent Backgrounder document, Dr. Wendy Carter had used the commercial software program JReview that gave her access to the viral load data as well as to a truncated version of our eDISH program. From it she had identified 10 cases of potential interest and one of some concern in the Japanese study 26,

despite the fact that the dual regimen of asunaprevir and daclatasvir had already been approved in Japan in July 2014, and a paper written by 15 Japanese investigators from 10 of the 24 sites where 222 patients had been treated was published in June 2014. The authors of that paper had noted serious adverse events in 13 of the 222 patients, and that elevated serum aminotransferase levels on study were the most frequent laboratory test abnormalities, at 16 and 13%, just behind nasopharyngitis and headache, were the reason for 10 of the 11 premature discontinuations for adverse events. Since no patient showed hepatic decompensation, their favorable conclusions led to approval for marketing of the combination regimen in Japan a month later. Dr. Carter's review was not so strongly favorable, and she found 10 cases by her JReview analyses that seemed to be worthy of closer inspection, hepatology consultation, and an advisory committee consideration, as confirmed by other members of the DAVP review team. A series of email messages in late July led to request to the sponsor (Bristol Myers Squibb) for submission of data from the three pivotal clinical trials 26, 28, and 29, for confirmation by our eDISH program. A request was sent on 7 August for consultation from Drs. Senior and Avigan. Dr. Guo then worked with BMS to obtain liver test data from the pivotal clinical trials during August before he left for China.

As summarized in the backgrounder document, research in many companies worldwide has led to a profusion of new DAA agents, and effective treatment rates have climbed to well over 90% for even the most resistant strains and subtypes. And now, the first of the combinations to be submitted for review by Bristol Myers Squibb (BMS) is being considered:

asunaprevir (ASV)	BMS-650032	(b) (4)	IND (b) (4) 12/21/2007	NDA 206844 3/31/2014
daclatasvir (DCV)	BMS-790052	DAKLINZA	IND (b) (4) 6/3/2010	NDA 206843 \\ 3/31/2014

This combination includes a protease inhibitor (ASV) and a novel HCV NS5A inhibitor (DCV), with P/R (QUAD) or without P/R (DUAL). The submission relies primarily on three Phase III studies of 1367 patients (867 on DUAL treatment in studies 26 and 28; 398 on QUAD treatment in study 29; and 102 on placebo (PLAC) in study 28, and is supported by 10 Phase II studies of 991 more patients who received the proposed dose and duration.

The safety questions that emerged from analyses involved possible drug-induced **hepatotoxicity** attributable to the ASV/DCV combination, and a syndrome of both **fever and eosinophilia**, with and without liver injury. Both of these safety problems are new to this combination regimen, and neither was found in the earlier reviews of the four novel DAA agents approved for treatment of chronic hepatitis C, as far as is known. The questions posed about these concerns are extremely complex, and not easily answered without considerable additional data analysis. A first step is to look at the hepatotoxicity data from the three pivotal studies 26, 28, 29 that have been described in the clinical review of Dr. Wendy Carter, filed into DARRTS on 29 August 2014. Dr. Carter used JReview as a tool to consider incidence and severity of the adverse effects, and correlations; I used our eDISH program to focus on the hepatotoxicity issue, with supplemental information from JReview provided by Dr. Carter.

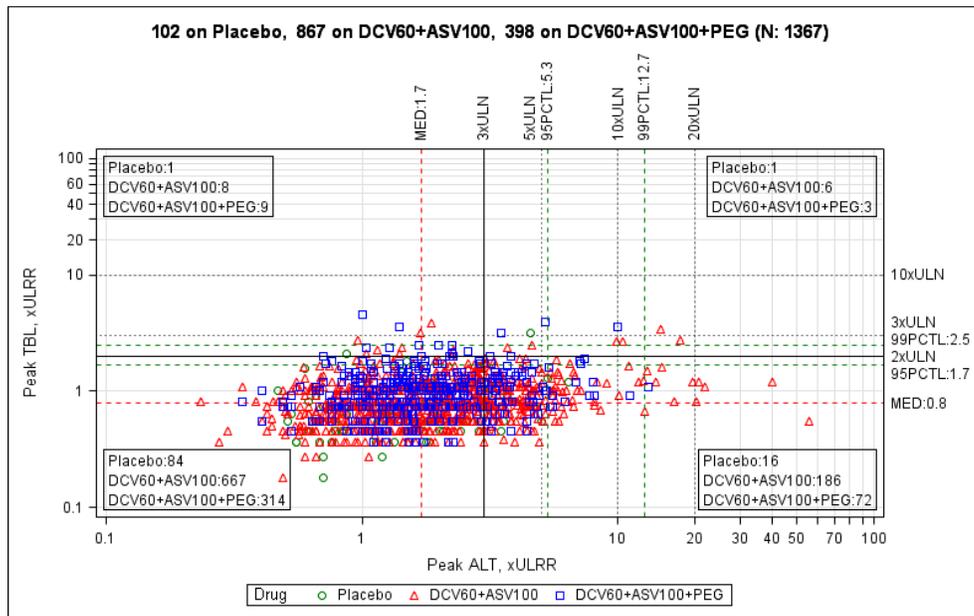
The eDISH program is meant to find those subjects in a study whose hepatocellular injury and whole liver dysfunction, measured on serum samples over their whole course of observation, are

taken to indicate a potentially serious drug toxicity. Hepatocellular *injury* (but not function) is estimated by rise in alanine aminotransferase (ALT) elevations more than three times the upper limit of a normal reference range ($>3xULN$), using the stated range for the particular laboratory where testing was done. Liver *dysfunction* is measured by rise in the total bilirubin concentration (TBL) over $2xULN$. This conservative set of lower limits for abnormalities is meant to increase the sensitivity of detecting cases of interest, and is *not intended to be diagnostic* by itself. Serum ALT increases are not specific just to liver injury, and they measure no function of the liver. The TBL level is more specifically a measure of the liver inability to clear plasma of bilirubin, and is a measure of the remaining whole liver function by uninjured hepatocytes. It may be caused by many processes. In order to conclude that the combination of liver injury and dysfunction have been *caused* by the drug in question, it is imperative to seek additional clinical information that allows medical differential diagnosis to be made or estimated as well as can be done; it *cannot* be made by serum chemistries alone. It is not enough to say that the finding of hepatocellular injury and liver dysfunction is thought “related to” or “associated with” the drug administration; what is required is that a drug may be considered at least **probably** the *cause* of the findings, meaning more likely than all the other possible causes combined. This is a process or exercise learned and practiced by physicians uniquely, and is not acceptably done by simply considering the numbers. There is no reliable test or finding, even by liver biopsy, that diagnoses drug-induced liver injury (DILI), and it is therefore a diagnosis of exclusion and estimation of relative likelihood. We now know that DILI may simulate any liver disease, is a heterogeneous disorder, depending not only on the drug causing it but on the great variability of individual reactions to the same dose of the same drug.

In these studies, there were 10 patients found whose serum chemistries suggested the need for closer attention, from Dr. Carter’s JReview analyses, for which an attempt at diagnosing the cause needed to be done. The eDISH program works in three steps successively: Step one is a graphic display of all patients in the study, with one symbol for each of them, divided into four quadrants by the vertical and horizontal cutoff lines of $3xULN$ ALT and $2xULN$ TBL, in which the highest value at any time for both variables in a single patient is used. Step two is done by pointing to and clicking on a single point in the first graph, to summon from the data file by the computer the data for ALT and TBL, as well as for alkaline phosphatase (ALP) and aspartate aminotransferase (AST), and display all four liver test variables each time they were measured for that person, a time-course of liver test values, plotted as \log_{10} values so that the greater variability of the serum enzyme activities is scaled down, for comparison to the less volatile bilirubin concentrations. Step three is a textual clinical narrative for differential diagnosis.

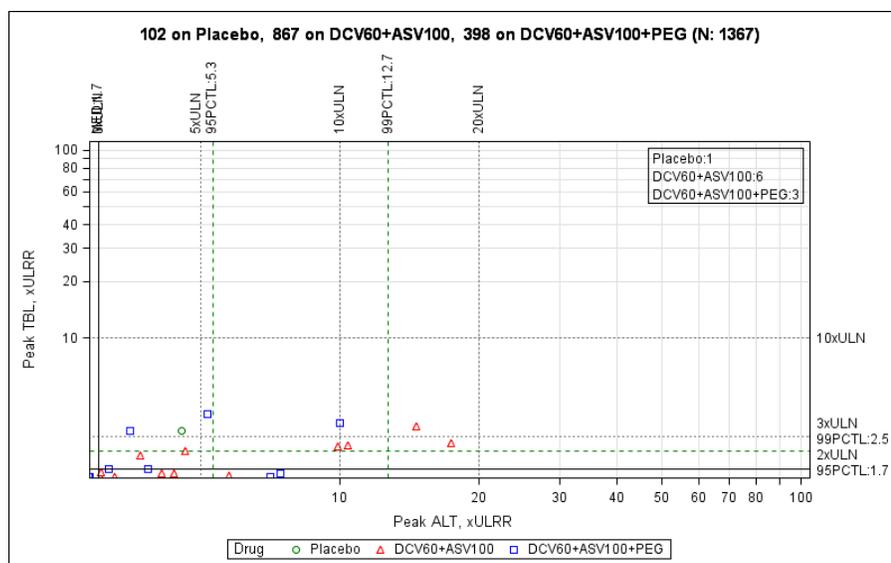
In the graph shown below are single points for all 1367 patients treated in these studies. The vertical line at ALT $3xULN$ separates those with notable elevations on the right from those without on the left; the horizontal line at TBL $2xULN$ separates those with bilirubin elevations above from those without below. Most patients are in the left lower quadrant, with peak values of both tests in or near the normal range. The left upper quadrant shows those with elevated peak serum bilirubins without much ALT increase, and the right lower quadrant those with elevated peak ALTs with much bilirubin elevation. We are most concerned with the few in the right upper quadrant who may have evidence of enough acute hepatocellular injury that the remaining liver cells are not able to function well enough to clear bilirubin from the plasma adequately. There were only 10 of them: 6 of the 867 on DUAL treatment (shown as red triangles), 3 of 398 on

QUAD treatment (blue squares), and 1/102 on placebo (green circle). It is necessary to find out the probable cause of these findings before concluding whether or not the changes were caused by the drug(s) being administered, or by some other process.



Comment: The power of the computer to search through all the data for 1367 patients in less than a second, then return a graph that a human can interpret at a glance to find the few patients of interest for additional close inspection, is what makes eDISH so useful.

The next step is to point to a given symbol on the first x-y log-log plot of peak ALT and TBL values to obtain the time course of all four liver tests for that individual patient over the whole time of observation in the study. The narrative is then considered, with the major aim to make the best possible diagnosis of probable cause, the most difficult step.



There were only 2 of the 10 who failed to achieve SVR: the placebo case in which it was not expected, and the serious index case in which the treatment was not long enough to suppress the virus for long enough and breakthrough occurred.

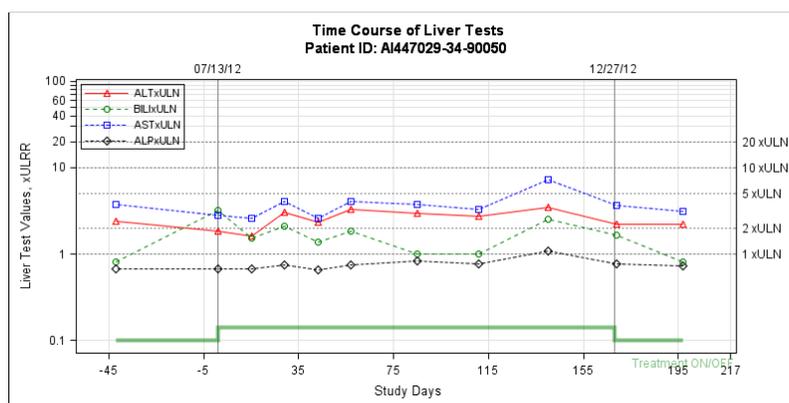
Listing the 10 patients, in order of their place on the above graph, from left to right, by (ALT_x,TBL_x), study number: patient number, country, sex age, treatment start date):

Possible Hy's Law Cases to be Adjudicated								
on graph ALT, TBL	study: patient	country	sex age	treat- ment	date started	severity	probable cause (JRS)	SVR
3.5, 3.2	29: 90050	France	M 46	QUAD	7/12/12	mild	cirrhosis	yes
3.7, 2.4	28: 80492	Taiwan	M 67	DUAL	10/2/12	mild	Gilbert's	yes
4.6, 3.2	28: 80827	USA	M 59	PLAC	10/3/12	mild	transfusions	no
4.7, 2.5	26: 10230	Japan	M 69	DUAL	3/23/12	mild	ASV/DCV	yes
5.2, 3.9	29: 90104	Canada	F 60	QUAD	7/24/12	moderate	QUAD	yes
9.9, 2.6	28: 80817	Australia	M 56	DUAL	9/14/12	mild	hepatocellular CA	yes
10.0, 3.6	29: 90110	Canada	M 61	QUAD	7/20/12	moderate	QUAD	yes
10.4, 3.3	26: 20265	Japan	M 72	DUAL	3/25/12	mild	ASV/DCV	yes
14.6, 3.4	28: 80975	Canada	M 26	DUAL	1/23/13	mild	Gilbert's	yes
17.4, 2.8	26: 10122	Japan	M 57	DUAL	3/9/12	serious	DCV/ASV	no

Therefore, of the 10 cases out of the 1367 total, there were several that were not true Hy's Law cases because alternative more likely causes were found. The definition of Hy's Law proposed initially by Bob Temple in 1999, and incorporated into the guidance of 2009, was not intended to be applied to patients with underlying active liver disease, such as chronic hepatitis C, and needs to be re-thought in this context. Dr. Zimmerman observed that having some liver disease did not increase the risk of having drug-induced injury, but he did not elaborate on whether it might have effects of recovering from DILI, or whether the course might be worse.

It may be seen that looking carefully at the time course of liver test changes, and especially at the narratives, other causes than the administered drug appeared to account for the changes seen in 5 of the 10, and only the other 5 appeared to be caused by the drug, or no alternative probable cause was reported. In 4 of those 5, the clinical severity was either mild or moderate, and in the QUAD cases attributed to the P/R components. The so-called Hy's Law criteria cannot really be used here, because the concept was meant to apply to patients with previously normal livers before drug treatment. This is obviously not true when treating patients with chronic hepatitis C, so we need to break new ground in considering apparent liver injury that might be caused by drug regimens intended to help the liver, not hurt it further. Patients enrolled and treated in these studies started out with variable levels of inflammatory activity, as estimated by pretreatment ALT levels. Dr. Carter's review and backgrounder mentioned pretreatment ALTs ranging from:

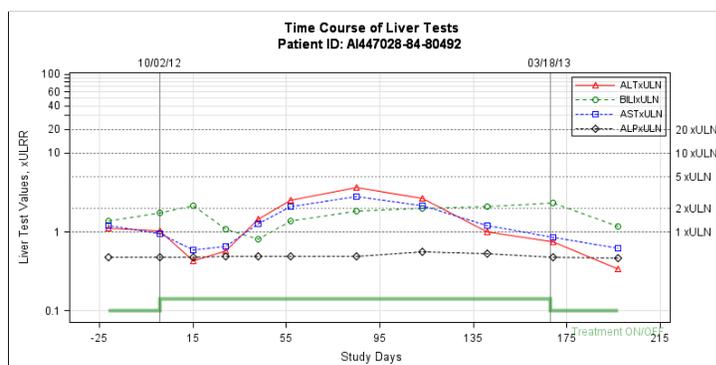
13 to 377 U/L, median 59 in 222 Japanese patients on DUAL regimen in Study 26;
12 to 364 U/L, median 66, in 398 worldwide patients on QUAD regimen in Study 29;
7 to 475 U/L, median 60, in 645 patients on DUAL and 102 patients on placebo in study 28.



The first, at (ALT 3.5, TBL 3.2) was that of a cirrhotic French male 46, #90050, Study 29 at site 34. He showed modest serum transaminase elevations before treatment, AST somewhat higher than ALT, as is often seen in cirrhotics. His serum bilirubin fluctuated considerably during the period of treatment, but was 3.5 mg/dL when the QUAD regimen was started and never increased to more than that for the 23 weeks he was treated. He was found to have SVR 12 and 24. Jaundice was not observed, but he showed a mild skin rash after 14 weeks of treatment, without fever or eosinophilia.

Comment: Treatment was continued despite borderline liver test elevations by an investigator who judged the treatment to be more important than the slight increase in AST after 20 weeks of treatment.

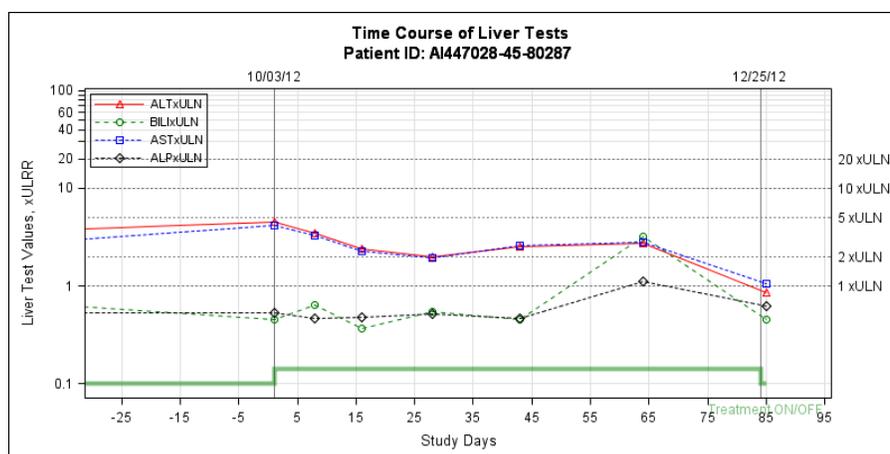
Let us point to the red triangle at (ALT 3.7, TBL 2.4), which then asks the computer to find all that data for all visits for that individual patient, a Taiwanese male 67 #80492 at site 84 in Study 28. The time course of serum ALT, AST, ALP, and TBL is shown, as log₁₀ values for multiples of the laboratory upper limit of normal range (log₁₀xULN). It is obvious that the bilirubin elevations were chronic, persistent, unrelated to ALT changes. The patient obviously had bilirubin elevations both before and after the mild rise in ALT and AST, and not increased when the transaminases rose.



He was continued on treatment and finished the 24-week planned period, and the transaminase increases subsided back to pre-treatment levels. The text narrative, visualized by clicking on the number, described no symptoms during course of treatment, no fever, eosinophilia, or other.

Comment: This is not a Hy's Law case, because the bilirubin elevations did not follow the ALT rise, and were probably due to Gilbert syndrome.

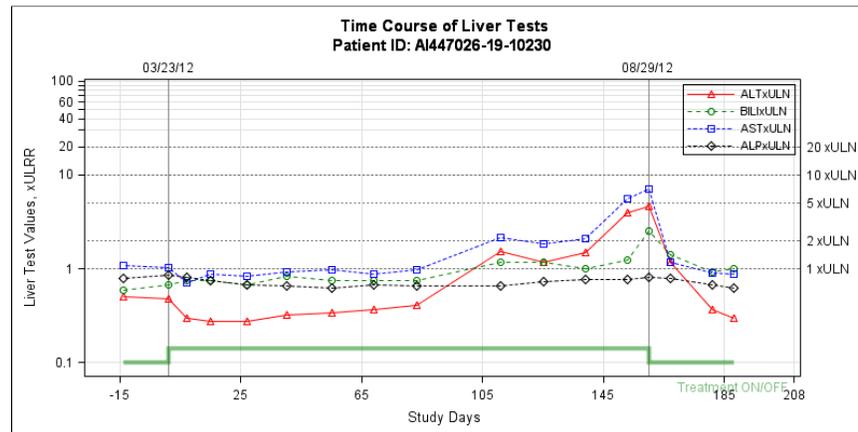
Let us look at the patient on **placebo** who appeared in the right-upper quadrant of the initial graph of all 1367 patients, the green circle at (ALT 4.6, TBL 3.2). He was a very obese US male 59 with body mass index of 34.4. He was treatment-naive for chronic hepatitis C genotype 1B. His ALT and AST were both greater than 4xULN before the study and never rose to higher for the 12 weeks of his observation on control placebo treatment, as #80287 at site 45 in Study 28. His bilirubin, however, rose sharply to 3.5 mg/dL on Day 64, which followed knee surgery on Day 55, followed by bleeding, hematoma formation, profound fatigue and blood transfusions on Days 58 and 59. He received no anti-viral treatment and showed no decline in his viral load.



Comment: This patient had no drug-induced liver injury whatsoever; the abnormal chemistries were from his untreated hepatitis C and the consequences of his knee surgery with post-operative bleeding, hematoma formation, transfusions, and the need to get rid of the load of heme and its metabolic products including bilirubin. It shows the hazard of making a "diagnosis" of DILI

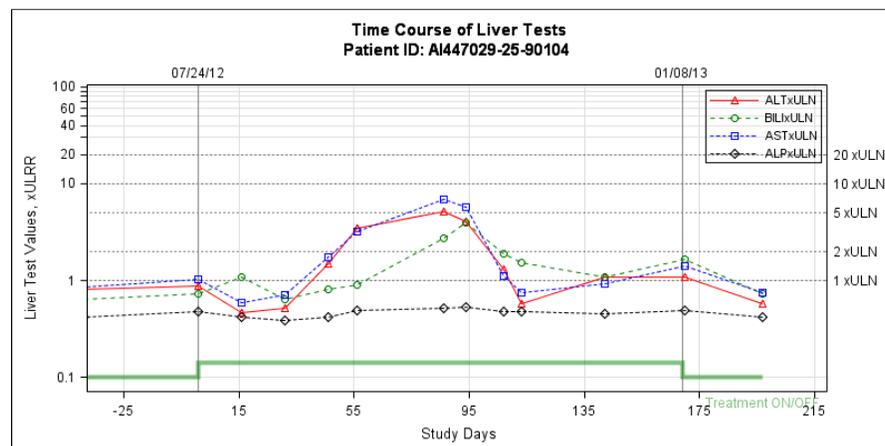
from serum chemistries alone, without considering what might have caused the abnormalities. Whether this patient may have had underlying steatohepatitis or not is uncertain, but certainly he might profit from viral load reduction.

The next case, with time course obtained by clicking on the next red triangle just to the right at (ALT 4.7, TBL 2.5) displays the course for a Japanese male 69 # 10230 in Study 26 at site 19. His tests showed an initial decline of ALTs, then a slow rise after 14 weeks but no interruption of anti-viral treatment until Day 160, about a week short of the intended 24-week treatment period, despite which he was found to have SVR 12 and 24.



Comment: The late rise in bilirubin after almost 23 weeks of treatment did not represent a serious case of DILI, although it appeared to be the consequence of the treatment given. The patients had no liver dysfunctional symptoms, and achieved the desired viral suppression by treatment.

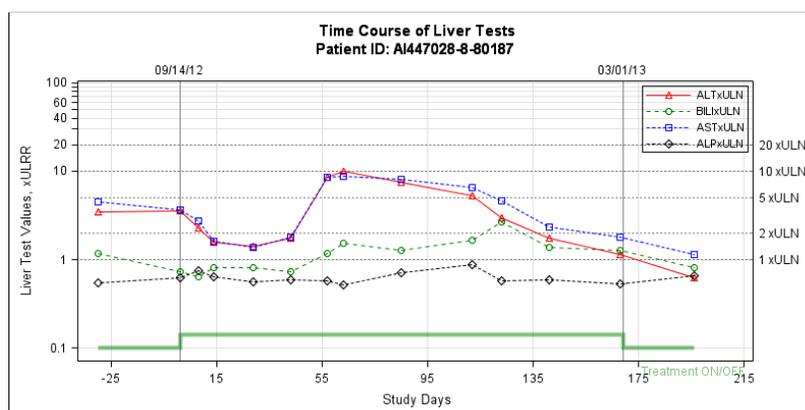
The next patient on QUAD treatment who was among the 10 selected for closer examination was a Canadian woman 60, # 90104 at site 25 in Study 29 (at ALT 5.2, TBL 3.9). She had a history of cholecystectomy but was not known to be cirrhotic.



After a month on QUAD treatment she developed fever, without rash or eosinophilia, followed by rising transaminases. Treatment was not interrupted and the serum enzyme peaked at Day 86, and the bilirubin a week later, but all the elevated liver tests declined despite continuing QUAD treatment and she completed the course of 163 days on treatment, with SVR 12 and 24.

Comment: The investigator considered the liver test elevations related to the treatment, but did not say to which component, and continued treatment. The patient's liver apparently adapted to the treatment regimen and become tolerant, with a successful outcome.

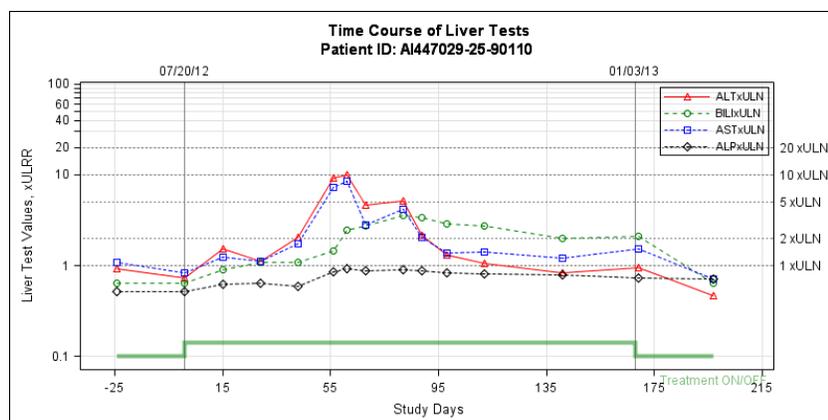
Next case: 28-2-80187



The next case shown above, was taken from the first graph somewhat farther to the right at (ALT 9.9, TBL 2.6). It was that of an Australian male 56, #80187 at site 8 in Study 28 who showed an initial drop of moderately elevated transaminase values then a sharp rise after about 8 weeks of treatment. Investigation by magnetic resonance imaging showed hepatocellular carcinoma, and treatment was interrupted for 5 days but resumed and completed. The slight bilirubin rise was seen just after a laparoscopic segmental resection on Day 116. Despite all this, he completed a full course of DUAL treatment and achieved SVR 12.

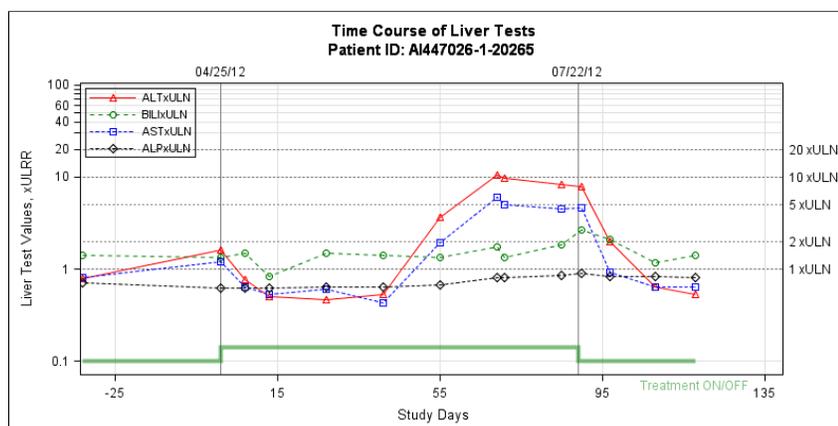
Comment: Here investigation revealed another cause for liver test elevations than the drugs used and appropriate action was taken and continued.

The last of the three patients on QUAD treatment selected (ALT 10.0, TBL 3.6) for inspection was a Canadian male 61, #90110 treated at site 25 in Study 29. He complained of mild fatigue after 4 weeks of treatment, followed by rising serum transaminases that peaked at Day 61, and his ASV dose was reduced to 100 mg daily for 10 days. The elevated serum enzyme levels began to fall when the bilirubin peaked 3 weeks later, and full treatment doses were resumed from Day 74 to Day 162 when treatment was completed. It was also noted that he developed anemia, and his ribavirin dose was reduced from 1200 to 600 mg/day. He also complained of pruritus and insomnia, and was treated with cholestyramine. All of the symptoms and findings were attributed to the mixture of study drugs, and dosing modified so that he completed the intended course of anti-viral treatment and showed SVR 12 and 24.



Comment: Although liver test abnormalities, symptoms, and other findings occurred, all of which were considered treatment-related, the investigator skillfully modified the regimen so that the drug-related abnormalities subsided, and the patient adapted to the regimen and completed the course successfully.

Case 26-1-20265 was a Japanese male 72 (ALT 10.4, TBL 3.3) who showed a somewhat more impressive rise of both transaminases after 8 weeks of DUAL therapy, which plateaued despite continued treatment but treatment was discontinued on Day 89 after over 12 weeks. Despite this he achieved SVR 12 and 24. The patient reported no fever or rash, but some fatigue and admitted to alcohol use. No liver biopsy was done.



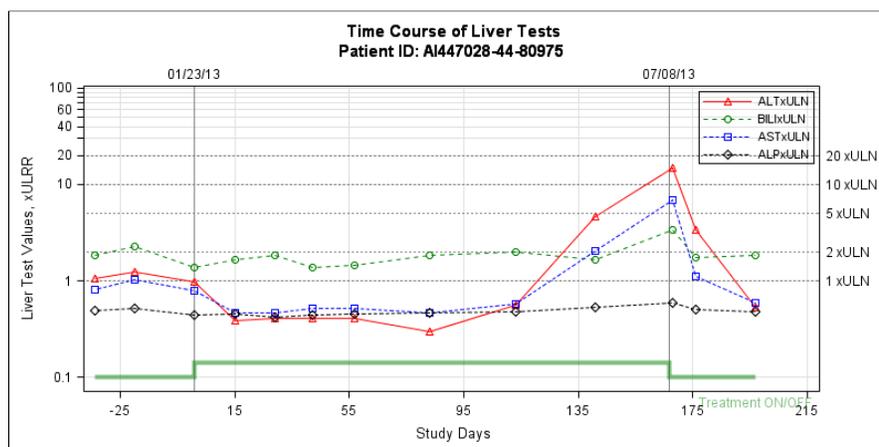
Comment: The main effect seen was a moderate increase in both serum transaminases, with little rise in bilirubin after over 12 weeks of treatment to 2.7xULN. Fortunately he had had enough DUAL treatment to get adequate viral suppression.

Even without adding the serial data for viral load, it may be seen that these few examples clearly demonstrate how the eDISH plots can enable clinical diagnosis of the most likely cause of the liver test abnormalities seen, often eliminating the case as a Hy's Law example. The first and most important requirement of the Hy's Law definition is that the liver problem be drug-induced and not caused by some other process. Simply using the elevated laboratory chemistry values of

>3xULN for peak ALT and >2xULN for TBL is not diagnostic, but requires additional clinical information and medical differential diagnosis, provided by the time course of all tests in step 2 of eDISH and the text narrative available by a simple click in the eDISH program. JReview, and even Dr. Carter, did not recognize that essential distinction. Although the FDA guidance of 2009 stated that point, it perhaps was not made sufficiently clear, leading to misinterpretation by many statisticians and preclinical scientists.

Let us now consider the two patients who showed the greatest ALT elevations:

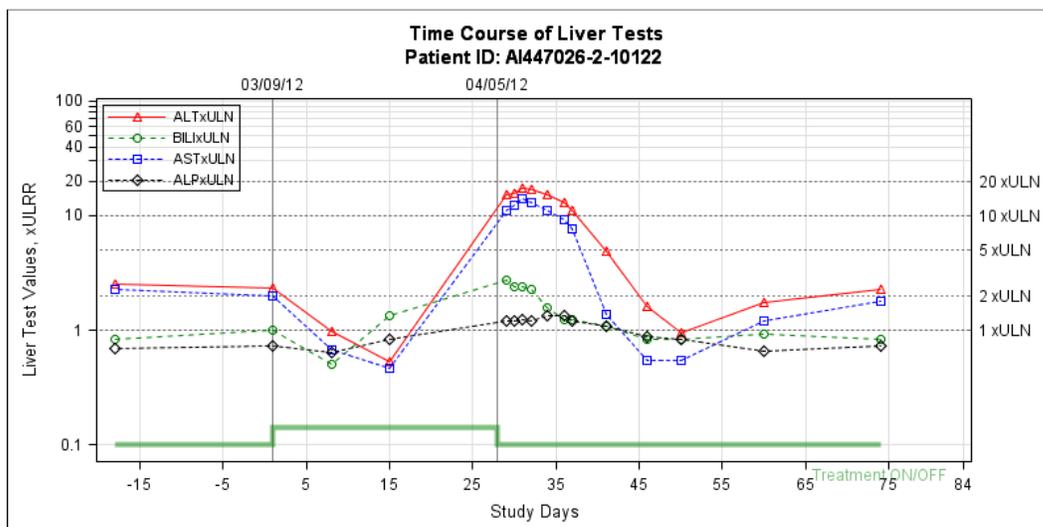
The first, on the Step 1 graph at (ALT 14.6, TBL 3.4), was a Canadian male 26, #80975 at site 44 in Study 28. He was known to have Gilbert's syndrome, with TBL fluctuating about 2 mg/dL. Immediately after starting on DUAL treatment he showed a small decrease in his ALT and AST, not previously elevated but then a rise after 20 weeks of treatment, and a small increase in TBL to 3.7 mg/dL on the last day of intended anti-viral treatment (Day 168). His viral load dropped immediately and remained undetectable thereafter, for SVR 12 and 24.



Comment: Another example brought about by an underlying mild abnormality of Gilbert's syndrome, and asymptomatic late serum transaminase increases. He may have had mild DILI but reached SVR, a very good trade-off.

The last of the 10 patients to be considered turned out to be the most serious, and only one of major concern. He was a Japanese male 57, #10122 at site 2 in Study 26, who was started on DUAL treatment on (b) (6) (Day 1). He had previously responded only partially to P/R therapy, was not known to be cirrhotic. His pre-treatment viral load was 12.6×10^6 ($\log_{10} 7.1$), that fell to 50 ($\log_{10} 1.7$) and 15 ($\log_{10} 1.17$) after 2 and 4 weeks of treatment. He reported he had nasopharyngitis on Day 11, then fever on Day 18 followed by sharp rise in ALT and AST to 14.0 and 10.2 xULN on Day 29, confirmed later that same day at as 15.2 and 11.0, with rise in TBL to 2.7xULN. Treatment was stopped, last doses on Day 28. Eosinophil increase was noted, but no rash or lymph node enlargement, and viral load was undetectable. The fever persisted until Day 34, peaking at 38.4 C (105° F). Investigation showed evidence of past cytomegalovirus and Epstein-Barr viruses, herpes virus, hepatitis viruses A, B, and E. He was admitted to hospital for liver biopsy on Day 36, which showed acute hepatocellular injury and eosinophilic infiltration.

He was diagnosed as having a hypersensitivity reaction, and was treated with prednisolone that was tapered down and stopped on Day 60 when all the liver test abnormalities had returned to normal. The viral load, however began to rise again, and when rechecked 4 weeks later was 6918 (\log_{10} 3.84), and at 8 weeks back to 17.8×10^6 (\log_{10} 7.25), and remained elevated at about that level.



Comment: This was a serious and alarming case, the “index” case for the consultation. The investigator was correct in stopping the drug immediately when these findings were observed, and treating it as an allergic-type, hypersensitivity reaction, of totally unpredictable possible course, but without skin lesions or lymphadenopathy. The four weeks of DUAL treatment were not enough to establish sustained viral suppression, and breakthrough followed. We can only speculate that the nasopharyngitis and fever should have provoked earlier recheck of serum enzymes (but it was not in the protocol), but the same response seems likely. At the end of the course of observation, he was back to where he had started, at the cost of a frightening acute hypersensitivity hepatitis that might have had a worse outcome if not promptly treated.

Because of the importance of this case, we shall comment further on it and its possible implications, after acquiring the data for viral load and merging them with the liver test data.

The ten cases above were those identified both by Dr. Carter and by eDISH confirmation. As discussed above, using the old eDISH program, they were ordered as shown on the overall graph on page 4 above. Shown below is a summary table for the ten cases, *but now ordered by study number and site*, including the serum viral load data on the day treatment was started, with the number of weeks of treatment and whether or not sustained viral response (SVRR) was obtained.

asunaprevir/daclatasvir NDAs 206844/3											
study	site	patient#	country	sex .age	Rx	peak,xULN ALT TBL	probable cause	VL log ₁₀	Rx wks	SVR	
26	1	20265	Japan	M 72	dual	10.40 2.67	DILI, not serious	6.50	12	yes	
26	2	10122	Japan	M 57	dual	17.43 2.72	ASV/DCV-sDILI	7.10	4	no	
26	19	10230	Japan	M 69	dual	4.61 2.50	DILI, nor serious	7.05	23	yes	
28	8	80187	Australia	M56	dual	9.89 2.64	hepatocellular CA	6.03	12	yes	
28	44	80975	Canada	M 26	dual	14.68 3.36	Gilbert syndrome	6.13	24	yes	
28	45	80287	USA	M 59	plac	4.53 3.18	no DILI, knee surg	6.96	12	no	
28	84	80492	Taiwan	M 67	dual	3.70 2.65	Gilbert syndrome	7.06	23	yes	
29	25	90104	Canada	F 60	quad	5.17 3.91	mild DILI, adapted	7.02	23	yes	
29	25	90110	Canada	M 61	quad	10.00 3.55	mild DILI, adapted	6.94	24	yes	
29	34	90050	France	M 46	quad	3.51 3.18	DILI, nor serious	5.41	23	yes	

It is evident that men were affected much more than women, that DILI from the DUAL regimen was much more seen among the Japanese, that other causes sometimes explained the abnormal chemistries, that those who received treatment for at least 12 weeks showed SVR, and that only one of the six patients with DILI was clinically serious, the index case 26-2-10122.

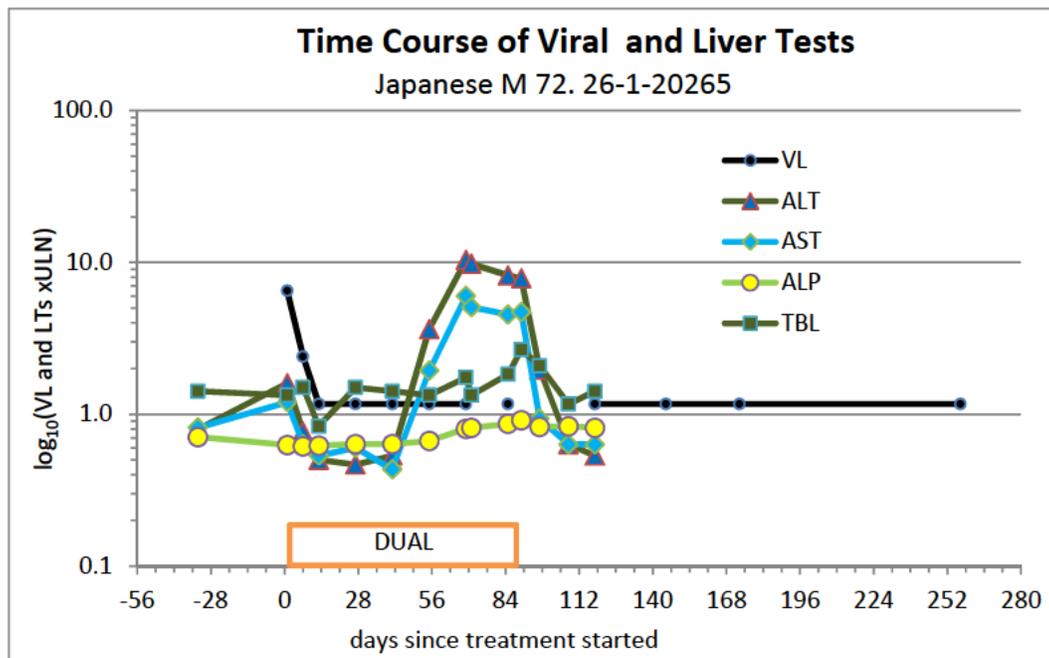
The above information was made available in July/early August to the consulting hepatologists Drs, (b) (4), in preparation for the late-cycle meeting of 22 September. The assessments made by them for each of the ten cases made by that BMS will be included with the new Excel graphs that include the serial measures of the serum viral load before, during, and after treatment with the two regimens.

When we obtained the viral load data (some from Dr. Carter but a complete set from the original NDA submissions by Dr. Guo after his return from China), we began on 9 October to merge the viral load (VL) information with the liver test information already in eDISH. But just before that, notice was received from the sponsor on 6 October requesting withdrawal of NDA 206844 for asunaprevir. (b) (4)

(b) (4) the scheduled Advisory Committee meeting for 17 November was cancelled. That gave us an opportunity during October to merge the serum VL and liver test data in a set of EXCEL graphs (not enough time to update eDISH). It also gave opportunity to prepare for the rapidly approaching annual meetings of the American Association for the Study of Liver Diseases (AASLD) in Boston 7-11 November, at which a great deal of information pertinent to these NDAs was expected to be presented and discussed, and possibly included in this consultation response. beclavubir

Let us look again at the 10 cases of interest and concern, using the newly constructed EXCEL graphs, plotting for each patient the serial VL and liver test findings, expressed as the log₁₀ values of the serum VL counts of RNA particles/mL and liver test results xULN. The cases will be shown below in the order they were presented and discussed at the 22 September late-cycle meeting, except that the index case 26-2-10122 will be shown last.

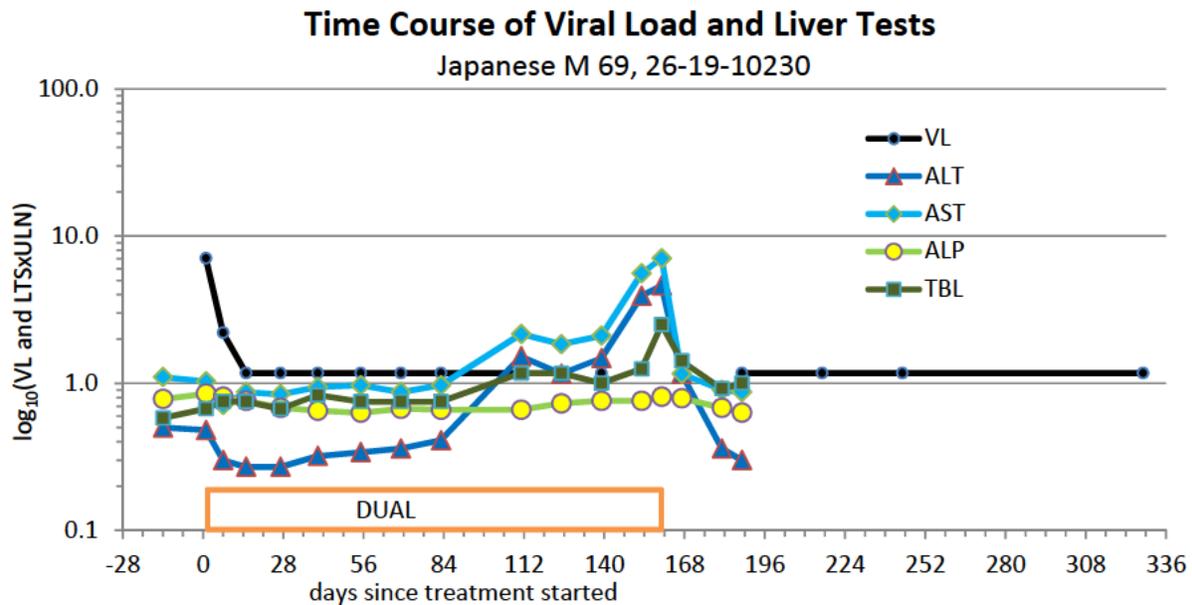
Case 2. 26-1-20265 Japanese M 71 ineligible for IFN, no cirrhosis. Showed ALT 3.6 xULN on Day 55 of DUAL therapy, increasing to ALT 10.4 on Day 69, then TBL 2,7 xULN on Day 90 when DUAL stopped after Day 89. The liver test abnormalities subsided to normal by Day 108 and SVT was achieved.



BMS Expert panel consensus assessment: Probable - with evidence of liver dysfunction.

JRS comment: Concur that this was probable DILI caused by the study drugs, but cannot say which of them. There was no increase in ALP to indicate obstructive liver injury, so the bilirubin rise was most likely evidence of hepatocellular dysfunction. The reaction was not early but started after 8 weeks of treatment, was asymptomatic, and not serious. Therefore, we all agree, including Prof. Joji Toyota at site 001 in Sapporo, who stated in the narrative that the case did not meet the protocol definition for pDILI and he did not report a SAE.

Case 3. 26-19-10230 Japanese M69, a previous partial responder to pegIFN/ribavirin with no cirrhosis. He showed a slight rise in aminotransferases, AST more than ALT, on Day 111, higher on Days 153 and 160, and was thought to have a non-tuberculosis infection with some mucobacteria, treated with carbocysteine and pentoxifyverine from Days 160-180. The DUAL treatment was stopped on Day 160, but SVR was achieved.



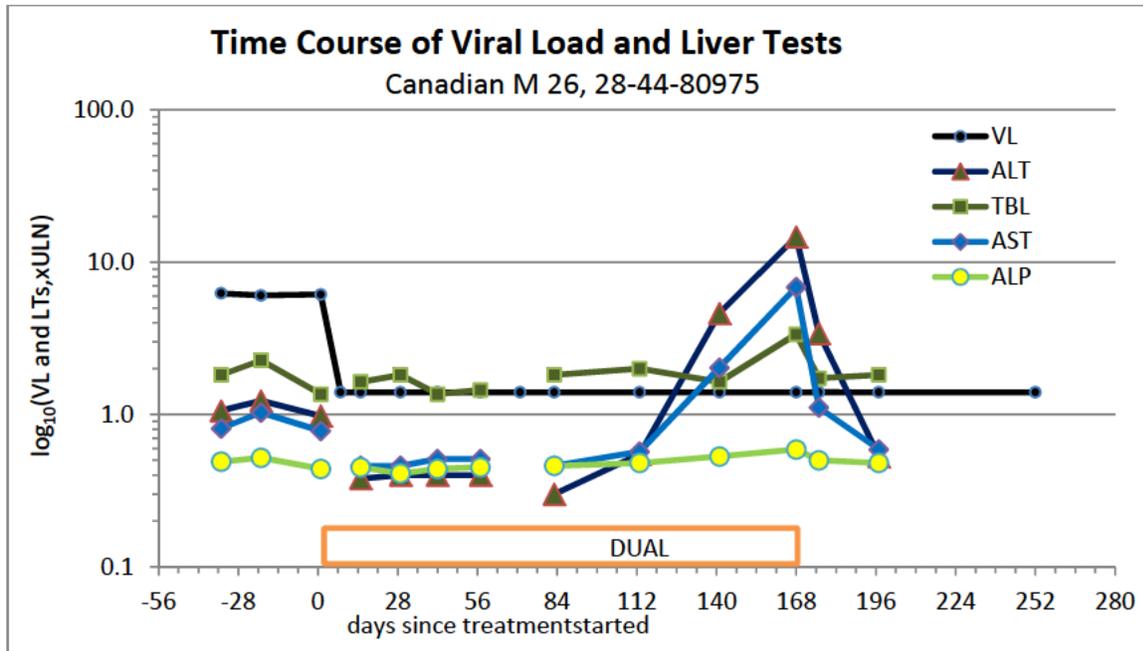
BMS Expert panel consensus assessment: Possible - without conclusive evidence of liver dysfunction. Biochemical abnormalities thought to be more likely due to mycobacterial infection.

JRS comment: Mildly disagree with the experts, and think the late rise in liver test abnormalities was induced by the study drugs, and doubt the mycobacterial infection of treatment from Days 160-180 caused the liver reaction. Therefore I agree more with the investigator, Dr. Koichi Takaguchi at site 019 in Kagawa, that the non-serious DILI was probably caused by the study drugs.

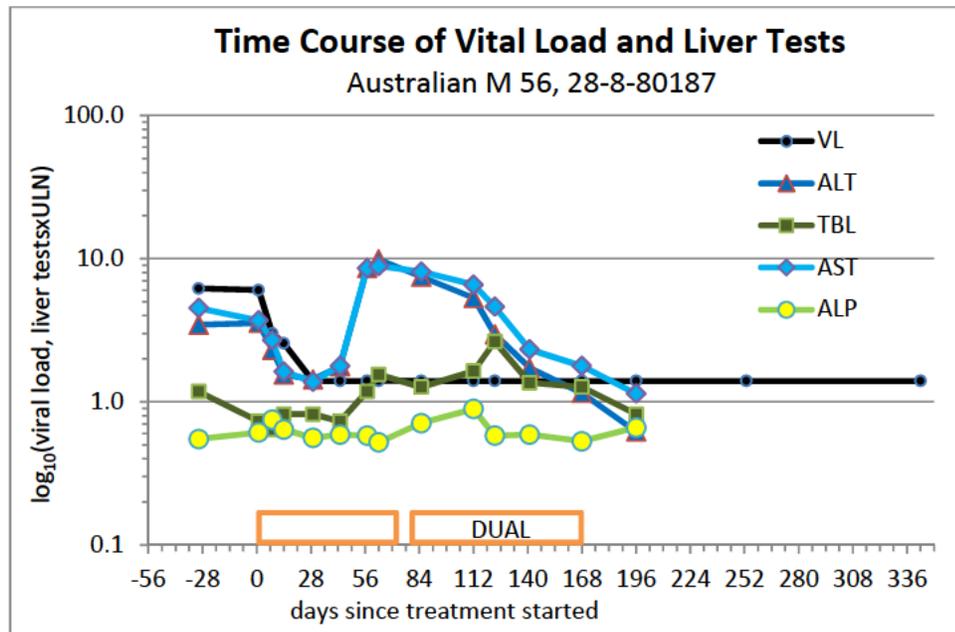
Case 4. 28-44-80975 Canadian M 26, a treatment-naïve young white male with known Gilbert syndrome, UGT1A1*28 TA7TA7. He showed fluctuating but low levels of TB, with normal levels of direct bilirubin.0.3 to 0.5 mg/dL Elevation,of ALT occurred after a full treatment course of 168 days, ALT 14.7, AST 6.8 xULN, and TBL3.4, asymptomatic. He completed the treatment and showed SVR (see graph below).

BMS Expert panel consensus assessment: Probable - no evidence of liver dysfunction (Patient has Gilbert's Syndrome).

JRS comment: Agree. Very minor DILI, after long delay, with slight drug-induced bilirubin Clearance atop Gilbert syndrome.



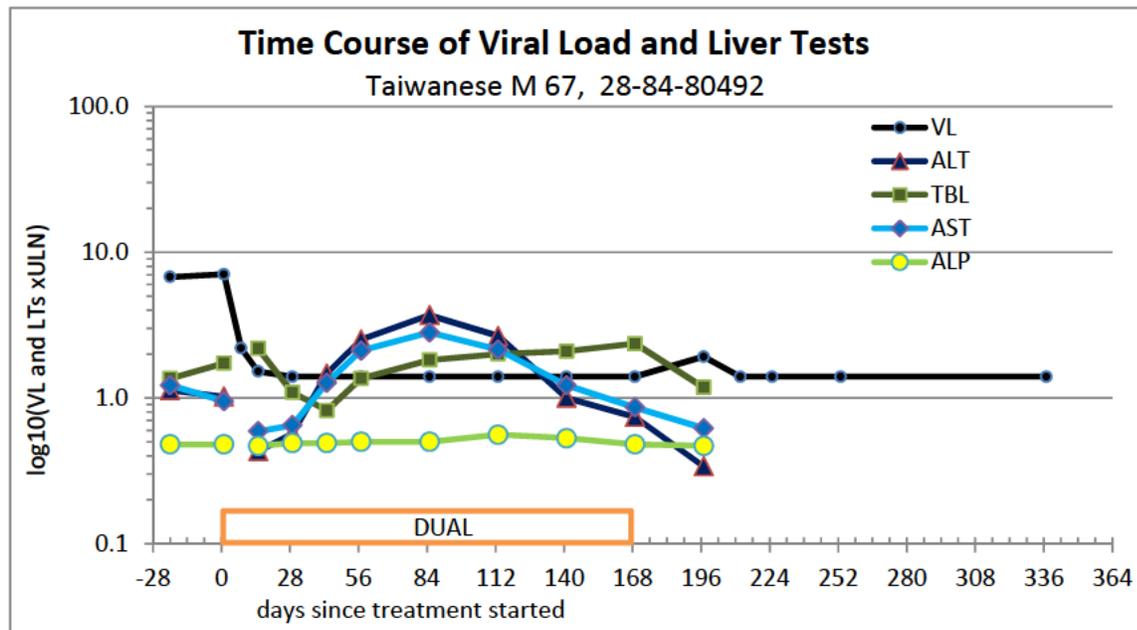
Case 5. 28-8-80187 Australian M 56, a non-responder to previous pegIFN/RBV treatment who had developed cirrhosis. After 8 weeks of treatment his aminotransferases rose and he was found to have hepatocellular CA. Treatment was interrupted for a week, but resumed and then completed. Laparoscopic segmental resection was done on Day 116, with only a small rise in TBL. After completion of treatment and SVR he later has transarterial chemoembolization of liver lesion segment VII.



BMS Expert panel consensus assessment: Probable – evidence for concomitant liver dysfunction although likely attributable to HCC requiring liver resection; the liver function appeared to ultimately improve despite resumption of treatment.

JRS comment: It seems unlikely that the hepatocellular CA, which had probably been there all along would suddenly cause a rise in transaminases, so DILI is probable. After resumption of treatment he maintained viral response and showed decline in the transaminases, probably due to adaptation of the liver to the drugs with development of tolerance.

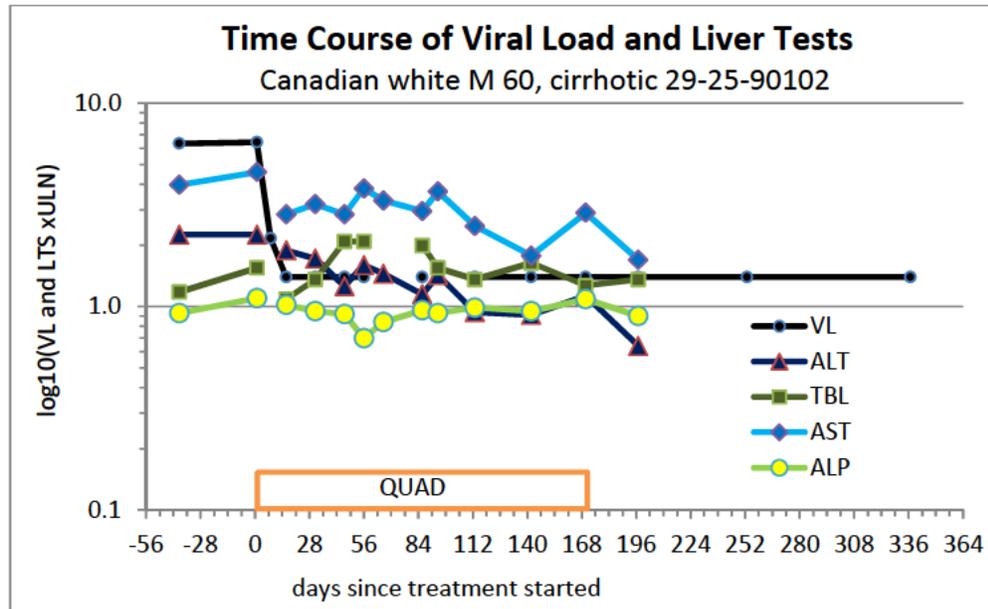
Case 6. 28-84-80492 Taiwanese M 67, prior non-responder to pegIFN/RBV, with cirrhosis and esophageal varices from HCV genotype 4, randomized in Study 28 to DUAL. He had a history of liver cysts, alcohol use, hypertension. His pretreatment TBL levels were mildly elevated, fell to normal on treatment but rose again to about the pretreatment level, with modest transient increases in aminotransferases. Treatment was continued and completed, and his transaminases normalized. SVR was achieved.



BMS Expert panel consensus assessment: Probable – no convincing evidence of liver dysfunction (bilirubin and INR were elevated throughout treatment course).

JRS comment: The small but persistent TBL elevations suggest Gilbert syndrome, although it was not diagnosed or confirmed. The transaminase elevations appear to have resuspended very mild DILI of no clinical significance, certainly not a Hy's Law case. The rise and fall of the serum transaminases also suggest that the patients showed hepatic adaptation to the drugs, with development of tolerance. Because the treatment was not aborted, he achieved SVR and its probable future benefits.

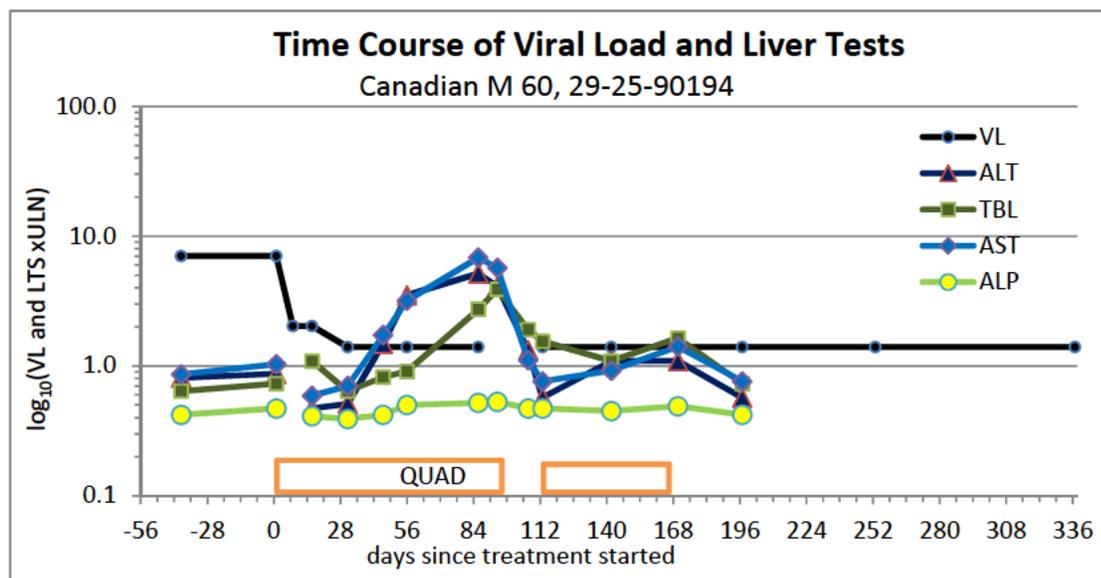
Case 7. 29-25-90192 Canadian M 60, prior non-responder to pegIFN/RBV, with cirrhosis and esophageal varices due to HCV genotype 4. Pretreatment aminotransferases were elevated, and both declined on QUAD treatment, along with a prompt drop in viral load. He completed the full course of treatment and achieved SVR



BMS Expert panel consensus assessment: Not a drug-induced liver injury case; there was a net decrease in ALT and AST levels throughout treatment.

JRS comment: It is not clear why this patient was considered at all. He did nothing but improve on QUAD treatment and there was no DILI, as agreed upon by the expert panel.

Case 8. 29-25-90104 Canadian F60, a null responder to pegIFN/RBV, with no cirrhosis.

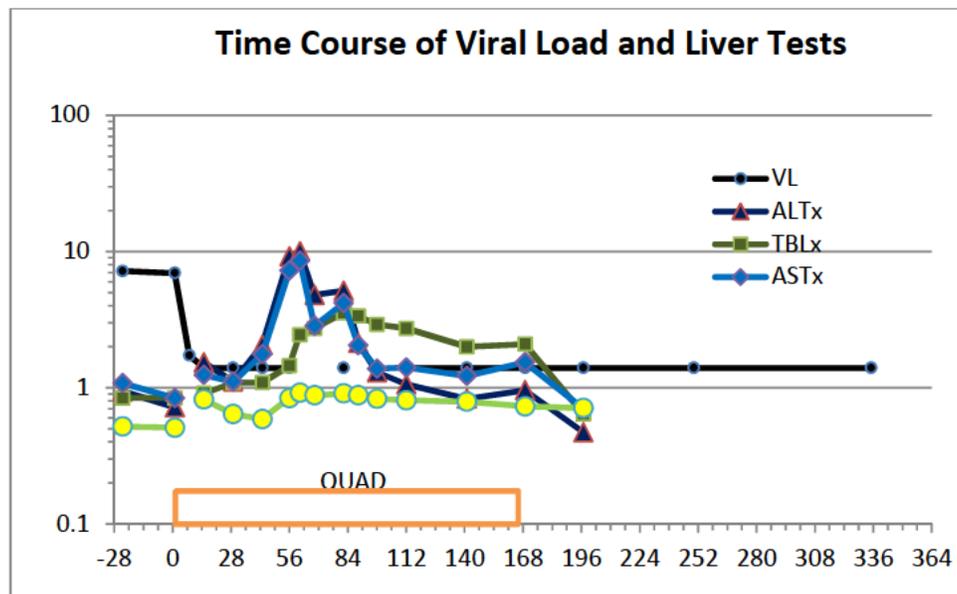


After starting QUAD treatment, she developed fever on Day 31, lasting 16 days . and het serum transaminase began to climb, peaking on Day 86 and TBL increased to 2,7 xULN. She was then asymptomatic and treatment was continued, with declines of the rlevated AST and ALT and peaking of TBL on Day 94 at 3, 9 xULN. Treatment with ASV was interrupted from Day 101 to 112, then resumed from Day 113 to 168, SVR was achieved, Her abnormal serumliver tests then declined rapidly, were only mildly elevated at the end of treatment, and normalized afterward.

BMS Expert panel consensus assessment: Probable with signs of liver dysfunction; however, it was possible to reintroduce ASV with only a small increase in ALT and the course of treatment was completed with return of serum total bilirubin and INR to normal limits.

JRS comments: This appeared to have been DILI due to the treatment regimen, and the liver Test abnormalities seemed to respond to withholding ASV for 12 days. It would be too much to say this proved that it was ASV and not DCV that caused the DILI, but it is suggested. Her liver seemed to adapt and recover and the ASV rechallenge did not cause recurrence, suggesting that Her liver had adapted and become tolerant.

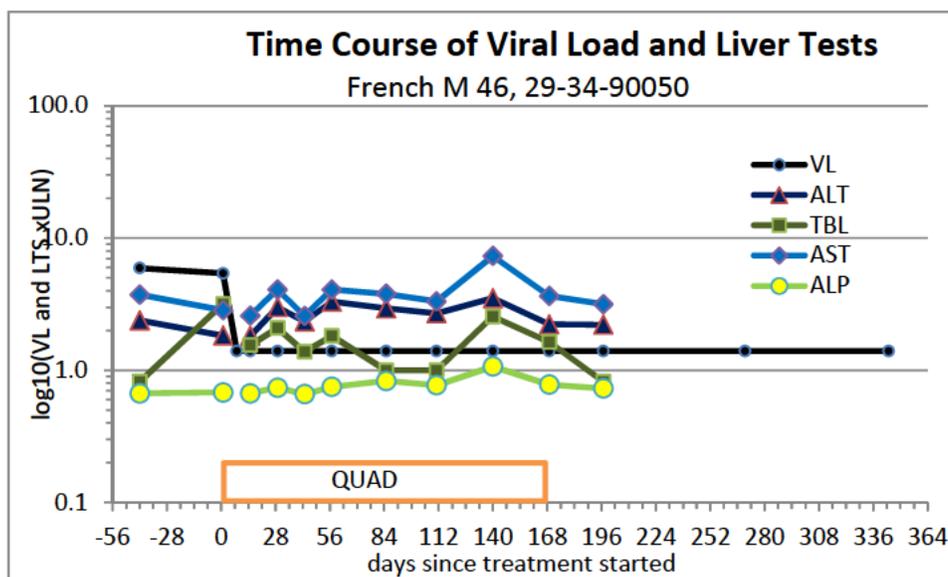
Case 9. 29-25-90110 Canadian M 61, a previous partial responder to pegIFN/RBV, with no cirrhosis, infected with HCV genotype 4e. On treatment, ALT and AST began to rise slightly on Day 43m then sharply on Day 56, followed by TBL increase that peaked on Day 82 espite falling aminotransferases. Treatment was not interrupted but ASV dose was reduced to 100 mg/day instead of b.i.d. from Days 64-73. Extra visits for liver tests were done on Days 61,68,89, and 98. The aminotransferases faster then the TBL. Treatment was completed and SVR was achieved.



BMS Expert panel consensus assessment: Probable with evidence of liver dysfunction; however, the injury and evidence of liver dysfunction appeared to resolve during treatment.

JRS comment: This was probable DILI, but reducing the ASV dose seemed to allow adaptation and development of tolerance. Not clinically serious.

Case 10. 29-34-90050 French M 46, previous null responder to prgIFN/RBV, cirrhotic with esophageal varices due to HCV genotype 4a/c/d, alcohol and tobacco use, hypertension. His serum AST, ALT, and TBL were elevated to begin, did not respond to treatment despite the reduction in viral load. He had pruritus on Day 88 unresponsive to hydroxyzine, worse on Day 127, for which cholestyramine was given. He completed treatment and achieved SVR.

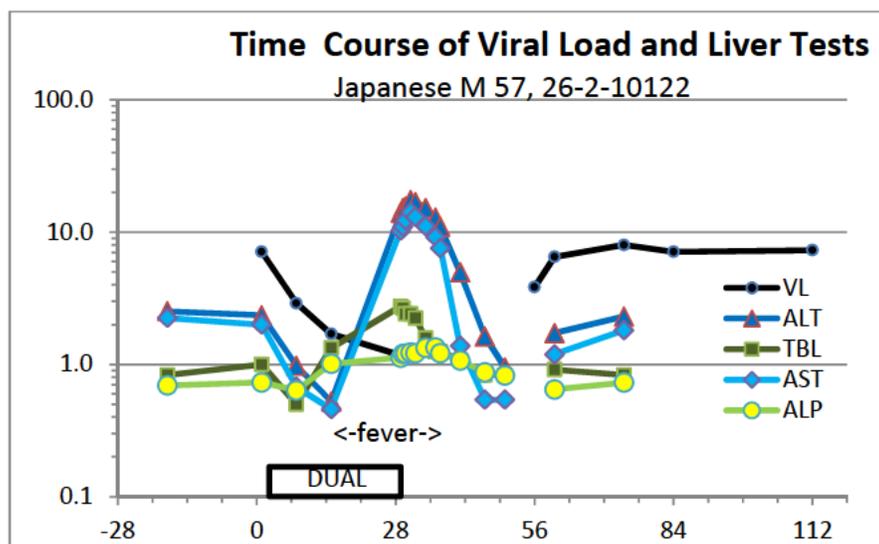


BMS Expert panel consensus assessment: Unlikely – an unidentified but pre-existing chronic liver disease (other than HCV) is likely to account for the persistently abnormal liver chemistries.

JRS comment: The AST>ALT elevation is consistent with cirrhosis and was not affected by the QUAD treatment or reduction in viral load. There was no effect on or elevated ALP, so it would be unlikely that the pruritus would respond to cholestyramine. No DILI.

Case 1. And now for the index case **26-2-10122**, the Japanese man of 57 who developed a rapid fever just 25 days after starting DUAL treatment. He had previously shown only a partial response to prgIFN/RBV, had not developed cirrhosis due to HCV infection with genotype 1b. He had a history of appendicitis and social use of sake, and previous smoking of 15 cigarettes/day stopped two years before. Pretreatment aminotransferases were mildly elevated but quickly normalized as the viral load fell to undetectable. His pretreatment level of gamma-glutamyltranspeptidase was also slightly elevated. He developed symptoms diagnosed as mild nasopharyngitis on Day 11, lasting about a week. He was then found to be febrile on Day 25, lasting until Day 34, with peak at 38.4 C., attributed to the DUAL therapy, and the ALT was found sharply elevated at 558 U/L, along with TBL 56.4 μM on Day 29. The patient was told to stop medication, so the last doses taken were on Day 28. It was found on inquiry that he was taking double doses of daclatasvir, 60 mg twice daily instead of once. His body weight was 60.4 kg (133 lb), height 1.72 m, (5'7.8"), BMI 20.4. Close observation was started, and it was found that his eosinophil count had risen, but he showed no skin rash or lymphadenopathy. Testing was positive for cytomegalovirus IgG and Epstein-Barr virus IgG. He was hospitalized for liver biopsy on Day 36, and results showed changes typical of an allergic reaction, for which

prednisolone was started on Day 37. He was discharged from hospital on Day 39, improving. The investigator, Prof. Satoshi Mochida at site 002 in Saitama (Tokyo suburb about 20 km northwest) felt that the adverse reaction was serious and had been caused by the DUAL treatment, but could not say to which of the two components. He made no attempt to rechallenge with either drug. The patient recovered from his acute liver injury without showing hepatic decompensation, but the viral infection relapsed.



BMS Expert panel consensus assessment: Probable with evidence of liver dysfunction. The experts noted that eosinophils in liver biopsies is characteristic of drug-induced liver injury (DILI) and is not a worrisome finding. Indeed, data from DILI registries suggest that the presence of eosinophils in the liver is associated with milder liver injuries.

JRS comment: The acute allergic-like reaction was totally unexpected, but the prompt action of the investigator may have prevented more serious injury and possible liver failure if the drugs had not been stopped. The importance of the daclatasvir overdose is unclear. This case was not reported in detail by the group of Japanese investigators who published results of Study 26 in Hepatology in June 2014, just before approval of the DUAL regimen in July 2014 for prescription and marketing.

It is interesting to ask why this case was of concern to Dr. Carter and the DAVP team, but was not so perceived by the sponsor, BMS. In this matter, why was the case glossed over by the 15 investigators who authored the paper in Hepatology? Closer reading of that publication, which seems to have been influential in the Japanese regulatory approval of the DUAL regimen just a month later, show that the 15 Japanese authors had studied patients at only 12 of the 24 sites for Study 26, including two authors from 3 of the sites. From information submitted with the NDAs on 31 March, Appendices 1.5 and 2.1B give the list and description of investigators, locations of the 24 sites in Japan, and the number of patients treated at each site. It may not be coincidental that investigators at the 12 sites where only 6 or fewer patients were treated were not authors of

the paper, but investigators at sites at which 8 or more patients were treated were shown as authors and two authors from sites where 20 or more patients were treated are listed as authors.

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PMID 24604476

Dacaltasvir plus asunaprevir for chronic HCV genotype 1b infection

<u>Authors</u>	<u>site, location</u>	<u>treated</u>	<u>Non-authors</u>	<u>site, location</u>	<u>treated</u>
H. Kumada	008, Tokyo (Toranomom)	20	S. Mochida	002, Saitama	6
Y. Suzuki	007, Tokyo (Toranomom)		O. Yokosuka	003, Chiba	6
K. Ikeda	007, Tokyo (Toranomom)	20	T. Ho	006, Tokyo (Showa)	6
J. Toyota	001, Sapporo		T. Shimikami	009, Ishikawa	5
Y. Karino	001, Sapporo	25	M. Sakamoto	010, Yamanashi	4
K. Chayama	018, Hiroshima		M. Ishigami	011, Aichi	6
Y. Kawakami	018, Hiroshima	21	H. Yoyoda	012, Ogaki	6
A. Ido	023, Kagoshima	12	T. Okanoue	013, Osaka	6
H. Yamamoto	017, Okayama	10	H. Hagawra	016, Hyogo	5
K. Takaguchi	019, Kagawa	8	M. Koda	021, Osaka	3
N. Izumi	004, Tokyo (Musashimi)	8	M. Nakamura	022, Fukuoka	6
K. Koike	005, Tokyo (U Tokyo)	8	K. Kondo	024, Nyagi	5
T. Takehara	014, Osaka	8			
N. Kawada	015, Osaka	8			
M. Sata	020, Fukuoka	8			
... of 222 treated		158			64

It is evident that 71% of the patients treated were at the 12 sites where at least 8 were treated, and the investigators at those sites were included as authors of the paper. Dr Mochida, at site 002 in Saitama, was not included as an author, and it of interest that he just submitted a paper to Hepatology reporting his case 26-2-10122, the index case for this consultation.

Fujii Y, Uchida Y, Mochida S. Drug-induced immunoallergic hepatitis during combination therapy with daclatasvir and asuaprevir.

Hepatology 2014 Oct 12; ePub ahead of print PMID 25308083

In his submission, he stated that the patient's fever had occurred at 15 days after starting therapy, not on day 25, and he provided a few more details, a graph showing the rise of ALT and eosinophils and duration of fever. He also included a picture of the liver biopsy, and cited the publications by Kumada et al on Study 26 in Hepatology June 2014, and that of Anna Lok et al. on Studies 28 and 29 that had been published in the Journal of Hepatology in April 2014.

JRS comment: It is obvious that Prof. Mochida was not entirely satisfied with the publications by the Tokyo group of investigators, and felt that his case was deserving of special attention. It will be of interest to see if the approval of this dual combination therapy for chronic hepatitis C in Japan leads to additional cases such as that he reported. English versions of the labeling were sent by the sponsor shortly after its approval in Japan in early July 2014. It may be that prescribers of this novel combination treatment may not be as astute as was Dr. Mochida, and more serious outcomes may result.

The most important aim of anti-viral treatment is to get rid of the infecting virus, and suppressing it long enough and hard enough that it doesn't recur after treatment. so that the damaged liver may heal, We do not know fully yet what long-term benefits may result from effective viral suppression but suspect they will be important. We presume that benefit will occur to the livers of patients in whom the virus is effectively suppressed (SVR), that such benefit will be long-lasting and very important in reducing progression to cirrhosis and hepatocellular carcinoma, and preventing need for liver transplantations.

Chronic hepatitis C is obviously a serious liver problem, and the aim of anti-viral treatment is to benefit patients with infected livers by getting rid of the virus without injuring or harming livers of those treated. This has not been a problem in the past, with the four agents approved, which did not appear to cause any liver injury and were increasingly successful in suppressing the C virus, or some of its genetic subtypes especially. Now we have a pair of agents used together, but some evidence of at least rare liver injury probably being caused by them. In all but one case, so far, the index case 26:10122, the balance was favorable, more benefit than harm.

APPEARS THIS WAY ON ORIGINAL

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Chronic hepatitis C is obviously a serious liver problem, and the aim of anti-viral treatment is to benefit patients with infected livers by getting rid of the virus without injuring or harming livers of those treated. This has not been a problem in the past, with the four agents approved, which did not appear to cause any liver injury and were increasingly successful in suppressing the C virus, or some of its genetic subtypes especially. Now we have a pair of agents used together, but some evidence of at least rare liver injury probably being caused by them. In all but one case, so far, the index case 26:10122, the balance was favorable, more benefit than harm.

How should we compare beneficial effects and harmful effects? Good and bad effects? Desired and undesired effects? We start with patients who are in highly variable states of their chronic disease, some early, some late, some already cirrhotic and others not. Trying to lump or group them into categories for statistical group analyses is very difficult or impossible, and therefore I

suggest considering each patient as an unique individual, and assess the effect of treatment in that single person. The sum of all individual net beneficial effects will build a group net effect. Note that I do not use the conventional term of “risk.” Risk is really not an effect. But the chance of finding an adverse, unwanted, bad effect, to be balanced against the chance of finding a beneficial, favorable, desired, good effect. Therefore, let us focus on the actual observed effects of treatment, good, bad or mixed, rather than on the chances that they might occur. These effects are not simply binary but quantitative, so a great benefit easily outweighs a slight harm, but a serious harm outweighs a minor benefit. These should logically be compared as a *difference*, but never as a ratio that becomes meaningless when one or the other is zero, or none. It is obvious that (5/0) and (1/0) are equally indeterminate but (5 – 0) is clearly better than (1 – 0). Placebo treatment is expected to confer neither benefit nor harm, if measured objectively, its net benefit is expected to be at or near (0 – 0). The National Cancer Institute has classified all test results and adverse symptoms or findings into five grades, for 1=mild, 2=moderate, 3=severe, 4=life-threatening, and 5=fatal.. These have become firmly established since first proposed in 1982, and are now in revision of version 4 to version 5. Comparable grades could be established for good or beneficial effects of treatment. For treatment of chronic hepatitis C with DAAs, the desired outcome is prompt, total, and permanent eradication of the C virus, suggesting a scale of good or beneficial outcomes from +1 to +5, with a scale of bad or adverse outcomes from -1 to -5. Let us propose a set of definitions for this:

- +5 prompt, complete, sustained viral eradication, with return of abnormal liver tests to normal
- +4 prompt, complete, sustained viral eradication, with stabilization of abnormal liver tests
- +3 slower but eventually effective viral eradication, with no worsening of liver tests
- +2 incomplete but substantial reduction in viral load, no apparent effect on chronic liver disease
- +1 very slight reduction in viral load, no apparent effect on chronic liver disease
- +0 no reduction viral load, no benefit on chronic liver disease
- 0 no harmful effect on liver observed during or present after treatment
- 1 slight or mild, reversible liver injury, such as serum transaminase elevations only
- 2 moderate liver injury, with recovery after treatment
- 3 serious or severe liver injury attributable to or caused by the drug treatment
- 4 life-threatening liver failure attributable to or caused by the drug treatment
- 5 fatal treatment-induced liver damage caused by the treatment

The net benefit of treatment in a single patient would range from +5 to -5, the positive values being desired or favorable, and negative values unwanted or adverse. For the 10 patients selected for detailed review, as shown above, 8 would have shown a net benefit of +2 to +4, the placebo-treated patient a net benefit of 0, and the index case -3. The last is given a seriously negative score, losing the initial transient benefit of viral load reduction because he developed a grade 3 serious liver reaction (acute hypersensitivity hepatitis caused by the combination or one of its components), with insufficient anti-viral treatment and recurrence and no final reduction of the viral load.

If we look at the 102 patients treated with placebo on Study 28, their individual net benefits were all zero or very nearly so. The 398 patients treated with the QUAD regimen nearly showed viral response of SVR, with very few suffering any residual bad effects at final outcome assessment, giving that group a very high number of heavily positive results, even considering the adverse

effects during treatment of the four agents used. The 222 Japanese patients of Study 26 and the 645 worldwide patients of Study 28 on the QUAD regimen were intermediate, with fewer ill or adverse effects but a lesser degree of SVR, but overall quite positive. When the groups, made up of net-benefit scored individuals, are compared, different patterns can be seen when all of the patients treated are considered. A high price is paid for discontinuation of treatment prematurely because of adverse reactions, in some of whom the time of treatment was not long enough to get SVR as an outcome. Additional analyses of those who discontinued treatment other than for lack of efficacy will be undertaken as time permits. It will also be important to look at the patients who showed significant peak ALT levels $>8xULN$ (eDISH right lower quadrant) to see what happened to their viral loads and net benefit scores.

The sharp-eyed readers of this discussion may note that the EXCEL graph shown above of the time course of liver tests in the index case 26:10122 with added viral load data, showed the liver tests plotted as multiples of the patients own baseline values (xB) instead of the upper limit of the normal reference range (ULN). This is consistent with the idea of focus on effects of the drug on each individual rather than comparison to some hypothetical normal population, whatever that may be and however determined.

While these concepts are being developed further with additional data analyses, it is appreciated that the other issue of the fever and eosinophilia syndrome has not been addressed, not have I any special knowledge about it. As time permits in coming days, I shall want to look at the notable pyrexia-eosinophilia cases, as well discussed by Dr. Carter in her review of 29 August. I shall want to look at liver test data in those patients, and effects on viral load to attempt to estimate net benefit. The class of allergic or hypersensitivity reactions is certainly something to worry about, a highly unpredictable but fortunately rare effect that in the full-blown expression such as toxic epidermal necrosis or liver necrosis may be very lethal. That such reactions were not discovered with the other protease inhibitors approved recently suggests the possibility that the novel agent daclatasvir (DCV) may be triggering in some patients an immune system response that is severe and excessive, and possibly dangerous.

This brings me to the set of 9 questions posed in the consultation request, which I tried to answer in early September, based on what I had learned so far. Since then, Dr. Mark Avigan provided (on 7 October 2014) a set of very thoughtful but quite long, complex answers to the questions, in 3 pages for question 1, a page for questions 3, 4 and 5, and somewhat briefer answers for the last 4 questions. Since then have obtained the viral load data and merged them with the liver test data, shown graphically above on pages 14-21 of this document, and have attended the meetings of the American Association for the Study of Liver Diseases in Boston 7-11 November, at which a stupendous amount of new information was presented and discussed, including hundreds of posters, scores of oral presentations on over 30 DAAs and combinations, from 129 studies on over 34,000 patients. In addition, there have been several papers published on these studies of asunaprevir/daclatasvir from the Japanese study 26, and from the worldwide studies 28 and 29 that were not cited in either the Backgrounder document provided in early August or the full clinical report of 29 August by Dr. Wendy Carter. The index case 26-2-10122 that aroused such concern in DAVP was not much mentioned in the large report by Kumada and colleagues from 12 of the 24 study centers in Japan, but has recently (October 12) been published separately by Dr. Moshida and colleagues from Saitama, Japan (see references and attachments).

So, back to the 9 tough questions, with **addenda in bold**, following the liver meetings in Boston:

1. Please provide your opinion regarding the overall hepatotoxicity signal and how the observed eosinophilia findings (with and without pyrexia) relate or do not relate to the observed hepatotoxicity signal. Specifically, in your opinion, do these findings represent a single clinical syndrome or event, or distinct events?

Comment 1: Although there are five cases that showed peak serum ALT >3xULN AND TBL >2xULN in the eDISH plot, confirmed by JReview, they occurred in patients who already had underlying chronic liver disease at variable stages in development, so these effects must be considered acute-on chronic injury and not as conventional "Hy's Law cases" So far, I have considered the liver effects and the viral load, but have yet to evaluate the relationship of the fever-eosinophilia with liver effects. This I shall try to do while this preliminary response sent on Sunday evening 7 September is being pondered before the 10 September discussion. So far there is only the one index case, and the question needs further consideration.

Further review suggests to me that the eosinophilia-fever syndrome seen only in the Japanese study does not constitute a consistent diagnostic signal for serious DILI caused by these drugs, but there were many who showed those effects who did not develop serious liver injury, and only one who did.

2. Please comment on a possible association with demographic factors (i.e., race) and any potential risk mitigation that may be considered for the safety concerns.

Comment 2: This concept was encountered for the first time in the case of ximelagatran, where it was ultimately found, several years after the drug was not approved, that European, especially Swedish, patients showed genetic HLA markers associated with increased susceptibility to DILI. As yet, I could only speculate on the point, lacking data. The Japanese study 26 may have been reflective of their cautious approach and conservative decision-making. It is conceivable that the hypersensitivity reaction might have occurred anywhere. The only mitigation is prompt discovery and appropriate action as was taken for 26-2-10122. After approval, when close observation and quick action might nnt be done as well as itr was at site 002, it could be worse.

This deserves further watching as many more patients are exposed in Japan following the approval in July 2014. There is not yet enough evidence to form a basis for genetic stuidies in that population, but they may be needed in the future.

3. Please provide your opinion whether or not pyrexia is a discriminating clinical symptom to potentially identify at-risk patients. If not, then provide comments on how to distinguish at-risk patients.

Comment 3: It was in the index case, but it is premature to generalize findings from one patient to all treated. In view of what has been learned, it should not be ignored, and should lead to more frequent assessment of liver injury, without waiting for the next routinely scheduled visit. It is a real problem and more experience and information is needed.

The Japanese labeling says to watch out for people with sensitivity to any component of the therapy, but how can one know in advance who will show it?

4. Please provide your assessment of the subjects who met Hy's Law laboratory criteria and specify subjects that you believe represent drug-induced liver injury and those that do not.

Comment 4: As explained, the usual criteria for and definition of Hy's Law are not applicable here. We defined it, and now need to redefine something to use in considering drugs used to treat chronic, active liver diseases such as that caused by the hepatitis C virus, I thought that 5 of the 10 subjects identified by both eDISH and JReveiw were most likely forms of DILI, as far as probable causality, but the interpretative predictions of how serious the reactions might be will require more experience and information. We hope to obtain it more quickly than did Drs. Zimmerman (in 1965-78) and Temple (1978-99).

Again, Hy's Law criteria are not just serum chemistries, but absolutely require evidence for most likely or probable causality by the drugs in question. Further, not all cases that meet even that more rigorous standard turn out to be clinically serious, as we have learned from many other drugs.

5. Do these events affect your risk/benefit assessment for the DUAL and QUAD regimens, and if so, how?

Comment 5: The best I can do is to use the net benefit scoring, based on my own experience as a physician, treating and observing effects of treatment in one patient at a time but building up concepts for many patients so evaluated from that experience.

We should distinguish between net benefit to one individual patient, as is the concern of the physician prescribing the treatment, from new benefit to a large group of patients. Clearly, it is almost certainly a benefit to patients to get rid of the infection that is causing chronic damage to their livers. In this series only one individual showed negative net benefit, the index case. In general, is a very good idea to suppress or cure the HCV infection.

6. Do you think there are enough data to show the safety events are related only to asunaprevir, only to daclatasvir or to the asunaprevir/daclatasvir combination?

Comment 6: This is a really tough question that was not fully answered in Phase II, The ASV is just one more protease inhibitor, and probably similar to the others. That is not true for DCV, which is a new agent, new mechanism, and perhaps new problems. I don't see any information and about the sensitizing potential of DCV and whether it might be a rare but maybe seriously dangerous drug for some people.

This cannot be answered, as even Prof. Mochida observed. There may be some concern that the inadvertent overdosing with daclatasvir may have played a role in the rapid and serious case of immunoallergic reaction shown by the index case. The favorable responses by two of the other who had temporary interruption or reduction in asunaprevir is inconclusive.

7. Does a potential association with (1) hepatotoxicity and (2) pyrexia/eosinophilia with and without liver involvement portend an increased risk when considering broad availability of these drugs?

Comment 7: It certainly could be so, but what we have to learn is how to use these drugs safely. It took over 20 years to learn how to use isoniazid safely and still keep its valuable benefit of

preventing tuberculosis, despite some early deaths from fatal DILI when it was used unwisely or unknowingly. The intense competition for marketing these new DAAs may speed development but not necessarily safety assessment.

Right now, we have just one case of serious harm from this combination therapy, out of 222 patients treated. That does not establish a reliable figure for incidence. There may be none in the next several cohorts of 200. Only time and further experience will establish and answer to the question.

8. [Considering the overall risks and benefits, do these cases present a serious approvability concern? If not, please comment on potential labeling for monitoring, discontinuation criteria and situations where asunaprevir/daclatasvir should not be administered.](#)

Comment 8: I do not know how labeling can be written so all physicians prescribing the drug really read and understand it, and even to follow the recommendations, nor how to get them to watch their patients closely and reduce, interrupt, or stop drug as appropriate. We don't really want to approve drugs that will soon after have to be taken off the market, which is learning the hard way.

The question is now moot, since asunaprevir has been withdrawn and the sponsor is consider just what to ask for in a resubmission of data for NDA 206843. It may be fortuitous that the only approval so far is in Japan, where there problem amy be most likely to occur.

9. [What additional data would be helpful to further characterize these events?](#)

Comment 9: We have some information, but a lot of hard questions, and only a few hundred patients treated with each of these regimens, but with tens or hundreds of thousands to be treated with less rigorous observation if the combination is approved. For starters, I shall want to have time to look more carefully at what we have so far regarding liver effects in patients showing the fever-eosinophilia syndrome or partial syndrome, and viral responses in patients showing only enzyme increases without dysfunctional hyperbilirubinemia.

Stay tuned. This is an exploding field, as you all know very well.

John R. Senior, M.D.

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/s/

SOHAIL MOSADDEGH
11/18/2014

JOHN R SENIOR
11/18/2014

From: Mark Avigan, MD CM; Associate Director, Office of Pharmacoeconomics and Epidemiology (OPE)/OSE

To: Debra Birkkrant, MD; Director, Division of Anti-Viral Products (DAVP)

Via: Solomon Iyasu, MD, Director OPE

Subject: Draft Responses to Questions Submitted by DAVP
NDA: 206843/206844: Asunaprevir; Daclatasvir: Potential Hepatotoxicity and Eosinophilia/Pyrexia

Date: October 7, 2014

1. Please provide your opinion regarding the overall hepatotoxicity signal and how the observed eosinophilia findings (with and without pyrexia) relate or do not relate to the observed hepatotoxicity signal. Specifically, in your opinion, do these findings represent a single clinical syndrome or event, or distinct events?

Response: *A causal link between ASV/DCV to hepatotoxicity is supported by strong evidence for clinically significant and other causally-related liver injuries in the clinical trial database. This footprint includes the following findings:*

- *Among 9 Dual Regimen (ASV/DCV) study subjects in Phase -3 trials who had biochemical findings consistent with Hy's Law, expert adjudication by the sponsor-hired consultants (Drs. [REDACTED]^{(b)(4)}) found that 5 were 'probable' (>50% likelihood) in their causal association with these agents. During the period of transient liver test abnormalities while on study drug, HCV RNA levels remained suppressed, suggesting that a resurgence of HCV viral activity could not be the basis of the new liver abnormalities. Nonetheless, it should be noted that there were important caveats or confounders in a number of these cases. Case 7028-44-80975 was marked by evidence of acute liver injury in a patient with Gilbert syndrome. During the transient rise in serum ALT and bilirubin on Day 168 reaching respective peak levels of 690 U/L and 6 µmol/L, the direct bilirubin value was 7 µmol/L, similar to baseline levels. Case 7028-8-80187 was marked by a transient episode of acute liver injury that began on Day 57 that was superimposed on abdominal imaging findings on Day 91 revealing HCC and a short treatment course with prescribed amoxicillin and APAP/codeine at week 4. That case and case 28-84-80492 were marked by the presence of underlying cirrhosis. The 'sentinel' case 26-2-1022 was marked by coincident transient rises of serum ALT, AST, ALP and bilirubin that began on Day 29 and were reversed upon discontinuation of ASV/DCV and initiation of prednisolone. Although the HCV viral load was suppressed at the time of liver biopsy, it subsequently increased, reflecting lack of a SVR. In this*

case, a confluence of drug-induced systemic hypersensitivity and hepatotoxicity was supported by findings of a liver biopsy performed on Day 36 that was coincident with peak liver test abnormalities and the presence of eosinophilia and pyrexia. At the time of the liver biopsy HCV viral levels were transiently suppressed prior to their resurgence after discontinuation of ASV/DCV on Day 28 and initiation of prednisolone on Day 37. The liver biopsy findings that were reported include interface hepatitis (piecemeal necrosis), bridging fibrosis, pockets of lobular hepatitis, and moderate infiltration of eosinophils. I was asked by DAVDP to review the biopsy using ImageScope software. Liver biopsy stains that were available were H&E, Masson Trichrome (to assess fibrosis) and silver stain (to assess collapse of reticulin-based hepatic trabeculae and thickening of hepatic cell plates for evidence of hepatocyte necrosis and active regeneration, respectively). My review of the biopsy findings revealed piecemeal necrosis with mononuclear cell and eosinophilic infiltrates, focal areas of lobular hepatitis, areas of reticulin collapse as well as thickened hepatocellular plates, consistent with ongoing hepatocyte necrosis and regeneration, and moderate bridging fibrosis between portal regions. Because of longstanding untreated or unresponsive chronic HCV until initiation of ASV/DCV, only 36 days prior to the date of the biopsy, and the later resurgence of HCV after discontinuation of the study drug(s), it is not possible to definitively determine the relative contributions of the viral infection vs drug toxicity in the aforementioned findings. With attention given to this case, it would be useful to confirm or modify my interpretation of the biopsy findings with input from a recognized expert in the histopathology of DILI.

- Some cases were marked by transient large increases of serum ALT and AST levels which improved upon interruption of ASV/DCV but which recurred after reinstatement of the study drug treatment. These included cases 28-80942, 28-80687, 28-80692 and 28-80419.
- A number of cases were marked by transient increases of ALT, AST, some associated with concomitant increases of bilirubin in Quad Regimen [(ASV and/or DCV) together with PEG/RBV] randomized patients who had previously been treated with PEG/RBV without evidence of DILI. During the period of transient liver test abnormalities while on study drug, HCV RNA levels remained suppressed, suggesting that a resurgence of HCV viral activity was not the basis of acute liver injuries in these cases. The sponsor's expert adjudicators classified 8 of these cases as 'probable' in their analysis of causal association with study drug(s).

With few or no exceptions, this reviewer agrees with the assessments made by the sponsor's expert panel.

From the clinical trial database, it appears that exposure to ASV/DCV is associated with a range of drug-induced injuries that are idiosyncratic and appear to be immunologically driven. In some cases the liver is the predominant organ of injury. As in the case of the panel's assessment, in my evaluation the identification and analysis of cases of liver injury with regards to severity and causal association with study drug(s) did not hinge on the presence or absence of markers of systemic hypersensitivity, including eosinophilia and pyrexia. It is notable that although eosinophilia was present in Case 7026-2-10122 (the 'sentinel case') most of the other cases of hepatotoxicity were not linked to reported eosinophilia or pyrexia. The consistent presence of diverse but frequent manifestations of classic drug-related hypersensitivity syndromes such as DRESS and SJS/TEN was not observed in the small clinical trial population who developed the adverse events of concern. Notably absent in the liver injury or eosinophilia case reports was the presence of concomitant rash, lymphadenopathy, or meningeal symptoms, etc, all cardinal elements of DRESS.

Whether the ensemble of cases of toxic reactions that have been identified, so far, across all the human clinical trials for ASV, DCV, or both agents in combination should be uniformly classified as diverse manifestations of a common syndrome cannot be determined at this time, given all the constraints of an incomplete understanding of these toxic events by academic experts and limitations in available information surrounding some of the individual cases. Other marketed drugs exemplified by drugs such as lamotrigine and phenytoin are known to cause DRESS. In addition to eosinophilia these reactions have been linked to different manifestations of hypersensitivity (across different organs) in different patients, with involvement of skin, lymph nodes, kidney, liver, meninges, etc. Importantly, exposure to these drugs can also cause non-DRESS idiosyncratic toxic reactions (e.g. SJS/TEN, isolated liver injury, etc.), highlighting inter-individual variation in the phenotypes of organ injuries that can occur after exposure to the same agents. After the pooling of phase II and phase III clinical studies the NDA safety database for ASV/DCV reflects study of these agents in ~2,200 study subjects. From this modest clinical trial exposure alone, the full potential range of organ involvement along with the liver as a target organ and laboratory manifestations of idiosyncratic toxic injuries in US patients that should be expected cannot be gauged and would only be determined in a larger domestic treatment population.

From phase II clinical trial data and case causality assessments by the expert panel (e.g. A1447016), with a finding of a rising frequency of hepatotoxicity with increasing doses of ASV (administered with fixed doses of PEG/RBV), it is likely, although not certain, that ASV was the cause of liver injury in many if not all of the study subjects treated with the DUAL regimen. However, differences of the DILI- inciting components between patients with liver injury or drug-drug potentiation of toxicity cannot be ruled out for patients treated with either the DUAL or QUAD regimens (see below).

2. Please comment on a possible association with demographic factors (i.e., race) and any potential risk mitigation that may be considered for the safety concerns.

Response: *Cases of ‘probable’ hepatotoxicity as adjudicated by the sponsor’s expert panel were present in trials that enrolled patients from different demographic groups across the globe. Although the current database analysis points to an increased susceptibility to eosinophilia and pyrexia in Japanese study subjects compared to other Asian groups, African Americans and Caucasians, there are a number of possible pitfalls to consider that prompt further investigation to address this possibility. First, Trial 7026 (performed in Japan) reported absolute eosinophils as percentages of total WBC counts compared to trials performed elsewhere which directly measured absolute eosinophil counts. With an inevitable lack of precision in the projections of eosinophil counts in Trial 7026 due to inconsistencies in the timing of the WBC sampling it is difficult to compare the eosinophil data across the clinical trials. Moreover, since there was no protocol-based regular monitoring of temperature in these trials and pyrexia was patient-reported with likely cultural and investigator-driven differences at play, ascertainment bias may largely underlie the more frequent reporting of pyrexia in the Japanese trial [Study 7026 (13%)], compared to the non-Japanese global trial [Study 7028 (4%)]. It is important to assess demographic differences among patients with increases of eosinophil counts when pyrexia was not reported. This analysis has been highlighted in Figures 17 and 20 of Dr. Carter’s Clinical Review. Although a more pronounced rise in mean eosinophil counts from baseline to peak (0.45 Standard units; Weeks 2-6) occurred in Study 7026 (Figure 17; standard units baseline: 0.15; peak: 0.45) when compared to Study 7028 (Figure 20; standard units baseline: 0.43; peak: 0.55), the substantial difference in the mean baseline levels of absolute eosinophil counts between these studies remains to be explained. As discussed above, the differences of baseline values may be partially explained by inconsistencies in how the measurements of eosinophil counts were performed. After the recent approval of ASV/DCV in Japan, it may be possible to clarify ambiguities concerning measurements of temperature, blood eosinophils and other parameters relevant to drug hypersensitivity in a future carefully performed study.*

3. Please provide your opinion whether or not pyrexia is a discriminating clinical symptom to potentially identify at-risk patients. If not, then provide comments on how to distinguish at-risk patients.

Response: *Patient-reported pyrexia alone is unlikely to identify patients at risk for hepatotoxicity or be a useful marker for ASV/DCV-induced hypersensitivity (see above). In addition, patients treated with PEG/RBV may get fever as a side effect, thus complicating the interpretation of pyrexia. In the ASV/DSV clinical trials, pyrexia recorded in individual case reports was often short-lasting, thus calling into question consistency in detection and documentation of an increased temperature. According to the displays of data of individual study subjects who were*

identified as having pyrexia and eosinophilia in JReview (Appendix B of Dr. Carter's Review), mild very transient episodes of pyrexia lasting less than one week occurred in 7/16 subjects and longer than one week in 5/16 subjects. Severe pyrexia only occurred in 4/16 subjects, 3 in which the fever lasted less than one week.

More investigation, presumably with sufficient statistical power, would be required to identify reliable predictors of increased risk for ASV/DCV hepatotoxicity or hypersensitivity. Whether and how applied routine periodic liver test monitoring would be a useful tool to reliably mitigate risk of serious outcomes to inform when HCV treatment with ASV/DCV should be modified, interrupted or discontinued at an early phase of reversible DILI requires further study and analysis. Routine testing to detect isolated eosinophilia without other symptoms or signs of drug-related toxicity does not appear to be a useful tool to guide treatment decisions.

4. Please provide your assessment of the subjects who met Hy's Law laboratory criteria and specify subjects that you believe represent drug-induced liver injury and those that do not.

Response: See above. Among the relatively small cohort of study subjects treated with ASV/DSV (~2,200 patients) the presence of 9 Dual Regimen subjects with drug-associated elevations of bilirubin in conjunction with rises of ALT/AST points to a potential risk for serious outcomes in a large post-market treatment population. Although all of the study subjects demonstrated reversibility of liver injury upon either discontinuation of the anti-HCV treatment or through a process of adaptation in the face of continued treatment, what the full range of outlier effects and outcomes would be among all post-marketing patients with idiosyncratic ASV/DSV-induced liver injury and consequent liver dysfunction is an open question. I note that the sponsor's expert panel members felt that the current criteria for a 'Hy's law' case (defined in the 2009 FDA guidance and dubbed by Robert Temple) has not been determined for individuals with pre-existing liver disease. Whether or not 'Hy's law' has been formally established in the context of pre-existing liver disease does not diminish concerns generated in a drug development program of cases of drug-induced acute hepatocellular damage accompanied by worsening liver function (such as reductions in bilirubin clearance). In the body of ASV/DSV cases of concern, HCV RNA levels remained suppressed during the phase of acute organ injury that occurred during exposure to the study drug(s). This finding precludes resurgent Hepatitis C as the reason to explain or predict outcomes of the observed drug-induced acute liver injury events.

It is unlikely that different liver disorders would be uniformly marked by the same levels of risk when a superimposed drug-induced injury occurs. In some, but not all liver diseases, the underlying condition may potentiate severity of the liver injury induced by a DILI-causing drug. Examples of increased severity of DILI due to underlying liver disease include the worsening of hepatotoxicity associated with HAART in the presence of Types B & C viral hepatitis, and with

anti-TB agents in the presence of Type B or Type C hepatitis. With these observations, it is unlikely that Hyman Zimmerman would have argued that the presence of pre-existing liver diseases would diminish the importance of identifying cases of acute hepatocellular DILI with drug-induced rising bilirubin levels or other manifestations of worsening liver function in clinical trials.

5. Do these events affect your risk/benefit assessment for the DUAL and QUAD regimens, and if so, how?

Response: *Yes, regards hepatotoxicity. No, regards eosinophilia. The finding of 5 cases of acute liver injury with elevations of bilirubin that were adjudicated as 'probable' in their causal association with the study drug(s) by the sponsor's expert panel in a relatively small database (~2,200 treated patients) is of concern. If the 1/440 risk were evenly distributed and the cases conform to Hy's Law established with other drugs such as troglitazone, INH, etc., the risk for drug-induced liver failure could be as high as 1/4,400 in a large treatment population, (assuming there is an absence of effective risk mitigation and that 1/10 cases will progress to liver failure). How this hypothetical possibility which remains untested impacts an overall assessment of benefits and risks depends on a number of factors. These include: 1. The presence or absence of alternative 24 week DAA treatments for HCV 1b and DAA + PEG/RBV for HCV 1a and 4 that are superior or non-inferior regards efficacy and have an advantageous safety profile. Of note, there are other HCV 1b regimens under study although not yet approved, such as sofosbuvir/ledipasvir. 2. The presence or absence of hepatotoxicity susceptibility markers that will possess sufficient predictive powers to reliably enable the avoidance of ASV/DCV treatment in all DILI susceptible individuals. Work by the sponsor has embarked on studies to identify individuals through a systematic analysis of HLA allelic polymorphisms in Japanese study subjects with DILI and their clinical trial controls. With the small number of bio-specimens that are available for a case-control analysis of candidate genetic markers this round of investigation will at best be exploratory and may only be relevant for specific demographic groups. At the very least, they will require further confirmatory studies. 3. The overall effectiveness of regular liver test monitoring to uncover early liver injuries in time to change course in the treatment while avoiding risk for serious ASV/DCV-induced liver injury. The utility of serum monitoring would depend on rates of progression of ASV/DCV – induced liver injury relative to the pre-specified time intervals of monitoring, patient and HCP adherence to instructions for regular visits and serum liver testing in conjunction with clinical evaluation, and a periodic comprehensive evaluation of the effectiveness of monitoring practices in different patient care environments across the nation. Although the expert panel has recommended biweekly testing for the first month of treatment, followed by monthly testing, there is no evidence provided by the sponsor that proves overall effectiveness or likely adherence to such an algorithm by patients and healthcare providers.*

6. Do you think there are enough data to show the safety events are related only to asunaprevir, only to daclatasvir or to the asunaprevir/daclatasvir combination?

Response: *Not completely. Although phase II studies point to ASV as the main cause of hepatotoxicity, in nonclinical species DCV has a very low safety margin. A key finding of toxicity in the rat and dog was the presence of drug-induced AST/ALT increases with hepatic lesions at high doses of DCV. In humans, PEG has been associated with elevations of serum aminotransferases, a reaction that is described in the product label. Therefore, how concomitant DCV and PEG exposure would affect or promote ASV associated DILI remains an open question.*

7. Does a potential association with (1) hepatotoxicity and (2) pyrexia/eosinophilia with and without liver involvement portend an increased risk when considering broad availability of these drugs?

Response: *See above. Based on the relatively small number of cases with these events in the clinical trial case series pyrexia/eosinophilia do not appear to be independent predictors or prognosticators of hepatotoxicity events linked to ASV/DCV. Whether eosinophilia in the clinical trial dataset does/does not portend more serious outcomes of hypersensitivity reactions in a smaller subset of patients after broad exposure of these drugs in a post-marketing setting will only be determined after the marketing of these agents, assuming that adequate pharmacovigilance and reporting practices are put into place.*

8. Considering the overall risks and benefits, do these cases present a serious approvability concern? If not, please comment on potential labeling for monitoring, discontinuation criteria and situations where asunaprevir/daclatasvir should not be administered.

Response: *Yes. See above. If these drugs are approved by FDA, the implementation of a number of labeling and risk mitigation tools should be considered.*

(b) (4)



9. What additional data would be helpful to further characterize these events?

Response: *Going forward, it is critically important to obtain adequate information around each new potential case of ASV/DCV associated hepatotoxicity or hypersensitivity and to document the baseline and time course of all pertinent clinical and lab findings. This proactive approach would enable adequate characterization of the phenotype, diagnosis and causal association of the adverse events with these agents. With regards to the finding of cases of drug-associated eosinophilia with/without pyrexia in the absence of other clinical features of systemic hypersensitivity, certain less likely drug-related effects other than hypersensitivity should be ruled out. These include transient drug-induced corticosteroid deficiency (Addison's disease) which can present with eosinophilia with/without pyrexia. Such an effect has been described in peer-reviewed publications regards short-term treatment with ketoconazole, an inhibitor of 21 and 17 hydroxylase activities in adrenal cells. [Although drug-associated Addison's disease can cause eosinophilia it is unlikely to have been the cause of eosinophilic infiltrates in the liver, as identified in the biopsy of case 7026-20-10122 (see above).] To definitively rule out transient drug-induced corticosteroid deficiency (Addison's disease) caused by ASV/DCV consideration may be given to perform a study of serum/urine cortisol and ACTH stimulation with these agents on board. Finally, as discussed previously, the prominence of case 7026-20-10122 points to the importance of seeking an expert histopathologist to review the liver biopsy materials that were obtained.*

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/s/

SOHAIL MOSADDEGH
10/09/2014

MARK I AVIGAN
10/09/2014

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: August 13, 2014

TO: Sohail Mosaddegh, PharmD, Regulatory Health Project Manager
Wendy Carter, D.O., Medical Officer
Division of Antiviral Products

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

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 206843/206844

APPLICANT: Bristol Myers Squibb Co.

DRUG: Daclatasvir

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority review
INDICATION: Treatment of chronic HCV-infection in adults
CONSULTATION REQUEST DATE: April 29, 2014
DIVISION ACTION GOAL DATE: November 28, 2014
PDUFA DATE: November 30, 2014

INSPECTION SUMMARY DUE DATE: October 1, 2014

I. BACKGROUND:

The Applicant conducted three pivotal trials in support of approval of a combination of daclatasvir and asunaprevir regimen because of a need for new compounds that may overcome the disadvantages of current HCV therapy. Both asunaprevir and daclatasvir (ASV and DCV) are designed as NME and are currently being reviewed in support of an application for HCV infected (b)(4) subjects.

The Applicant sponsored three pivotal clinical studies: Protocols A1447026, A1447028, and A1447029 were conducted to support the pending application.

Protocols: A1447026 entitled “A Phase 3 Japanese Study-790052 Plus BMS-650032 Combination Therapy in Chronic Hepatitis C Genotype 1b Infected Subjects Who are Non-Responsive to Interferon Plus Ribavirin and Interferon Based Therapy Ineligible Naïve/Intolerant”,

A1447028 entitled “A Phase 3 Study with Asunaprevir and Daclatasvir (DUAL) for Null or Partial Responders to Peginterferon Alfa and Ribavirin(P/R), Intolerant or Ineligible to P/R Subjects and Treatment-Naïve Subjects with Chronic Hepatitis C genotype 1b Infection”, and

A1447029 entitled “A Phase 3, Open-Label Study with Asunaprevir and Daclatasvir Plus Peginterferon Alfa-2a (Pegasys) and Ribavirin (Copegus) (P/R)(QUAD) for Subjects Who are Null or Partial Responders to Peginterferon Alfa 2a or 2b Plus Ribavirin with Chronic Hepatitis C Genotypes 1 or 4”.

Protocol A1447026

The objective of this study was to assess antiviral activity as determined by the proportion of subjects with SVR 24 for each population.

The secondary objectives of this study were: 1) to assess safety, as measured by the frequency of serious adverse events (SAEs), discontinuation due to AEs, AEs, and abnormalities observed from clinical laboratory tests, and 2) to assess the proportion of subjects with HCV RNA below the lower limit of quantification (LLOQ: 15 IU/mL), Target detected (TD) or target not detected (TND), at weeks: 1, 2, 4, 6, 8,10 and 12; Weeks: 4 and 12; end of treatment (EOT) or post-treatment week 12.

This protocol was an open-label, Phase 3 study of subjects with HCV GT-1b infection. Two parallel populations were enrolled: prior non-responders (null and partial responder) and IFN-based therapy ineligible-naïve/intolerant. A total of 200 subjects (approximately 80 prior non-responders and maximum 120 IFN-based therapy ineligible-naïve/intolerant subjects) will receive 60 mg of DCV QD and 100 mg ASV BID in combination for 24 weeks and then followed for 24 weeks, regardless of HCV RNA status at the EOT. For both populations,

subjects with viral relapse will be followed for up to Week 24 without any antiviral therapy. Thus, maximum study duration was 48 weeks. A total of 24 sites in Japan enrolled subjects on this study.

Protocol A1447028

The objectives of this study were: 1) For prior null or partial responders to P/R cohort: to estimate efficacy, as determined by the proportion of subjects with SVR, defined as HCV RNA < LOQ at post-treatment Week 12, and 2) For treatment naïve cohort: To determine whether the SVR rate in subjects treated with DUAL therapy was similar to the historical SVR rate for TVR on combination with P/R in previously untreated, genotype 1b, HCV patients.

The secondary objectives of this study were: 1) to estimate efficacy, as determined by the proportion of subjects with SVR, defined as HCV RNA < LOQ at post-treatment Week 12 for subjects who are intolerant or ineligible to P/R, and 2) to estimate the rate of anemia and rash.

This protocol was a phase 3 study with asunaprevir (ASV) and daclatasvir (DCV)(DUAL) for Null or Partial responders to P/R, were intolerant or ineligible to P/R, the co-administration of ASV and DCV for 24 weeks for the treatment of chronic HCV genotype 1b infection was safe, tolerable and efficacious where efficacy was based on SVR 12, defined as HCV RNA < LOQ at post-treatment Week 12. It was planned to include a total of 625 HCV genotype 1b-infected subjects. Treatment of subjects received ASV +DCV and approximately 100 genotype 1b subjects received PBO in this study. Subjects meeting pre-specified rescue criteria in the treatment naïve cohort and in the null or partial responder cohort had therapeutic rescue instituted with QUAD regimen (ASV and DCV plus P/R).

Protocol A1447029

The Primary objectives of this study was to assess efficacy, as determined by the proportion of subjects with SVR 12, defined as HCV RNA < LOQ at post-treatment Week 12.

This was a phase 3, open- label study with ASV and DCV plus Peginterferon alfa 2a and ribavirin (P/R (QUAD) in subjects who are null/partial responders to P/R, co-administration with P/R for 24 weeks for the treatment of chronic HCV genotype 1 infection is safe, tolerable and efficacious where efficacy was based on SVR 12, defined as HCV RNA < LOQ at post-treatment Week 12. Approximately 390 HCV genotype 1 and 4 subjects were treated in this open-label study. Enrollment of Genotype 4 subjects was capped at 10%. The study enrolled a minimum of 40% of each HCV subtype: 1a and non-1a (subtype was capped at 60%).

The review division requested inspection of six clinical investigators for the pivotal studies noted above 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 submitted to these original NDAs (three trials) for a 2-NME drug regimen, and 2) the need to determine if sites conducted the trial ethically and were in compliance with GCP and local regulations. It is for these reasons that it is critical that international sites be included in the inspection. (b) (4)

(b) (4) It would be desirable to include foreign sites in the OSI inspections to verify the quality of the conduct of the studies.

II. RESULTS (by protocol/site):

Name of CI, Location, and Site #	Protocol and # of subjects randomized	Inspection Dates	Final Classification
Joji Toyota, M.D. 8-5 Higashikita 3jyo Japan Site #001	Protocol A1147026 Number of subjects: 25	7/28-31/2014	Pending (preliminary classification NAI)
Yoshiiku Kawakami, M.D. 1-2-3 Kasumi, Minmi ku Hiroshim 7348551 Japan Site# 0018	Protocol A1447026 Number of subjects: 21	August 4-7/ 2014	Pending (preliminary classification NAI)
Ira Jacobson, M.D 1305 York Ave,4th floor New York, NY 10021 Site #0015	Protocol A1447028 Number of subjects: 18	July 23- 29/2014	Pending (preliminary classification NAI)
William Towner, M.D. 1505 North Edgemont St. Los Angeles, CA 90027 Site #0020	Protocol A1447028 Number of subjects: 13	July 30- August 8/2014	Pending (preliminary classification NAI)
Velmir Luketic, M.D 1201 Broad Rock Blv Richmond, VA 23249 Site #015	Protocol A1447029 Number of subjects: 9	June 2- 3/2014	NAI
Ziad Younes, M.D. 1310 Wolf Park Dr. Germantown, TN38138 Site #0039	Protocol A1447029 Number of Subjects 10	June 9- 10/2014	NAI

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; the Establishment Inspectional Report (EIR) has not been received from the field and complete

review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

1. Joji Toyota, M.D.
Hokkaido 060033, Japan

- a. What Was Inspected:** This inspection was performed as a data audit for NDAs 206-843/206844 Study Protocol A1447026. At this site, a total of 26 subjects were screened, one subject was reported as a screen failure, 25 subjects were randomized into the study, and 23 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for 12 subjects were reviewed and compared to data listings. The review included drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for all subjects were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings. No deficiencies were noted.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Toyota. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.
- c. Assessment of Data Integrity:** The data generated by this site are considered reliable and appear acceptable in support of the pending applications.

2. Yoshiku Kawakami, M.D.
Hiroshim, Japan

- a. What Was Inspected:** This inspection was performed as a data audit for NDA 206843/206844 and inspected Study Protocol 1447026. At this site, a total of 24 subjects were screened, three subjects were reported as screen failures, 21 subjects were randomized into the study, and 21 subjects completed the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for 11 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/endpoint values to the data listings for primary efficacy endpoints, and no discrepancies were noted.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Kawakami. The medical records reviewed were found to be in order and the data verifiable. However, our investigator noted that there was no documentation to show that the sub-investigator received adequate training for protocol changes and no contact information between the Head of the Hospital/IRB and the sponsor in regards to informed consent document and adverse events reporting. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.
- c. Assessment of Data Integrity:** Although minor deviations noted at this site, the findings appear to be isolated and unlikely to impact the outcome of the study. The data in support of the clinical efficacy and safety at Dr. Kawakami's site are considered reliable and may be used in support of the pending applications

3. Ira Jacobson, M.D.
New York, NY10021

- a. What Was Inspected:** This inspection was performed as a data audit for NDA 206843/206844 and inspected Study Protocol 1447028. At this site, a total of 25 subjects were screened, 7 subjects were reported as screen failures, 18 subjects were randomized into the study, and 16 subjects completed treatment. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for 18 subjects were reviewed for primary/secondary endpoints, informed consent including drug accountability records, vital signs, IRB records, prior and current medications, and inclusion/exclusion criteria. Source documents for all subjects were compared to data listings for primary efficacy endpoints and adverse events listing. There was no evidence of under-reporting of adverse events at this site. Few concomitant medications and one adverse event were not recorded into the e-CRFs; were entered during the inspection.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Jacobson. However, minor deficiencies were discussed with the clinical investigator and the records were corrected accordingly.

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

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

4. William Towner, M.D.
Los Angeles, CA 90027

- a. What Was Inspected:** This inspection was performed as a data audit for NDA 206-6219, Study Protocol A1447028. At this site, a total of 15 subjects were screened, two subjects were reported as screen failures, 13 subjects were randomized into the study, and 13 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment. However, one subject signed informed consent three days after the liver biopsy; explanation given the liver biopsy was done as standard of care.

The medical records/source data for 15 subjects were reviewed. The review included randomization, adverse events, and concomitant medication for all 15 subjects. The records for six subjects were compared source document 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, sponsor correspondence, and adverse events.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Towner. The medical records were found to be in order, organized, and the data verifiable; however, the medical records regarding the use concomitant medications and hyperkeratosis were not reported in the case report forms for two subjects. There were no deaths and no evidence of under-reporting of adverse events (exception one subject with hyperkeratosis). There were no known limitations to the inspection.
- c. Assessment of Data Integrity:** With the exception of the missing or incomplete reporting of concomitant medications and adverse event for two subjects, the data generated in support of the clinical efficacy and safety at Dr. Towner's site are considered reliable and may be used in support of the pending application.

5. VelimirA. Luketic, M.D.
Richmond, VA 23249

- a. What was Inspected:** This inspection was performed as a data audit for NDAs 206843/206844 and inspected Study A1447029. At this site, a total of 12 subjects were screened, 3 subjects were reported as screen failures, 9 subjects were randomized into the study, and all nine subjects completed the study. Review of the Informed Consent Documents for all subjects verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for all subjects enrolled were reviewed. The review included drug accountability records, vital signs, IRB files, inclusion/exclusion criteria, study procedures, financial disclosure, monitoring procedures, and use of concomitant medications. Source documents were compared to CRFs and data listings, to include primary efficacy endpoints and adverse events. No deficiencies were noted.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Luketic. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.
- c. Assessment of Data Integrity:** The data generated in support of the clinical efficacy and safety at Dr. Luketic's site are reliable and may be used in support of the pending applications.

**6. Ziad Younes, M.D.
Germantown, TN 38138**

- a. What was Inspected:** This inspection was performed as a data audit for NDA 206843/206844 and inspected Study 1447029. At this site, a total of 13 subjects were screened, 3 subjects were reported as screen failures, 10 subjects were randomized into the study, one subject withdrew consent, and nine subjects completed the study. Review of the Informed Consent Documents for all subjects verified that all subjects signed informed consent forms prior to enrollment.

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

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Younes. The medical records reviewed were found adequate and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.
- c. Assessment of Data Integrity:** Overall, the data generated at this site in support of the clinical efficacy and safety are considered reliable and may be used in support of the pending applications.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Six clinical investigator sites were inspected in support of this application. The inspection of the six clinical investigators listed above revealed no regulatory violations. The pending classification for Drs. Toyota, Kawakami, Jacobson, and Towner sites are No Action Indicated (NAI) and the final classification for Drs. Luketic and Younes sites are No Action Indicated (NAI). For the pending classifications, a summary addendum will be generated if conclusions change upon receipt and review of the EIRs. Overall, the data submitted from these six sites are considered acceptable and may be used in support of the pending application.

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

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

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/s/

ANTOINE N EL HAGE
08/15/2014

KASSA AYALEW
08/15/2014

LABEL AND LABELING REVIEW

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

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

Date of This Review: June 29, 2014
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: NDA 206843
Product Name and Strength: Daklinza (daclatasvir) Tablets, 30 mg and 60 mg
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Bristol-Myers Squibb
Submission Date: March 31, 2014
OSE RCM #: 2014-672
DMEPA Primary Reviewer: Mónica Calderón, PharmD, BCPS
DMEPA Associate Director: Irene Chan, PharmD, BCPS

1 REASON FOR REVIEW

Bristol Myers Squibb (BMS) is developing Daklinza for the treatment of Hepatitis C under NDA 206843. Thus, the Division of Antiviral Products (DAVP) requested that DMEPA evaluate the Applicant's proposed container label and full prescribing information (FPI) for 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
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C (N/A)
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing multiple strength (30 mg and 60 mg), single ingredient tablets. The daily dose is 60 mg; however, a 30 mg tablet is being proposed to be utilized for dose reduction during concomitant therapy with a strong cytochrome P450 enzyme 3A4 inhibitor. The product will be packaged in 28-count bottles, which is supported by the dosage and administration of this product. DMEPA performed a risk assessment of the proposed container label and FPI and notes the strengths are clearly differentiated and the Dosage and Administration section is clearly stated, respectively. The FPI states (b) (4); however, the "How should I take Daklinza" section of the Patient Package Insert does not make any mention regarding (b) (4) tablets. This information should be added for consistency. We provide recommendations in (b) (4) to address this.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes the Applicant's proposed Dosage and Administration section of the FPI is acceptable. However, we recommend a statement be added in the Patient Package Insert indicating that patients (b) (4) for consistency with the insert labeling and

to minimize the risk for wrong technique errors. Additionally, the Applicant should replace the “<TRADE-NAME-DCV>” statement with the conditionally acceptable proprietary name, Daklinza, throughout the labels and labeling. We advise the recommendations below are implemented prior to approval of this application.

4.1 RECOMMENDATIONS FOR THE APPLICANT

A. All Labels

Replace the “<TRADE-NAME-DCV>” statement with the conditionally acceptable proprietary name, Daklinza, throughout the labels and labeling.

4.2 RECOMMENDATIONS FOR THE DIVISION

A. Patient Package Insert

Add the following bulleted statement [REDACTED] (b) (4) [REDACTED] to the “How do I take Daklinza?” section to minimize wrong technique errors.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Daklinza that Bristol-Myers Squibb submitted on April 29, 2014.

Table 2. Relevant Product Information for Daklinza	
Active Ingredient	daclatasvir
Indication	In combination with other agents for the treatment of chronic hepatitis C infection.
Route of Administration	Oral
Dosage Form	Tablet
Strength	30 mg and 60 mg
Dose and Frequency	60 mg once daily
How Supplied	Bottles of 28 tablets
Storage	25°C (77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F)

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

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/s/

MONICA M CALDERON
07/29/2014

IRENE Z CHAN
07/29/2014

**Selected Requirements of Prescribing Information
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: 206843

Application Type: New NDA

Name of Drug/Dosage Form: daclatasvir, 30mg and 60 mg tablets.

Applicant: Bristol-Myers Squibb Company

Receipt Date: March 31, 2014 (label reviewed was submitted 04/29/2014)

Goal Date: November 30, 2014 (goal date November 28, 2014)

1. Regulatory History and Applicant's Main Proposals

The new molecular entity (NME) NDA was submitted to provide data to support the use of daclatasvir (b)(4) for the treatment of (b)(4), chronic hepatitis C infection (b)(4)

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by June 15, 2014. 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: *some of the lines appear dashed, BMS will be asked to correct*

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *not enough white space before each heading*

- 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

Selected Requirements of Prescribing Information

• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

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

Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

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:

Selected Requirements of Prescribing Information

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *Web link not in italics*

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:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

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:

- 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)*]”.

Comment: 12.4 reference should be *Microbiology*

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 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

Selected Requirements of Prescribing Information

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/

SOHAIL MOSADDEGH
05/28/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 206843 BLA#	NDA Supplement #:S- 000 BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Daclatasvir Dosage Form: oral tablet Strengths: 30 & 60 mg		
Applicant: Bristol-Myers Squibb Company Agent for Applicant (if applicable):		
Date of Application: March 31, 2014 Date of Receipt: March 31, 2014 Date clock started after UN:		
PDUFA Goal Date: 11/30/2014	Action Goal Date (if different): 11/28/2014	
Filing Date: 05/30/2014	Date of Filing Meeting: 05/09/2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Treatment of chronic hepatitis C infection.		
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: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</i>		
Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<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)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input checked="" 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 checked="" 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 [21 CFR 314.55(b)/21 CFR 601.27(b)] <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)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 79599, 100932, 101977				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA 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 proprietary, 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 to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <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: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><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></p>	<p>Payment for this application:</p> <p><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</p>																			
<p><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></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>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)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>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)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<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 type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</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"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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), 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)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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	<input checked="" type="checkbox"/>	<input type="checkbox"/>		03/31/14 financial

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

included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <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>				discourse doc
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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, <u>both</u> 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 RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Agreed to PSP submitted
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	SDN 3, 04/04/2014
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<u>Prescription Labeling</u>	<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)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) 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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	OSI – 05/05/14 Methods Validation 04/25/14 by CMC
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 07/09/2011, 02/27/2013(daclatasvir IND 79599) CMC 11/06/2013 (asunaprevir IND (b)(4)) <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 07/09/2011, 02/27/2013(daclatasvir IND 79599) <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): 02/23/2011, 02/25/2011 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 05/09/2014

BLA/NDA/Supp #: 206843 SDN 2

PROPRIETARY NAME: TBD

ESTABLISHED/PROPER NAME: daclatasvir

DOSAGE FORM/STRENGTH: oral tablet

APPLICANT: BRISTOL-MYERS SQUIBB CO

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of Hepatitis C virus

BACKGROUND: This new molecular entity (NME) NDA was submitted to support the use of this product for the treatment of chronic hepatitis C virus infection.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sohail Mosaddegh	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Kim Struble		Y
Clinical	Reviewer:	Wendy Carter	Y
	TL:	Kim Struble	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:	Lalji Mishra	Y
	TL:	Julian O'Rear	Y

Clinical Pharmacology	Reviewer:	Stanley Au	Y
	TL:	Shirley Seo	Y
Biostatistics	Reviewer:	Wen Zeng	Y
	TL:	Fraser Smith	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Peyton Myers	Y
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Chunchun Zhang (DS/DP)	Y
	TL:	Steve Miller	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Krishna Ghosh	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Mónica Calderón,	Y
	TL:	Irene Chan	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Patient labeling	Karen Dowdy (Barbara Fuller TL)		Y/N
OPDP labeling reviewer (marketing)	Kemi Asante		Y
Biopharmaceutics	Sandra Suarez (Angelica Dorantes TL)		Y/N
Pharmacometrics	Fang Li (Jeff Florian TL)		Y/Y
Other attendees			

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

If no, explain:	
<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: <i>the application did not raise significant safety or efficacy issues</i>
<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
<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>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>	<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 pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIostatistics</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<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
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<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
PRODUCT QUALITY (CMC) Comments:	<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
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <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? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <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><u>CMC Labeling Review</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 checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>CMC</p>
<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	
<p>Signatory Authority: Office Director, Ed Cox</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 06/26/2014</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<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"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

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

/s/

SOHAIL MOSADDEGH
05/28/2014

KAREN D WINESTOCK
05/28/2014