

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206843Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 206843

SUPPL #

HFD #

Trade Name Daklinza

Generic Name daclatasvir

Applicant Name Bristol-Myers Squibb Co

Approval Date, If Known 07/24/15

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

5 years

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

interest provided substantial support for the study?

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

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

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

YES NO

If yes, explain:

Name of person completing form: Sohail Mosaddegh
Title: regulatory Project Manager
Date: 07/22/15

Name of Office/Division Director signing form: Debra Birnkrant
Title: Director, Division of Antiviral Products

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/s/

SOHAIL MOSADDEGH
07/24/2015

DEBRA B BIRNKRANT
07/24/2015

From: Mosaddegh, Sohail
To: "[Frost, Marianne](#)"
Subject: RE: PMR for BMS
Date: Friday, July 10, 2015 10:18:00 AM

The intention of PMR#3 is to provide information on the persistence of resistance-associated substitutions through 1 year or longer. We understand that the -046 protocol may follow patients longer than this, but PMR#3 can be addressed by submitting an interim report from HCV GT3 infected subjects once a sufficient number of subjects have been followed for a minimum of 1 year. Because daclatasvir resistance in HCV GT3 appears to be driven primarily by a single substitution (NS5A Y93H), analyses from a relatively small number of subjects (at least ~5 subjects with treatment-emergent Y93H) through 1 year of follow-up should be sufficient for the purposes of addressing the PMR. Based on our understanding of the ALLY-3, ALLY-3+ and PMR#1 timelines, it should be reasonable to submit these results no later than mid- to late 2018?

*Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
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Silver Spring, MD 20993-0002
Phone: (301) 796-4876
Fax: (301) 796-9883
Email: Sohail.Mosaddegh@FDA.HHS.GOV*

From: Frost, Marianne [<mailto:marianne.frost@bms.com>]
Sent: Thursday, July 09, 2015 4:17 PM
To: Mosaddegh, Sohail
Subject: RE: PMR for BMS

Hi Sohail,

There are not many GT-3 failures in the AI444046 study currently, so we are thinking that patients from ALLY-3+ and PMR#1 will need to roll into 046 for a more robust assessment. We project submission of the report for PMR#3 to be 1 year from 046 last patient last visit (sNDA submission assumed in the event that labeling changes are warranted). Please let me know if you need further information.

Regards,

Marianne

Study Milestones	Date	Assumptions
PMR1 Study Completion	(b) (4)	(b) (4)
046 LPLV		
046 Final DBL		
046 CSR		

From: Mosaddegh, Sohail [<mailto:Sohail.Mosaddegh@fda.hhs.gov>]
Sent: Thursday, July 09, 2015 3:27 PM
To: Frost, Marianne
Subject: RE: PMR for BMS

Can you comment on PMR3 dates, if you have this already ongoing to look at persistence for at least one year, then why does it take until 2022 to get a final report??

PMR3:

Characterize the long-term (≥ 1 year) persistence of treatment-emergent, daclatasvir resistance-associated substitutions in HCV genotype 3 infected subjects ^{(b) (4)}
PMR/PMC Description:

PMR/PMC Schedule Milestones:	Final Protocol Submission:	Submitted to IND 79,599 11/23/2011, Seq #0327
	Study/Trial Completion:	02/16/2021
	Final Report Submission:	02/16/2022

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Email: Sohail.Mosaddegh@FDA.HHS.GOV

From: Frost, Marianne [<mailto:marianne.frost@bms.com>]
Sent: Thursday, July 09, 2015 2:53 PM
To: Mosaddegh, Sohail
Subject: RE: PMR for BMS

Hi Sohail,
Please find attached dates for the PMRs listed below. Please let me know if you would like the assumptions around any of the dates provided.
Kind regards,
Marianne

From: Mosaddegh, Sohail [<mailto:Sohail.Mosaddegh@fda.hhs.gov>]
Sent: Tuesday, July 07, 2015 9:19 AM
To: Frost, Marianne
Subject: PMR for BMS
Importance: High

Hello:
here are the three PMR's for DCV, please complete/verify the dates below:

PMR1

PMR/PMC Description: Conduct a trial to determine if a longer duration of treatment or addition of ribavirin improves the efficacy (i.e., sustained virologic response rate) of daclatasvir plus sofosbuvir for hepatitis C virus genotype 3 infected subjects with cirrhosis.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	02/xx/2016
	Study/Trial Completion:	05/xx/2017
	Final Report Submission:	11/xx/2017
Other:	MM/DD/YYYY	

PMR2

NDA/BLA
206843
Product Daclatasvir

Name:

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/XX/2019
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	12/XX/2023
Other:	MM/DD/YYYY	

PMR3:

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:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
Other:	MM/DD/YYYY	

Please email your response by COB 07/09/2015. Thank you

*Sohail Mosaddegh, Pharm.D.
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/s/

SOHAIL MOSADDEGH
07/10/2015

Electronic Mail Correspondence – Information Request/Advice



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

DATE: July 6, 2015

TO: **Marianne Frost**
Director Global Regulatory, Safety & Biometrics
Bristol- Myers Squibb

SPONSOR: **Bristol- Myers Squibb**

SUBJECT: **NDA 206843**

We are requesting your assistance in populating the attached tables for your New Molecular Entity, daclatasvir, currently under review in the Division.

As part of FDASIA 2012, information on demographic subgroups in clinical trials for newly-approved drugs and biologics will be made publicly available on www.fda.gov/drugtrialssnapshot.

The website will include information on study design, results of efficacy and safety studies, and whether there were any differences in efficacy and side effects within sex, race, and age subgroups. The website is not intended to replace or replicate the package insert (PI), which is intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language
- “MORE INFORMATION” sections that provide more technical, data-heavy information
- Information that focuses on subgroup data and analyses
- Links to the PI for the product and to the FDA reviews at Drugs@FDA

Thank you in advance for your cooperation and please respond to this request by July 16, 2015. Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

Table 7.5.3-a. Subgroup Analysis of AEs, Phase 3 population--please provide this table

Subgroup	Treatment 1 (N=50) n(%)	
	x (%)**	Total, n
Any TEAEs*	40 (80.0)	50
Sex		
Male	25 (83.3)	30
Female	15 (75.0)	20
Age Group		
<17 years		
17 - 64 years		
>=65 years		
Race		
White		
Black or African American		
Asian		
American Indian or Alaska Native		
Native Hawaiian or Other Pacific Islander		
Other		
Ethnicity		
Hispanic or Latino		
Not Hispanic or Latino		
Source:		

*Designate per review, other options are SAEs or AEs of special interest (for instance, a

** Percentages are calculated based on the number of subjects in the subgroup per arm

***Designated per review, other options are Risk Difference, Hazard Ratios, etc

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Table 6.1.2-a. Baseline Demographics, Single Trial

Demographic Parameters	Treatment Group(s)		Total (N=200) n (%)
	Treatment Group 1 (N=50) n (%)*	Treatment Group 2 (N=50) n (%)*	
Sex			
Male			
Female			
Age			
Mean years (SD)			
Median (years)			
Min, Max (years)			
Age Group			
<17 years			
17 - 64 years			
>=65 years			
Race			
White			
Black or African American			
Asian			
American Indian or Alaska Native			
Native Hawaiian or Other Pacific Islander			
Other			
Ethnicity			
Hispanic or Latino			
Not Hispanic or Latino			
Region			
United States			
Rest of the World			
Canada			
South America			
Europe			
Asia			
Africa			

Source:

* Percentages are calculated based on the total number of subjects in the respective arm. For example, percentag

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Percentage of males in Treatment Group 1 = 25/50

Table 6.1.7 Subgroup Analysis of Primary Endpoint, Pivotal Efficacy Trials

Subgroup	Treatment 1 (N=50)	
	x (%)*	Total, n
Overall Response/All patients	35 (70.0)	50
Sex		
Male	20 (66.7)	30
Female	15 (75.0)	20
Age Group		
<17 years		
17 - 64 years		
>=65 years		
Race		
White		
Black or African American		
Asian		
American Indian or Alaska Native		
Native Hawaiian or Other Pacific Islander		
Other		
Ethnicity		
Hispanic or Latino		
Not Hispanic or Latino		
Source:		

*Percentages are calculated based on the number of subjects in the subgroup per arm. For

**Designated per review, other options are Risk Difference, Relative Risk, etc

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/s/

SOHAIL MOSADDEGH
07/06/2015

From: Mosaddegh, Sohail
To: "[Frost, Marianne](#)"
Subject: RE: Draft PMR NDA 206843
Date: Friday, June 12, 2015 1:27:00 PM

Hello:

DAVP has considered your request regarding the language you proposed for the PMR. However, because of the inherent bias of observational data, we do not agree that observational data can substitute for a clinical trial. We do agree that observational data can provide important supportive data and encourage you to conduct a trial **and** provide observational study data to support your proposed optimal regimen for hepatitis C genotype 3 infected subjects with cirrhosis.

With respect to the proposed PMR Schedule Milestones, we request that the Final Protocol Submission be completed before the end of December, 2015. Please adjust your timelines accordingly.

Thank you

*Sohail Mosaddegh, Pharm.D.
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From: Frost, Marianne [<mailto:marianne.frost@bms.com>]
Sent: Friday, May 29, 2015 10:44 AM
To: Mosaddegh, Sohail
Subject: RE: Draft PMR NDA 206843

Hi Sohail,

Attached is a BMS response with proposed dates included. Please let me know if you would like to discuss or need further information.

Kind regards,
Marianne

From: Mosaddegh, Sohail [<mailto:Sohail.Mosaddegh@fda.hhs.gov>]
Sent: Thursday, May 21, 2015 10:49 AM
To: Frost, Marianne
Subject: Draft PMR NDA 206843
Importance: High

Hello:

please see the draft PMR and provide the needed dates:

NDA/BLA # 206843:
Product Name: Daclatasvir

PMR/PMC Description:

Conduct a trial to determine if a longer duration of treatment or addition of ribavirin (b) (4) of daclatasvir plus sofosbuvir for hepatitis C virus genotype 3 infected subjects with cirrhosis.

PMR/PMC Schedule
Milestones:

Final Protocol Submission:

MM/DD/YYYY

Study/Trial Completion:

MM/DD/YYYY

Final Report Submission:

MM/DD/YYYY

Other: _____

MM/DD/YYYY

Sohail Mosaddegh, Pharm.D.

Lieutenant Commander, USPHS

Regulatory Health Project Manager

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/s/

SOHAIL MOSADDEGH
06/12/2015

**PeRC Meeting Minutes
June 3, 2015**

PeRC Members Attending:

Lynne Yao

Linda Lewis (Did not review Daklinza, Non-Responsive)

Gettie Audain

Gregory Reaman

Hari Cheryl Sachs

Wiley Chambers

Lily Mulugeta

Kevin Krudys

Thomas Smith

Peter Stark

Gilbert Burckart

Robert 'Skip' Nelson

Dianne Murphy

Andrew Mulbert

Olivia Ziolkowski

Agenda

IND	Non-Responsive		
NDA	206843	Daklinza (daclatasvir) Partial Waiver/Deferral/Plan	In combination with sofosbuvir in treatment-naïve and treatment-experienced adults with HCV genotype 3 infection and compensated liver disease including cirrhosis
NDA	Non-Responsive		
NDA			
IND			
PIND			
IND			
IND			
IND			

Non-Responsive

Daklinza (daclatasvir) Partial Waiver/Deferral/Plan

- NDA 206843 seeks marketing approval for Daklinza (daclatasvir) in combination with sofosbuvir for treatment-naïve and treatment-experienced adults with HCV genotype 3 infection and compensated liver disease including cirrhosis.
- The application triggers PREA as directed to a new active ingredient.
- The PDUFA goal date is August 13, 2015.
- The division clarified that the agreed iPSP included a plan to study this product in combination with asenapavir. However, the sponsor voluntarily withdrew asenapavir from the market, and intends to study this drug with another DAA, sofosbuvir. However, sofosbuvir is owned by a different company, Gilead. Gilead is currently completing PREA studies for sofosbuvir in pediatric patients and is not expected to complete these studies until 2019. Additionally, there are no other DAA's that have been approved that can be studied with daclatasvir. Furthermore, daclatasvir cannot be used as a single agent to treat HCV. Therefore, PREA studies for daclatasvir cannot be initiated until sofosbuvir has been approved in pediatric patients.
- The division acknowledged that the agreed iPSP is no longer a valid (see comment above). However, the division is able to use the iPSP to develop an appropriate pediatric plan for this product. The PeRC agreed, and recommended that formal amendments to the agreed iPSP would not be necessary at this point even

though the agreed iPSP is no longer valid because PREA PMRs will be established for the product.

- *PeRC Recommendations:*
 - The PeRC agreed with the plan for w waivers and deferrals as agreed upon in the iPSP: waiver of PREA studies for pediatric patients less than 3 years of age because studies would be impossible or highly impracticable; deferral of studies in pediatric patients 3 to less than 18 years of age because adult studies have been completed and the product is ready for approval.

(b) (4)

Pages has been withheld in full as Non-Responsive

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/s/

GEORGE E GREELEY
06/18/2015

From: Mosaddegh, Sohail
To: marianne.frost@bms.com
Subject: BMS NDA 206843 -cases for DDI amiodarone
Date: Tuesday, June 02, 2015 11:56:00 AM

Hello:

1. Please clarify if case BMS-2015-003146 (61 year old female with cardio-respiratory arrest after single dose DCV/SOF with background of amiodarone, report via BMS sales rep in France) which was submitted to IND 121165 was submitted to NDA 206843. This case does not appear in the EMA Question and Response Report that provides the cases of cardiac arrhythmia associated with DCV/SOF and concomitant amiodarone use. Please submit this case to the NDA or indicate where it is available. This case would increase the total to 6 reports of cardiac arrhythmia with severe bradycardia/arrest in patients receiving amiodarone with combination therapy of DCV/SOF.

2. Please submit case BMS-2015-015803 to the NDA (Submitted to IND 121165; 35 year old male with 2nd degree AV block). Additionally, within the report of this case there is mention of online posting about the potential for cardiac arrhythmia (MCN#BMS-2015-014240) which was described by the facilitator of the BMS HCV Connection community and within this is a comment made by the BMS Medical Evaluation stating the following: "A male patient was reported to have developed sinus bradyarrhythmia and atrioventricular conduction disorder while on concomitant amiodarone and daclatasvir and asunaprevir treatment." The EMA Question and Response report states that there are no cardiac arrhythmia reports for DCV in combination other HCV antiviral drugs such as ASV, in patients also receiving amiodarone. Please clarify and submit all cases of cardiac arrhythmia associated with use of DCV and amiodarone without concomitant use of SOF.

Thank you

*Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
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/s/

SOHAIL MOSADDEGH
06/02/2015

From: Mosaddegh, Sohail
To: marianne.frost@bms.com
Subject: Draft PMR NDA 206843
Date: Thursday, May 21, 2015 10:49:00 AM
Importance: High

Hello:

please see the draft PMR and provide the needed dates:

NDA/BLA # 206843:

Product Name: Daclatasvir

PMR/PMC Description:

Conduct a trial to determine if a longer duration of treatment or addition of ribavirin ^{(b)(4)} (i.e., sustained virologic response rate) of daclatasvir plus sofosbuvir for hepatitis C virus genotype 3 infected subjects with cirrhosis.

PMR/PMC Schedule
Milestones:

Final Protocol Submission:

MM/DD/YYYY

Study/Trial Completion:

MM/DD/YYYY

Final Report Submission:

MM/DD/YYYY

Other: _____

MM/DD/YYYY

Sohail Mosaddegh, Pharm.D.

Lieutenant Commander, USPHS

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/s/

SOHAIL MOSADDEGH
05/21/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: May 18, 2015

Application Number: 206843

Product Name: daclatasvir (DAKLINZA)

Sponsor/Applicant Name: Bristol-Myers Squibb

Subject: Daclatasvir review status update

FDA Participants

- John Farley, MD, Deputy Director, Office of Antimicrobial Products
- Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
- Jeffrey Murray, MD, MPH, Deputy Director (DAVP)
- Fang Li, PhD, Pharmacometrics Reviewer, Office of Clinical Pharmacology
- Felicia Duffy, RN, BSN, MEd, Division of Risk Management, Office of Surveillance and Epidemiology
- Fraser Smith, PhD, Statistician, Division of Biometric
- Jeffry Florian, PhD, Pharmacometrics Team Lead, OCP, Division of Pharmacometrics
- Julian O'Rear, PhD, Virology Team Lead, DAVP
- Karen Winestock, Chief, Project Management Staff, DAVP
- Kim Struble, PharmD, Medical Team Lead, DAVP
- Lalji Mishra, PhD, Virology Reviewer, DAVP
- Patrick Harrington, PhD, Virology Reviewer, DAVP
- Peter Verma, PhD, Pharmacologist, DAVP
- Shirley K Seo, PhD, Clinical Pharmacology Team Lead, Office of Clinical Pharmacology
- Sohail Mosaddegh, PharmD, Regulatory Project Manager, DAVP
- Stanley Au, PharmD, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology
- Wen Zeng, PhD, Statistician, Division of Biometric
- Wendy Carter, DO, Medical Officer, DAVP

Applicant Participants

- Philip Yin, MD PhD, HCV DAA Clinical Lead, Global Clinical Research (GCR) - Virology
- Stephanie Noviello, MD, MPH, Group Director, GCR - Virology
- Eugene Scott Swenson, MD, Associate Director, GCR - Virology
- Beatrice Anduze-Faris, MD, Group Director, HCV Lead, US Medical
- Melissa Harris, PharmD, Worldwide Medical Lead, HCV
- Frank LaCreta, PhD, Executive Director, Clinical Pharmacology and Pharmacometrics
- Timothy Eley, PhD, Director, Clinical Pharmacology and Pharmacometrics
- Tushar Garimella, PhD, Director, Clinical Pharmacology and Pharmacometrics

- Thomas Kelleher, PhD, Group Director, Global Regulatory Sciences & Biostatistics (GRSB) - Virology
- Navdeep Boparai, MS, Associate Director, GRSB - Virology
- Tao Duan, PhD, Associate Director, GRSB - Virology
- Fiona McPhee, PhD, Senior Principal Scientist, Biology Infectious Disease
- Wenying Li, PhD, Principal Scientist, Biotransformation
- Daniel Seekins, MD, Group Medical Director, Medical Safety Assessment Lead, Virology
- Carrie Kefalas, MD, MPH, Medical Director, Global Safety Surveillance and Epidemiology
- Ambarish Singh, PhD, Director, GRSB - CMC
- Margo Heath-Chiozzi, MD, Head, Specialty Regulatory Strategy, GRSB
- Joan Fung-Tomc, PhD, Executive Director, GRSB, Virology
- Marianne Frost, MA, Director, GRSB - U.S.
- Rebecca Skinner, Director, Labeling Content Development
- Jonathan Nguyen Diep, PharmD, Manager, GRSB

BACKGROUND:

A teleconference was held between DAVP and BMS on May 18, 2015. The purpose of the meeting was for DAVP to provide a status update on the DCV resubmission and discuss review issues identified.

DISCUSSION:

Substantial Review Issues:

FDA stated:

- As stated in previous discussions prior to the NDA resubmission, the main review issue was whether sufficient data from ALLY-3 are available to recommend dosing for patients with cirrhosis. At this time we are uncertain whether the indication will be limited to non-cirrhotics. We do not agree with your proposal to state, (b) (4) " These regimens were not evaluated in ALLY-3. The data from the ATU are limited and not conclusive to determine the appropriate dosage recommendation, whether it is the addition of RBV and/or extending the duration. Additionally, the data from the ATU are not from an adequate and well-controlled trial which limits the ability to include the data in Section 14 of the prescribing information to support a dosing recommendation.
- At this time, a PMR is recommended to conduct a trial to determine which treatment strategy (b) (4) would support a dosing recommendation that improves SVR rates and decreases treatment failure. We consider treatment failure and development of resistance a safety issue. After the PMR is established we can discuss the amount of information from ALLY-3 to be displayed in labeling with regards to patients with cirrhosis during this NDA review cycle.

- Also, as you are aware the efficacy of daclatasvir plus sofosbuvir was reduced in HCV genotype 3 infected subjects who had the NS5A Y93H polymorphism. We will recommend this information is described under limitations of use with supporting data included in Sections 12.4 (Microbiology) and 14 (Clinical Studies).

Summary:

- The FDA is uncertain about how to manage cirrhotic patients in the indication section.
 - The Division does not agree with the BMS proposed recommendation in the dosage and administration section to add [REDACTED] (b) (4)
 - The Division acknowledged the data [REDACTED] (b) (4) not conclusive or adequate to support the proposed labeling.
 - As FDA considers treatment failures and development of resistance to be safety issues, a post marketing requirement (PMR) is needed in order to determine the appropriate dosing recommendation for cirrhotic patients and minimize treatment failure.
 - The Division stated that once a PMR is agreed upon we can discuss a recommendation for cirrhotics in labeling.
 - FDA stated that they are taking into consideration the existing approved regimen for GT3 cirrhotics and noted that, although the overall results are similar with ALLY-3, there are differences observed whether patients were treatment naive or treatment experienced versus current standard of care.
 - BMS stated that there is an ongoing study (ALLY-3+) with 50 patients enrolled in France and Australia evaluating DCV+SOF+RBV for 12 or 16 weeks in patients with advanced fibrosis and cirrhosis. SVR4 for this study will be available at the end of June for patients treated for 12 weeks and in July for patients treated for 16 weeks, with final database lock for SVR4 in August. Final SVR12 results will be available by October.
 - The Division said the study would not be sufficient to address the question of minimization of treatment failure due to the small sample size and the fact not all subjects had cirrhosis. However, BMS indicated that these data might help to inform the design of the PMR for GT-3 infected patients with cirrhosis.
- A decrease in SVR was observed in GT-3 infected subjects with NS5A-Y93H at baseline, both in cirrhotic and noncirrhotic subjects, although sample size was limited for these groups.
 - The Division recommends a limitation of use to state that efficacy is reduced in this population with a reference to the clinical trials and microbiology sections of the label. FDA also indicated that because the trend in decreased SVR is based on small numbers of subjects with Y93H, additional major NS5A resistance substitutions do not appear to emerge in virologic failures who started with the Y93H polymorphism, and because there are questions about the potential availability of a commercial assay, the data will be noted in the label but pretreatment screening of NS5A polymorphism in GT-3 patients will not be mandated.

- FDA indicated that should the longer treatment duration or the addition of RBV improve the SVR rates in GT-3 patients with Y93H baseline polymorphism, the labeling can be amended with this information.
- BMS commented that the virologic failures with the Y93H polymorphism represented only 2.6% of the noncirrhotic population in ALLY-3, questioning whether this is a significant finding that warrants a limitations of use statement. FDA commented that the limitations of use statement is based on the frequency of Y93H detected in the study population overall (~9%) and the fact that SVR rates were lower in both cirrhotic and noncirrhotic subjects with this polymorphism.
- BMS further requested if a “(b)(4)” statement could be included in the label to describe the impact of the Y93H polymorphism, in place of a limitations of use statement. FDA responded that current best labeling practice is to consistently use the term “Limitation of Use” and move away from “(b)(4)” language. All labels with (b)(4) terminology will be revised to limitations of use terminology in future updates.
- There are no additional substantial review issues at this time.
- The Division was able to reproduce BMS efficacy and safety results with minimal differences.
- The Division has determined that a REMS will not be needed.
- Regarding a PMR for Pediatrics, FDA stated that they wanted to take a staged approach and focus on the PMR for GT3 cirrhotics first. A PMR for pediatrics will be issued shortly. It will likely be broad language (i.e., DCV containing regimen rather than DCV/SOF).
- Compassionate use data has been challenging for the Division because the data are not from adequate and well controlled studies. Additionally, the dosage recommendations proposed by BMS were not evaluated in adequate and well-controlled clinical trials. Data from compassionate use can be used as supportive information (b)(4) (b)(4) in the absence of data from adequate and well-controlled clinical trials.

ACTION ITEMS:

- BMS will send the ALLY-3+ protocol and projected timelines on data availability to the Division.
- The Division will send the PMR to conduct a trial to determine which treatment strategy in GT-3 patients with cirrhosis (addition of RBV and/or extending treatment duration up to 24 weeks) would support a dosing recommendation that improves SVR rates and decreases treatment failure.

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/s/

SOHAIL MOSADDEGH
05/20/2015

From: Mosaddegh, Sohail
To: marianne.frost@bms.com
Subject: DCV mid cycle communication agenda
Date: Friday, May 15, 2015 2:13:00 PM
Importance: High

Here is the agenda/talking points for Monday:

Substantial Review Issues:

- Reduced SVR rates in subjects with cirrhosis and in subjects who have the NS5A polymorphism at baseline and how the data will be presented in labeling. Currently, we propose these issues are included as Limitations of Use in Section 1 of the product labeling.
- Dosing recommendations for patients with cirrhosis
 - o Proposed regimens were not evaluated in ALLY-3 and limited data from ATU
 - o Indication may be limited to patients (b) (4)
 - o PMR to conduct trial to determine which treatment strategy (addition of RBV and/or extending treatment duration up to 24 weeks) would support a dosing recommendation that improves SVR rates and decreases treatment failure.

Take care

*Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
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Silver Spring, MD 20993-0002
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Fax: (301) 796-9883
Email: Sohail.Mosaddegh@FDA.HHS.GOV*

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/s/

SOHAIL MOSADDEGH
05/15/2015

From: Mosaddegh, Sohail
To: marianne.frost@bms.com
Subject: Info Request to BMS ; NDA 206843
Date: Friday, May 08, 2015 12:41:00 PM

Hello:

1. Please provide a revised cell culture resistance section describing results for GT3 only. Site-directed mutagenesis results may be included.
2. Please provide a summary and the supporting data for the section or provide a reference(s) to the relevant section(s) in your NDA.
3. Please provide a revised cross-resistance section and the data/reference on cross resistance of daclatasvir resistant GT-3 variants to sofosbuvir and of variants containing S282T substitution to daclatasvir

Take care

*Sohail Mosaddegh, Pharm.D.
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/s/

SOHAIL MOSADDEGH
05/08/2015



NDA 206843

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Bristol-Myers Squibb
5 Research Parkway
Wallingford, CT 06492

ATTENTION: Marianne Frost
Director, Global Regulatory, Safety & Biometrics - US

Dear Ms. Frost:

Please refer to your New Drug Application (NDA) dated March 29, 2014, received March 31, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Daclatasvir Tablets, 30 mg and 60 mg.

We also refer to your correspondence dated and received February 13, 2015, requesting review of your proposed proprietary name, Daklinza. We have completed our review of the proposed proprietary name Daklinza, and have concluded that this name is acceptable.

If **any** of the proposed product characteristics as stated in your February 13, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager Sohail Mosaddegh, at (301) 796-4876.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
04/14/2015

TODD D BRIDGES
04/14/2015

Electronic Mail Correspondence – Information Request/Advice



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

DATE: March 25, 2015

TO: Marianne Frost
Director Global Regulatory, Safety & Biometrics
Bristol- Myers Squibb

SPONSOR: Bristol- Myers Squibb

SUBJECT: Reply to February 13, 2015 submission to NDA 206843

In reference to our prior inquiry regarding study visits on Saturdays and Sundays as well as holidays we have detected the issue which resulted in these reports. In your SV dataset (tabulation), the start dates and end dates for the assigned study dates should be the same, as these dates should represent single outpatient site visit dates. However, there are multiple cases where the start date and end date define a range of dates. This is most frequently observed for the pre-screen visit, however, it is also seen for other visits on treatment and for follow-up. This date range for some instances is what is driving the results that reported both weekend and holiday site visits. Please see the attached screen shots that identify the instances where the dates do not match and instead provide a date range. Please note that these occur not only for pre-screen visits but also for some on-treatment and follow-up visits.

Please provide your explanation for this variation in the dataset. If a short teleconference would be helpful to explain the issue further we would be agreeable to determining a time to have a short call.

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
03/25/2015

From: Mosaddegh, Sohail
To: marianne.frost@bms.com
Subject: NDA 206843
Date: Friday, March 20, 2015 9:50:00 AM

Hello:

1. Analysis of site visits on weekdays and holidays showed 3802 visits on Saturday and 3801 visits on Sunday. Additionally, there were numerous site visits on various holidays including 64 site visits on Thanksgiving Day and 72 site visits each on Christmas Day and New Year's Day. Please provide the reasons for site visits on days that would not usually be expected to be open and/or operational.

2. Your proposed Dosage and Administration labeling for patients with cirrhosis states to "^{(b) (4)} . . .". Please clearly specify all available and reviewable data to support labeling ^{(b) (4)} . Please also provide a detailed rationale for proposing ^{(b) (4)} .

Also provide a status update on any outstanding information requests.

Thank you

*Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
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SOHAIL MOSADDEGH
03/25/2015

From: Mosaddegh, Sohail
To: marianne.frost@bms.com
Subject: NDA 206843 resubmission Information request
Date: Tuesday, March 10, 2015 2:58:00 PM

Please refer to Table 3, Page 16 of Addendum 01 to Resistance Profile Summary for Daclatasvir and Asunaprevir in HCV Infected Subjects (DCN: 930086934).

Please provide the mean EC₅₀ values of daclatasvir for each genotype and each genotype/subtype, i.e. 1a, 1b, 2, 3a, 3b, 4, 5 and 6, isolates with and without NS5A polymorphisms listed in Table 3, Page 16 of the above report. Please provide a spreadsheet with the individual values and GT/subtype identified.

*Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
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/s/

SOHAIL MOSADDEGH
03/10/2015

Electronic Mail Correspondence – Information Request/Advice



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

DATE: March 17, 2015

TO: Marianne Frost
Director Global Regulatory, Safety & Biometrics
Bristol- Myers Squibb

SPONSOR: Bristol- Myers Squibb

SUBJECT: Reply to February 13, 2015 submission to NDA 206843

Based on the EMA report submitted, we request you provide any ECGs that are available from subjects who experienced cardiac events while receiving DCV/SOF and amiodarone. Specifically, we are requesting clarification if any ECG recordings are available that document the resolution of the event following discontinuation of HCV treatment or reoccurrence of the event when HCV treatment was restarted. If available, we request that these ECG recordings are submitted to the DCV NDA and FDA ECG Warehouse along with cross-referencing information linking them to the index cases we are currently evaluating as referenced above.

Regarding the cases of bradycardia observed with DCV/SOF and amiodarone, please provide a complete summary of your plans to investigate possible mechanisms including a timeline for conducting experiments and the availability of results.

Please conduct the following subgroup analyses from Ally 1, 2 and 3 with SOF/DCV and we request you submit the results to the DCV NDA by April 7, 2015:

- In subjects on a stable beta-blocker regimen, perform assessment of change from baseline heart rate at all on-treatment time points where heart rate data are available. It is important to ensure subjects in this analysis do not have a change in their beta-blocker regimen while on treatment. Please comment on any subjects on beta-blockers who may have experienced arrhythmias, cardiac adverse events, syncope, or dizziness within the first two weeks of initiating HCV treatment.
- In subjects on a stable calcium channel blocker, perform assessment of change from baseline heart rate at all on-treatment time points where heart rate data are available. It is important to ensure subjects in this analysis do not have a change in their calcium channel blocker regimen while on treatment. Please comment on any subjects on calcium channel blocker who may have experienced arrhythmias, cardiac adverse events, syncope, or dizziness within the first two weeks of initiating HCV treatment.

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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SOHAIL MOSADDEGH
03/17/2015

Electronic Mail Correspondence – Information Request/Advice



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

DATE: February 27, 2015

TO: Marianne Frost
Director Global Regulatory, Safety & Biometrics
Bristol- Myers Squibb

SPONSOR: Bristol- Myers Squibb

SUBJECT: Reply to February 13, 2015 submission to NDA 206843

Please provide data on median EC₅₀ values of daclatasvir for genotype 3 subtypes, EC₅₀ value ranges and number of isolates tested with and without NS5A polymorphisms.

Please submit your responses/data by COB March 04, 2015 and contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
02/27/2015

Electronic Mail Correspondence – Information Request/Advice



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

DATE: February 23, 2015

TO: Marianne Frost
Director Global Regulatory, Safety & Biometrics
Bristol- Myers Squibb

SPONSOR: Bristol- Myers Squibb

SUBJECT: Reply to February 13, 2015 submission to NDA 206843

1. The report “Addendum 01 to Supplementary Resistance Data to Clinical Scientific Report AI444218” provides additional NS5A and NS5B sequence data that were not available at the time of the SVR12 database lock, and apparently were not included in the main resistance datasets (e.g., res5a3.xpt). Since the total number of HCV GT3 subjects available for analysis is relatively small, and the additional data were obtained from samples collected at timepoints within the Pre-treatment through SVR12 analysis timeframe, we would like to include these data in our independent resistance analyses of AI444218. Please provide these additional data in a reviewable spreadsheet format. If it helps to expedite submission, it would be acceptable if the supplementary dataset included only (1) USUBJID, (2) VISIT, and (3) data for the individual amino acid position columns. A complete and cumulative dataset including these and any other additional data could then be submitted to the NDA at a later date.
2. The next generation sequencing data from AI444218 submitted to IND 121165 could not be opened, possibly due to an unsupported zip protocol. Please correct the format and resubmit the data. Also, please submit/link the data to IND 121165 and also to NDA 206843.
3. There are 10 subjects in the AI444218 viral load dataset who had 5-7 Pre-Treatment/VLDY=1 sample timepoints with HCV RNA results reported. Some of the results varied significantly ($>2\text{-log}_{10}$ IU/mL) for the same sample timepoints from the same subject. Please provide an explanation for these data, or if such an explanation is already provided in the NDA please indicate where it can be found.

Please submit your responses/data by COB March 02, 2015 and contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD

Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
02/23/2015

Electronic Mail Correspondence – Information Request/Advice



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

DATE: February 20, 2015

**TO: Marianne Frost
Director Global Regulatory, Safety & Biometrics
Bristol- Myers Squibb**

SPONSOR: Bristol- Myers Squibb

SUBJECT: Reply to February 13, 2015 submission to NDA 206843

We are aware the EMA requested a comprehensive cumulative safety review of cardiac arrhythmias for DCV/SOF containing regimens. Please provide this safety review by March 7, 2015. Please also provide a cumulative safety review of cardiac failure, cardiomyopathy and related events for DCV/SOF containing regimens. Please provide this review within 30 days. For both reviews please include pertinent case narratives and literature reports.

Please also provide your assessment on potential pharmacokinetic or pharmacodynamic interactions of DCV with amiodarone (including potential mechanism, if applicable) and related cardiac adverse events. Please provide your assessment within 30 days.

For all three requests please address why or why not labeling is warranted, if warranted please amend your current proposed labeling within 30 days.

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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SOHAIL MOSADDEGH
02/20/2015

Electronic Mail Correspondence – Information Request/Advice



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

DATE: December 12, 2014

TO: Charles Wolleben, PhD
Group Director, Global Regulatory Sciences – US
Bristol- Myers Squibb

SPONSOR: Bristol- Myers Squibb

SUBJECT: reply to 12/05/2015 email (attached) regarding Resubmission Safety Update and 11/19/14 submission regarding resubmission for NDA 206843

We have the following response regarding your comments response emailed 12/05/2014 to the resubmission safety update:

We acknowledge that the Phase 2 data for DCV/P/R compared to PBO/P/R was included in the original NDA 206843; however, based on the emphasis on liver safety, we request that the safety resubmission include a complete liver toxicity assessment for DCV/P/R compared to PBO/P/R.

We recommend that the analyses for DCV/SOF vs. DCV/SOF/RBV are completed separately from the DCV/P/R vs. PBO/P/R for the more specific or drilled down safety analyses (e.g. most common adverse events, grade 3 or 4 events, laboratory abnormalities etc.). The rationale for this request is to avoid the P/R portion of the regimen from driving the overall safety results for the non-P/R containing regimens and potentially diluting the observed safety data of the DCV/SOF +/- RBV regimens. Additionally, we are not planning on displaying in product labeling the P/R containing regimen data in Section 6 safety tables because this is not the indication being sought. When appropriate, display of the regimens in a side-by-side presentation (as in your example Tables 2 and 3) may be acceptable for ease of presentation.

Please clarify exactly what type of safety data (i.e. line listings, safety narratives, datasets) you plan to submit from ALLY-1 and -2 trials when you state “high level safety data” will be included.

In your response to FDA comment 4, you re-state the BMS definition of hypersensitivity events. In the protocols, this definition is limited by timing of laboratory draws (eosinophilia and elevation of ALT and AST must be same day). For the resubmission and future NDA and sNDA submissions, we recommend that your overall assessment of hypersensitivity not

be constrained by only this definition and those cases with rash or lymphadenopathy or other clinical symptoms potentially concerning for hypersensitivity be closely evaluated and included in the overall clinical assessments when appropriate.

In reference to your 11/19/2014 submission regarding resubmission:

Please clarify if the first and or second interim EAP safety data report from the ATU cohort (due October 2014 and January 2015, respectively) could be included in the resubmission as additional supportive data for DCV/SOF +/- RBV.

In regards, to the pooled safety dataset comprised of the 8 trials AI444010, AI444011, AI444014, AI444021, AI444022, AI444031, AI444040, AI444218, please clarify that you intend to provide at minimum, the BMS legacy analysis datasets to allow for safety and efficacy analyses (adae, DM, LB, SVR etc.) in addition to the adsl (ADAM) dataset. Please provide a sample dataset of the pooled data.

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

SAFETY UPDATE

FDA COMMENT

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

BMS RESPONSE

The nonclinical portion of NDA 206843 will remain unchanged from what was submitted in Module 4 of the original NDA with the following exception: a repeat study on a transporter (BCRP) that does not change any of the existing conclusions in the nonclinical documents.

As stated in the proposed resubmission plan submitted to NDA 206843 on November 19, 2014 (Seq #0029), BMS proposes to include only DCV regimens that do not contain ASV in the safety update as described in Table 1 (table extracted from NDA 206843 Seq#0029 Table 2). Safety of DCV is established based upon the total safety experience with DCV which represents exposure of over 5500 patients. The safety profile of DCV was explored as part of the Phase 2 program. DCV administered at the recommended dose was well tolerated and has a favorable safety profile in patients with chronic hepatitis C. DCV was evaluated in combination with a number of other agents including P/R, asunaprevir (ASV), SOF, and simeprevir (SMV). This experience documented that the safety profile of the DCV-containing combination was driven by the safety profile of the other agent(s) in the regimen. For example, when combined with ASV the safety profile of DCV/ASV was marked by elevated ALT which is associated with ASV. Likewise, when combined with P/R the safety profile of DCV/P/R is consistent with the safety profile of P/R. While this broader safety profile currently reflected in NDA 206843 will be noted in the NDA resubmission, a detailed safety assessment only for the DCV/SOF regimen will be provided in the NDA resubmission since that is the regimen that will be reflected in labeling. In addition, we intend to include the safety profile of DCV/SOF ± RBV data from AI444040 and describe the Phase 2 data (already in NDA 206843) comparing DCV/P/R and PBO/P/R to help contextualize the overall safety profile of DCV.

In the resubmission for the initial DCV NDA, BMS proposes that the safety of DCV be based on a side-by-side presentation of the DCV/SOF ± RBV regimen and the Phase 2 DCV/P/R studies (the latter being already included in the initial submission). Although the Phase 3 DCV/P/R studies (AI444052, AI444042, AI444038, AI444043 referred to in NDA 206843 Seq #0029 Table 2) are completed/near completion, these Phase 3 studies do not change the safety profile observed in the Phase 2 DCV/P/R studies or the safety profile observed with the DCV/SOF regimen under consideration and, therefore, will not be added to the resubmission. The CSRs for AI444052 and AI444042 referred to above were submitted to the DCV IND 79,599 (Seq 0876 and 0743 respectively) and the CSR for AI444038 will be submitted to IND 79,599. If needed, these CSRs can also be submitted to the DCV NDA 206843 as post-marketing commitments as BMS does not intend to request for an indicated use of DCV/P/R.

High level safety data from ALLY-1 and -2 studies will be included in the DCV resubmission as data from ongoing studies to support the safety evaluation of the DCV/SOF regimen. As stated in the proposed resubmission plan (NDA 206843 Seq#0029), BMS proposes to submit a parallel NDA with ALLY-1 and -2 data mid-2015 during the review of the DCV NDA 206843 containing ALLY-3.

Table 1 **Number of Subjects Treated in DCV-containing (non-ASV) Regimens at the Recommended DCV dose of 60 mg QD for 12 Weeks or Longer**

Regimen	Duration	N	Comments
In planned NDA resubmission (target submission ~Feb-2015)			
DCV/SOF			
ALLY-3 (AI444218)	12 weeks	152	
AI444040	12 weeks	41	
	24 weeks	80	
DCV/SOF +RBV			
AI444040	12 weeks	41	
	24 weeks	49	
TOTAL	12 to 24 weeks	363	Total safety database for DCV = 868
DCV (60 mg only) + P/R			
AI444014	48 weeks	12	
AI444010	12 or 24 weeks	158	
AI444011	24 weeks	199	
AI444021	24 weeks	19	
AI444022	24 weeks	17	
AI444031	12 or 16 weeks	100	
TOTAL	12 weeks or longer	505	
Available during review (propose separate, parallel NDA - Mid 2015)			
DCV/SOF			
ALLY-2 (AI444216)	12 weeks	203	December 2014 - SVR12 topline April 2015 - CSR
DCV/SOF + RBV			
ALLY-1 (AI444215)	12 weeks	113	January 2015 - SVR12 topline April 2015 - CSR
TOTAL	12 weeks	316	

FDA COMMENT 1

Describe in detail any significant changes or findings in the safety profile.

BMS RESPONSE

BMS agrees to provide this information.

FDA COMMENT 2

When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- *Present new safety data from the studies/clinical trials (from the on-treatment period) for the proposed indication using a format that DAVP agrees upon prior to submission.*

BMS RESPONSE

BMS proposes to focus on the ALLY program with ALLY-3 included as a new study in the resubmission and ALLY-1 and -2 as ongoing studies. However, as described above, BMS proposes to submit a parallel NDA with ALLY-1 and -2 data mid-2015 (during the review of the DCV NDA 206843 containing ALLY-3). BMS proposes to present safety data as indicated in Tables 2 and 3 below.

- **Present tabulations of the new safety data combined with the original NDA data.**
- **Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.**

BMS RESPONSE

BMS proposes to prepare tables to compare safety data from AI444040 (which was included in the original NDA and updated in the 90-day safety update report) to AI444218 (ALLY-3) alone, and to integrated data from AI444040 + AI444218 (ALLY-3). Comparison tables will include SAEs, AEs leading to discontinuation, common AEs, treatment related AEs, and Grade 3 or 4 AEs. For these events only, there will be a comparison to data previously submitted in the NDA (Table 2).

Template for summary table of SAEs, all AEs, AEs leading to discontinuation, treatment related AEs, grade 3-4 AEs:

Table 2 Protocol: AI444010, AI444011, AI444014, AI444021, AI444022, AI444031, AI444040, AI444218							
Title							
Treated Subjects							
Number (%) ³							
Safety Event	AI444040 DCV/SOF N=**	AI444218 DCV/SOF N=**	Total DCV/SOF N=**	AI444040 DCV/SOF/RBV N=**	Total ¹ N=**	DCV/pegIFNalpha /RBV ² N=**	PBO/pegIFN alfa/RBV ² N=**
			xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
			xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)

Recommended dose of DCV is 60 mg QD

¹ Includes studies: AI444040, AI444218

² Includes studies: AI444010, AI444011, AI444014, AI444021, AI444022, AI444031

³ Does not include assessments during or after rescue therapy

- **For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.**

BMS RESPONSE

For indications other than the proposed indication, BMS will capture frequencies of adverse events as part of the safety data display as illustrated in Table 3.

Template for all tables:

Table 3 Protocol: AI444010, AI444011, AI444014, AI444021, AI444022, AI444031, AI444040, AI444218					
Title					
Treated Subjects					
	Number (%)⁴				
Safety Event	DCV/SOF¹ N=**	DCV/SOF/RBV² N=**	Total¹ N=**	DCV/pegIFNalpha/RBV³ N=**	PBO/pegIFNalpha/RBV³ N=**
	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)

Recommended dose of DCV is 60 mg QD

¹ *Includes studies: AI444040, AI444218*

² *Includes study AI444040*

³ *Includes studies: AI444010, AI444011, AI444014, AI444021, AI444022, AI444031*

⁴ *Does not include assessments during or after rescue therapy*

- ***Please note that safety data from the original NDA includes the safety data provided in the safety update report and only safety data subsequent to the safety update report cut dates would be considered new safety data. Additionally, we are requesting that only on-treatment safety data be provided in detail as highlighted in this section and only important new safety findings or trends during the post-treatment period be highlighted in a separate post-treatment safety findings section.***

BMS RESPONSE

BMS proposes to provide new on-treatment safety data from AI444218 and data from the final AI444040 database lock (on-treatment data from AI444040 was provided in the original DCV dossier).

FDA COMMENT 3

Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

BMS RESPONSE

BMS agrees to provide this information for the ALLY-3 AI444218 study.

FDA COMMENT 4

Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events, any grade 3 or 4 liver event not otherwise covered by discontinuation, SAE or death and any hypersensitivity events with or without liver involvement.

BMS RESPONSE

Assuming the Division agrees that the resubmission will focus on non-ASV containing regimens, narratives for all deaths, serious adverse events, adverse events leading to discontinuation of study therapy and any hypersensitivity events (defined as pyrexia $\geq 38.7^{\circ}\text{C}$ with concurrent [i.e. occurring on the same day within 28 days after the onset date of pyrexia] eosinophilia defined as absolute eosinophil count of 1.5×10^3 cells/ μL [or $>1.5 \times 10^9$ cells/L] and ALT and AST $\geq 5 \times \text{ULN}$, and no evidence of

acute viral, bacterial, or parasitic infection) for the AI444218, AI444040, and Phase 2 DCV/pegIFN/RBV studies outlined in Table 1 will be provided. Note that in the original DCV US NDA submission, narratives for all deaths, serious adverse events, adverse events leading to discontinuation of study therapy and hypersensitivity events were previously included for the AI444040 study as well as the Phase 2 DCV/pegIFN/RBV studies listed in Table 1.

As requested, Grade 3 or 4 liver events of the preferred terms in the MedDRA System Organ Class (SOC) of “Hepatobiliary disorders” and hepatic events in “Investigations”, as well as Grade 3 or 4 ALT laboratory abnormalities will be included for the studies to be submitted as outlined in Table 1.

FDA COMMENT 5

Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

BMS RESPONSE

BMS agrees to provide this information.

FDA COMMENT 6

Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

BMS RESPONSE

BMS agrees to provide this information.

FDA COMMENT 7

Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

BMS RESPONSE

BMS agrees to provide post-marketing worldwide safety experience with DCV with an estimate of patient exposure.

FDA COMMENT 8

Provide English translations of current approved foreign labeling not previously submitted.

BMS RESPONSE

BMS agrees to provide this information.

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/s/

SOHAIL MOSADDEGH
12/12/2014

From: Mosaddegh, Sohail
To: charles.wolleben@bms.com
Subject: NDA 206843 Right of Reference issues
Date: Monday, November 17, 2014 11:32:00 AM

Before we can respond to your question regarding resubmission of NDA 206843 we need to understand the following:

- (1) how do you propose to bridge ALLY3 and study 040
- (2) do you intend to rely on the 040 data to support Dosage and Administration in labeling?
- (3) what exactly do you want to display in the label from study 040.

Thank you

Sohail Mosaddegh, Pharm.D.

Lieutenant Commander, USPHS

Regulatory Health Project Manager

FDA/CDER/OND/OAP/Division of Antiviral Products

10903 New Hampshire Ave., Bldg. 22, Room 6223

Silver Spring, MD 20993-0002

Phone: (301) 796-4876

Fax: (301) 796-9883

Email: Sohail.Mosaddegh@FDA.HHS.GOV

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/s/

SOHAIL MOSADDEGH
11/17/2014

Electronic Mail Correspondence – Information Request/Advice



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

DATE: October 31, 2014

TO: Charles Wolleben, PhD
Group Director, Global Regulatory Sciences – US
Bristol- Myers Squibb

SPONSOR: Bristol- Myers Squibb

SUBJECT: NDA 206843

In advance of the November 7, 2014, teleconference to discuss daclatasvir post NDA actions we are providing you the following comments and recommendations.

- We have determined resubmission of requested data to NDA 206843 is appropriate and a new NDA for daclatasvir is not needed.
- We do not agree with your plans to submit only the ALLY-3 data to support the use of daclatasvir/sofosbuvir combination for genotype 3 HCV infection. Based on the preliminary data submitted from ALLY-3 more data are needed to assess the optimal treatment regimen and duration for treatment-naïve and treatment-experienced cirrhotic patients. Recommendations in treatment-naïve and treatment-experienced non-cirrhotic patients could be considered with other supportive data (see comment below).
- We encourage you to submit a meeting request when you have topline SVR12 data for trials ALLY-1, ALLY-2, ALLY-3 and (b)(4). These trials will be a starting point to discuss potential resubmission plans and appropriate data to support recommendations for specific genotypes, prior treatment status and cirrhosis status. Please submit the following information in the meeting background package.
 - The numbers of subjects and SVR12 data overall and by genotype/subtype, prior treatment status and cirrhosis status for each trial regimen and duration. Please also include the point estimate and 95% CI for each requested result. These data are important to assess the precision around the point estimate to support recommendations for specific genotypes and subpopulations.
 - SVR12 data according to the detection of baseline NS5A polymorphisms, especially for the (b)(4) trial.

- Please clarify your plans for daclatasvir expanded access/compassionate use data for a resubmission. Specifically do you have any SVR12 data from the French ATU cohort? Data from the French ATU cohort from daclatasvir/sofosbuvir +/- ribavirin for 12 or 24 weeks could provide supportive data for a given genotype. We note a total of 3594 subjects have received treatment. Please provide the number of subjects by genotype who received the 12 or 24 week regimen +/- ribavirin, including prior treatment status and cirrhosis status.

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
10/31/2014

Electronic Mail Correspondence – Information Request/Advice



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

DATE: October 17, 2014

TO: Charles Wolleben, PhD
Group Director, Global Regulatory Sciences – US
Bristol- Myers Squibb

SPONSOR: Bristol- Myers Squibb

SUBJECT: NDA 206843/206844 and IND (b) (4)

Future NDA recommendations.

Based on review of your NDAs 206843 and 206844 we have the following comments and recommendations for subsequent NDA submissions.

In general, your clinical integration of the safety data was difficult to navigate and to assess. The presentation by regimen was agreed upon previously; however, there was little to no overall discussion of the overall DCV and ASV regimen compared to the PR containing regimens and clinical assessment of the rationale for contribution of DCV or ASV to the main safety issues. Additionally, while the NDAs were adequately hyperlinked, often the format was a statement regarding the safety event and proportions followed by multiple hyperlinks and little to no text discussing the findings or interpretation of the data. Once a hyperlink would be clicked, you may have to scroll many pages to find the single safety finding that was being discussed or listed. Overall, the NDAs were more similar to a statistical analysis report and not an integrated clinical safety analysis.

We recommend specifically listing the findings that are being discussed by identifying the reported events, the number of subjects with the event and when appropriate the patient ID numbers. This was done in some places but not in others. Additionally, our expectation is a clinical discussion of the data. For example discuss the events with an appropriate level of detail and provide the hyperlinks for further reference. For example, section 2A.1.3 discussed Treatment-Related SAEs and provides a listing of the events with proportions and brief narratives. However, there is no discussion of the overall assessment of the SAEs for DUAL regimen and how this compares to the other regimens or what BMS' interpretation of the data is for the regimen. Additionally, similar issues were found in the reporting of special search categories where the ISS was more similar to a statistical report than an integrated summary discussing the rationale for the search categories, the findings from the trials and BMS' interpretation of the safety data.

We recognize that this was a complicated NDA with multiple regimens and trials to be integrated; however, we want to provide this feedback in attempts to help you provide more clinically oriented NDA submissions in the future. Also, this process may help identify specific safety areas that will need additional attention and discussion throughout the NDA in order to provide an integrated assessment of the safety of the proposed treatment regimen. Of note, your data quality was excellent and in general, your data, including the legacy datasets, were easily navigated and used in the available reviewer tools.

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
10/17/2014

Electronic Mail Correspondence – Information Request/Advice



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

DATE: September 03, 2014

TO: Charles Wolleben, PhD
Group Director, Global Regulatory Sciences – US
Bristol- Myers Squibb

SPONSOR: Bristol- Myers Squibb

SUBJECT: 206843/206844 Questions

Based on FDA findings associated with pyrexia and eosinophilia, you conducted similar analyses of pyrexia and eosinophilia within 2 weeks which were used for your external consultants' backgrounder. Overall, the analyses resulted in similar findings; however, there are some minor discrepancies regarding the identified subjects that we would like to address to ensure we understand the reasons for the differences in the analyses that were conducted. One difference in method of analyses between the BMS and FDA analyses was that for the original broad FDA analysis, any eosinophil count above ULN and BMS used any treatment-emergent absolute eosinophil count of 0.5×10^9 /c/L (Grade 1 or higher). Additionally, FDA included cases in which pyrexia followed an elevation of eosinophil count as long as it was within 2 weeks. While FDA agrees with the subsequent eosinophilia grading scale that was employed for the analyses, we want to ensure we understand the reasons for the small discrepancies in the identified subjects. By COB Monday, 09/08/2014, please provide us with your rationale for the differences highlighted below for each subject.

BMS' analysis of phase 3 subjects with pyrexia and eosinophilia within 2 weeks did not include the following 4 subjects which were included in the FDA analysis:

- **Subject AI447026-1-20265:** This subject reported pyrexia at Day 6 and had an elevation of eosinophils to 13% at Week 2.
- **Subject AI447026-7-10193:** This subject had an eosinophil count of 9.1% at Week 4 with pyrexia following at Week 6. (pyrexia followed the eosinophil elevation)
- **Subject AI447026-1-10059:** This subject had an elevation of eosinophils to 10% at Week 4 and a few days later AE report of pyrexia. (pyrexia followed the eosinophil elevation)
- **Subject AI447026-23-20272:** This subject had an elevation of eosinophils to 9.4% at Week 6 with AE reporting of pyrexia at Week 4 ending at Week 10.

Additionally, the following differences from phase 2 trials were identified:

From trial **AI444011**: Subject 78-392 was not included

From trial **AI444021**: Subjects 4-21102 and 4-21108 were not included

From trial **AI447017**: Subject 3-3017 is not included

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
09/03/2014

From: Mosaddegh, Sohail
To: charles.wolleben@bms.com
Subject: assay comment
Date: Tuesday, August 26, 2014 9:16:00 AM

During the mid-cycle teleconference on 7/10/2014 we informed you that we have concerns about the impact of certain baseline NS5A polymorphisms on the efficacy of the daclatasvir/asunaprevir (DUAL) regimen in HCV genotype 1b infected patients. We will be recommending a limitation of use statement for the daclatasvir and asunaprevir labels that screening for the presence of NS5A L31F/I/M/V or Y93H polymorphisms is recommended for this treatment regimen, and alternative therapy should be considered for patients with these NS5A polymorphisms. We strongly recommend that you share this information with one or more diagnostic companies that may be able to make a validated NS5A sequence analysis assay commercially available. This process should be initiated immediately to ensure the timely availability of a diagnostic assay if asunaprevir and daclatasvir are approved, as it may take a significant amount of lead time to make an assay commercially available.

*Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6223
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/s/

SOHAIL MOSADDEGH

08/26/2014

From: Mosaddegh, Sohail
To: charles.wolleben@bms.com
Subject: BMS IR
Date: Tuesday, August 19, 2014 11:16:00 AM

Please refer to your submission dated 08/14/14 providing the narratives for cases meeting Hy's Law laboratory criteria with DCV/PegIFN/RBV or DCV in any other combinations (excluding trials with ASV). Please provide a summary of these cases along with your assessment for hepatotoxicity potential with DCV. Please also provide a similar summary and assessment for the Phase 2 cases with ASV/PegIFN/RBV.

Please respond by COB Thursday 8/21/2014.

Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
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/s/

SOHAIL MOSADDEGH

08/19/2014

Cuff, Althea

From: Cuff, Althea
Sent: Monday, August 18, 2014 4:55 PM
To: Wolleben, Charles (Charles.Wolleben@bms.com)
Subject: NDA 206843 and 206844- Information Request

Dear Mr. Wolleben,

Please respond to the following request by Monday August 25th.

NDA 206 844 (Asunaprevir (b) (4))

Provide stability update for clinical batches 2L68261 and 2H62987 manufactured at (b) (4) site.

NDA 206 843 (Daclastavir Tablets)

Provide stability update for commercial image batches 3A9009X for Daclatasvir Tablets 30 mg), 3A9010X and 2K9011X for Daclatasvir Tablets 60 mg manufactured at Mt. Vernon site.

Thanks, Althea

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/s/

ALTHEA CUFF
08/18/2014

From: Mosaddegh, Sohail
To: charles.wolleben@bms.com
Subject: IR for 206843/206844
Date: Thursday, August 07, 2014 10:14:00 AM

Hello:

Please provide an evaluation of your safety database for DCV in combination with PegIFN/RBV from the phase 2 trials or DCV in any other DAA combinations (excluding trials that subjects are also exposed to ASV) for cases meeting Hy's Law laboratory criteria. Please include available placebo comparisons and any placebo cases also meeting these criteria.

Also, provide a description and timeline of your pending responses to the action items identified at the midcycle and post-midcycle communication.

Thank you

*Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
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SOHAIL MOSADDEGH
08/07/2014

From: Mosaddegh, Sohail
To: ["Wolleben, Charles"](#)
Subject: RE: eDISHdataRequirements.xls
Date: Tuesday, August 05, 2014 10:45:00 AM

Hello:

here are the responses from our eDSIH contact:

1. The criteria specified in eDISH-Data Requirements should be used. Under this criteria, the clinical narratives are required for subjects located in the NE quadrant of the eDISH graph.
2. I do not have knowledge about the BMS analysis data sets, but the sponsor needs to strictly follow the eDISH-Data Requirements regardless of the original data source.
3. If the sponsor follows the eDISH-Data Requirements, I do not need any define.doc. However, the eDISH data sets should be put in a folder named eDISH.

*Sohail Mosaddegh, Pharm.D.
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Fax: (301) 796-9883
Email: Sohail.Mosaddegh@FDA.HHS.GOV*

From: Wolleben, Charles [mailto:Charles.Wolleben@bms.com]
Sent: Friday, August 01, 2014 12:13 PM
To: Onaga, Linda
Cc: Mosaddegh, Sohail
Subject: RE: eDISHdataRequirements.xls

Hi Linda,

Thanks. This has been very helpful but has generated 3 questions from our programming/stats group.

Hy's law criteria are as follows:

[REDACTED] (b) (4)

The criteria in the [REDACTED] (b) (4) requirements for the narratives are:

Questions:

1. We would like to know if Hy's law criteria above (vs eDISH requirement) can be used for identifying subjects to have narrative data (we have narratives for all Hy's law cases)?
2. We would like to know if data is expected to be sourced from SDTM or BMS analysis data sets (prefer BMS)?
3. Are define.doc needed for the 3 data sets per protocol?

Feedback on these questions would be appreciated as we are now constructing the datasets for the Division.

Regards,
Chuck

From: Onaga, Linda [<mailto:Linda.Onaga@fda.hhs.gov>]
Sent: Thursday, July 31, 2014 7:36 AM
To: Wolleben, Charles
Cc: Mosaddegh, Sohail
Subject: eDISHdataRequirements.xls

Chuck,

Here is the excel file. I was under the assumption that you could see this site. Edish is a graphic tool that we use to evaluate special cases of liver injury possible due to drug exposure. The information needed for this tool is listed in excel sheet attached.

Let me know if you have any additional questions.

Linda

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/s/

SOHAIL MOSADDEGH
08/05/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 206843 and 206844
Drug: daclatasvir and asunaprevir
Date: July 30, 2014
To: Charles Wolleben, Ph.D. Group Director, Regulatory Sciences - US
Sponsor: Bristol-Myers Squibb
Subject: NDA comments

Please refer to NDA 206843 and NDA 206844. We have the following non clinical comments:

Please submit the following studies in eDISH format:

- AI 447028
- AI 447029
- AI 447026

For eDISH-data requirements, please visit <http://eReview/eDISH> and download the requirements sheet (xls) for you to use.

Please submit your response by COB August 8, 2014.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
07/30/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 206843
Drug: daclatasvir
Date: July 29, 2014
To: Charles Wolleben, Ph.D. Group Director, Regulatory Sciences - US
Sponsor: Bristol-Myers Squibb
Subject: Non-clinical comments

Please refer to NDA 206843. We have the following non clinical comments:

Non Clinical

1. Please submit the Ames assay study report for [REDACTED] (b)(4). If this information was previously submitted, indicate the submission number and date.
2. [REDACTED] (b)(4) appears to be effectively purged from the daclatasvir drug substance; however, please note that [REDACTED] (b)(4) is mutagenic and not considered a routine impurity under ICH Q3A(R2). If necessary to support a proposed specification in future applications, results of in vivo genotoxicity testing with [REDACTED] (b)(4) could be used to justify limits exceeding the default TTC described in ICH M7. This comment is for your information and requires no additional follow-up.

Please submit your response by COB August 6, 2014.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
07/29/2014

Please note that these remain preliminary analyses from our draft document and are subject to change. In addition, further analyses may be necessary.

Questions:

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?
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.
3. Please provide your opinion whether or not pyrexia is a discriminating clinical symptom to potentially identify at-risk patients.
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.
5. Do these events affect your risk/benefit assessment for the DUAL and QUAD regimens, and if so, how?
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?
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?
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.
9. What additional data would be helpful to further characterize these events?

I. Hepatic Safety Assessment

Graded Liver Biochemistry Analyses

Treatment-Emergent Liver Biochemistry Laboratories by Toxicity Grade for the Phase 3 Trials.

Lab Test and Emergent Toxicity Grade		AI447026	AI447028	AI447029	
		DUAL	DUAL	QUAD	
		DCV 60mg QD + ASV 100 mg BID (24W) N=222	DCV 60mg QD + ASV 100 mg BID (24W) N=645	PLACEBO (12W) N=102	DCV 60mg + ASV 100mg BID+ PegIFN + RBV (24W) N=398
ALT	Grade 1 (1.25 to 2.5 x ULN)	28 (13%)	84 (13%)	17 (17%)	40 (10%)
	Grade 2 (>2.5 to 5 x ULN)	30 (14%)	40 (6%)	9 (9%)	25 (6%)
	Grade 3 (>5 to 10 x ULN)	15 (7%)	14 (2%)	2 (2%)	12 (3%)
	Grade 4 (> 10x ULN)	8 (4%)	8 (1%)	0	2 (1%)
AST	Grade 1 (1.25 to 2.5 x ULN)	33 (15%)	82 (13%)	13 (13%)	44 (11%)
	Grade 2 (>2.5 to 5 x ULN)	17 (8%)	30 (5%)	7 (7%)	27 (7%)
	Grade 3 (>5 to 10 x ULN)	11 (5%)	12 (2%)	1 (1%)	13 (3%)
	Grade 4 (> 10x ULN)	5 (2%)	4 (1%)	0	2 (1%)
ALK Phos	Grade 1 (1.25 to 2.5 x ULN)	21 (9%)	19 (3%)	0	11 (3%)
	Grade 2 (>2.5 to 5 x ULN)	1 (<1%)	0	0	0
Total Bilirubin	Grade 1 (1.1 to 1.5x ULN)	39 (18%)	58 (9%)	8 (8%)	91 (23%)
	Grade 2 (>1.5 to 2.5 x ULN)	13 (6%)	20 (3%)	2 (2%)	34 (9%)
	Grade 3 (>2.5 to 5 x ULN)	2 (1%)	4 (1%)	1 (1%)	4 (1%)
	Grade 4 (>5.0 x ULN)	0	0	0	0

Source: Laboratory and Subject Level Analysis Datasets

Shift Analyses

Table 7: Summary of Shift Analyses: Maximum Post-Baseline versus Baseline Liver Biochemistries for Phase 3 Trials

		A1447026 - DUAL				A1447028 - DUAL				A1447029 - QUAD															
ALT Baseline		DCV 60mg QD + ASV 100mg BID (24W) N = 222				DCV 60mg QD + ASV 100 mg BID N = 645				DCV 60mg + ASV 100mg BID + PegIFN + RBV (24W) N = 398															
		ALT < 2x ULN	2x ≤ ALT < 5x ULN	5x ≤ ALT < 10x ULN	ALT ≥ 10x ULN	ALT < 2x ULN	2x ≤ ALT < 5x ULN	5x ≤ ALT < 10x ULN	ALT ≥ 10x ULN	ALT < 2x ULN	2x ≤ ALT < 5x ULN	5x ≤ ALT < 10x ULN	ALT ≥ 10x ULN												
ALT Maximum		Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%												
ALT < 2x ULN		99	44.59	63	28.38	1	0.45	0	0.00	426	66.05	118	18.29	1	0.16	0	0.00	266	66.83	59	14.82	1	0.25	0	0.00
2x ≤ ALT < 5x ULN		22	9.91	15	6.76	4	1.80	1	0.45	47	7.29	26	4.03	7	1.09	1	0.16	26	6.53	30	7.54	3	0.75	0	0.00
5x ≤ ALT < 10x ULN		6	2.70	3	1.35	1	0.45	0	0.00	6	0.93	3	0.47	0	0.00	0	0.00	5	1.26	5	1.26	0	0.00	0	0.00
10x ≤ ALT < 20x ULN		4	1.80	3	1.35	0	0.00	0	0.00	4	0.62	0	0.00	0	0.00	0	0.00	2	0.50	1	0.25	0	0.00	0	0.00
ALT ≥ 20x ULN		1	0.45	0	0.00	0	0.00	0	0.00	4	0.62	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

		DCV 60mg QD + ASV 100mg BID (24W) N = 222				DCV 60mg QD + ASV 100 mg BID N = 645				DCV 60mg + ASV 100mg BID + PegIFN + RBV (24W) N = 398															
AST Baseline		AST < 2x ULN	2x ≤ AST < 5x ULN	5x ≤ AST < 10x ULN	AST ≥ 10x ULN	AST < 2x ULN	2x ≤ AST < 5x ULN	5x ≤ AST < 10x ULN	AST ≥ 10x ULN	AST < 2x ULN	2x ≤ AST < 5x ULN	5x ≤ AST < 10x ULN	AST ≥ 10x ULN												
AST Maximum		Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%												
AST < 2x ULN		115	51.80	62	27.93	3	1.35	0	0.00	404	62.64	149	23.10	6	0.93	0	0.00	246	61.81	58	14.57	7	1.76	0	0.00
2x ≤ AST < 5x ULN		16	7.21	11	4.95	1	0.45	1	0.45	30	4.65	32	4.96	8	1.24	0	0.00	30	7.54	40	10.05	3	0.75	0	0.00
5x ≤ AST < 10x ULN		5	2.25	2	0.90	0	0.00	0	0.00	6	0.93	4	0.62	0	0.00	0	0.00	5	1.26	6	1.51	1	0.25	0	0.00
10x ≤ AST < 20x ULN		3	1.35	2	0.90	0	0.00	0	0.00	2	0.31	0	0.00	0	0.00	0	0.00	1	0.25	1	0.25	0	0.00	0	0.00
AST ≥ 20x ULN		0	0.00	0	0.00	0	0.00	0	0.00	2	0.31	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

		DCV 60mg QD + ASV 100mg BID (24W) N = 222				DCV 60mg QD + ASV 100 mg BID N = 645				DCV 60mg + ASV 100mg BID + PegIFN + RBV (24W) N = 398															
ALP Baseline		ALP < 2x ULN	2x ≤ ALP < 5x ULN	5x ≤ ALP < 10x ULN	ALP ≥ 10x ULN	ALP < 2x ULN	2x ≤ ALP < 5x ULN	5x ≤ ALP < 10x ULN	ALP ≥ 10x ULN	ALP < 2x ULN	2x ≤ ALP < 5x ULN	5x ≤ ALP < 10x ULN	ALP ≥ 10x ULN												
ALP Maximum		Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%												
ALP < 2x ULN		217	97.75	0	0.00	0	0.00	0	0.00	641	99.38	0	0.00	0	0.00	0	0.00	396	99.50	0	0.00	0	0.00	0	0.00
2x ≤ ALP < 5x ULN		4	1.80	1	0.45	0	0.00	0	0.00	2	0.31	0	0.00	0	0.00	0	0.00	2	0.50	0	0.00	0	0.00	0	0.00
5x ≤ ALP < 10x ULN		0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
10x ≤ ALP < 20x ULN		0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
ALP ≥ 20x ULN		0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

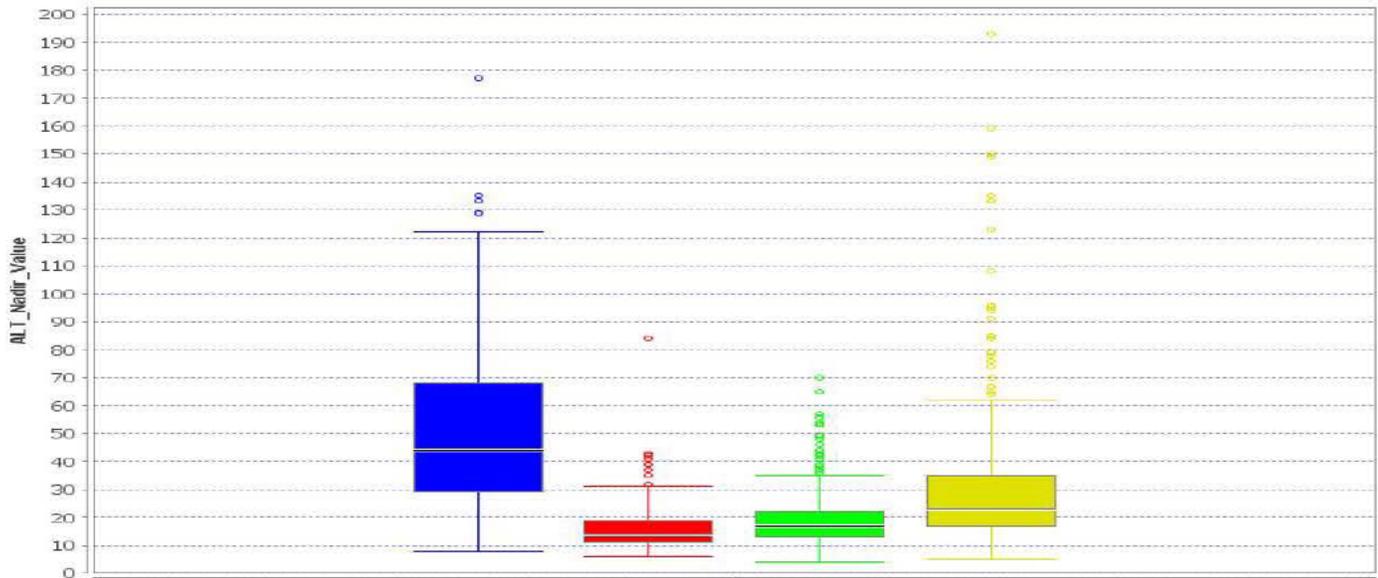
		DCV 60mg QD + ASV 100mg BID (24W) N = 222				DCV 60mg QD + ASV 100 mg BID N = 645				DCV 60mg + ASV 100mg BID + PegIFN + RBV (24W) N = 398															
TB Baseline		TB < 2x ULN	2x ≤ TB < 5x ULN	5x ≤ TB < 10x ULN	TB ≥ 10x ULN	TB < 2x ULN	2x ≤ TB < 5x ULN	5x ≤ TB < 10x ULN	TB ≥ 10x ULN	TB < 2x ULN	2x ≤ TB < 5x ULN	5x ≤ TB < 10x ULN	TB ≥ 10x ULN												
TB Maximum		Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%												
TB < 2x ULN		218	98.20	0	0.00	0	0.00	0	0.00	633	98.14	0	0.00	0	0.00	0	0.00	381	95.73	1	0.25	0	0.00	0	0.00
2x ≤ TB < 5x ULN		4	1.80	0	0.00	0	0.00	0	0.00	9	1.40	1	0.16	0	0.00	0	0.00	12	3.02	4	1.01	0	0.00	0	0.00
5x ≤ TB < 10x ULN		0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
10x ≤ TB < 20x ULN		0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
TB ≥ 20x ULN		0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Note: Subjects who have only baseline visit information or who were missing a baseline visit but had post baseline visits were not included in the Subject Counts, therefore, percents may not add up to 100.

ALT Nadir Analyses

Mean and Median Values for ALT nadir by Phase 3 trial

ALT NADIR Summary Box Whiskers Plot Safety Population - Subset of patients
LBTESTCD: ALT



	ALT Nadir			
	Placebo 028	Dual 026	Dual 028	Quad 029
Mean	53.23	16.09	18.59	30.71
Median	44.00	14.00	17.00	23.00
Q1	29.00	11.00	13.00	17.00
Q3	68.00	19.00	22.00	35.00
N	102	222	642	398

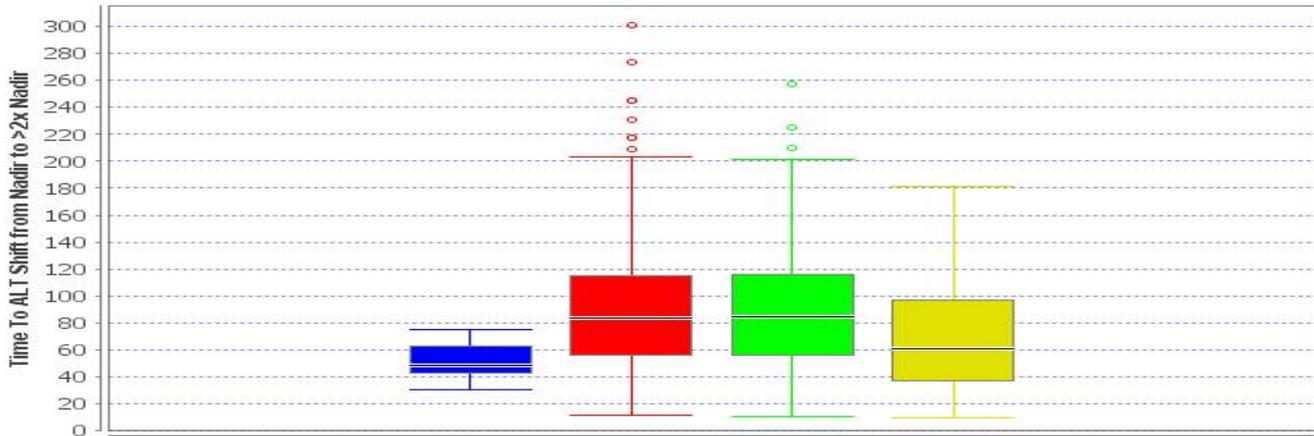


Patient Selection Criteria: Subject-Level Analysis Dataset Safety Population Flag =Y

Time (in Days) from ALT Nadir to 2x Nadir Value

Time to ALT Shift from Nadir to 2x Nadir post Nadir - Subset of patients

LBTESTCD: ALT



ALT Shift from Nadir

	Placebo 028	Dual 026	Dual 028	Quad 029
Mean	52.14	88.01	88.19	68.64
Median	49.00	84.00	85.00	61.00
Q1	42.50	56.00	56.00	37.00
Q3	62.50	115.00	116.00	96.50
N	4	94	207	86

ALT_Shift

Series

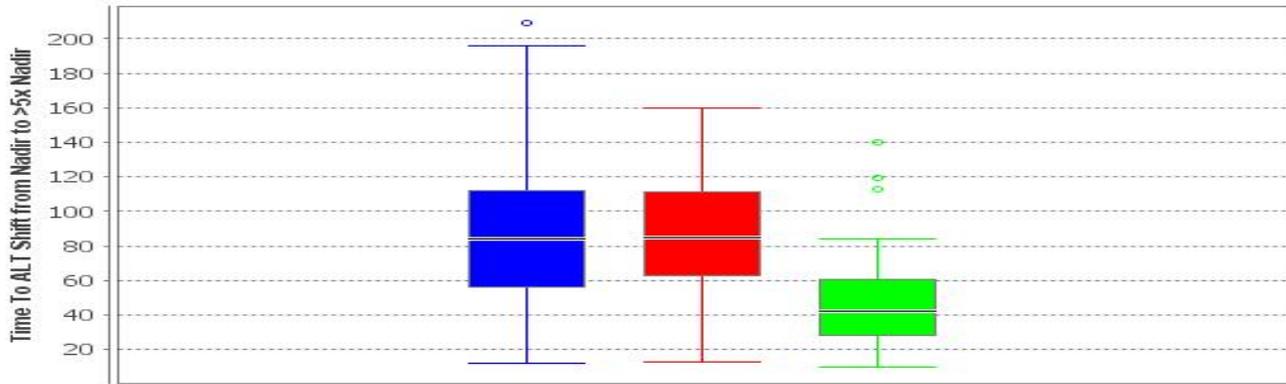
■ Placebo 028 ■ Dual 026 ■ Dual 028 ■ Quad 029

Patient Selection Criteria: Subject-Level Analysis Dataset.Safety Population Flag =Y
 Output Filter: ALT results with Nadir.Post_Nadir_Value =1

Proportions of Subjects who met criteria of 2x nadir: PBO: 4%; DUAL 7026: 42%; DUAL 7028: 32%; QUAD 7029: 22%

Time (in Days) from ALT Nadir to 5x Nadir Value

Time To ALT Shift from Nadir to >5x Nadir - Subset of patients
LBTESTCD: ALT



	ALT Shift from Nadir		
	Dual 026	Dual 028	Quad 029
Mean	84.94	85.66	50.97
Median	84.00	84.50	42.00
Q1	56.00	63.00	28.00
Q3	112.00	111.00	60.50
N	41	75	22

ALT_Shift
Series
■ Dual 026 ■ Dual 028 ■ Quad 029

Patient Selection Criteria: Subject-Level Analysis Dataset.Safety Population Flag =Y

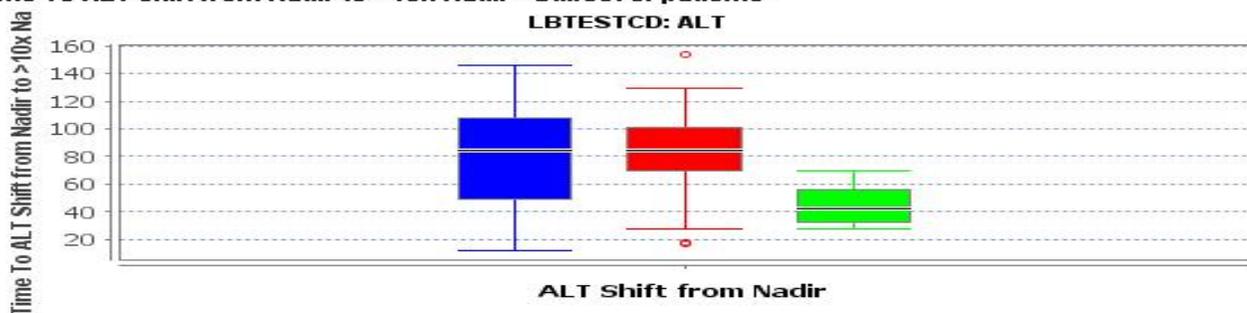
Output Filter: ALT results with Nadir.Post_Nadir_Value =1 AND ALT results with Nadir.Time_To_ALT_gr_5x...

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Proportions of Subjects who met criteria of 5 x nadir: DUAL 7026:18%; DUAL 7028: 12%; QUAD 7029: 6%

Time (in Days) from ALT Nadir to 10x Nadir Value

Time To ALT shift from Nadir to >10x Nadir - Subset of patients
LBTESTCD: ALT



	ALT Shift from Nadir		
	Dual 026	Dual 028	Quad 029
Mean	77.87	81.96	44.88
Median	84.00	84.50	42.00
Q1	49.50	70.00	32.50
Q3	107.50	101.00	56.00
N	23	24	6

ALT_Shift
Series
■ Dual 026 ■ Dual 028 ■ Quad 029

Patient Selection Criteria: Subject-Level Analysis Dataset.Safety Population Flag =Y

Output Filter: ALT results with Nadir.Post_Nadir_Value =1 AND ALT results with Nadir.Time_To_ALT_gr...

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Proportions of Subjects who met criteria of 10x nadir: DUAL 7026: 10%; DUAL 7028: 4%; QUAD 7029: 2%

II. Overview of Potential Drug-Induced Liver Injury and Hy's Law Cases

In the protocols, pDILI was defined as concurrent ALT \geq 5x Baseline or nadir value, whichever is lower, **and** \geq 10 x ULN **and** TBILI \geq 2 x ULN on study (on treatment or during follow-up) for treated subjects. Concurrent was defined as the bilirubin elevation occurring within 30 days subsequent to the ALT elevation. In total, 4 subjects from the phase 3 clinical trials met these criteria [Subjects AI447026-2-10122, AI447026-1-20265, AI477028-44-80975 and AI447029-95-90110].

Hy's Law Analyses

The definition used by the FDA as indicator of clinical concern for drug-induced liver injury includes: ALT or AST $>$ 3x upper limit of normal (ULN), total bilirubin $>$ 2x ULN without an initial increase in alkaline phosphatase. Overall from the Phase 3 trials, there were 9 DCV/ASV exposed subjects (0.7%; 9/1265) who met the laboratory criteria for Hy's Law as discussed above, and 1 subject (1%; 1/102) who was randomized to placebo in trial 7028.

Subject IDs:

AI447026-19-10230

AI447026-2-10122

AI447026-1-20265

AI447028-45-80287 (placebo)

AI447028-44-80975

AI447028-8-80187

AI447028-84-80492

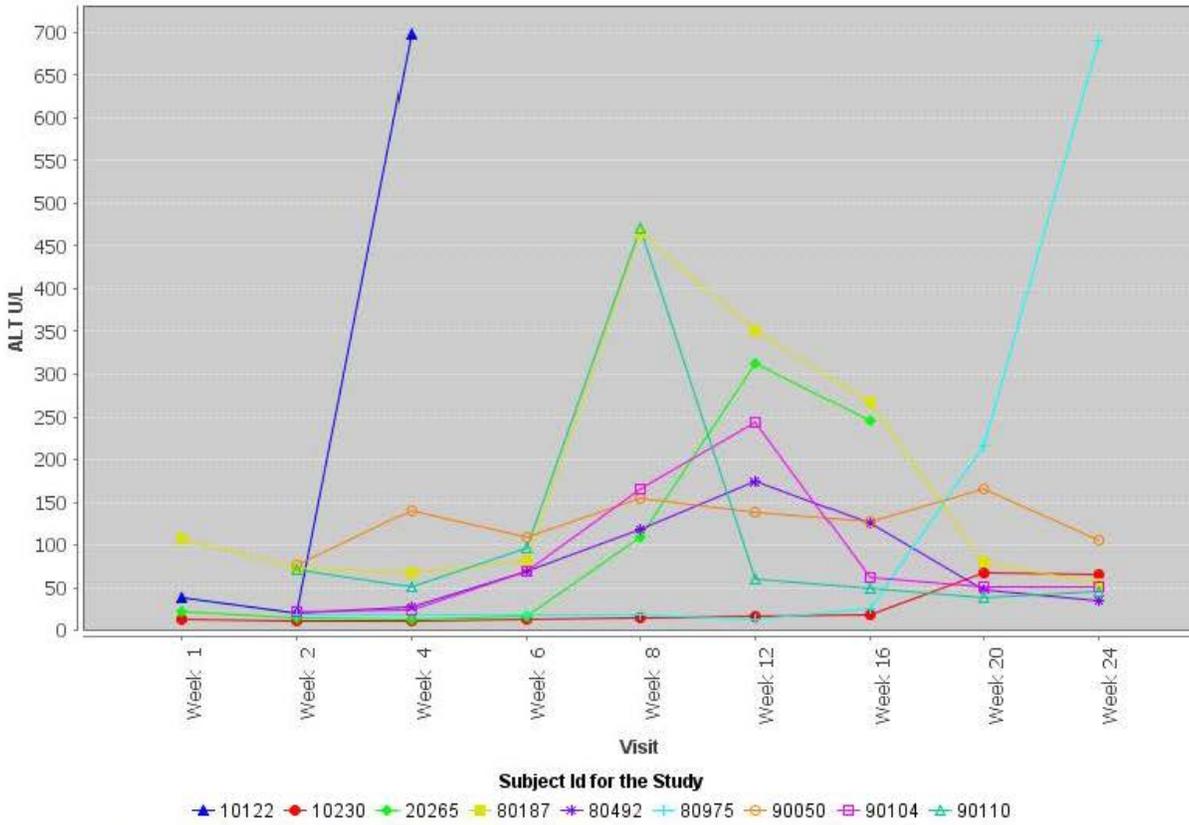
AI447029-25-90104

AI447029-25-90110

AI447029-34-90050

ALT by Study Visit for Hy's Law Subjects

- Subset of patients

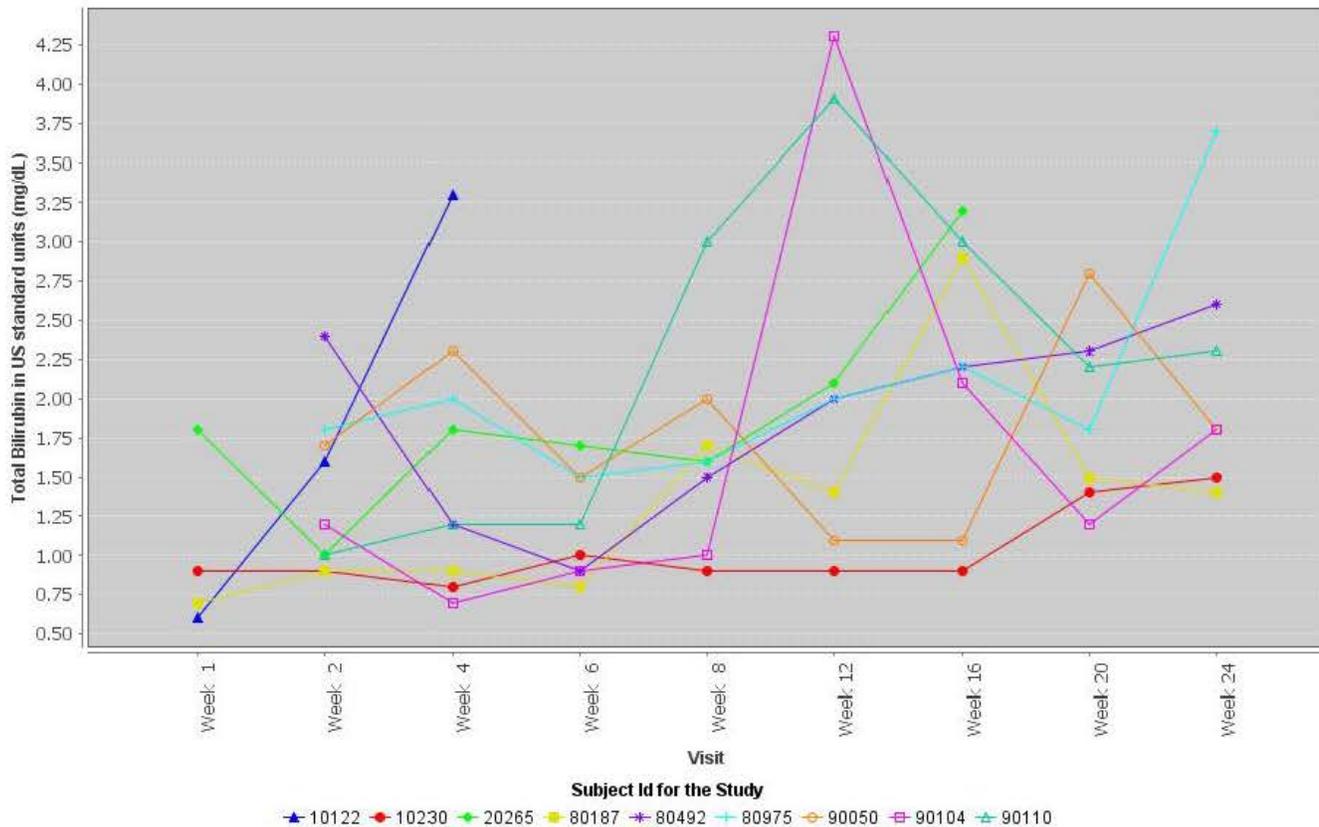


ALT by Study Visit for 9 subjects who met Hy's Law lab criteria

Patient Selection Criteria: <html> Demographics.Unique Subject Identifier=AI447026-1-20265,AI447026-19-10230,AI447026-2-10122 \$ OR D...
 Output Filter: Laboratory Results with US Units.Drv: Lab Test or Examination Code =Alanine AminoTransferase (ALT) AND Laboratory Results ...

TBILI by Study Visit for Hy's Law Subjects

- Subset of patients



Total Bilirubin (mg/dL) by Study Visit for 9 subjects who met Hy's Law lab criteria

Patient Selection Criteria: <html> Demographics.Unique Subject Identifier=AI447026-1-20265,AI447026-19-10230,AI447026-2-10122 \$ OR Demographics.Unique Su...

Output Filter: Laboratory Results with US Units.Drv: Period=On Treat AND Laboratory Results with US Units.Drv: Visit Number=DAY 1,WEEK 1,WEEK 12,WEEK 16,WE...

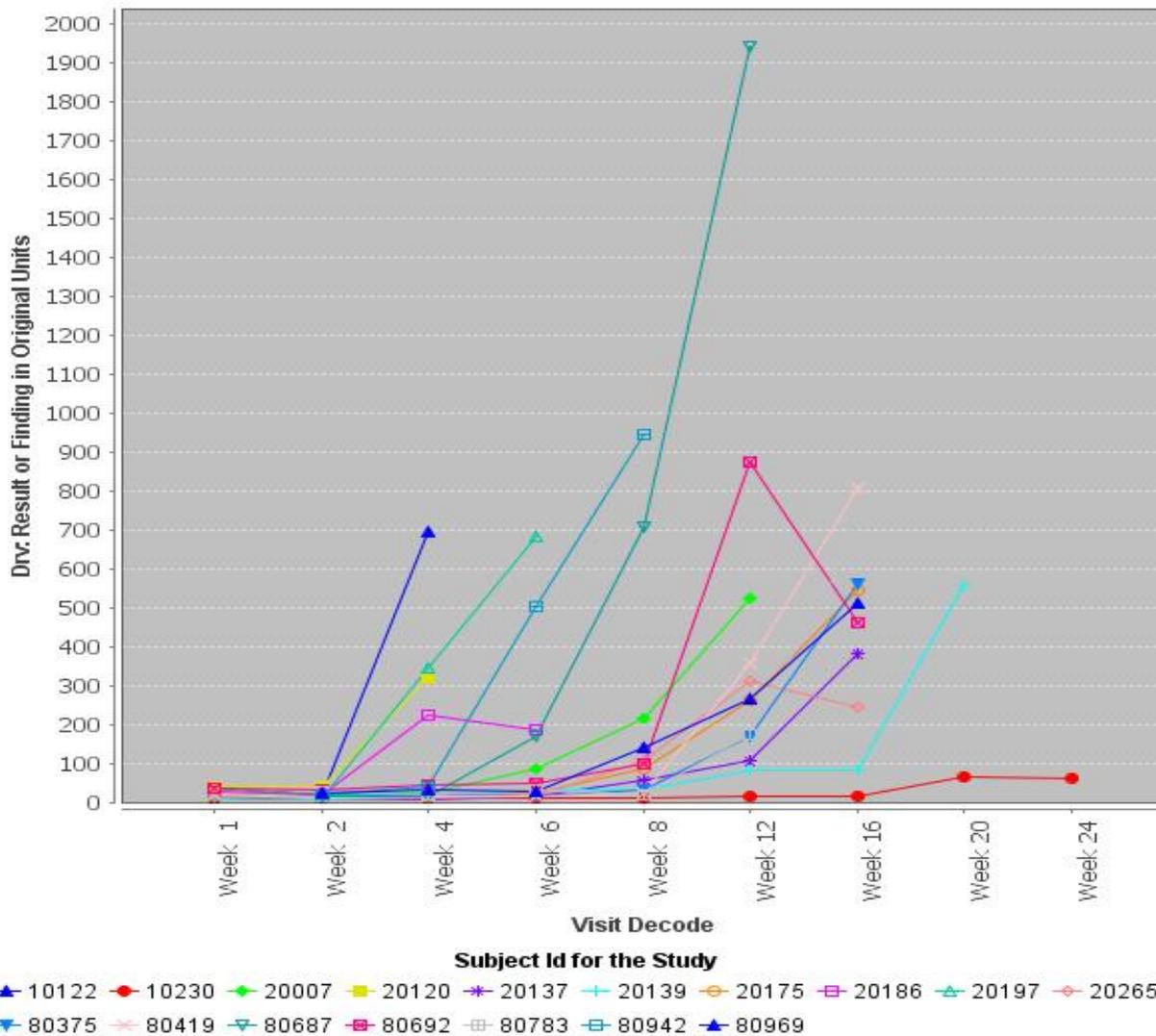
Liver-Related Events Leading to Discontinuation

Table 8: Summary of Liver-Related AEs Leading to Study Drug Dose Modification, Interruption or Withdraw

		AI447026	AI447028	AI447029
Action With Drug		DCV 60 mg QD + ASV 100 mg BID (24 W) N=222	DCV 60 mg QD + ASV 100 mg BID (24 W) N=645	DCV 60 mg QD + ASV 100 mg BID + PegIFN + RBV (24W) N=398
Subjects with an Event		14 (6%)	8 (1%)	5 (1%)
Subjects who Withdraw due to an Event		10 (5%)	7 (1%)	1 (<1%)
ALANINE AMINOTRANSFERASE INCREASED	Interrupted	2 (1%)	4 (1%)	0
	Withdrawn	10 (5%)	4 (1%)	0
ASPARTATE AMINOTRANSFERASE INCREASED	Interrupted	2 (1%)	0	0
	Withdrawn	10 (5%)	1 (<1%)	0
BLOOD BILIRUBIN INCREASED	Interrupted	1 (<1%)	0	0
	Withdrawn	3 (1%)	0	0
HEPATIC ENZYME INCREASED	Interrupted	0	0	3 (1%)
	Withdrawn	0	0	1 (<1%)
HYPERTRANSAMINASAEMIA	Interrupted	0	1 (<1%)	0
	Withdrawn	0	1 (<1%)	0
LIVER DISORDER	Interrupted	1 (<1%)	0	0
PROTHROMBIN TIME PROLONGED		1 (<1%)	0	0
TRANSAMINASES INCREASED	Dose Reduced	0	0	1 (<1%)
	Interrupted	0	1 (<1%)	0
	Withdrawn	0	2 (<1%)	0

ALT over Time for Subjects Who Discontinued Due to Liver-Related AEs

ALT by visit for 17 Subjects who Discontinued for Liver Biochemistry Abnormalities - Subset of patients



Patient Selection Criteria: <html> Subject-Level Analysis Dataset.Safety Population Flag =Y \$ AND Adverse E...
 Output Filter: Laboratory Results with US Units.Dvr: Lab Test or Examination Code =Alanine Aminotransfera...
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III. Analyses for Further Characterization of Pyrexia and Eosinophilia

FDA conducted a broad evaluation to identify subjects who may meet clinical characteristics of a drug hypersensitivity reaction by evaluating any subject with an AE report of pyrexia (note: temperature was not routinely collected during trials, and had at least one laboratory eosinophil count above normal. Based on these broad criteria, 37 subjects were identified from the Phase 3 trials (7026, 7028 and 7029). Subsequently, each subject's data was examined to determine other pertinent clinical findings that may support or confound a case of possible pyrexia with eosinophilia. Cases were evaluated to determine if, after the AE of pyrexia with an accompanying eosinophila, rash was a part of the clinical syndrome or whether subjects had any ALT increase over normal levels or any elevations or bilirubin or AE reports consistent with significant liver injury.

The following tables provide a summary of these analyses. Table 9 summarizes the clinical findings of those subjects who met the criteria of an AE report of pyrexia and had an elevated eosinophil count by laboratory

data within 2 weeks. Table 10 summarizes the clinical findings of those subjects who did not meet the criteria of an AE report of pyrexia with an elevated eosinophil count within 2 weeks. It is important to note that although all 3 trials were evaluated with the same criteria, only subjects from the Japanese trial 7026 met the criteria for inclusion in Table 9. Similarly, the same analysis was done with the supportive Phase 2 data for DCV and ASV included the Integrated Safety Summary (ISS) datasets. Evaluation of the 994 subjects from this database, found 19 subjects who met the broad criteria of pyrexia and elevated eosinophil count. Of these 19 subjects, 7 met the criteria of an AE report of pyrexia and had an elevated eosinophil count by laboratory data within 2 weeks, and 6 of the 7 subjects are Japanese. The single subject who is not Japanese had a baseline elevated eosinophil count which is higher than those observed while on therapy, and therefore, has a different clinical presentation than the other cases. These subjects are summarized in Table 11.

For reference, a general scale for fraction of eosinophils is provided here. Almost uniformly, subjects did not have wbc counts above normal levels at the time of eosinophil elevations. For the few exceptions, wbc elevations were generally at most $10\text{-}12 \times 10^9$ cells/L. Additionally, the Phase 3 trials reported absolute eosinophils in various unit formats (7026 as percentage, 7028 and 7029 as $\times 10^3$ c/uL or $\times 10^9$ c/L). Standardized grading scale was not available for eosinophilia for the clinical trials.

The reference scale used for the eosinophil counts which were reported as absolute eosinophil values and provided as % the datasets was generalized and is provided here:

- 0 to 6% [0.00-0.06] (normal)
- 7 to 10% [0.07-0.10] (slightly elevated) **GREEN in tables**
- 11-20% [0.11-0.20] (elevated) **BLUE in tables**
- Over 20% [0.20] (high) **RED in tables**

A summary of findings is provided following the tables.

Table 9: Subjects with AE Report of Pyrexia and Increased Eosinophils (above nl) within 2 weeks

Subj ID	Pyrexia and Eosinophilia (within 2W)	Race	Confounding Factors	ALT increase (over nl)	Max Grade ALT	Time to Max Grade ALT	Inc Bili or symptomatic?	Rash?	D/C?	SVR 12?
AI447026 (16 subjects of 222 total=7%)										
2-10122	Yes (Eos 54% W4) (liver bx, eosinophilic DILI)	Japanese	High Levels of ASV and DCV, taking 2x DCV dosing	Yes	GD 4 (peak 697)	W4, resolved by W7 on prednisone	GD 2 (2.9)	No	Yes	No
1-20265	Yes (Eos 13% W2)	Japanese	-	Yes	GD 3 (312)	W9	GD 3	No	Yes	Yes
8-20120*	Yes (pyrexia moderate, Eos 34% W3)	Japanese	Cefotiam, Teprenone (hepatic warning)	Yes	GD 3 (323)	W5, resolved by W7	-	No	Yes (W5; achieves SVR12)	Yes
7-20200**	Yes (Eos 22.5% W4)	Japanese	-	Yes	GD 2 (114)	W4, resolved W6 on Tx	-	Yes	No	Yes
11-10115	Yes (Eos 15.8% W4)	Japanese	-	Yes	GD 2 (155)	W22	GD 2 (1 blip then returns to nl)	No	No	No
14-10161	Yes (Eos 26% W4)	Japanese	-	Yes	GD 1 (112)	W24	-	No	No	Yes
7-10193	Yes (Eos 9.1% W4)	Japanese	PR rescue	Yes	GD 1 (50)	W8	-	No	Yes-lack of efficacy	No
9-10087	Yes (Eos 37.6% W3)	Japanese	Also PT of lymphadenopathy, Prolonged PT and Thrombocytopenia but by labs data all nl or G0	Yes	GD 1 (43)	W2, resolved W3	-	No	No	Yes

9-20248	Yes (Eos 10.9% W3)	Japanese	Malaise, PT prolonged, Thrombocytopenia (plt 127- GD0)-	Yes	GD 1 (99)	W16, resolved W20	G2 blip at W2, ALT trend down, INR GD1 (1.4) W2	No	No	Yes
15-20271	Yes (Eos 12% W4)	Japanese	-	Yes	GD 0 (41)	W4	GD 1 (1 time) W2	No	No	Yes
18-20093	Yes (Eos 25.9% W4)	Japanese	-	No	-	-	-	No	No	Yes
19-20273	Yes (Eos 15.4% W10) Pyrexia late at W6, then W10-16	Japanese	Conjunctivitis Allergic (W6-24)	No	-	-	-	No	No	No
1-10059	Yes (Eos 10% W3)	Japanese	Second degree burns/wound complication	No	-	-	-	No	No	Yes
23-20272	Yes (Eos 9.4% W6)	Japanese	-	No	-	-	-	No	No	Yes
10-10062	Yes (Eos 16% W4)	Japanese	-	No	-	-	-	No	No	Yes
8-20032	Yes (Eos 22% W2, moderate pyrexia)	Japanese	-	No	-	-	-	No	No	Yes

*This case has elevated EOS, ALT and AST at same week

**This case has elevated EOS, ALT and AST with Pyrexia all at Week 4, and develops Arthralgia at W12-W24 (D92-169); all considered related

Table 10: Subjects With Events of Pyrexia and Eosinophilia But Not Within 2 Weeks of Reported Pyrexia

Subj ID	Pyrexia and Eosinophilia (within 2W)	Race	Confounding Factors	ALT increase	Max Grade ALT	Time to Max Grade ALT	Inc Bili or symptomatic	Rash	D/C	SVR?
AI447026 (N=12)										
11-10095	No	Japanese	-	No	-	-	-	No	No	Yes
11-10207	No	Japanese	-	No	-	-	-	No	No	Yes
12-10023	No	Japanese	PR rescue	No	-	-	-	No	No	No
17-20256	No	Japanese	-	No	-	-	-	No	No	Yes
18-10044	No	Japanese	PR rescue	Yes	Gd1	W30	-	No	No	Yes
18-10060	No	Japanese	PR rescue	No	-	-	-	No	Yes...Lack of efficacy	No
18-10257	No	Japanese	-		-	-	-	No	No	Yes
19-20145	No	Japanese	-	No	-	-	-	No	No	Yes
3-10130	No	Japanese	PR rescue	Yes	Gd0	W36 on rescue	-	Yes	No	Yes
4-10090	No	Japanese	PR rescue	No	-	-	-	No	No	No
8-10037	No	Japanese	-	No	-	-	-	No	No	Yes
8-20160	No	Japanese	-	No	-	-	-	No	No	Yes

AI447028- Global Dual (N=3)

111-80376	No	White	-	No	-	-	-	No	No	Yes
14-80974	No	White	-	No	-	-	-	No	No	Yes
54-80098	No	White	Cough, dysphonia, rhinorrhea	No	-	-	-	No	No	Yes

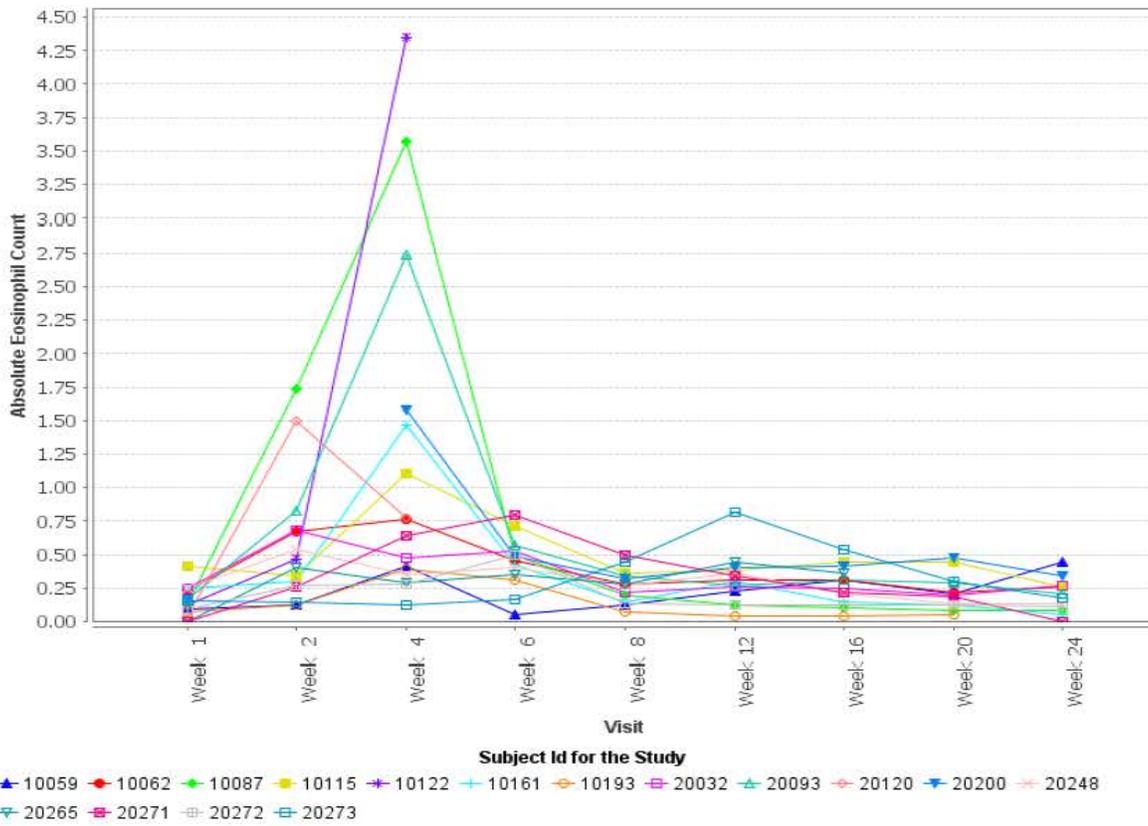
AI447029 – QUAD (N=6)

11-90289	No	White	Peg/RBV	No	-	-	-	No	No	Yes
22-90452	No	White	Peg/RBV	No	-	-	-	No	No	Yes
30-90093	No	White	Peg/RBV	No	-	-	-	Yes	No	Yes
41-90194	No	White	Peg/RBV	No	-	-	-	Yes	No	Yes
7-90306	No	White	Peg/RBV	Yes	GD1	W20	GD2 W16	No	No	Yes
96-90490	No	White	Peg/RBV	Yes	GD2	W20	GD2 W2	No	No	Yes

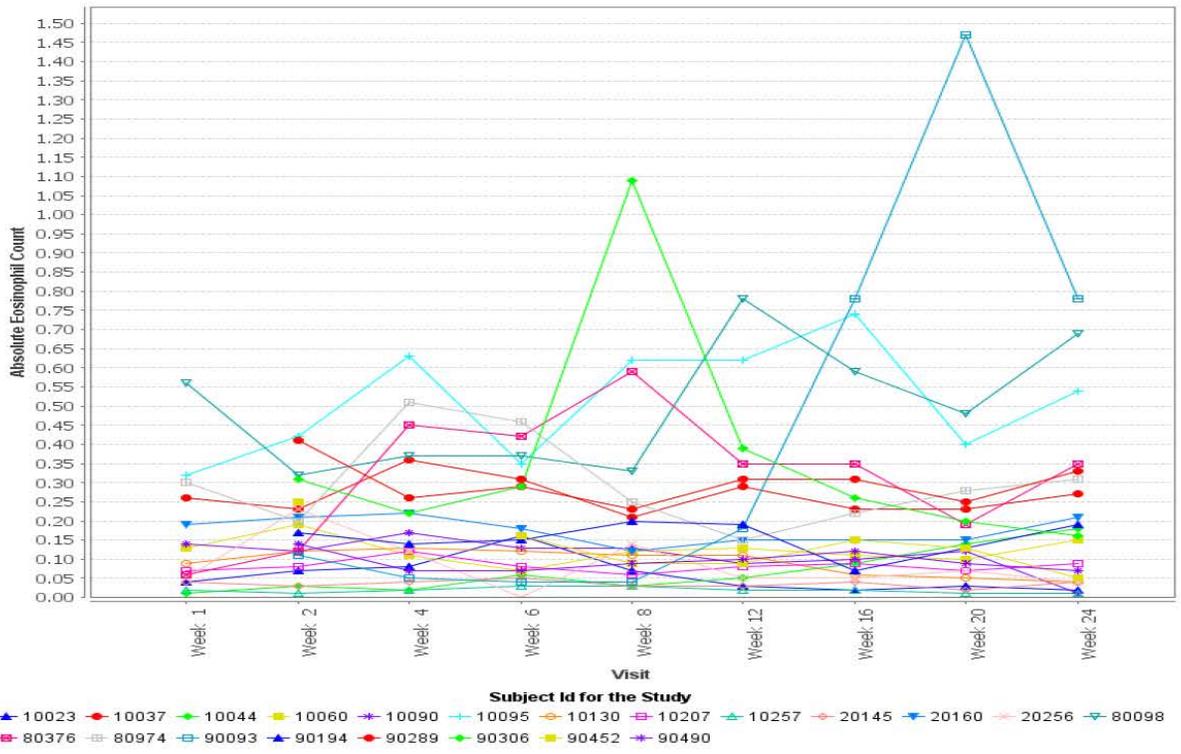
Table 11: 7 Subjects From Phase 2 trials (ISS dataset) Who Met Criteria of Pyrexia and Eosinophilia within 2 weeks

Subj ID	Pyrexia and Eosinophilia (within 2W)	Race	Confounding Factors	ALT increase	Max Grade ALT	Time to Max Grade ALT	Inc Bili or symptomatic	Rash?	D/C?
AI444011 (Phase 2 DCV 60 mg + PR)									
78-392*	Yes (Eos 0.77A; peak 1.02 at W51,BUT 1.07 at Baseline)	White/Argentina	PR, rash that is GD2 & persists W10-W51, No eos above BL level	Yes	GD 1 (75 and not above BL	W28	-	Yes	No
AI444021 (Phase 2 DCV 60 mg + PR)									
4-21102	Yes (Eos 10.5%, .354 A) at W1	Asian/Japan	PR, rash	No	-	-	-	Yes	No
4-21108	Yes (Eos 9%, .215A) at W11	Asian/Japan	PR	No	-	-	-	No	No
AI447017 (Phase 2 DUAL DCV/ASV) (4 subjects of total 33 in this arm=12%)									
1-1008	Yes (Eos 27.8%) W4	Asian/Japan	-	Yes	GD1 (68)	W2	GD1	No	No
3-3005	Yes (Eos 35.4%) W3	Asian/Japan	-	Yes	GD2 (143)	W2/nl W4	GD2 (W2)/nl W4	No	No
3-3015	Yes (Eos 24%) W3	Asian/Japan	-	Yes	GD1 (56)	W3	No	No	No
3-3017	Yes (Eos 8.5%)	Asian/Japan	-	Yes	GD1 (61)	W25/GD0 at W3 (39)	No	No	No

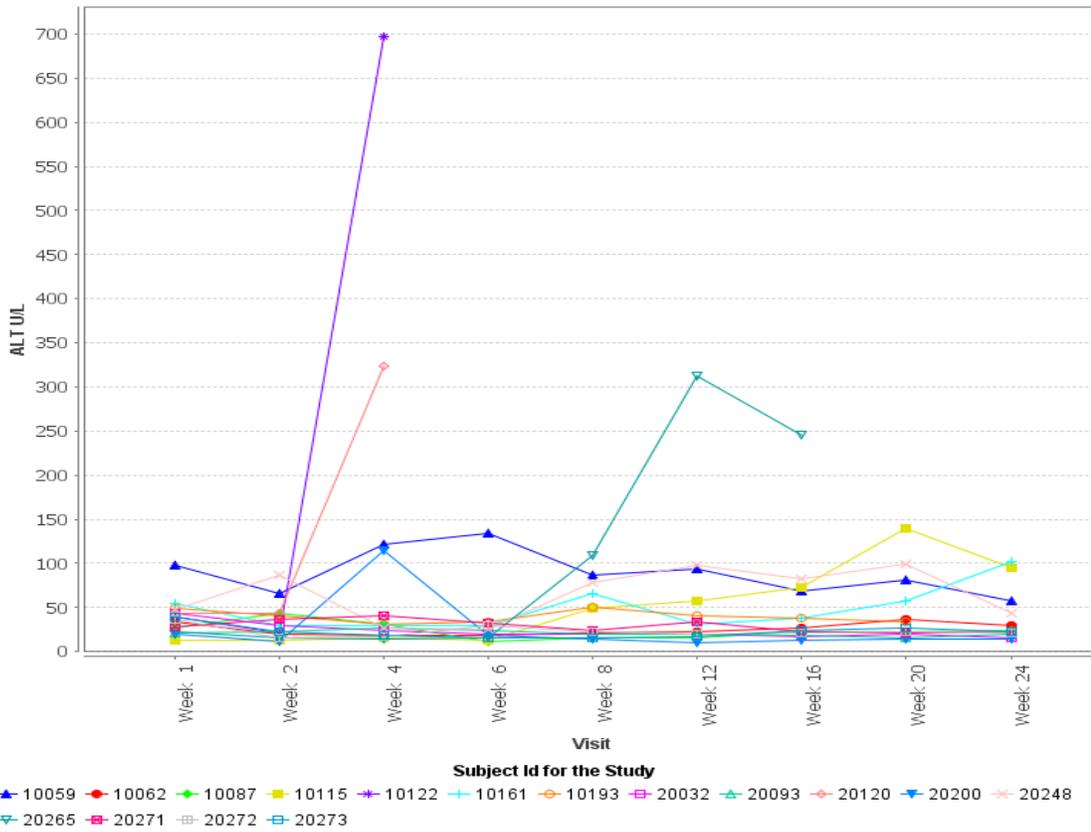
Absolute Eosinophils for 16 Subjects with Pyrexia and Eosinophilia Within 2 Weeks



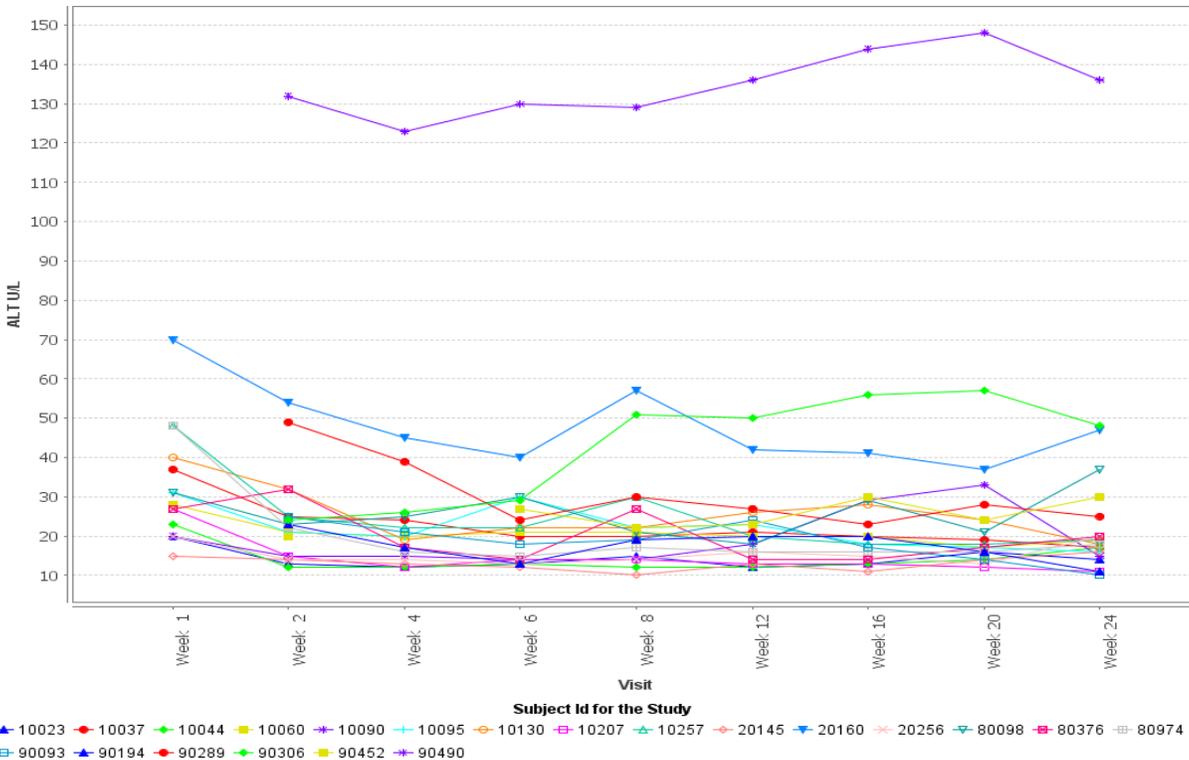
Absolute Eosinophils for 21 Subjects With Pyrexia and Eosinophilia Not Within 2 Weeks



ALT by Visit for 16 Subjects with Pyrexia and Eosinophilia Within 2 Weeks



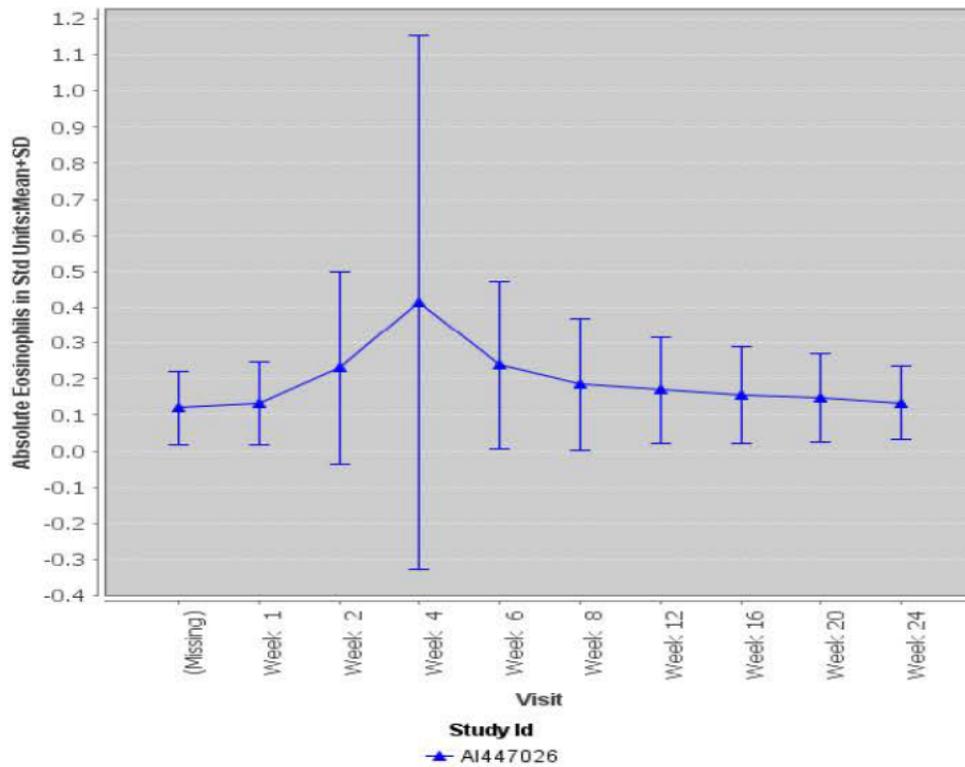
ALT by Visit for 21 Subjects With Pyrexia and Eosinophilia Not Within 2 Weeks



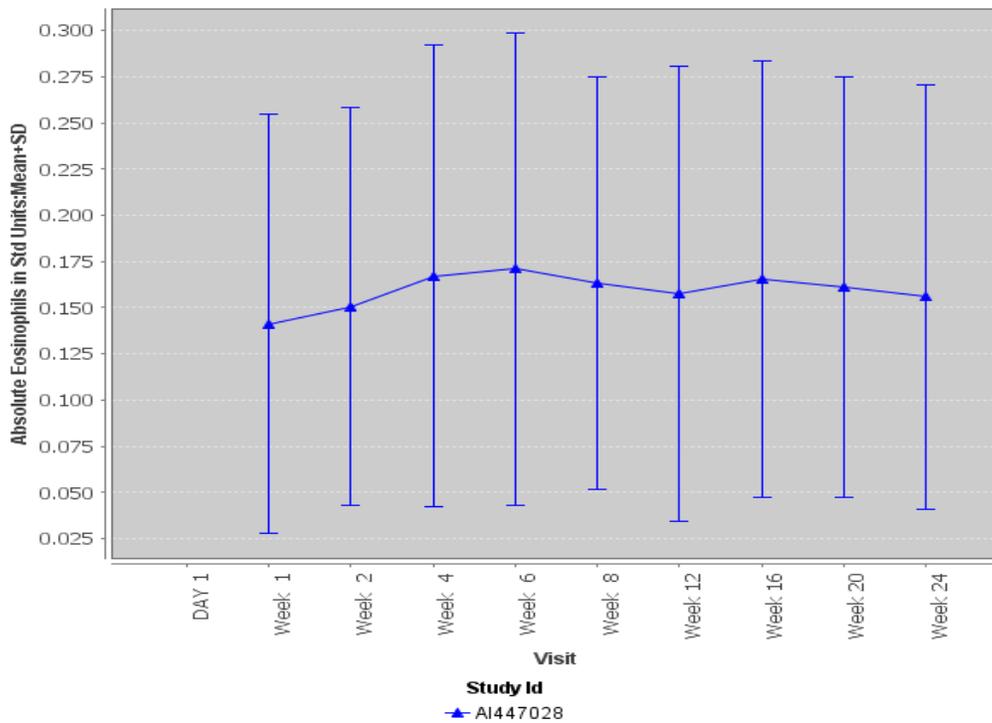
Assessment of Japanese Prevalence of Pyrexia and Eosinophilia

Analyses of the mean and standard deviation of absolute eosinophils were completed to evaluate the overall trend of eosinophils in the Japanese DUAL trial 7026 compared to the global DUAL trial 7028.

Absolute Eosinophils Mean and SD by Visit for Trial 7026



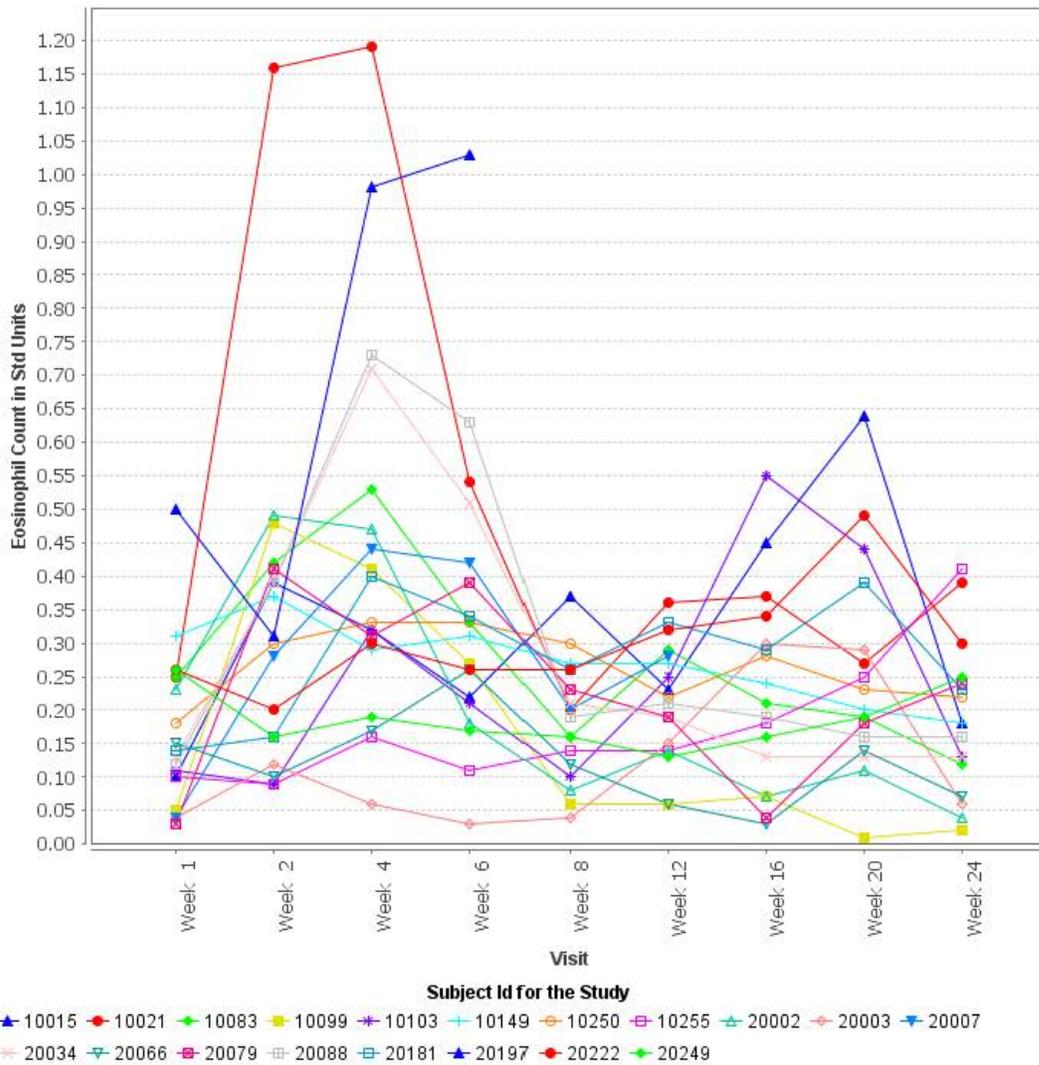
Absolute Eosinophils Mean and SD by Visit for Trial 7028



A. Adverse Event Reporting of Pyrexia

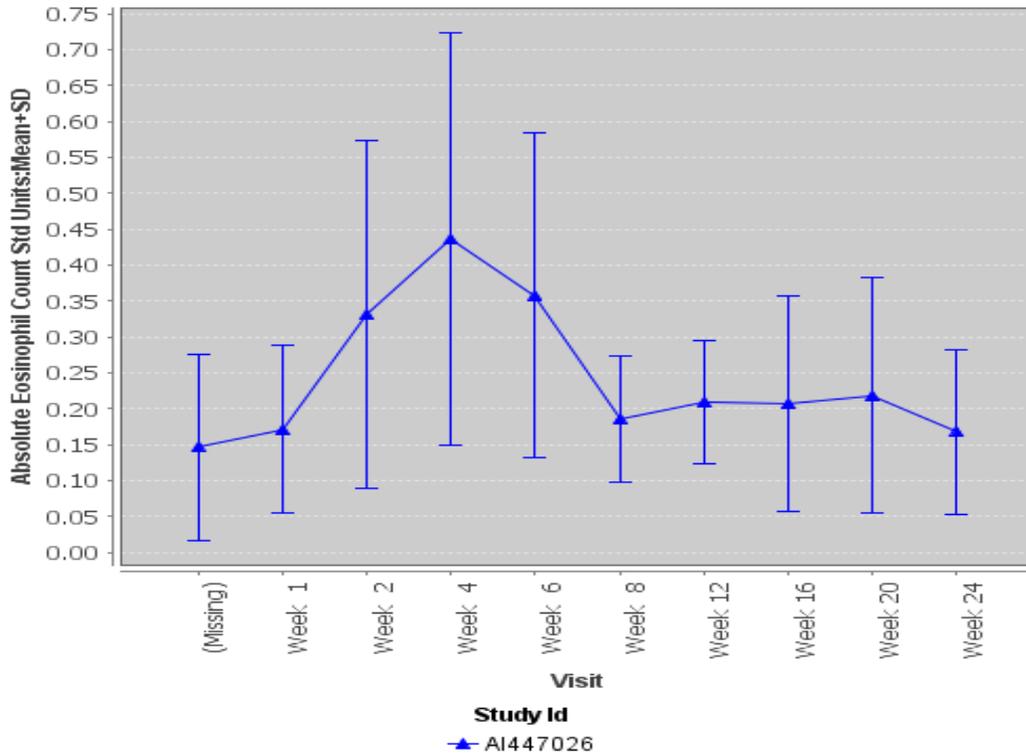
To further characterize whether a similar pattern of eosinophilia with and without liver involvement were observed in subjects without pyrexia, additional analyses of the DUAL trials 7026 and 7028 were completed. The QUAD trial 7029 was excluded from these analyses due to the concomitant use of PegIFN/RBV. Any subject with an elevated absolute eosinophil count (>9%) while on treatment for subjects in trial 7026 and > 0.7×10^9 c/L (reported as original units for 7028, and standard units are $\times 10^3$ c/uL) for subjects in trial 7028 were included in the analyses. Note the differences in the eosinophil units are a function of the reported data; trial 7026 reported absolute eosinophils as a percentage unit and 7028 used 10^9 c/L or 10^3 c/uL. Additionally, subjects who had reported an AE of pyrexia were excluded.

Absolute Eosinophil Count by Visit for Subjects with Elevated Absolute Eosinophils without Pyrexia—

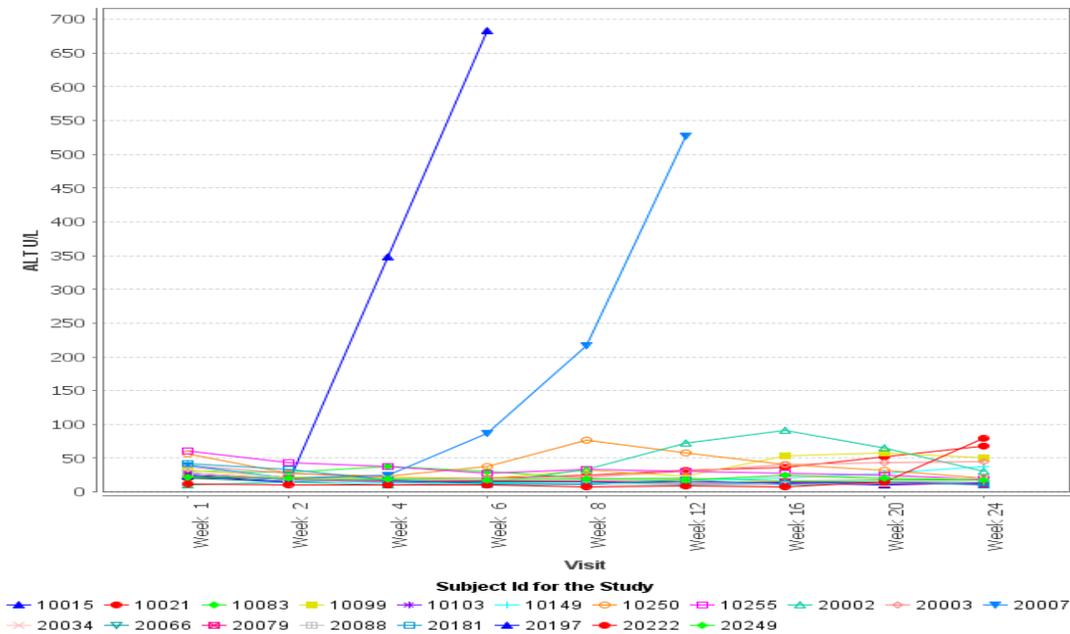


Trial 7026

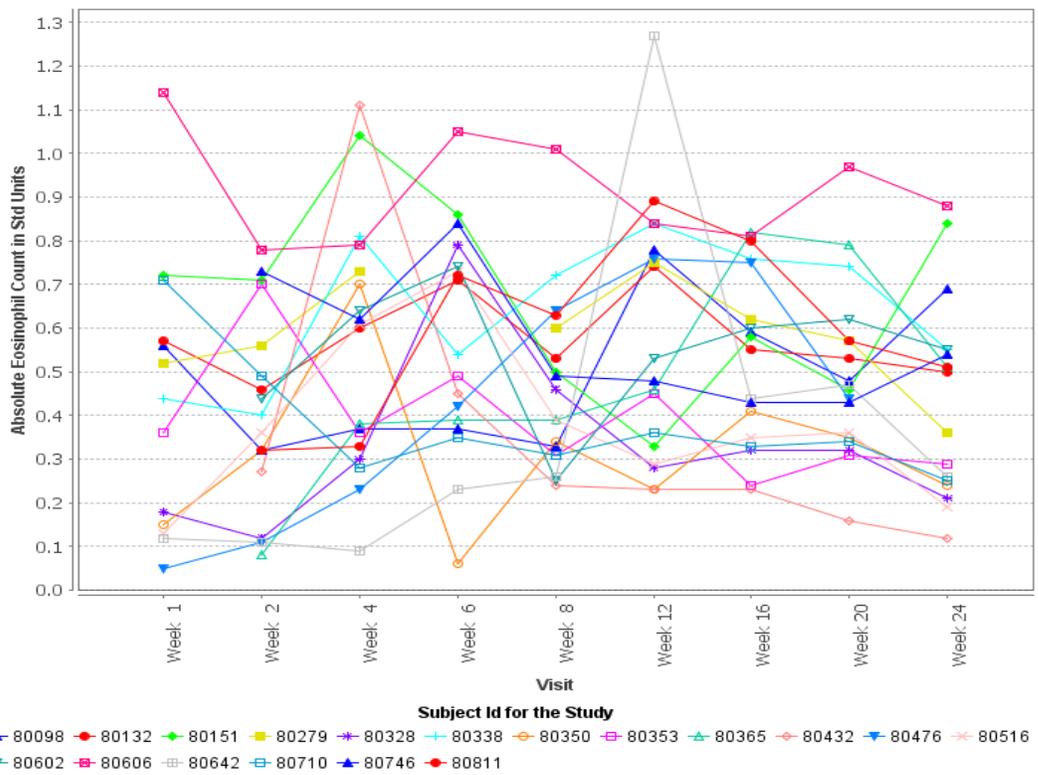
Mean and SD of Absolute Eosinophil Count by Visit for Subjects with Elevated Absolute Eosinophils without Pyrexia—Trial 7026



ALT by Visit for Subjects with Elevated Absolute Eosinophils without Pyrexia—Trial 7026

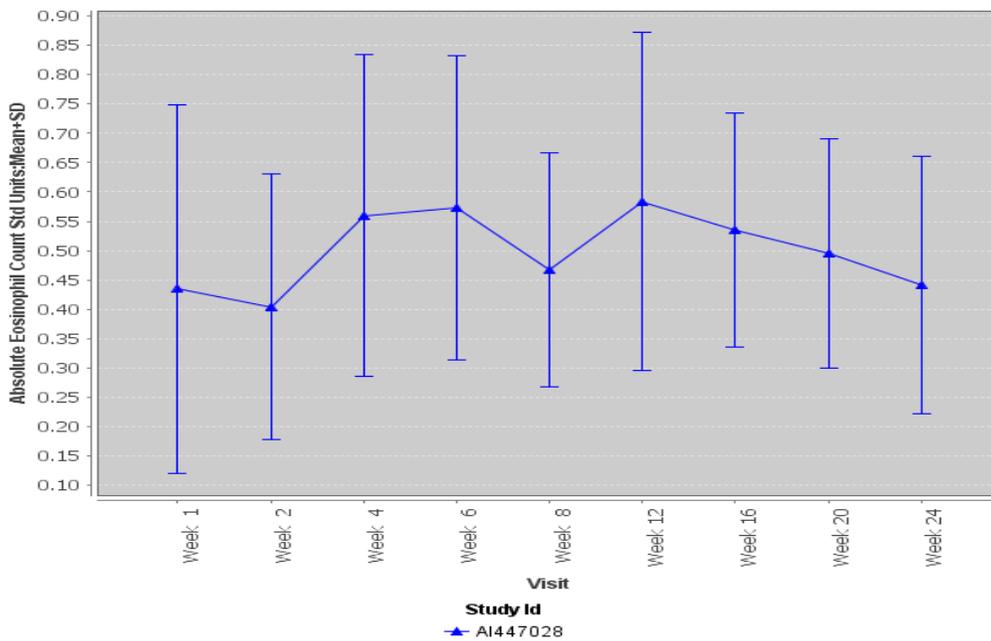


Absolute Eosinophil Count by Visit for Subjects with Elevated Absolute Eosinophils without Pyrexia—

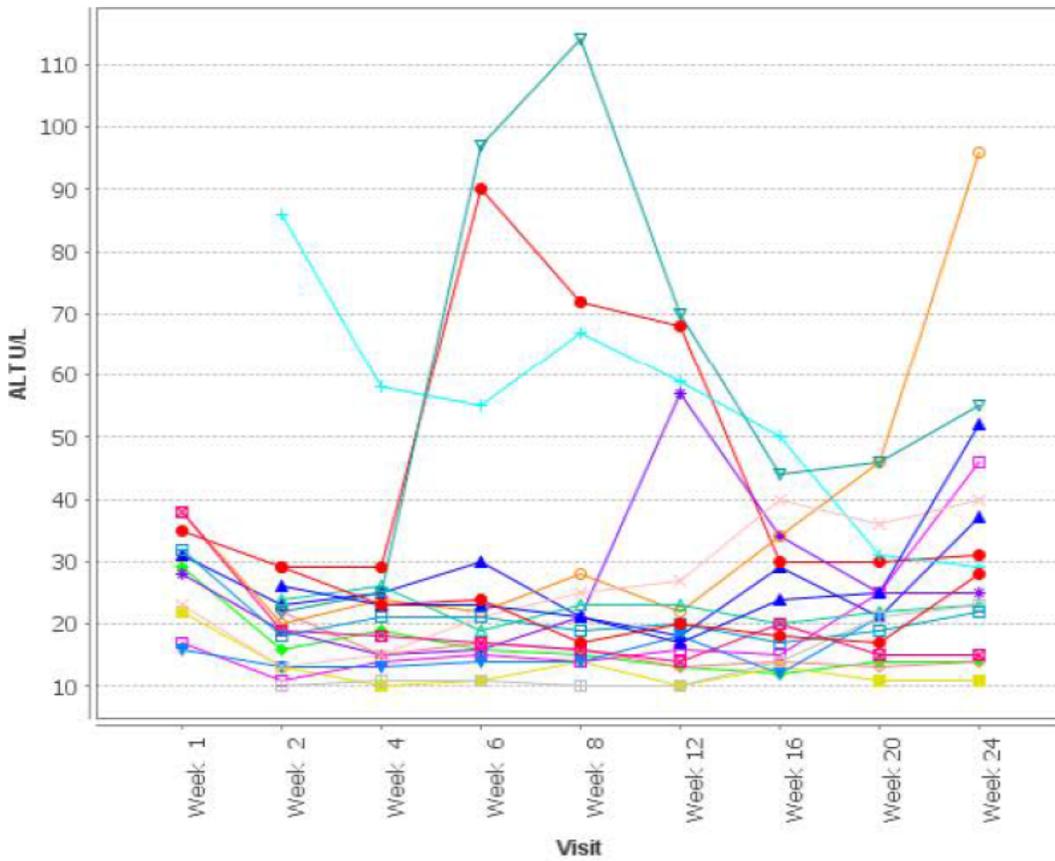


Trial 7028

Mean and SD of Absolute Eosinophil Count by Visit for Subjects with Elevated Absolute Eosinophils without Pyrexia—Trial 7028



ALT by study Visit for Subjects with Elevated Absolute Eosinophils without Pyrexia—Trial 7028



Subject Id for the Study

- ▲ 80098 ● 80132 ▲ 80151 ● 80279 ▲ 80328 ▲ 80338 ● 80350 ▲ 80353 ▲ 80365 ● 80432
- ▲ 80476 ● 80516 ▲ 80602 ● 80606 ▲ 80642 ▲ 80710 ▲ 80746 ● 80811

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/s/

SOHAIL MOSADDEGH
07/25/2014



NDA 206844
NDA 206843

MID-CYCLE COMMUNICATION

Bristol-Myers Squibb Company
Attention: Charles D. Wolleben, PhD
Group Director, Global Regulatory Sciences - US
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Wolleben:

Please refer to your New Drug Applications (NDAs) dated March 31, 2014, received March 31, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for asunaprevir [REDACTED] (b) (4) and daclatasvir tablets 30 and 60 mg.

We also refer to the teleconference between representatives of your firm and the FDA on July 10, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Sohail Mosaddegh, PharmD, Regulatory Project Manager, at (301) 796-4876 or (301) 796-1500.

Sincerely yours,

{See appended electronic signature page}

Kim Struble, PharmD
Medical Team Leader
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

MID-CYCLE COMMUNICATION

Meeting Date and Time: July 10, 2014, 10:10 AM to 12:00 PM

Application Number: NDA 206843 & 206844
Product Name: asunaprevir & daclatasvir
Indication: Treatment of Chronic Hepatitis C Infection
Applicant Name: Bristol-Myers Squibb Company

Meeting Chair: Kim Struble, PharmD
Meeting Recorder: Sohail Mosaddegh, PharmD

FDA ATTENDEES

1. Edward M Cox, MD, MPH, Director, Office of Antimicrobial Products
2. John Farley, MD, Deputy Director, Office of Antimicrobial Products
3. Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
4. Jeffrey Murray, MD, MPH, Deputy Director, DAVP
5. Wendy Carter, DO, Medical Officer, DAVP
6. Kim Struble, PharmD, Medical Team Lead, DAVP
7. Adam I Sherwat, MD, Medical Officer, DAVP
8. Christopher Ellis, PhD, Pharmacology/Toxicology Reviewer, DAVP
9. Julian O'Rear, PhD, Virology Team Lead, DAVP
10. Karen Winestock, Chief, Project Management Staff, DAVP
11. Lalji Mishra, PhD, Virology Reviewer, DAVP
12. Mary Singer, MD, PhD, Medical Team Lead, DAVP
13. Patrick Harrington, PhD, Virology Reviewer, DAVP
14. Peyton Myers, PhD, Pharmacologist/Toxicologist, DAVP
15. Shirley K Seo, PhD, Clinical Pharmacology Team Lead, Office of Clinical Pharmacology
16. Sohail Mosaddegh, PharmD, Regulatory Project Manager, DAVP
17. Stanley Au, PharmD, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology
18. Stephen Miller, PhD, CMC-Lead, Office Of New Drug Quality Assessment
19. Wen Zeng, PhD, Statistician, Division of Biometric
20. Dave Roeder, Associate Director Regulatory Affairs, Office of Antimicrobial Products
21. Kemi Asante, PharmD. Senior Regulatory Review Officer, Office of Prescription Drug Promotion
22. Monica Calderon, PharmD, Safety Evaluator, Division of Medication Error Prevention and Analysis
23. Chih-Ying (Natasha) Chen, PhD, Visiting Scientist/Epidemiologist, Division of Epidemiology
24. Fang Li, PhD, Pharmacometrics Reviewer, Office of Clinical Pharmacology
25. Jeff Florian, PhD, Acting Team Leader, Division of Pharmacometrics
26. Camille Dusserre, Pharmacy Student Intern, DAVP
27. Suzanne Strayhorn, MSc, Regulatory Health Project Manager, DAVP
28. Naomi S. Redd, PharmD, Drug Risk Management Analyst, Office of Medication Error Prevention and Risk Management

29. Karen Dowdy, Patent Labeling Reviewer, Division of Medical Policy Programs

EASTERN RESEARCH GROUP ATTENDEES

30. Patrick Zhou, Independent Assessor

APPLICANT ATTENDEES

31. Steven Schnittman, VP Global Development Lead – HCV, Global Clinical Research (GCR)
32. Stephanie Noviello, Director, GCR – Virology
33. Scott Swenson, Associate Director, GCR - Virology
34. Dessislava Dimitrova, Global Medical Director, Global Pharmacovigilance and Epidemiology
35. Tushar Garimella, Associate Director, Clinical Pharmacology and Pharmacometrics
36. Timothy Eley, Director, Clinical Pharmacology and Pharmacometrics
37. Marc Bifano, Director, Clinical Pharmacology and Pharmacometrics
38. Frank LaCreta, Executive Director, Clinical Pharmacology and Pharmacometrics
39. Beatrice Anduze-Faris, US Medical Virology Lead, US Medical
40. Fiona McPhee, Research Fellow, Research & Development – Virology
41. Mark Arnold, Executive Director, Analytical & Bioanalytical Development
42. Theodora Salcedo, Senior Principal Scientist, DSE – Toxicology
43. Robert Lange, Senior Research Investigator, DSE – Toxicology
44. Prashant Deshpande, Research Fellow, Pharmaceutical Development
45. Margo Heath-Chiozzi, VP, Global Regulatory Safety & Biometrics (GRSB), Virology
46. Thomas Kelleher, Group Director, GRSB, Virology
47. Andrew Damokosh, Director, GRSB
48. Joan Fung-Tomc, Group Director, GRSB – Virology
49. Charles Wolleben, Group Director, GRSB – US
50. Chirag Patel, Manager, Global Regulatory Strategy Management, GRSB
51. Angelina Verna, Associate Director, GRSB-CMC
52. Rebecca Skinner, Director, GRSB – Labeling
53. Eric Hughes, Exec Director, GCR – Virology

INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

SIGNIFICANT ISSUES

Major Safety Concerns

- We have identified significant safety issues that may affect approvability of this application. Specifically we are concerned that there is a signal for eosinophilic hepatitis associated with asunaprevir, daclatasvir or the combination. Our findings include (1) hepatotoxicity and (2) pyrexia/eosinophilia with and without liver involvement. In the upcoming weeks we will consult external experts regarding these findings.
- At this time we are not certain if these events represent a single clinical presentation or distinct events. Further work is needed to characterize the event or events, research possible mechanisms and conduct pharmacogenomic analyses. We are uncertain if these review activities can be completed within the current review cycle. Additionally, advisory committee input may be needed for a final assessment of risk benefit, but is unlikely possible during this review cycle.
- We acknowledge the hepatotoxicity signal noted in phase 2 development and the actions taken during development; asunaprevir dose reduction and conservative stopping rules and definition for potential DILI cases. Additionally the case that you refer to as possible hypersensitivity reaction in subject AI447026-2-1022 is concerning following a more detailed review. Our analyses included any subject with an AE report of pyrexia and a laboratory eosinophil count above normal. Based on this broad criteria we identified 37 subjects from the phase 3 trials. Then, each subject's data was examined to determine other pertinent clinical findings that may support or confound a case of possible pyrexia with eosinophilia. Cases were evaluated to determine if, after the AE of pyrexia with an accompanying eosinophilia within 2 weeks, rash was a part of the clinical syndrome or whether subjects had any ALT increase over normal levels or any elevations or bilirubin or AE reports consistent with significant liver injury. From the phase 3 trials, 16 subjects from the Japanese trial 7026 met the criteria. We are further evaluating these cases to determine if any represent eosinophilic hepatic injury. The cases are seen in the subjects from Japan and at this time we are not certain whether race is a predisposing factor or if the event(s) would occur in a broader population. We also requested submission of the pharmacogenomics reports for subjects with events from trial AI447026, which you mentioned during the teleconference, as part of the ongoing review cycle.
- There are many unresolved questions at this time and our approach is to share our analyses and preliminary findings and have future discussions and a meeting. We will further outline the criteria and approach we took for the various analyses and request you reproduce these analyses to further investigate this issue. We will send additional information requests in efforts to characterize the event(s) and develop a path forward. Although not the subject of this teleconference, we will be making similar requests for your ongoing and completed trials with your triple FDC.

Virology/Clinical/Statistics:

- Baseline NS5A polymorphisms reduced the efficacy of the ASV/DCV DUAL regimen in HCV genotype 1b subjects based on analyses of pooled Phase 3 trials. Screening out those with baseline NS5A polymorphisms increases SVR12 rates with the DUAL regimen to 87-95% (depending on specific polymorphism).
- The detection of certain baseline NS5A polymorphisms is associated with a high likelihood of virologic failure (up to ~60%), as well as the emergence of resistance-associated substitutions in NS3 and also additional substitutions in NS5A. DAVP is considering a limitation of use to state the efficacy is reduced in HCV genotype 1b patients with HCV NS5A sequence polymorphisms detected at positions L31(F,I,M or V) or Y93 (H). Screening for the presence of these polymorphisms is recommended and alternative therapy should be considered for patients with NS5A L31F/I/M/V or Y93H.
- We also have concerns regarding the availability of an assay to detect baseline polymorphisms in NS5A.
- Given the clear impact of baseline NS5A polymorphisms on ASV/DCV efficacy, and the low SVR rates for those who received rescue therapy with ASV/DCV/Peg-IFN α /RBV, we are considering labeling recommending against using the ASV/DCV-based regimen in subjects who have previously failed ASV/DCV or other NS3/4A protease inhibitors or NS5A inhibitors.
- BMS inquired whether the lack of an available NS5A sequencing assay would impact approvability of the ASV/DCV NDAs, or whether the issue would be addressed in drug labeling. The Division responded that it is premature to make that determination at this time. The Division asked BMS if they have reached out to any diagnostic companies regarding the development of a commercial assay, and BMS responded that they have been in contact with some companies, but did not indicate any formal plans for the development or release of an assay.

Clinical Pharmacology (Ongoing review of DDI information and labeling):

- OC recommendations-based on the drug-drug interaction results with high dose ethinyl estradiol and norethindrone in combination with ASV and DCV, DAVP is discussing whether use of low dose ethinyl estradiol and norethindrone is also appropriate. Also being discussed is the appropriateness of including OC labeling recommendations for ASV or DCV as single entities.
- Use of DCV with strong CYP3A inhibitors and moderate CYP inducers-the rationale for the proposed dosage adjustments and the specific labeling language, if dosage adjustments are warranted, are being reviewed.
- ASV: (b) (4)
- SOF DDI info due to lack of right of reference for the sofosbuvir method report-the DCV label will not include drug-drug interaction data for sofosbuvir in section 12.3 but a general comment regarding the predicted sofosbuvir-daclatasvir DDI may be included in section 7.
- Your responses to our information request regarding discrepancies in dosing for the population PK datasets are currently being reviewed.

Product Quality:

- We may have additional topics for discussion (e.g., control strategy for mutagenic impurities), so additional communication may be needed.

Non Clinical Pharmacology/Toxicology

- No issues identified

INFORMATION REQUESTS

No information requests at this time.

MAJOR SAFETY CONCERNS/RISK MANAGEMENT

Will need to further evaluate safety as previously discussed.

ADVISORY COMMITTEE MEETING

Advisory committee meeting is currently being planned. Potential dates forthcoming.

LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The proposed dates for:

Late Cycle Meeting is September 22, 2014

Late Cycle Meeting Background Package due to you by September 10, 2014

PMR/PMC/labeling negotiations by September 07, 2014

Action Date: November 28, 2014

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/s/

KIMBERLY A STRUBLE
07/21/2014

From: Mosaddegh, Sohail
To: charles.wolleben@bms.com
Subject: ASV/DCV NDAs-follow up Clin Pharm comments
Date: Tuesday, July 15, 2014 9:30:00 AM

Please submit a response to the following to your NDAs by 07/29/2014:

1) For the following analytes: a) norelgestromin (372), b) ethinyl estradiol and norethindrone method (255), c) caffeine and the caffeine metabolite paraxanthine, d) dextromethorphan and the dextromethorphan metabolite dextrorphan, and e) losartan and the losartan metabolite E-3174, please clarify whether the differences in the calibration curve and/or QC concentrations for the bioanalytical reports compared to the submitted validation reports were evaluated in partial validation experiments. If yes, please provide the relevant reports, addendums or amendments for the partial validation experiments.

2) For NDA 206844, [REDACTED] (b) (4)

3) [REDACTED] (b) (4)

4) For NDA 206843, please provide the information outlined in question 1 from the May 30, 2014 information request for the AI444039 and AI444044 trials.

5) For NDA 206843 and NDA 206844, please clarify the following in regards to the responses to question 1 from the May 30, 2014 information request:

a) For the sample storage information at the bioanalytical laboratory, are “receipt to analysis” defined as the maximum duration of storage from the time subject samples are received at the bioanalytical laboratory to sample analysis and “collection to analysis” defined as the maximum duration of storage from the time subject samples are collected at the trial site to sample analysis?

b) If the terms are as described above, the reported maximum duration of storage under “collection to analysis” does not appear to be consistent with the reported information. For example, in the AI447011 trial, the daclatasvir maximum duration of storage for “collection to analysis” was reported as 526 days, however the maximum duration of storage at the trial site, the central lab and the bioanalytical lab (2, 495, and 280 days, respectively) when totaled together equals 777 days, which exceeds 526 days.

c) Please clarify whether daclatasvir samples were stored at -70C or -20C in AI444040.

6) For the 930057408 daclatasvir method, please provide the CV% values for the long term stability experiments at 154 days for both the non stable labeled and the stable labeled daclatasvir analyte.

*Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6223
Silver Spring, MD 20993-0002*

Phone: (301) 796-4876

Fax: (301) 796-9883

Email: Sohail.Mosaddegh@FDA.HHS.GOV

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/s/

SOHAIL MOSADDEGH
07/15/2014

Electronic Mail Correspondence – Information Request/Advice



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

DATE: July 11, 2014

TO: Charles Wolleben, PhD
Group Director, Global Regulatory Sciences – US
Bristol- Myers Squibb

SPONSOR: Bristol- Myers Squibb

SUBJECT: 206843/206844 Questions/Recommendations

CLINICAL

1. Prior to sending you our detailed analyses and findings, we are providing you an outline of our review activities for NDAs 206843 and 206844 to further investigate hepatotoxicity and pyrexia/eosinophilia with and without liver involvement. This will give you an opportunity to begin conducting similar analyses and provide your interpretation to the Division regarding these findings in relation to the overall risk benefit assessment for the ASV/DCV combination. For the analyses, please provide integrated analyses of the phase 3 trials (AI447026, AI447028 and AI447029; n=1367) and separately present supportive data available from the phase 2 trials (n=991; or n=745 excluding placebo). Please also provide your plans to further characterize the event(s), research possible mechanisms and conduct pharmacogenomics analyses.
2. Additionally, please provide data based on the outline below from your 3 DAA FDC program (completed and ongoing trials). Please also provide the data by trial and an integrated clinical assessment and rationale as to whether or not changes to the current 3 DAA FDC program are needed.

Review Outline

Evaluation of proportion of subjects with:

- Hepatic-related AEs
- Grade 1-4 ALT/AST/Alk phos/Total bilirubin
- ALT > 3 x ULN and Total bilirubin > 2 x ULN
- pDILI definition
- Increase in ALT/AST 2, 5 and 10 x baseline
- Increase in ALT/AST 2, 5 and 10 x nadir
- Pyrexia
- Eosinophilia above baseline
- Pyrexia and eosinophilia within 2 weeks

- Of the subjects meeting these criteria, indicate if rash was also present at any time point and if subject developed any increase in ALT/AST/total bilirubin or hepatic related AEs at any time point.
 - Subject narratives for pyrexia and eosinophilia within 2 weeks with either rash or ALT/AST/total bilirubin increases
 - Discontinuations due to hepatic- related AEs or laboratory abnormalities
 - Subject narratives for hepatic-related SAEs, discontinuations due to hepatic- related AEs or laboratory abnormalities, subjects meeting the pDILI definition and any subject with pyrexia and eosinophilia within 2 weeks and rash or any increase in ALT/AST/total bilirubin or hepatic-related AE at any timepoint
3. Finally, please provide an integrated clinical analysis, incorporating the data from the DUAL and QUAD phase 3 trials with any supportive data from the phase 2 program to provide your overall assessment, your risk-benefit assessment and any additional work planned to further characterize, monitor and label these safety findings.

PRODUCT QUALITY

4. Please provide a plausible mechanistic explanation for hepatotoxicity including the observed case of eosinophilic hepatic injury, including the potential role of asunaprevir, its major metabolites and whether any reactive intermediates/metabolites may exist that are able to modify hepatic proteins covalently. Based on preliminary information available to us, we are wondering if you have any evidence for, or against, the generation of a reactive intermediate by metabolism of the (b) (4) substructure?

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
07/11/2014



NDA 206843
NDA 206844

INFORMATION REQUEST

Bristol-Myers Squibb Company
Attention: Charles D. Wolleben, PhD
Group Director, Global Regulatory Sciences - US
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Wolleben:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for daclatasvir, tablets 30 mg and 60 mg) and asunaprevir

(b) (4)

We are reviewing the chemistry, manufacturing and controls section of your submission and have the following comments and information requests. We request a prompt written response by July 23, 2014, in order to continue our evaluation of your NDA's.

NDA 206844 (Asunaprevir (b) (6)

(b) (4)

NDA 206 843 (Daclastavir Tablets)

Biopharmaceutics Comments

1. Provide dissolution profile as a function of tablet weight gain for both strengths.
2. Provide dissolution profiles as a function of D10, D50, and D90.
3. Provide the particle size distribution (D10, D50 and D90) of batches tested in pivotal phase 3 trials and pivotal BA/BE studies which included the Phase 3 formulation.
4. Submit the individual and mean (n=12) dissolution profiles (tabulated and graphical form) for 60 mg tablet batches tested in pivotal phase 3 trials and pivotal BA/BE studies which included the phase 3 formulation.
5. Submit the individual and mean (n=12) dissolution profiles (tabulated and graphical form) for the 30 mg tablet batches (registration batches).

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

Sincerely,

{See appended electronic signature page}

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

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/s/

STEPHEN MILLER
07/09/2014
For R.Madurawe

Electronic Mail Correspondence – Information Request/Advice



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

DATE: July 3, 2014

TO: Charles Wolleben, PhD
Group Director, Global Regulatory Sciences – US
Bristol- Myers Squibb

SPONSOR: Bristol- Myers Squibb

SUBJECT: 206843/206844 Questions/Recommendations

1. Please provide the liver biopsy complete report from patient AI447026-2-10122. In addition, please verify with the Investigator, if not previously done, regarding the dosing of ASV in the first 2 weeks. Documented overdosing of DCV in the first two weeks was provided; however, no mention of ASV dosing is given. Please also confirm whether the patient was taking any over the counter or herbal medications, and if so, what ones? Please provide timing of the elevated PK draws, are they pre-dose? Lastly, please provide BMS' rationale for the high PK levels of ASV and DCV.
2. Please provide a narrative for subject 7-20200. This patient has a complaint of pyrexia and rash, with elevated eosinophils (22.5%), and a grade2 ALT elevation at Week 4 followed by an AE report of arthralgia at W12-24 (D92-169). Please provide your assessment of this case for potential hypersensitivity.
3. Please provide your rationale for not including language regarding hepatotoxicity in the DCV label.
4. Please provide analyses of the median time to onset (including range) for any subject who had a 2x nadir, 5x nadir and 10x nadir and a 2x Baseline increase in ALT from the pooled phase 3 data (AI447026, AI447028 and AI447029). Additionally, please provide an analysis for the median time to normalization for each of these subgroups.
5. Please provide an exposure response analysis for 16 subjects from AI447026 and the 17 subjects from AI447028 who had ALT grade 3 or 4 elevations reported and are included in the narratives. Also include an exposure response of bilirubin elevation for these same subjects.

Please submit a response to the NDAs by July 09, 2014 and contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
07/03/2014

From: Mosaddegh, Sohail
To: charles.wolleben@bms.com
Subject: NDA 206843/206844 PT IR
Date: Thursday, June 19, 2014 1:46:00 PM

Hello:

- **NDA#206-844**

(b) (4)

NDA#206-843

Additional details are needed from the (Q)SAR evaluation of structures briefly mentioned in section 3.2.S.2.6.5 (Development of Genotoxic Impurity Control Strategy). Please provide a description of the methodology used (e.g., software used, versions, etc.) and a table of structures evaluated for potential mutagenicity and the corresponding (Q)SAR predictions. If this information was previously provided, please indicate the submission number and date.

Please provide the requested information by 7/14/14.

Thank you

*Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6223
Silver Spring, MD 20993-0002
Phone: (301) 796-4876
Fax: (301) 796-9883
Email: Sohail.Mosaddegh@FDA.HHS.GOV*

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/s/

SOHAIL MOSADDEGH
06/19/2014

Electronic Mail Correspondence – Information Request/Advice



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

DATE: June 16, 2014

TO: Charles Wolleben, PhD
Group Director, Global Regulatory Sciences – US
Bristol- Myers Squibb

SPONSOR: Bristol- Myers Squibb

SUBJECT: 206843/206844 Questions/Recommendations

CLINICAL:

In the Exposure Analysis datasets (EX2) for the phase 3 trials, there are some noted inconsistencies for how asunaprevir and daclatasvir dosing is displayed. For AI447026 and AI447028, it is noted that asunaprevir is listed as (b) (4). In AI447026 and AI447029, EXDOS and EXDOSTOT provide the same data for asunaprevir dosing. Please clarify the intended difference between the EXDOS (dose quantity) and EXDOSTOT (total dose exposure). In contrast, in AI447028, there are 2 variables EXDOS and EXDOS1. The data in EXDOS are inconsistent for asunaprevir and provide dose quantity as (b) (4) and EXDOSE1 provides dose quantity as missing, (b) (4) (similar issues are observed for DCV). For asunaprevir, it seems that for the DUAL trials the EXDOS should be (b) (4)

Please note that similar discrepancies are observed for daclatasvir in the phase 3 trials. Please clarify these discrepancies.

CLINICAL PHARMACOLOGY:

1. For the ASV NDA, (b) (4)

2. For all subjects included in the population PK datasets (DSV or ASV), in addition to NONMEM ID, please provide unique subject ID that will link to the source clinical trial datasets.
3. During the review of the ASV and DCV NDAs, the review team noticed discrepancies regarding the dosing information in your population PK datasets. In the Phase 3 trials AI447026 and AI447028, the specified dosing regimen was DCV 60 mg QD (using a 60 mg tablet formulation) and ASV 100 mg BID (using a 100 mg (b) (4) formulation) for 24 weeks. The protocols for the trials did not include information permitting dose adjustments for DCV or ASV throughout the duration of the trials. However, in your population PK dataset "asvpkmm.xpt" for ASV, we noticed numerous subjects in the AI447026 and AI447028 trials that received an ASV dose other than 100 mg. For example, we identified (b) (4)

Please clarify and provide further information regarding whether the identified discrepancies were due to data assembly issues, dose adjustments, or other issues that are not specified in the trial reports.

Please submit a response to the NDAs by 06/26/2014 and contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
06/16/2014



NDA 206843

INFORMATION REQUEST

Bristol-Myers Squibb Company
Attention: Charles D. Wolleben, PhD
Group Director, Global Regulatory Sciences - US
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Wolleben:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for daclatasvir, tablets 30 mg and 60 mg).

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

Drug Substance

1. In Section 3.2.S.2.6, several open-ended parameter temperatures settings such as (b) (4) etc. are used in the process descriptions. Revise these to include specific ranges for the operating parameters (i.e., with both lower and upper limits) or provide a scientific rationale as to why a one-sided parameter is acceptable.
2. Include residual solvents in the specification of the starting material (b) (4) and clarify if residual solvents are carried over into the drug substance.
3. In your impurity control on starting material (b) (4), there was no discussion on impurities (b) (4). Please provide information on these impurities, including their structures, if known.

Drug Product

4. The "critical in-process controls" listed in Section 3.2.P.3.4-1 have the potential to impact critical quality attributes. Please identify the critical process parameters for the proposed manufacturing process based on preselection of operating ranges or magnitude of product quality response. Please note that changes from the preselected targets/ranges (i.e.

changes outside of the Proven Acceptable Ranges) could have a minor, moderate or substantial potential to adversely affect product quality. The Agency's expectation is that the potential impact of changes to process parameters and in-process controls, including those designated as non-critical process parameters, as well as the parameters in Master Batch Record, be assessed under the firm's quality system at the time of the change. As appropriate, changes with a potential to adversely affect product quality should be notified to the Agency in accordance with 21 CFR 314.70.

5. Confirm the proposed 30-months shelf life for the 28-ct HDPE bottles is calculated from the date of manufacture (DOM).

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

Sincerely,

{See appended electronic signature page}

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

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/s/

STEPHEN MILLER

06/10/2014

For R.Madurawe

From: Mosaddegh, Sohail
To: charles.wolleben@bms.com
Subject: FW: response to NDA 206844/206843 (BMS) Information Request (COR-NDAIR-01)
Date: Friday, June 06, 2014 8:49:00 AM

Please see our response below:

QUESTION 4: Presentation of Treatment-Emergent Resistance Data in Labeling For the ASV/DCV (DUAL) and ASV/DCV + P/R (QUAD) treatment-emergent resistance data in the ASV and DCV prescribing information, specifically the data summarized in Table 8 of each draft label, we prefer the data presented focus on the three pivotal Phase 3 trials. Data from the Phase 2 trials will be considered in our reviews of ASV and DCV drug resistance, but the numbers of virologic failure subjects from these trials are small and do not add significantly to the numbers from the Phase 3 trials, and only a subset of Phase 2 DUAL/QUAD virologic failure subjects received dosing regimens/schedules that were analogous to the Phase 3 dosing regimens. Focusing the DUAL/QUAD resistance analyses on the Phase 3 trials would also be consistent with the presentation of efficacy data in Clinical Studies Section 14.

We anticipate providing labeling recommendations accordingly, and therefore recommend that you reproduce the results in Table 8 for each draft label considering data only from the Phase 3 trials.

-
BMS Response:

We acknowledge the Division's preference to focus on the data from the three pivotal Phase 3 studies for the presentation of treatment-emergent resistance data in the ASV and DCV prescribing information (PI). As a result, we will prepare revised versions of Table 8 for both the DCV and ASV draft PIs based solely on the three pivotal Phase 3 studies and provide them to you in the coming weeks, for your information. Later in review of the applications, when we expect to be submitting revised labeling on the basis of comments from the Agency, we will insert these revised versions of Table 8 into the draft labeling and remind the Agency of these updates. Please alert us if this is not acceptable.

-
DAVP Follow-up Response:

It is not necessary for you to submit revised versions of the tables before we provide our specific labeling comments since we expect we will also recommend some formatting changes to the tables. We will include these formatting recommendations as well as the results from our resistance analyses of the Phase 3 trials, which you can use to compare with the results from your analyses.

*Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products*

10903 New Hampshire Ave., Bldg. 22, Room 6223
Silver Spring, MD 20993-0002
Phone: (301) 796-4876
Fax: (301) 796-9883
Email: Sohail.Mosaddegh@FDA.HHS.GOV

From: Wolleben, Charles [<mailto:Charles.Wolleben@bms.com>]
Sent: Monday, June 02, 2014 1:34 PM
To: Mosaddegh, Sohail
Subject: RE: NDA 206844 Information Request (COR-NDAIR-01)

Sohail,

Attached is a response to this information request. As before, once the response is published here I will submit it to NDA 206844.

Regards,
Chuck

From: Mosaddegh, Sohail [<mailto:Sohail.Mosaddegh@fda.hhs.gov>]
Sent: Wednesday, May 28, 2014 9:19 AM
To: Wolleben, Charles
Subject: NDA 206844 Information Request (COR-NDAIR-01)

Hello:
Please see attached.
Thanks

*Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6223
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Phone: (301) 796-4876
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SOHAIL MOSADDEGH
06/06/2014

From: Mosaddegh, Sohail
To: charles.wolleben@bms.com
Subject: NDA-206843/206844 No Filing Review Issues Identified and IR
Date: Friday, June 06, 2014 1:13:00 PM

Hello:

Please see our responses below.

thanks

Sohail Mosaddegh, Pharm.D.

Lieutenant Commander, USPHS

Regulatory Health Project Manager

FDA/CDER/OND/OAP/Division of Antiviral Products

10903 New Hampshire Ave., Bldg. 22, Room 6223

Silver Spring, MD 20993-0002

Phone: (301) 796-4876

Fax: (301) 796-9883

Email: Sohail.Mosaddegh@FDA.HHS.GOV

From: Wolleben, Charles [<mailto:Charles.Wolleben@bms.com>]
Sent: Thursday, June 05, 2014 10:35 PM
To: Mosaddegh, Sohail
Subject: RE: NDA-206843/206844 No Filing Review Issues Identified and IR

Sohail:

I have received a couple of questions regarding the May 30 Information Request from the team here.

Question 13 is the following:

QUESTION 13

For the tenofovir method validation (TSLR08-327), certain pages from the Amendment 1 and 2 memos have been redacted. Please provide a description of the redacted contents. If the information is not related to details regarding the analytical method, if possible, please submit the information to the FDA.

We used (b) (4) proprietary method. When they submitted the method validation reports to us they redacted text related to the method details. Our interpretation of Question 13 is that since the redacted sections of the report are related to the details of the analytical method there is no need to provide anything further. Can you confirm that our interpretation of Question 13 is

accurate? DAVP response: Yes

For Questions 5 and 21 below, are the long term stability experiments referred to for matrix (e.g., plasma) or stock solution (solvent)? DAVP response: Matrix (e.g. Plasma)

QUESTION 5

For the following method validation reports, information was not provided on whether current reference standards were used during the method validation, including for long term stability experiments. Please provide further information on this issue.

QUESTION 21

For the following method validation reports, information was not provided on whether current (non expired) standards were used during the method validation, including for long term stability experiments. Please provide further information on this issue.

Also, we are aware of the conclusion of pre approval inspection of the Mt Vernon facility for daclatasvir. Do you know if there is an inspection planned for the asunaprevir (b)(4) facility at (b)(4)? Finally, our CMC team has asked if they can expect CMC questions in the near future. DAVP response: CMC IR pending, no update on inspections at this time.

Regards,
Chuck

From: Mosaddegh, Sohail [<mailto:Sohail.Mosaddegh@fda.hhs.gov>]
Sent: Friday, May 30, 2014 11:46 AM
To: Wolleben, Charles
Subject: NDA-206843/206844 No Filing Review Issues Identified and IR

Hello:
Please see attached.
Take care

*Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS*

Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6223
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/s/

SOHAIL MOSADDEGH
06/06/2014



NDA 206843

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

Bristol-Myers Squibb Company
Attention: Charles D. Wolleben, PhD
Group Director, Global Regulatory Sciences - US
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Wolleben:

Please refer to your New Drug Application (NDA) dated March 31, 2014, received March 31, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for daclatasvir, tablets 30 mg and 60 mg.

We also refer to your amendments dated: April 04, 2014, April 10, 2014, April 28, 2014, April 29, 2014, May 02, 2014, and May 20, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is November 30, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 31, 2014. In addition, the planned date for our internal mid-cycle review meeting is June 26, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

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

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of

administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

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

If you have any questions, call Sohail Mosaddegh, PharmD, Regulatory Project Manager, at (301) 796-4876 or (301) 796-1500.

Sincerely yours,

{See appended electronic signature page}

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

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/s/

DEBRA B BIRNKRANT
05/30/2014

Electronic Mail Correspondence – Information Request/Advice



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

DATE: May 30, 2014

TO: Charles Wolleben, PhD
Group Director, Global Regulatory Sciences – US
Bristol- Myers Squibb

SPONSOR: Bristol- Myers Squibb

SUBJECT: NDA 206843/206844 Questions/Recommendations

CLINICAL PHARMACOLOGY:

NDA 206843

- 1) In order to independently determine whether the submitted long term stability data in plasma (or other matrices) for daclatasvir (and concomitant medications that were evaluated in drug-drug interaction trials) sufficiently covers the actual duration and storage temperature for plasma samples (or other matrices), please provide a table that lists the information below. The table should include Phase 2 and Phase 3 trials included in the daclatasvir population PK analysis and any Phase 1 trials with exposure information that is included in the proposed daclatasvir U.S. prescribing information, including drug-drug interaction, hepatic or renal impairment trials.

Trial number and analyte	Temperature and maximum duration of sample storage at clinical site	Temperature and duration of sample storage at central laboratory (if not stored at a central laboratory for a specific trial, list "NA")	Temperature and maximum duration of sample storage at bioanalytical site	Temperature(s) and maximum duration of long term stability data
--------------------------	---	--	--	---

- 2) For the daclatasvir-simeprevir drug-drug interaction trial (TMC435HPC1005), please submit the relevant method validation and bioanalytical reports for both the daclatasvir and simeprevir analytes.

- 3) For the daclatasvir-telaprevir drug-drug interaction trial (AI444067), please submit the relevant method validation report for the telaprevir analyte.
- 4) The AI444084 trial report states that pharmacokinetic data for escitalopram (the S enantiomer of racemic citalopram) was evaluated. However, the method validation reports (LCMS-332) and the AI444084 bioanalytical reports measured the racemic citalopram analyte.

Please provide further information explaining the rationale for not using a validated assay that measures only escitalopram concentrations for the AI444084 trial. Additionally, the AI444084 bioanalytical report states that there is no chiral inversion of escitalopram to the R enantiomer of racemic citalopram. Please provide information to support this statement for the escitalopram samples that were analyzed in the AI444084 trial.

- 5) For the following method validation reports, information was not provided on whether current reference standards were used during the method validation, including for long term stability experiments. Please provide further information on this issue.
 - a) LCMSC-393: rosuvastatin
 - b) LCMSC-356: tacrolimus
 - c) LCMSC-372: norelgestromin
- 6) For the AI444065 trial, only Addendum 1 for the cyclosporine bioanalytical report was submitted. Please submit the main portion of the cyclosporine bioanalytical report, including any other addendums, plus information on whether a current (non expired) cyclosporine reference standard was used during bioanalysis. Please also confirm that the method validated in the ARCYC2 report was the method that was used to analyze cyclosporine whole blood samples and cyclosporine blood samples were drawn in K2EDTA anticoagulated tubes for the AI444065 trial.
- 7) For the daclatasvir-sofosbuvir trial (AI444040), please submit the relevant method validation report ((b) (4) 86-0938) for the sofosbuvir and sofosbuvir metabolite analytes.
- 8) For the analysis of the (b) (4) -6206 (GS-331007) analyte from the AI444040 trial:
 - a) The reference material expired on July 8, 2012. Please provide information to support the analysis of the (b) (4) -6206 analyte until January 26, 2013.
 - b) In run #34, both of the LLOQ (b) (4) -6206 calibration standards failed. Please specify whether the LLOQ was raised to 20 ng/mL and any samples from run #34 were reassayed for (b) (4) -6206 concentrations that were less than 20 ng/mL.
- 9) For the analysis of the daclatasvir analyte from the AI444014 trial, in run #6, both of the LLOQ daclatasvir calibration standards failed. Please specify whether the LLOQ was raised to 1 ng/mL and any samples from run #6 were reassayed for daclatasvir concentrations that were less than 1 ng/mL.
- 10) For the analysis of the norethindrone analyte from the AI447039 trial, in run #9, both of the LLOQ norethindrone calibration standards failed. Please specify whether the LLOQ was raised to 100 ng/mL and any samples from run #9 were reassayed for norethindrone concentrations that were less than 100 ng/mL.

- 11) For the rosuvastatin method validation, the long term stability was evaluated using a different high QC (75 ng/mL) that was not evaluated as part of the initial validation. Please clarify whether the same rosuvastatin calibration curve concentrations were used for the initial validation in the long term stability experiments: 0.1, 0.2, 0.4, 1.6, 25, 80 and 100 ng/mL.
- 12) For the analysis of the rosuvastatin analyte from the AI444054 trial, in run #9 and run #10, both of the LLOQ rosuvastatin calibration standards failed. Please specify whether the LLOQ was raised to 0.2 ng/mL and any samples from run #9 or run #10 were reanalyzed for rosuvastatin concentrations that were less than 0.2 ng/mL.
- 13) For the tenofovir method validation (TSLR08-327), certain pages from the Amendment 1 and 2 memos have been redacted. Please provide a description of the redacted contents. If the information is not related to details regarding the analytical method, if possible, please submit the information to the FDA.
- 14) Please submit information to support the following statement in the proposed U.S prescribing information in the absence of drug-drug interaction data from a P-gp inhibitor with no simultaneous CYP3A inhibition effects: “coadministration of agents that modify P-gp activities alone (without concurrent effect on CYP3A4) is unlikely to have a clinically meaningful effect on daclatasvir exposure”.
- 15) In multiple assays that measured concentrations of concomitant medications, the following differences were observed. Please provide information to support the acceptability of the concentration data for the following scenarios:
 - a) Different calibration curve concentrations and QC concentrations during bioanalysis compared to the validated calibration curve concentrations and/or QC concentrations using a linear regression.
 - b) Different QC concentrations during bioanalysis compared to the validated calibration curve concentrations and/or QC concentrations using a quadratic regression.

NDA206844

(b) (4)

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BIOPHARMACEUTICS**NDA 206843**

To support the approval of the proposed dissolution method provide the following:

- 26) A list of the Critical Material Attributes (CMA) and Critical Process Parameters (CPP) affecting dissolution with supporting data. For this purpose, provide dissolution profiles (graphical and tabular form) of drug substance particle size, water content, hardness, weight gain, film coating, and other relevant attributes identified using the proposed QC method.

- 27) Provide multipoint dissolution profile comparison data (n=12) for the 30 mg vs. 60 mg strengths in three different pH media and the medium proposed in the QC dissolution method using the same testing conditions. Note that you should use only one unit per vessel of each strength (e.g., one 30 mg tablet vs. one 60 mg tablet). Use an appropriate statistical test (e.g.,

f2 test) to evaluate the similarity of the dissolution profiles of the strengths. Use the 60 mg as the reference product.

NDA 206844

(b) (4)

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
05/30/2014

Electronic Mail Correspondence – Information Request/Advice



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

DATE: May 28, 2014

TO: Charles Wolleben, PhD
Group Director, Global Regulatory Sciences – US
Bristol- Myers Squibb

SPONSOR: Bristol- Myers Squibb

SUBJECT: NDA 206843/ 206844 Clinical Virology Questions/Recommendations

The Clinical Virology review team has two sets of questions/recommendations related to the drug resistance analysis data for NDAs 206843 and 206844. The first set of questions pertains to the analysis of the persistence of resistance-associated substitutions, and the second pertains to the reporting of treatment-emergent resistance data in the ASV and DCV prescribing information.

Analysis of Persistence of Resistance-Associated Substitutions

We have some questions about the formatting of the resistance datasets for these analyses. The following questions/issues arose from our initial review of the genotype 1b NS5A datasets, and we assume will also apply to related datasets for both targets (i.e., NS3 and NS5A) and genotypes/subtypes (i.e., 1a and 1b). **Please respond to these questions by COB 6/2/2014.** We are also open to having an informal teleconference if it is easier to discuss these questions.

1. Comparing the integrated genotype 1b NS5A resistance dataset (2013 format) alongside the AI444046 genotype 1b NS5A dataset (long-term follow-up study, 2006 format), **please confirm our understanding of how the data are presented in these datasets:**
 - a. For subjects who enrolled in the AI444046 long-term follow-up study, all available resistance data from the parent trials are included in the AI444046 dataset.
 - b. Resistance data rows that are unique to the AI444046 study (i.e., resistance data collected only in the context of the AI444046 long term follow-up study) have blank cells for columns related to treatment in the parent trials, such as ARM, TRTCD, RFENDN and RFSTDN. Is there any other specific flag to highlight the AI444046-specific resistance data rows?
 - c. VISIT in the AI444046 resistance datasets can mean two different things, referring either to (1) visits from the parent trials for the resistance data rows that

carried over from the parent trials, or (2) visits that are unique to AI444046. For example, as implied in point (b) above, VISIT=DAY 1 refers to Day 1 in AI444046 if ARM, TRTCD, RFENDN and RFSTDN results are blank.

- d. RFENDN in the AI444046 datasets refers to the end date of treatment, including any rescue therapy. In other words, subtracting RFENDN from ISOLDN will provide the number of days of drug-free follow-up.
2. Please clarify what “EXT” means in VISIT, for example from the AI444046 resistance dataset:

USUBJID	CONSDN	ISOLDN	VISIT
AI447017-1-1011	12/17/2012	11/22/2011	F/U WEEK 24
AI447017-1-1011	12/17/2012	2/13/2012	F/U WEEK 24 EXT
AI447017-1-1011	12/17/2012	5/7/2012	F/U WEEK 24 EXT

3. It is our understanding that the following dataset formats are not available, please confirm: (1) Resistance datasets that pool results from the parent trials and AI444046, including all subjects who did or did not enroll in AI444046, or (2) resistance datasets for AI444046 in the 2013 format.

Presentation of Treatment-Emergent Resistance Data in Labeling

4. For the ASV/DCV (DUAL) and ASV/DCV + P/R (QUAD) treatment-emergent resistance data in the ASV and DCV prescribing information, specifically the data summarized in Table 8 of each draft label, we prefer the data presented focus on the three pivotal Phase 3 trials. Data from the Phase 2 trials will be considered in our reviews of ASV and DCV drug resistance, but the numbers of virologic failure subjects from these trials are small and do not add significantly to the numbers from the Phase 3 trials, and only a subset of Phase 2 DUAL/QUAD virologic failure subjects received dosing regimens/schedules that were analogous to the Phase 3 dosing regimens. Focusing the DUAL/QUAD resistance analyses on the Phase 3 trials would also be consistent with the presentation of efficacy data in Clinical Studies Section 14.

We anticipate providing labeling recommendations accordingly, and therefore recommend that you reproduce the results in Table 8 for each draft label considering data only from the Phase 3 trials.

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
05/28/2014



NDA 206843

**METHODS VALIDATION
MATERIALS RECEIVED**

Bristol-Myers Squibb Company
Attention: Charles D. Wolleben
5 Research Parkway
Wallingford, CT 06492

Dear Charles Wolleben:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Daclatasvir Dihydrochloride (b) (4) Tablets, 30 mg and 60 mg and to our April 25, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on May 6, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

MICHAEL L TREHY
05/06/2014

From: Mosaddegh, Sohail
To: charles.woleben@bms.com
Subject: NDA-206844 Information Request (COR-NDAIR-01) - NS5A Polymorphism Analysis
Date: Monday, May 05, 2014 11:56:00 AM

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/s/

SOHAIL MOSADDEGH
05/05/2014



NDA 206843

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Bristol-Myers Squibb
5 Research Parkway
Wallingford, CT 06492

ATTENTION: Charles D. Wolleben, Ph.D.
Group Director, Global Regulatory Sciences - US

Dear Dr. Wolleben:

Please refer to your New Drug Application (NDA) dated March 29, 2014, received March 31, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Daclatasvir Tablets, 30 mg and 60 mg.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager Sohail Mosaddegh, at (301) 796-4876.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
05/01/2014

TODD D BRIDGES on behalf of KELLIE A TAYLOR
05/02/2014

Executive CAC

Date of Meeting: April 22, 2014

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Lynnda Reid, Ph.D., DBRUP, Alternate Member
Hanan Ghantous, Ph.D., DAVP, Pharm Tox Supervisor
L. Peyton Myers, Ph.D., DAVP, Presenting Reviewer

Author of Minutes: L. Peyton Myers, Ph.D.

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

NDA # 206-843

Drug Name: Daclatasvir, DCV

Sponsor: BMS

Background

BMS-790052 (Daclatasvir, or DCV) is a Hepatitis C Virus (HCV) NS5A “replication complex” inhibitor currently under review for oral use for chronic Hepatitis C in combination with other HCV medications. Notably, it will be combined with an NS3/4A inhibitor, Asunaprevir, NDA 206-844 which is also from BMS. BMS submitted the final study reports for the rat and mouse carcinogenicity studies in the current NDA.

TWO YEAR CARCINOGENICITY STUDY IN RATS

- Species/strain: Sprague Dawley rats/CRL
- Doses: daily doses of 0 (water), 0 (vehicle), 5, 15, 50 (males); 0 (water), 0 (vehicle), 5, 15, 50 (females)
- Vehicle: 60% polyethylene glycol 400 (PEG-400) and 40% Vitamin E-d- α -tocopheryl polyethylene glycol 1000 succinate (TPGS).
- Route: Oral gavage
- Basis of dose selection: MTD

The doses used were those recommended by Executive CAC .

(See Exec. CAC minutes from April 6, 2011)

Study findings

On December 14, 2012, BMS submitted questions via email regarding an increase in deaths on a 2-year Carcinogenicity Study. BMS stated that it was anticipated that the intermediate- and high-dose male groups (Groups 4 and 5) would likely reach 20 survivors at approximately Weeks 84 to 88 (03-Jan-2013 through 31-Jan-2013). BMS also anticipated that control females (Groups 2 and/or 3) may have 20 survivors at approximately the same time or shortly after.

DAVP consulted the Exec. CAC (Dec 19, 2012) and provided responses to BMS on early termination on Dec 27, 2012.

Due to the early termination, males were dosed for a minimum of 94 weeks and females were dosed for a minimum of 92 weeks. Administration of BMS-790052 did not have a negative impact on survival, and sufficient numbers of animals survived to adequately evaluate carcinogenicity.

No significant neoplastic findings were noted.

Non-neoplastic findings were limited to treatment related lesions in the adrenal glands at the high dose level.

Statistical evaluation

The FDA statistical analysis did not demonstrate any effect of BMS-790052 on the incidence, distribution or nature of the neoplastic changes seen during the course of this study.

TG.RASH2 MOUSE CARCINOGENICITY STUDY

- Species/strain: CByB6F1/Tg rasH2 hemizygous
- Doses: daily dosing of 0 (water), 0 (vehicle), 30, 100, 300 (males) and 0 (water), 0 (vehicle), 30, 100, 300 (females)
- Vehicle: 60% polyethylene glycol 400 (PEG-400) and 40% Vitamin E-d- α -tocopheryl polyethylene glycol 1000 succinate (TPGS).
- Route: Oral gavage
- Basis of dose selection: MTD.
- Positive control: single intraperitoneal injection of N-Nitrosomethylurea at 75 mg/kg

Executive CAC concurred with the dose selection.

(See Exec. CAC minutes from April 6, 2011.)

Study findings

There were no BMS-790052-related macroscopic lesions. Occasional skin papillomas at similar incidence in control (water and vehicle) and BMS-790052 groups were noted on the right pinna (associated with the metal ear tag) with an increased incidence in NMU-treated mice. NMU treatment also caused an increase in the incidence of lymphoma.

Tumor incidences in the water- and vehicle-control groups were similar and there were no BMS-790052-related neoplastic microscopic findings at any dose.

Non-neoplastic findings were limited to minor increased incidences of splenic extramedullary hematopoiesis in females at ≤ 100 mg/kg/day.

Statistical evaluation

The FDA statistical analysis detected no significant positive trend and/or BMS-790052-related increase in neoplasms compared to the vehicle control. There was also no significant difference in neoplastic lesion incidence between the vehicle and water controls.

Executive CAC Recommendations and Conclusions:

Rats:

- The Committee concurred that the study was acceptable, noting prior Exec CAC recommendations.
- The Committee concurred that there were no drug-related neoplasms in male and female rats at any of the doses tested.

Mice:

- The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplastic findings in male and female mice at any of the doses tested.

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

cc:\

/Division File, DAVP, NDA 206-843
/Team leader, HGhantous, DAVP
/Reviewer, LMyers, DAVP
/PM, SMosaddegh, DAVP
/ASeifried, OND-IO

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/s/

ADELE S SEIFRIED
04/25/2014

ABIGAIL C JACOBS
04/25/2014

Memo of informal teleconference between BMS and DAVP on 05/12/2014 regarding status of AI444040 in NDA 206843

NDA 206843/206844
Daclatasvir/Asunaprevir

DAVP Attendees:

1. Dave Roeder, Associate Director Regulatory Affairs, Office of Antimicrobial Products
2. Debra Birnkrant, MD, Director
3. Karen Winestock, Chief, Project Management Staff, DAVP
4. Kim Struble, PharmD, Medical Team Lead
5. Mammah Sia Borbor, MS, MBA, Regulatory Project Manager
6. Sohail Mosaddegh, PharmD, Regulatory Project Manager
7. Stanley Au, PharmD, Clinical Pharmacology Reviewer
8. Wendy Carter, DO, Medical Officer

BMS attendees:

1. Steven Schnittman, MD, VP Global Development Lead – HCV, GCR
2. Eric Hughes, MD, PhD, Exec Director, GCR – Virology
3. Stephanie Noviello, MD, Director, GCR – Virology
4. Timothy Eley, PhD, Director, Clinical Pharmacology and Pharmacometrics
5. Margo Heath-Chiozzi, MD, VP, GRSS – Virology
6. Joan Fung-Tomc, PhD, Group Director, GRSS – Virology
7. Joseph Lamendola, PhD, VP, U.S. Regulatory Sciences and Regulatory Relations & Policy
8. Charles Wolleben, PhD, Group Director, GRSS – US

This teleconference was held to be sure there is a common understanding between BMS and DAVP related to the potential consideration of reflecting study AI444040 in the initial daclatasvir USPI following interactions between BMS' legal staff and representatives from the FDA's Office of Chief Counsel on the issue referencing the EU Public Assessment Report for the approval of Sovaldi (sofosbuvir) for information regarding the comparability of the formulation of sofosbuvir used in study AI444040 and the commercial form of Sovaldi approved in the US. Those discussions concluded that there was no legal obstacle to this strategy.

BMS stated that while the NDA was in an early stage of review the issue of AI444040 is important not just due to the compelling results but also due to the fact that the regimen will likely be used regardless of the labeling.

DAVP stated that there are no objections to BMS referencing the European public information for identifying formulations used in the Sovaldi development program, but these facts alone do not provide enough data to allow labeling of the combination and we cannot refer to the safety and/or efficacy data from the Sovaldi NDA without a right of reference.

Based on statements in the publically available Sovaldi clinical pharmacology review, the 90% CIs were not within 80%-125% when comparing Form 1 to Form 2 with respect to the sofosbuvir analyte. Therefore, without a Right of Reference from Gilead to the Sovaldi NDA, DAVP cannot determine the comparability of the safety and efficacy of the two formulations in question.

BMS asked if the recent sNDA for the combination of Olysio /Sovaldi was not a similar example. DAVP responded that we cannot comment on such a question, but we have made extraordinary efforts to deal with all parties involved in a very fair and balanced way.

BMS asked about the possibility of qualifying any representation of AI444040 in the daclatasvir USPI with a factual statement that it was conducted with a non-commercial form of sofosbuvir. DAVP responded that this was not acceptable as it would be labeling the combination of daclatasvir and sofosbuvir without knowledge of the comparable safety and efficacy of the sofosbuvir product used in AI444040 vs. the one commercially marketed in the US.

In summary, it was concluded that without a Right of Reference to the Sovaldi NDA BMS cannot anticipate any reference to study AI444040 in the initial USPI for daclatasvir.

DAVP asked if after the European approval of daclatasvir BMS intended to make any public comments regarding the inability to obtain a Right of Reference to allow the incorporation of study AI444040 in the USPI. BMS said they have not reached an opinion on this, but would keep DAVP aware of any public communications on the topic. DAVP stated that any question we received regarding the discrepancy between Europe and the US labeling for daclatasvir would be deferred to BMS.

DAVP will send comments regarding the PSPs for daclatasvir and asunaprevir.

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/s/

SOHAIL MOSADDEGH
05/19/2014



NDA 206843

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Bristol-Myers Squibb Company
Attention: Charles D. Wolleben
5 Research Parkway
Wallingford, CT 06492
FAX: (203) 677-7435

Dear Charles D. Wolleben:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Daclatasvir Dihydrochloride (b)(6) Tablets, 30 mg and 60 mg.

We will be performing methods validation studies on Daclatasvir Dihydrochloride, as described in NDA 206843.

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

Method, current version

Method ID 95012802; BMS-790052 HPLC test method for Daclatasvir (BMS-790052-05) drug substance.

Samples and Reference Standards

- 2 * 250 mg Daclatasvir Dihydrochloride drug substance
- 2 * 250 mg Daclatasvir Dihydrochloride reference standard
- 1 impurity cocktail solution if available or

(b)(4)

Equipment

- 1 (b)(4) particle size

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

Forward these materials via express or overnight mail to:

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

MICHAEL L TREHY
04/25/2014

Electronic Mail Correspondence – Information Request/Advice



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

DATE: April 24, 2014

TO: Charles Wolleben, PhD
Group Director, Global Regulatory Sciences – US
Bristol- Myers Squibb

SPONSOR: Bristol- Myers Squibb

SUBJECT: NDA 206843/ 206844

As discussed at the 1/31/2014 pre-NDA meeting, the impact of Baseline NS5A resistance-associated polymorphisms on the efficacy of the DCV/ASV (DUAL) regimen in genotype 1b subjects will be an important review issue. Table 1 below summarizes our initial analyses of the Baseline prevalence of key NS5A polymorphisms in your genotypic resistance dataset, along with the SVR rates in the pooled Phase 3 trials (AI447026/AI447028) for subjects carrying these polymorphisms.

The independent analysis presented in Table 1 differs from your analyses presented in the integrated resistance report. Because this analysis will be an important point of focus for our review, we request that you conduct a similar analysis to confirm that you can reproduce these results. **Please note that we have not yet had any formal internal discussions on how to interpret these results and how this information should be presented in drug prescribing information.** At this time we are simply asking that BMS reproduce these results.

Table 1. Prevalence of NS5A polymorphisms L28M, R30Q, L31F/I/M/V and Y93H in genotype 1b subjects and their impact on SVR rates in the Phase 3 ASV/DCV (DUAL) trials.

Polymorphism(s)	NS5A Polymorphism Prevalence (Pooled GT1b Datasets)			SVR in Phase 3 DUAL Trials (Non-VF-Censored, n=806)	
	All Sites (n=1,393)	N. America (n=307)	U.S. (n=236)	with RAP(s)	without RAP(s)
L28M	48 (3%)	1 (0.3%)	0 (0%)	20/29 (69%)	676/777 (87%)
R30Q	112 (8%)	15 (5%)	13 (6%)	53/69 (77%)	643/737 (87%)
L31F/I/M/V	73 (5%)	15 (5%)	11 (5%)	14/36 (39%)	682/770 (89%)
Y93H	127 (9%)	20 (7%)	15 (6%)	31/76 (41%)	665/730 (91%)
Subgroup Analyses					
L28M or R30Q	132 (9%)	16 (5%)	13 (6%)	62/83 (75%)	634/723 (88%)
L28M or R30Q (no L31F/I/M/V or Y93H)	115 (8%)	13 (4%)	11 (5%)	61/72 (85%)	591/625 (95%)
L31F/I/M/V or Y93H	193 (14%)	32 (10%)	24 (10%)	44/109 (40%)	652/697 (94%)
L28M, R30Q, L31F/I/M/V, or Y93H	308 (22%)	45 (15%)	35 (15%)	105/181 (58%)	591/625 (95%)
				Overall SVR rate in dataset: 696/806 (86%)	

Important details regarding the analysis in Table 1 include the following:

- For the SVR analyses, only the Phase 3 trials (AI447026/AI447028) were considered.
- SVR rates are based on SVR12, except that 2 subjects (AI447026-18-20035 and AI447028-109-80359) who experienced post-SVR12 relapse were considered virologic failures. Later follow-up results were used to impute SVR for any subjects with missing data at Follow-up Week 12.
- SVR rates were calculated using a non-virologic-failure-censored dataset. In other words, subjects who failed to achieve SVR for non-virologic reasons were censored in this analysis. Table 2 lists the subjects who were censored and the reasons for censoring.
- It appears that Subject AI447028-2-80120 did not have NS5A sequence data for VISIT="PRE TREAT", but did have data for VISIT="DAY 1" which was considered a Baseline isolate for our analyses (no polymorphisms at NS5A positions 28, 30, 31 or 93). Otherwise, all other Baseline data considered were flagged as RESBLFL=Y and RSANAL=Y.
- For analysis of Baseline prevalence, all subjects included in the integrated NS5A genotype 1b dataset PLUS the genotype 1b NS5A dataset for clinical trial AI447029 (QUAD) were considered.

Table 2. Subjects censored for Baseline resistance analyses of Phase 3 DUAL trials.

USUBJID	Reason for Censoring
AI447026-2-10122	Virologic relapse after stopping treatment early at Day 28
AI447026-2-20186	Discontinued at Day 34 while responding to treatment
AI447026-7-20104	Virologic relapse after stopping treatment early at Day 71 (also no Baseline NS5A data)
AI447026-9-20051	Virologic relapse after stopping treatment early at Day 16
AI447028-12-80804	Discontinued at Day 6 (also no Baseline NS5A data)
AI447028-55-80788	Achieved SVR4 but no subsequent follow-up HCV RNA results available
AI447028-61-80586	Discontinued at Day 2
AI447028-87-80851	Discontinued at Day 12
AI447028-91-80712	Discontinued at Day 16
AI447028-135-80872	Discontinued at Day 12 and no HCV RNA results

Please respond by COB 5/12/2014.

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
04/24/2014

From: Mosaddegh, Sohail
To: charles.wolleben@bms.com
Subject: NDAs 206843 and 206844 IR
Date: Thursday, April 24, 2014 3:40:00 PM

Hello:

By 04/28/2014 please clarify the dataset variable or variables BMS used to provide comparisons for the first 12 Weeks of treatment for the DUAL treatment arm versus placebo arm in trial A1447028.

Thank you

*Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6223
Silver Spring, MD 20993-0002
Phone: (301) 796-4876
Fax: (301) 796-9883
Email: Sohail.Mosaddegh@FDA.HHS.GOV*

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/s/

SOHAIL MOSADDEGH
04/24/2014



NDA 206843

NDA ACKNOWLEDGMENT

Bristol-Myers Squibb Company
Attention: Charles D. Wolleben, PhD
Group Director, Global Regulatory Sciences - US
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Wolleben:

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

Name of Drug Product: daclatasvir, 30 & 60 mg tablets

Date of Application: March 31, 2014

Date of Receipt: March 31, 2014

Our Reference Number: NDA 206843

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 30, 2014, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

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

If you have any questions, call me at 301-796-4876 or 301-796-1500.

Sincerely,

{See appended electronic signature page}

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SOHAIL MOSADDEGH
04/17/2014

Electronic Mail Correspondence – Information Request/Advice



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

DATE: April 16, 2014

TO: Charles Wolleben, PhD
Group Director, Global Regulatory Sciences – US
Bristol- Myers Squibb

SPONSOR: Bristol- Myers Squibb

SUBJECT: SDN 001 (SN 000, dated 02/28/14) NDA 206843/ 206844

FINANCIAL DISCLOSURE:

We recognize you have provided a financial disclosure document that provides the financial disclosure information for both NDA's; however, due to the table format, it is difficult to review and confirm the specific numbers of investigators overall and for some other specific criteria listed below. For both NDA's (206843 and 206844) please provide the following information related to financial disclosures:

1. Total number of investigators identified. (This total should include all Primary Investigators as well as sub-Investigators for all covered studies)
2. Number of investigators who are sponsor employees (including both full-time and part-time employees).
3. Number of investigators with disclosable financial interests/arrangements (Form FDA 3455).
4. If there are investigators with disclosable financial interests/arrangements, identify the **number of investigators** with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):
 - a. Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:
 - b. Significant payments of other sorts:
 - c. Proprietary interest in the product tested held by investigator:

- d. Significant equity interest held by investigator in sponsor of covered study:
5. Number of investigators with certification of due diligence (Form FDA 3454, box 3)

CODING DICTIONARY:

6. For both NDAs, please provide the location of the coding dictionary. We are aware that you are using MedDRA version 16.1. The “coding dictionary” should consist of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
04/16/2014



NDA 206843

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Bristol-Myers Squibb
5 Research Parkway
Wallingford, CT 06492

ATTENTION: Charles D. Wolleben, Ph.D.
Group Director, Global Regulatory Sciences - US

Dear Dr. Wolleben:

Please refer to your New Drug Application (NDA) dated March 29, 2014, received March 31, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Daclatasvir Tablets, 30 mg and 60 mg.

We also refer to your correspondence dated and received April 4, 2014, requesting a review of your proposed proprietary name, Daklinza. Upon preliminary review of your submission, we have determined that it is a complete submission as described in our Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*.

Therefore, the user fee goal date is July 3, 2014.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact Sohail Mosaddegh, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4876.

Sincerely,

{See appended electronic signature page}

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

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/s/

AZEEM D CHAUDHRY
04/09/2014



NDA 206843

ACKNOWLEDGE NDA PRESUBMISSION

Bristol-Myers Squibb Company
Attention: Charles D. Wolleben, PhD
Group Director, Global Regulatory Sciences - US
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Wolleben:

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

Name of Drug Product: daclatasvir, 30 & 60 mg tablets

Date of Submission: February 28, 2014

Date of Receipt: February 28, 2014

Our Reference Number: NDA 206843

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

Please cite the NDA number listed above at the top of the first page of any communications concerning this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

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

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

If you have any questions, call me at 301-796-4876 or 301-796-1500.

Sincerely,

[{See appended electronic signature page}](#)

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SOHAIL MOSADDEGH
03/26/2014

Electronic Mail Correspondence – Information Request/Advice



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

DATE: March 21, 2014

TO: Charles Wolleben, PhD
Group Director, Global Regulatory Sciences – US
Bristol- Myers Squibb

SPONSOR: Bristol- Myers Squibb

SUBJECT: SDN 001 (SN 000, dated 02/28/14) NDA 206843/ 206844

-
- 1) Please correct the file structure for NDA 206844 (for drug BMS-650032). The 2-Year Rat Carcinogenicity study for BMS-790052 appears to be included in the NDA 206844 by mistake.
 - 2) Please explain the statement from the 2 year rat study for BMS-650032

(b) (4)

(b) (4)

Please contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
03/21/2014



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

Record of Electronic Mail Transmission

DATE: March 10, 2014

To: Charles Wolleben, Ph.D.	From: Mammah Sia Borbor, M.S., M.B.A.
Company: Bristol- Myers Squibb	Title: Regulatory Project Manager
Fax number: 203-677-7453	Fax number: 301-796-9885 or 9883
Phone number: 203-677-5480	Phone number: 301-796-7731
Subject: NDA 206843/ 206844 Clinical Comments	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

Electronic Mail Correspondence – Information Request/Advice



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

DATE: March 10, 2014

TO: Charles Wolleben, Ph.D.
Group Director, Global Regulatory Sciences – US
Bristol- Myers Squibb

From: Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager
Division of Antiviral Products

SPONSOR: Bristol- Myers Squibb

SUBJECT: NDA 206843/ 206844 Clinical Comments

Please refer to NDAs 206843/ 206844 and your submission dated February 28, 2014 (eCTD number 0000). We have the following clinical comments:

Clinical

1. Please clarify if your planned DCV and ASV NDAs contain Trial Design (or trial summary) datasets. As stated in the draft FDA Technical conformance guide (<http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>) on page 12, “Trial Design datasets provide a standard way to describe the planned conduct of a clinical trial and should be included in SDTM submissions”. If feasible, without delaying the filing of the NDAs, please include trial design datasets for the DCV and ASV NDAs.

We are providing this above information via electronic mail for your convenience. PLEASE REPLY BY EMAIL (mammah.borbor@fda.hhs.gov) to confirm receipt. Please feel free to contact me at 301-796-7731 or 301-796-1500 if you have any questions regarding the contents of this transmission.

See electronic signature page

Mammah Sia Borbor, M.S., M.B.A., RPM

APPEARS THIS WAY ON ORIGINAL

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/s/

MAMMAH S BORBOR
03/10/2014

Electronic Mail Correspondence – Information Request/Advice



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

DATE: March 10, 2014

TO: Charles Wolleben, Ph.D.
Group Director, Global Regulatory Sciences – US
Bristol- Myers Squibb

From: Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager
Division of Antiviral Products

SPONSOR: Bristol- Myers Squibb

SUBJECT: NDA 206843/ 206844 Clinical Comments

Please refer to NDAs 206843/ 206844 and your submission dated February 28, 2014 (eCTD number 0000). We have the following clinical comments:

Clinical

1. Please clarify if your planned DCV and ASV NDAs contain Trial Design (or trial summary) datasets. As stated in the draft FDA Technical conformance guide (<http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>) on page 12, “Trial Design datasets provide a standard way to describe the planned conduct of a clinical trial and should be included in SDTM submissions”. If feasible, without delaying the filing of the NDAs, please include trial design datasets for the DCV and ASV NDAs.

We are providing this above information via electronic mail for your convenience. PLEASE REPLY BY EMAIL (mammah.borbor@fda.hhs.gov) to confirm receipt. Please feel free to contact me at 301-796-7731 or 301-796-1500 if you have any questions regarding the contents of this transmission.

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Mammah Sia Borbor, M.S., M.B.A., RPM

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/s/

MAMMAH S BORBOR

03/10/2014



IND 79599
IND (b) (4)

MEETING MINUTES

Bristol-Myers Squibb Company
Attention: Charles D. Wolleben, PhD
Group Director, Global Regulatory Sciences-US
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Wolleben:

Please refer to your Investigational New Drug Applications (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMS-790052 daclatasvir (IND 79599) and BMS-650032 asunaprevir (IND (b) (4)).

We also refer to the meeting between representatives of your firm and the FDA on January 31, 2014. The purpose of the meeting was to discuss the adequacy of the data that will be submitted to support the two NDAs forthcoming and the requirements for submission of complete NDAs for daclatasvir (DCV) and asunaprevir (ASV).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mammah Sia Borbor, M.S., M.B.A., Regulatory Project Manager, at (301) 796-7731 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

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

IND 79599
IND (b) (4)
Meeting Minutes
Type B
Page 2

OAP
DAVP

Enclosure:
Meeting Minutes

APPEARS THIS WAY ON ORIGINAL



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: January 31, 2014, 9:30 AM – 11:00 AM (EST)
Meeting Location: White Oak Building 22, Conference Room: 2205

Application Number: 79599 and (b) (4)
Product Name: BMS-790052, daclatasvir, and BMS-650032, asunaprevir
Indication: Treatment of chronic hepatitis C virus infection
Sponsor/Applicant Name: Bristol-Myers Squibb Company

Meeting Chair: Debra Birnkrant, MD, Director
Meeting Recorder: Mammah Sia Borbor, M.S., M.B.A.

FDA ATTENDEES

Edward Cox, MD, MPH, Director, Office of Antimicrobial Products (OAP)
Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, MD, MPH, Deputy Director DAVP
David Roeder, Associate Director of Regulatory Affairs, OAP
Kendall Marcus, MD, Deputy Director for Safety
Kimberly Struble, PharmD, Medical Team Leader DAVP
Wendy Carter, DO, Medical Officer DAVP
Hanan Ghantous, PhD, DABT, Pharmacology/Toxicology Team Leader DAVP
Peyton Myers, PhD, Pharmacologist DAVP
Shirley K. Seo, PhD, Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology IV (DCP IV)
Fang Li, PhD, Pharmacometrics Reviewer, OCP, Division of Pharmacometrics
Stanley Au, PharmD, Clinical Pharmacology Reviewer (OCP) (DCP IV),
Julian O'Rear, PhD Virology Team Leader DAVP
Lalji Mishra, PhD, Virology Reviewer DAVP
Patrick Harrington, PhD, Virology Reviewer DAVP
Wen Zeng, PhD, Statistician, OB, DB IV
Fraser Smith, PhD, Statistician, OB, DBIV
Antoine El-Hage, PhD, Office of Scientific Investigations
Karen Winestock, Chief, Project Management Staff, DAVP
Mammah Borbor, MS, MBA, Regulatory Project Manager DAVP
Nina Mani, PhD, MPH, Regulatory Project Manager DAVP
George, Lunn, PhD, Chemist, ONDQA
Christopher Sese, ERG

Carolyn L. Yancey, OSE/DRISK
Kellie Reynolds, Pharm.D., Deputy Director, Division of Clinical Pharmacology 4, Team Lead,
Antiviral Products Team
Mary Singer, M.D., Ph.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer

SPONSOR ATTENDEES

Steven Schnittman, MD, VP Global Development Lead – HCV, Global Clinical Research (GCR)
Eric Hughes, MD, PhD, Exec Director, GCR – Virology
Stephanie Noviello, MD, Director, GCR – Virology
Dessislava Dimitrova, MD, Global Medical Director, Medical Safety Assessment, Global Pharmacovigilance and Epidemiology (GPV&E)
Tushar Garimella, PhD, Associate Director, Clinical Pharmacology and Pharmacometrics
Timothy Eley, PhD, Director, Clinical Pharmacology and Pharmacometrics
David Gardiner, MD, Group Director, Exploratory Clinical & Translational Research
Min Gao, PhD, Research Fellow, Research & Development – Virology
Fiona McPhee, DPhil, Research Fellow, Research & Development – Virology
Thomas Kelleher, PhD, Group Director, Global Biometric Sciences (GBS), Virology
Andrew Damokosh, PhD, Director, GBS
Theodora Salcedo, PhD, Senior Principal Scientist, DSE – Toxicology
Robert Lange, PhD, Senior Research Investigator, DSE – Toxicology
Margo Heath-Chiozzi, MD, Vice President, Global Regulatory & Safety Sciences (GRSS) – Virology
Joan Fung-Tomc, PhD, Group Director, GRSS – Virology
Joseph Lamendola, PhD, VP, U.S. Regulatory Sciences and Regulatory Relations & Policy
Charles Wolleben, PhD, Group Director, GRSS – US
Chirag Patel, MS, Manager, Global Regulatory Strategy Management, GRSS
Angelina Verna, Associate Director, GRSS-CMC
Donald Oleksak, Associate Director, GRSS-CMC

1.0 BACKGROUND

Bristol-Myers Squibb has been developing daclatasvir (DCV) and asunaprevir (ASV) for the treatment of chronic hepatitis C. Their Phase 3 development program investigating the use of these two products in combination with peginterferon/ribavirin (PR) and other direct-acting antivirals (DAA) is nearing completion and they believe they have data to support submission of two NDAs. On November 27, 2013, Bristol-Myers Squibb (BMS) submitted a Type B, PreNDA meeting request for both DCV and ASV to discuss the adequacy of the data that will be submitted to support ASV in combination with DCV (DUAL therapy); ASV and DCV in combination with PR (QUAD therapy); and DCV in combination with sofosbuvir. Because the two products will be used as a combination therapy, the meeting is intended to serve as the Pre-NDA meeting for DCV and ASV applications. BMS is targeting a goal date of March 31, 2014 to submit these NDAs to the Agency. As a result BMS is seeking advice along with detailed feedback from the Division on a series of questions as they relate to their upcoming NDAs.

On November 27, 2013, BMS requested a type B, PreNDA meeting with the Division to discuss the requirements for submission of complete NDAs for DCV and ASV.

The Division's preliminary comments (Attachment 1) were sent to BMS on January 28, 2014 and Dr. Wolleben followed up with an electronic mail (email) communication on January 30, 2014 that provided BMS' responses (Attachment 2) and a request to focus the meeting on DCV questions 1, 4, 8b, 10, 11, 12, 13, 15, 16, and the additional Clinical Virology Comments on pages 12-13 of the Meeting Preliminary Comments communication.

2.0 DISCUSSION

2.1. IND 79599 DCV Questions Chemistry, Manufacturing, and Controls (CMC)

Question 1: Does FDA agree to accept additional stability data within 30 days of submission of the DCV NDA without impacting the review clock of the application?

DAVP's Preliminary Response: Yes, we concur with the plan to submit 12 months of long-term data in the initial submission (including 5°C, 25°C/60%RH, and 30°/75%RH conditions), with an 18-month update within 30 days. We confirm that this schedule would not alter the review clock for the application.

Discussion: DAVP confirmed that as a rolling submission it would be acceptable to submit stability data within 30 days of the original application that starts the review clock.

Clinical

Question 3: Does FDA agree with the proposed strategy as laid out in the SAP

included in the Meeting Background Document for analysis of efficacy data for the Summary of Clinical Efficacy for DCV?

DAVP's Preliminary Response: In general, we agree with your approach for analyses for the Summary of Clinical Efficacy for DCV. As noted, plans for analysis of QUAD and DCV/SOF data are not included in the SAP in the Background Document but will be incorporated into the SCE and SCS using data from the CSRs. In addition, we have the following clinical virology comments:

- Please provide a pooled summary of available SVR and virologic failure data for P/R add-on rescue therapy in genotype 1b subjects who experienced virologic failure on DCV/ASV DUAL therapy in Phase 2 or Phase 3 trials.
- We are concerned about the apparent association between Baseline NS5A Y93H and treatment outcome for the DCV/ASV DUAL regimen. The Summary of Clinical Efficacy (or alternatively, the Integrated Resistance Summary) should address whether patients should be screened for the Y93H polymorphism or other NS5A polymorphisms (e.g., L31M/V) associated with poor treatment efficacy prior to initiating treatment with the DCV/ASV DUAL regimen. Please specifically report the pooled SVR rates for subjects with or without Y93H (or any additional polymorphisms associated with poor treatment efficacy, e.g. L31M/V), as well as the frequency of these polymorphisms in the U.S. genotype 1b population across all of your studies.

Discussion: BMS summarized data on the impact and prevalence of the NS5A L31x (with x indicating 'any' change) and Y93H polymorphisms, pooling Baseline sequence and SVR data from Phase 2 and Phase 3 DCV/ASV trials in HCV genotype 1b subjects. DAVP's understanding of these data is as follows:

- Subjects with L31x polymorphisms had an SVR rate of ~35%, compared to ~90% for those without L31x polymorphisms.
- Subjects with the Y93H polymorphism had an SVR rate of 40%, compared to ~90% for those without the Y93H polymorphism.
- Specifically for North American subjects in the Phase 3 AI447028 trial:
 - Subjects with L31x polymorphisms had an SVR rate of ~35%, compared to ~90% for those without L31x polymorphisms.
 - Subjects with the Y93H polymorphism had an SVR rate of 20%, compared to ~90% for those without the Y93H polymorphism; BMS commented that the 20% SVR rate comes from only 5 subjects.
- The prevalence of the Y93H polymorphism in North America was 3.3%, compared with 10% globally.
- The prevalence of L31x polymorphisms in North America was 6% (global prevalence not reported).
- Approximately ~9% of North American subjects had L31x or Y93H polymorphisms (with a small number having both).

DAVP thanked BMS for providing these data and stated that the SVR results are concerning. The prevalence of these polymorphisms is not high, but the association with treatment outcome is clear, and it will be important to describe these data and the implications in labeling. DAVP added that excluding patients with these polymorphisms will improve SVR rates for the DCV/ASV regimen. DAVP stated that the precise language in the labeling will be a review issue, and requested that BMS propose some language. DAVP asked BMS if there have been any additional concerning data with respect to resistance-associated polymorphisms, and BMS responded, in general, no.

BMS also asked for clarification about DAVP's request for summarized data from subjects who have received the DCV/ASV + P/R "rescue" regimen. DAVP clarified that they are interested in a pooled summary of data for the efficacy of the DCV/ASV + P/R "rescue" treatment approach for HCV genotype 1b subjects who have experienced virologic failure on the DCV/ASV regimen. DAVP has received brief summaries from individual trials that studied this approach, but would like a single pooled summary of the data. DAVP clarified that only a summary of pooled data are requested and datasets are not needed.

Question 4: Does FDA agree with the proposed strategy as laid out in the SAP included in the Meeting Background Document for analysis of safety data for the Summary of Clinical Safety for DCV?

DAVP's Preliminary Response: The proposed strategy is acceptable for the planned analysis of safety data for the SCS for DCV. We have the following additional comments based on review of the SAP:

- We note that you have defined the on-treatment period as the day of the last dose of study drug + 7 days. For the safety datasets please provide a flag for treatment-emergent adverse events occurring only while on study drug (i.e. excluding the +7 days after last dose).

Discussion: DAVP clarified to BMS that the request to add an additional flag is a request and is not mandatory. However, the flag will allow for ease of review. BMS agreed to provide the flag in the appropriate adverse event (AE) and laboratory datasets.

- Please clarify why your hypersensitivity analysis plan does not consider inclusion of rash as part of the analysis.

Discussion: BMS clarified their rationale for not considering the inclusion of rash as part of the analysis was based on the lack of any rash signal across the overall safety database for the development program.

Pharmacovigilance

Question 8b: Taking into consideration the extent of the safety database and described safety specifications for DCV, does FDA concur with BMS that routine pharmacovigilance appears sufficient for this NDA submission?

DAVP's Preliminary Response: Yes, currently we agree with the plans for routine pharmacovigilance, but as you are aware a full safety evaluation will be completed during the review which could alter this recommendation.

FDA encourages sponsors to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with DCV and ASV following market approval. Guidance for pharmacovigilance planning is included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the plan is available, please include it in the NDA application in the appropriate module so it can be reviewed accordingly.

Discussion: DAVP agreed that based on summary data to date a Risk Evaluation and Mitigation Strategy (REMS) for DCV or ASV is not expected.

Question 10: Does FDA agree with the proposal and timeline as presented in Module 2 of the draft Table of Contents for the DCV NDA in Appendix 10 for rolling submissions to the DCV NDA?

DAVP's Preliminary Response: We acknowledge your request to roll-in sections of Module 2, however, the Agency would prefer to receive data that will assist in making the review process more efficient. Prior to submitting your formal request to the IND, we strongly recommend you consider including additional sections of your NDA in your rolling review proposal. For example, we would accept the following:

- a. Module 3 as follows:
 - entire drug substance section
 - entire drug product section, except the 18-month stability update that will be submitted within 30 days of receipt of the application.
- b. Module 4 - The entire module
- c. Module 5 - Completed clinical study reports with any available associated completed datasets

When submitting rolling submissions, please follow the below format:

1. The original US Regional.xml file should be coded as "original application"
2. Cover letter and form should state "presubmission to rolling submission – part 1 of XXX
(depending on how many parts before the final submission)

3. The subsequent sequences prior to the final sequence should be coded as "amendment" in the us-regional.xml, relating to the original application (including the final part of the submission)
4. The cover letter and form of the final submission should state "original application" – this starts the clock for review

Discussion: BMS agreed to submit the requested information in Module 3 and 4 of the NDA by the end of February for each application. The information will be accompanied by the relevant Quality and Nonclinical summaries provided in Module 2 and any necessary components for Module 1. Should the summaries in Module 2 reference any Clinical Study Reports (CSRs), BMS would then include those CSRs in Module 5 without accompanying datasets/CRFs. The full component of datasets and CRFs for these CSRs would be provided in the original application submission. BMS informed DAVP that the content required in section 3.2.R.oft Module 3 will not be available until March 31, 2014. The Division agreed that the March 31, 2014 date is acceptable.

Question 11: While BMS realizes that labeling is a review issue, does FDA agree to our proposal for a broad Indication, with guidance provided to prescribers in the Dosage and Administration section as reflected in the draft USPI for DCV in Appendix 8?

DAVP's Preliminary Response: We agree it is reasonable to evaluate DCV for a broad indication during the review. Based on review of your draft USPI we have the following comments:

- The Indication should specify the drug class
- The Points to consider language should be improved to more fully inform and guide prescribers in clinical decision making, particularly for genotype 1. Use recent labels from other approved DAAs to model your approach.
- A detailed rationale needs to be provided for the proposed durations, in particular for (b) (4)
- The Dosage and Administration section will be viewed as an important review issue based on the data and rationale to support your proposed populations and durations, in particular, for the combination of DCV/SOF.

Discussion: See Attachment 3- Slides and discussion summary under Question 12.

Question 12: Does FDA agree that while the data from the (b) (4) may be supportive of broad labeling for DCV, the strength of the evidence in this study warrants its inclusion in the DCV USPI?

DAVP's Preliminary Response: As stated previously, labeling with respect to proposed (b) (4)

(b) (4)

Lastly, in the Integrated Resistance Summary please summarize resistance analyses to support your proposed labeling. For example, what is the impact of Baseline NS5A resistance-associated polymorphisms on efficacy for each of the proposed treatment regimens, durations, and treatment populations (i.e., HCV genotypes (b) (4)).

Discussion: BMS presented their proposal for the extrapolations and rationale to support the 12 week duration that was not studied in HCV genotypes (b) (4)

(b) (4)

(b) (4)

Additionally, DAVP asked BMS about the formulation of sofosbuvir used in the phase 2 trial AI444040 and how it compares to the approved sofosbuvir formulation.

BMS was advised to request a right of reference from Gilead for the sofosbuvir data to support daclatasvir labeling. DAVP informed BMS that they are seeking advice from General Counsel as to the potential regulatory pathways (b) (4) if BMS is refused right of reference from Gilead. DAVP also inquired if BMS had any sofosbuvir clinical trial material left from AI444040. BMS was unsure whether any material was left from the clinical trial but was very doubtful that they could use the material for additional trials. BMS stated they will contact Gilead regarding the request for right of reference to the sofosbuvir data. However, BMS expressed uncertainty if they would be able to resolve these issues by the March 31, 2014 submission goal date. DAVP made it clear to BMS that they could still submit their NDA as planned, however for the proposed daclatasvir/sofosbuvir indication appropriate linking between the different sofosbuvir formulations is a regulatory review issue that requires further discussion in order to include data from the AI444040 trial (b) (4) BMS indicated

the desire to include all proposed regimens (b) (4), but emphasized that the most important goal is to first receive DCV marketing approval.

BMS inquired about the status of Breakthrough Therapy designation for the DUAL therapy and Pediatric Study Plans (PSP) submitted for DCV and ASV. DAVP informed BMS that a decision would be made shortly regarding the Breakthrough Therapy designation request and they would follow up with BMS regarding the response for the PSPs. In addition, DAVP informed BMS that at the present time we do not expect a need for an Advisory Committee Meeting for these incoming NDAs. DAVP noted further that Advisory Committee Meetings may not be held for some drugs with Breakthrough Therapy Designation because a goal of the program is to ensure a rapid and efficient review of the NDAs.

Question 13: Does FDA agree with the incorporation of the 30-mg tablet of DCV in the DCV USPIs?

DAVP's Preliminary Response: Yes, the proposal to include a 30 mg tablet strength as part of the daclatasvir U.S. prescribing information is reasonable. The appropriateness of the proposed daclatasvir dosage adjustments will be a review issue. Please also provide responses for the following related issues:

- a) Please clarify whether the proposed dosage adjustment will include recommendations for strong CYP3A inducers.
- b) Please clarify whether a biowaiver or a relative bioavailability trial will be submitted to link the daclatasvir 30 mg tablet strength to the daclatasvir 60 mg tablet strength that was administered in the Phase 3 trials (AI447028 and AI447029).
- c) Please provide information regarding whether the daclatasvir 60 mg tablet formulation that was administered in the Phase 3 trials (AI447026, AI447028 and AI447029) is identical to the proposed U.S. marketed commercial formulation.
- d) Please provide information regarding whether the asunaprevir 100 mg (b) (4) formulation that was administered in the Phase 3 trial (AI447026, AI447028) (b) (4) (b) (4)

Discussion: BMS confirmed that for daclatasvir, there are no relative bioavailability data that directly links the proposed U.S. commercially marketed 30 mg tablets to the proposed U.S. commercially marketed 60 mg tablets. In vitro information, including dissolution data, is available to link the proposed U.S. commercially marketed 30 mg tablets to the proposed U.S. commercially marketed 60 mg tablets. DAVP recommended that BMS submit to the NDA a biowaiver request for the proposed U.S. commercially marketed 30 mg tablets.

BMS agreed to include a biowaiver request in the March 31, 2014, NDA submission..

Question 15: Does FDA agree with how BMS plans to reflect (b) (4) in the Clinical Studies section of the DCV USPI?

DAVP's Preliminary Response: As stated previously, how the trial will be presented in Section 14 will be a review issue. Please provide your rationale and supportive data for pooling of the populations, regimens and durations as you have presented in your draft USPL.

Discussion: See discussion summary under Question 12.

Question 16: Does FDA agree with BMS' proposal for managing cross referencing between the DCV and ASV NDAs?

DAVP's Preliminary Response: From a technical standpoint, providing cross reference information under List of References is not an acceptable approach.

Sponsors options of cross referencing information submitted to another application would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

1. To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), and (5) the submission identification (e.g., submission serial number, volume number, electronic folder, and file name) of the referenced document. Hyperlinks to those documents are optional, but could be of help to reviewers, if provided.
2. To use the second option (cross application links), both applications would need to be in eCTD format and reside on the same server which is the case, for both NDAs. The applications need to include the appropriate prefix in the href links (e.g. nda, ind,). Also, when cross application links are used, it's strongly recommended that a cross reference document be placed in m1.4.4, in case any of the links don't work and in the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference" and application number (e.g. Cross Ref to nda123456). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application and the application that is being referenced.

Prior to using cross application linking in an application, it is recommended that the sponsor submits an "eCTD cross application links" sample to ensure successful use of cross application links.

To submit an eCTD cross application link sample, sponsors would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. Please refer to the Sample Process web page which is located

at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

Discussion: BMS informed the Division that they will provide all reports cited in an application, even though they may also reside in the other NDA. The Division advised BMS to clearly specify the identical information in the related NDA. BMS should provide a written statement in the cover letter indicating that the information is identical and specify what information is repeated and its location.

2.2. Additional Clinical Virology Comments

1. Based on a previous communication (IND (b) (4) SN 046) it is our understanding that Baseline amino acid sequence data will be submitted for all subjects from Phase 3 trials, but post-Baseline data may not be available for all virologic failures (particularly relapsers) in time for inclusion in the NDA. Also, at the time of this previous communication there were no plans to submit resistance data from the QUAD trial AI447029. Please provide a brief update on your plans for submission of resistance data and summarize the number of DCV/ASV treated subjects (summarized by all study sites and within U.S.-only) who received either the DUAL or QUAD regimens and experienced virologic failure, and for whom post-Baseline resistance data will be included.

Discussion: BMS responded to the pre-meeting comment by noting that resistance analyses were conducted for all subjects who met the virologic failure definitions in the Phase 3 DUAL and QUAD trials, except that for some subjects data could not be obtained due to technical reasons. DAVP acknowledged that sometimes resistance data cannot be obtained due to technical issues.

2. Based on previous informal communications it is our understanding that deep sequencing data are available from one virologic failure subject from clinical trial AI444040. Please submit summary frequency tables from your analyses, and also submit the raw data as fastq files on a DVD or portable hard drive. Additional guidelines are provided in the attached document. (4.30.2013 NGS data submission guidelines).

Discussion: BMS stated they would prefer to submit the fastq deep sequencing data separately “outside the application” on a DVD or hard drive. DAVP stated that they prefer the data are submitted in the eCTD submission. BMS responded that they are not sure how to submit it to the eCTD. BMS and DAVP both acknowledged that the data are for only a single subject, and were generated by an academic collaborator who used a format that differs from the Agency’s requirements. DAVP stated it is not their intention to have this submission issue interfere with the assembly and submission of other parts of the NDA. BMS inquired if the data can first be submitted to the daclatasvir IND for DAVP to review and provide further guidance, and DAVP agreed. DAVP suggested placing the file(s) in Module 5.3.5.4 of the daclatasvir IND.

3. Please include the following virology/resistance reports and datasets in the requested

locations in the eCTD:

- **Module 2.7.2.4-Virology Summary:** Includes a summary of nonclinical and clinical virology data, with a listing and hyperlinks to nonclinical virology reports and also the Integrated Resistance Profile/Summary report. Since there will be a separate integrated resistance report, the clinical virology summary can be brief. One summary for each DAA/NDA.
- **Module 5.3.5.4-Integrated Resistance Profile/Summary:** Includes a summary of genotypic and phenotypic drug resistance data from clinical trials, with a listing and hyperlinks to submitted resistance dataset files. Please also provide compiled tables showing the phenotype data for all site-directed mutant HCV replicons that have been evaluated for phenotypic susceptibility to ASV or DCV. If one summary is written for both DAAs, the same summary can be included in both the ASV and DCV NDAs.
- **Module 5.3.5.4-Resistance datasets for Phase 3 and key Phase 2 trials assembled according to February 2013 Draft Guidance.** Based on a previous communication (IND (b) (4) SN 046) it is our understanding that resistance data from multiple trials will be pooled, which is acceptable as long as the datasets are not too large to open. For datasets that include data from trials studying both ASV and DCV (i.e., DUAL/QUAD regimens), please include the same datasets in both the ASV and DCV NDAs.
- **Module 5.3.5 Clinical Study Report Folders:** Clinical resistance reports and resistance datasets (previously referred to as “June 2006” format) generated for single clinical trials can be placed in the folders for the individual clinical study reports.
- **Module 5.3.5.4:** Please also provide a .xpt file showing the alignment of NS5A amino acid sequences (N-terminal (b) (4) aa) for all isolates that have been evaluated for susceptibility to DCV in the HCV replicon system (i.e., isolates summarized in Table 6.1.1-1 of meeting package), and include columns for the corresponding genotypes/subtypes and EC₅₀ values. Please report amino acid sequences in reference to the genotype 1a H77 strain.

Discussion Re: Module 5.3.5.4 Request: BMS asked for clarification of the request for a .xpt file of clinical isolate phenotype data for DCV. BMS stated that many clinical isolates have been evaluated beyond those summarized in Table 6.1.1-1 of the meeting package, and could put together a compiled table for these. BMS stated that most of the data are from HCV genotype 1 infected subjects. DAVP stated that the plan was acceptable, and noted that the interest in these data is to understand the relationship between phenotype results and NS5A sequences, particularly across different HCV genotypes.

2.3. Additional Clinical Pharmacology comments for daclatasvir and asunaprevir NDAs

1. Please specify whether the bioanalytical information that will be included at the time of the initial NDA submission for all clinical trials that will be used to support the proposed labels for daclatasvir and asunaprevir will include all the items outlined in the draft Guidance for Industry, Bioanalytical Method Validation, September 2013, section IX

(Appendix), Tables 1 to 4, including long term stability data and information on the storage temperature and the duration of storage at each site (e.g. trial site, secondary storage sites, the bioanalytical laboratory) that pharmacokinetic samples were stored at. This information should be available for daclatasvir, asunaprevir, sofosbuvir and any concomitant medications that were evaluated.

2. In the Summary of Biopharmaceutic Studies and Associated Analytical Methods, please include a table that lists the specific daclatasvir and asunaprevir formulations that were administered for each of the clinical trials that will be submitted for the daclatasvir and asunaprevir NDAs. The information should be categorized by the phase of the clinical development program (e.g. trials where the Phase 1 formulation was administered, etc). Please also include summaries of the relative bioavailability data linking the different daclatasvir or asunaprevir formulations.

Discussion: BMS proposed to submit a separate document in the NDAs with the information requested. DAVP agreed that BMS' proposal is acceptable.

3. For the drug interactions trials that will be submitted for the daclatasvir and asunaprevir NDAs, in the Summary of Clinical Pharmacology Studies, please specify whether any of the concomitant medications were evaluated using a non U.S. marketed formulation and provide information regarding the difference in bioavailability from the U.S. marketed formulation.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. DAVP agreed that the information BMS plans to include in both NDAs will constitute complete applications.

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

- A preliminary discussion on the need for a REMS was held and it was concluded that there are no safety signals that warrant a REMS at this time..
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
 - The (b) (4) stability data for asunaprevir.
 - The 18-month stability data for daclatasvir.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA NUMBER: LATE COMPONENT - QUALITY

4.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

5.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements of Prescribing Information* website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents, and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

6.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

7.0 ISSUES REQUIRING FURTHER DISCUSSION

- The appropriate pathway for submitting the fastq deep sequencing data to the daclatasvir NDA.

8.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Provide status of Break Through Therapy Request for IND (b) (4) (ASV and DCV)	FDA	Week of 2/2/2014
Provide status of iPSP	FDA	Week of 2/2/2014

submitted to INDs 79599 and (b) (4)		
Contact Gilead regarding a right of reference to the sofosbuvir NDA	BMS	As soon as possible
Include a Biowaiver Request in the DCV NDA	BMS	March 31, 2014
Submission of fastq deep sequencing data to daclatasvir IND	BMS	As soon as possible
Provide feedback on how to submit fastq deep sequencing data in the NDA	FDA	As soon as possible
Submit a consult request to the Office of Regulatory Policy	FDA	As soon as possible

6.0 ATTACHMENTS AND HANDOUTS

Attachment 1 - FDA's January 28, 2014 Preliminary Comments

Attachment 2 – Bristol Myers Squibb's January 30, 2014 Preliminary Responses

Attachment 3- Bristol Myers Squibb Slide Presentation

ATTACHEMENT 1



IND 79599
IND (b) (4)

MEETING PRELIMINARY COMMENTS

Bristol-Myers Squibb Company
Attention: Charles D. Wolleben, PhD
Group Director, Global Regulatory Sciences-US
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Wolleben:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMS-790052 daclatasvir (IND 79599) and BMS-650032 asunaprevir (IND (b) (4)).

We also refer to your November 27, 2013, correspondence, received November 27, 2013, requesting a meeting to discuss the requirements for submission of complete NDA applications for these two products.

Our preliminary responses to your meeting questions are enclosed.

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

If you have any questions, call Mammah Sia Borbor, M.S., M.B.A., Regulatory Project Manager, at (301) 796-7731 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

IND 79599
IND (b) (4)
Page 2

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: January 31, 2014 9:30 AM – 11:00 AM (EST)
Meeting Location: White Oak Building 22, Conference Room: 2205

Application Number: 79599 and (b) (4)
Product Name: BMS-790052, daclatasvir and BMS-650032, asunaprevir
Indication: Chronic Hepatitis C
Sponsor/Applicant Name: Bristol-Myers Squibb Company

FDA ATTENDEES

Edward Cox, MD, MPH, Director, Office of Antimicrobial Products (OAP)
David Roeder, Associate Director of Regulatory Affairs, OAP
Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, MD, MPH Deputy Director DAVP
Kendall Marcus, MD, Deputy Director for Safety
Kimberly Struble, PharmD, Medical Team Lead DAVP
Hanan Ghantous, PhD, DABT, Pharmacology/Toxicology Team Leader DAVP
Julian O'Rear, PhD Virology Team Lead DAVP
Shirley K. Seo, PhD, Clinical Pharmacology Team Lead, Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology IV (DCP IV)
Rapti Madurawe, PhD, Branch Chief, Office of New Drug Quality Assessment (ONDQA)
Stephen Miller, PhD, CMC Team Leader ONDQA
Greg Soon, PhD, Statistical Team Lead, Office of Translational Sciences- Division of Biometrics IV
Wendy Carter, DO, Medical Officer DAVP
Stanley Au, PharmD, Clinical Pharmacology Reviewer (OCP) (DCP IV),
Lalji Mishra, PhD, Virology Reviewer DAVP
Patrick Harrington, PhD, Virology Reviewer DAVP
Jeffrey Florian, PhD, Pharmacometrics Reviewer, OCP, Division of Pharmacometrics
Mark Powley, PhD, Pharmacologist DAVP
Sandra Suarez, PhD, Biopharmaceutics Reviewer, ONDQA
Milton Sloan, PhD, Chemist, ONDQA
George, Lunn, PhD, Chemist, ONDQA
Wen Zeng, PhD, Statistician, OB, DB IV
Fraser Smith, PhD, Statistician, OB, DBIV
Antoine El-Hage, PhD, Office of Scientific Investigations
Krishnakali Ghosh, PhD, Office of Manufacturing and Product Quality

Karen Winestock, Chief, Project Management Staff, DAVP
Danyal Chaudhry, MPH, Regulatory Project Management Staff, Office of Surveillance and Epidemiology
Mammah Borbor, MS, MBA, Regulatory Project Manager DAVP
Nina Mani, PhD MPH, Regulatory Project Manager DAVP

SPONSOR ATTENDEES

Steven Schnittman, MD, VP Global Development Lead – HCV, Global Clinical Research (GCR)
Douglas Manion, MD, Senior VP Development, Neuroscience, Virology and Japan, GCR
Eric Hughes, MD, PhD, Exec Director, GCR – Virology
Stephanie Noviello, MD, Director, GCR – Virology
Dessislava Dimitrova, MD, Global Medical Director, Medical Safety Assessment, Global Pharmacovigilance and Epidemiology (GPV&E)
Tushar Garimella, PhD, Associate Director, Clinical Pharmacology and Pharmacometrics
Timothy Eley, PhD, Director, Clinical Pharmacology and Pharmacometrics
David Gardiner, MD, Group Director, Exploratory Clinical & Translational Research
Richard Bertz, PhD, Vice President, Clinical Pharmacology & Pharmacometrics
Min Gao, PhD, Research Fellow, Research & Development – Virology
Fiona McPhee, DPhil, Research Fellow, Research & Development – Virology
Thomas Kelleher, PhD, Group Director, Global Biometric Sciences (GBS), Virology
Andrew Damokosh, PhD, Director, GBS
Marc Davies, Ph.D., DABT, Group Director, Drug Safety Evaluation (DSE)
Theodora Salcedo, PhD, Senior Principal Scientist, DSE – Toxicology
Robert Lange, PhD, Senior Research Investigator, DSE – Toxicology
Margo Heath-Chiozzi, MD, Vice President, Global Regulatory & Safety Sciences (GRSS) – Virology
Joan Fung-Tome, PhD, Group Director, GRSS – Virology
Joseph Lamendola, PhD, VP, U.S. Regulatory Sciences and Regulatory Relations & Policy
Charles Wolleben, PhD, Group Director, GRSS – US
Chirag Patel, MS, Manager, Global Regulatory Strategy Management, GRSS

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 31, 2014, 9:30 AM – 11:00 AM (EST), 10903 New Hampshire Avenue, White Oak Building #22, Conference Room: 2205 between Bristol-Myers Squibb Company and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the

meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Bristol-Myers Squibb has been developing daclatasvir (DCV) and asunaprevir (ASV) for the treatment of chronic hepatitis C. Their Phase 3 development program investigating the use of these two products in combination with peginterferon/ribavirin (PR) and other direct acting antivirals (DAA) is nearing completion and they believe they have data to support submission of two NDAs. On November 27, 2013, Bristol-Myers Squibb (BMS) submitted a Type B, PreNDA meeting request for both DCV and ASV to discuss the adequacy of the data that will be submitted to support ASV in combination with DCV (DUAL therapy); ASV and DCV in combination with PR (QUAD therapy); and DCV in combination with sofosbuvir. Because the two products will be used as a combination therapy, the meeting is intended to serve as the pre-NDA meeting for DCV and ASV applications. BMS is targeting a goal date of March 31, 2014 to submit these NDAs to the Division for review. As a result BMS is seeking advice along with detailed feedback from the Division on a series of questions as it relates to their upcoming NDA submissions.

2. TOPICS FOR DISCUSSION

IND 79599 DCV Questions Chemistry, Manufacturing, and Controls (CMC)

Question 1: Does FDA agree to accept additional stability data within 30 days of submission of the DCV NDA without impacting the review clock of the application?

DAVP's Preliminary Response: Yes, we concur with the plan to submit 12 months of long-term data in the initial submission (including 5°C, 25°C/60%RH, and 30°/75%RH conditions), with an 18-month update within 30 days. We confirm that this schedule would not alter the review clock for the application.

Clinical

Question 2: Assuming that the efficacy data from AI447028 and AI447029 are consistent with the DCV/ASV and DCV Quad Regimen data from Japanese Phase 3 and global Phase 2 experience, respectively, does FDA agree that these 4 studies (AI447028 [N = 747], AI447026 [N = 222], AI444040 [N = 211], and AI447029 [N = 398]) would represent sufficient efficacy data to support the filing of the proposed DCV NDA?

DAVP's Preliminary Response: Based on the preliminary data provided and your proposed plan, the trials outlined above are acceptable for submission of the DCV NDA. The specifics of the indication and populations included in the indication will be a review issue based on the data package you submit. In particular, we identify the proposed dosage and administration with respect to genotypes and treatment durations for DCV/SOF, as a review issue.

Question 3: Does FDA agree with the proposed strategy as laid out in the SAP included in the Meeting Background Document for analysis of efficacy data for the Summary of Clinical Efficacy for DCV?

DAVP's Preliminary Response: In general, we agree with your approach for analyses for the Summary of Clinical Efficacy for DCV. As noted, plans for analysis of QUAD and DCV/SOF data are not included in the SAP in the Background Document but will be incorporated into the SCE and SCS using data from the CSRs. In addition, we have the following clinical virology comments:

- Please provide a pooled summary of available SVR and virologic failure data for P/R add-on rescue therapy in genotype 1b subjects who experienced virologic failure on DCV/ASV DUAL therapy in Phase 2 or Phase 3 trials.
- We are concerned about the apparent association between Baseline NS5A Y93H and treatment outcome for the DCV/ASV DUAL regimen. The Summary of Clinical Efficacy (or alternatively, the Integrated Resistance Summary) should address whether patients should be screened for the Y93H polymorphism or other NS5A polymorphisms (e.g., L31M/V) associated with poor treatment efficacy prior to initiating treatment with the DCV/ASV DUAL regimen. Please specifically report the pooled SVR rates for subjects with or without Y93H (or any additional polymorphisms associated with poor treatment efficacy, e.g. L31M/V), as well as the frequency of these polymorphisms in the U.S. genotype 1b population across all of your studies.

Question 4: Does FDA agree with the proposed strategy as laid out in the SAP included in the Meeting Background Document for analysis of safety data for the Summary of Clinical Safety for DCV?

DAVP's Preliminary Response: The proposed strategy is acceptable for the planned analysis of safety data for the SCS for DCV. We have the following additional comments based on review of the SAP:

- We note that you have defined the on-treatment period as the day of the last dose of study drug + 7 days. For the safety datasets please provide a flag for treatment-emergent adverse events occurring only while on study drug (i.e. excluding the +7 days after last dose).
- Please clarify why your hypersensitivity analysis plan does not consider inclusion of rash as part of the analysis.

Question 5: Does FDA agree with the content and the proposed timeframe for submission of the Safety Update Report during the review of the DCV NDA?

DAVP's Preliminary Response: Your plan for the content and proposed timeframe for submission of the Safety Update Report is generally acceptable. However, please group the

trials by those with only post-treatment data and those with on-treatment data for ease of review. Please also organize by SOC according to MedDRA for ease of review. In addition, we request you provide narratives for all deaths, SAEs or discontinuations due to adverse drug reactions. Additional narratives may be requested as necessary for review. Although you may choose to submit the Case Report Forms, we are not requiring that you submit them for this Safety Update Report.

Question 6: Does FDA agree with BMS' proposal not to include BMS-986094 in the Summary of Clinical Safety or in the safety update for the DCV NDA?

DAVP's Preliminary Response: We agree with your proposal to not include BMS-986094 in the SCS or the SUR for the DCV NDA.

Question 7: Does FDA agree with the inclusion of an integrated PPK and exposure-safety analysis in the initial DCV NDA, which does not incorporate data from the DCV Quad Regimen Phase 3 study AI447029, but that an updated analysis including AI447029 will be submitted during the 90-day safety update?

DAVP's Preliminary Response:

The current plan to submit an integrated population PK and exposure-safety analyses for DCV and ASV which does not include data from the Phase 3 DCV QUAD trial is acceptable. However, the proposal to submit additional PK data during the review cycle is not acceptable.

All data that you intend to submit for the NDA, including pharmacokinetic data must be available at the time of the initial NDA submission. In addition, any pharmacokinetic data or analyses submitted after the initial NDA submission will be acknowledged, but may not be reviewed.

Pharmacovigilance

Question 8a: Does FDA agree that the anticipated safety experience for DCV represents sufficient safety data to support the filing of the proposed DCV NDA?

DAVP's Preliminary Response: Yes, we agree there are sufficient safety data to support submission of the DCV NDA.

Question 8b: Taking into consideration the extent of the safety database and described safety specifications for DCV, does FDA concur with BMS that routine pharmacovigilance appears sufficient for this NDA submission?

DAVP's Preliminary Response: Yes, currently we agree with the plans for routine pharmacovigilance, but as you are aware a full safety evaluation will be completed during the review which could alter this recommendation.

FDA encourages sponsors to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with DCV and ASV following market approval. Guidance for pharmacovigilance planning is included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the plan is available, please include it in the NDA application in the appropriate module so it can be reviewed accordingly.

Question 9: Does FDA agree that inclusion of these 3 regimens (DCV/ASV, DCV/SOF, and DCV Quad) that are expected to yield high efficacy and have an acceptable safety profile in several patient populations, including those with limited or no treatment options, in the DCV NDA, warrant consideration for priority review of this application?

DAVP's Preliminary Response: Yes, we agree that the planned NDA package warrants consideration for a priority review.

Question 10: Does FDA agree with the proposal and timeline as presented in Module 2 of the draft Table of Contents for the DCV NDA in Appendix 10 for rolling submissions to the DCV NDA?

DAVP's Preliminary Response: We acknowledge your request to roll-in sections of Module 2, however, the Agency would prefer to receive data that will assist in making the review process more efficient. Prior to submitting your formal request to the IND, we strongly recommend you consider including additional sections of your NDA in your rolling review proposal. For example, we would accept the following:

- a. Module 3 as follows:
 - entire drug substance section
 - entire drug product section, except the 18-month stability update that will be submitted within 30 days of receipt of the application.
- b. Module 4 - The entire module
- c. Module 5 - Completed clinical study reports with any available associated completed datasets

When submitting rolling submissions, please follow the below format:

1. The original US Regional.xml file should be coded as "original application"
2. Cover letter and form should state "presubmission to rolling submission – part 1 of XXX (depending on how many parts before the final submission)"
3. The subsequent sequences prior to the final sequence should be coded as "amendment" in the us-regional.xml, relating to the original application (including the final part of the submission)
4. The cover letter and form of the final submission should state "original application" – this starts the clock for review

Question 11: While BMS realizes that labeling is a review issue, does FDA agree

to our proposal for a broad Indication, with guidance provided to prescribers in the Dosage and Administration section as reflected in the draft USPI for DCV in Appendix 8?

DAVP's Preliminary Response: We agree it is reasonable to evaluate DCV for a broad indication during the review. Based on review of your draft USPI we have the following comments:

- The Indication should specify the drug class
- The Points to consider language should be improved to more fully inform and guide prescribers in clinical decision making, particularly for genotype 1. Use recent labels from other approved DAAs to model your approach.
- A detailed rationale needs to be provided for the proposed durations, in particular for (b) (4)
- The Dosage and Administration section will be viewed as an important review issue based on the data and rationale to support your proposed populations and durations, in particular, for the combination of DCV/SOF.

Question 12: Does FDA agree that while the data from the (b) (4) may be supportive of broad labeling for DCV, the strength of the evidence in this study warrants its inclusion in the DCV USPI?

DAVP's Preliminary Response: As stated previously, labeling with respect to proposed (b) (4)

Lastly, in the Integrated Resistance Summary please summarize resistance analyses to support your proposed labeling. For example, what is the impact of Baseline NS5A resistance-associated polymorphisms on efficacy for each of the proposed treatment regimens, durations, and treatment populations (i.e., HCV genotypes (b) (4)).

Question 13: Does FDA agree with the incorporation of the 30-mg tablet of DCV in the DCV USPIs?

DAVP's Preliminary Response: Yes, the proposal to include a 30 mg tablet strength as part of the daclatasvir U.S. prescribing information is reasonable. The appropriateness of the proposed daclatasvir dosage adjustments will be a review issue. Please also provide responses for the following related issues:

- a) Please clarify whether the proposed dosage adjustment will include recommendations for strong CYP3A inducers.

b) Please clarify whether a biowaiver or a relative bioavailability trial will be submitted to link the daclatasvir 30 mg tablet strength to the daclatasvir 60 mg tablet strength that was administered in the Phase 3 trials (AI447028 and AI447029).

c) Please provide information regarding whether the daclatasvir 60 mg tablet formulation that was administered in the Phase 3 trials (AI447026, AI447028 and AI447029) is identical to the proposed U.S. marketed commercial formulation.

d) Please provide information regarding whether the asunaprevir 100 mg (b) (4) formulation that was administered in the Phase 3 trial (AI447026, AI447028) (b) (4)

Question 14: Does FDA agree with how BMS plans to present the Adverse Reactions sections of the DCV draft USPI?

DAVP's Preliminary Response: In general, the presentation of the Adverse Reactions section in the draft label is appropriate, but the content and format of the section, including the tables, will be a review issue.

Question 15: Does FDA agree with how BMS plans to reflect (b) (4) in the Clinical Studies section of the DCV USPI?

DAVP's Preliminary Response: As stated previously, how the trial will be presented in Section 14 will be a review issue. Please provide your rationale and supportive data for pooling of the populations, regimens and durations as you have presented in your draft USPI.

Question 16: Does FDA agree with BMS' proposal for managing cross referencing between the DCV and ASV NDAs?

DAVP's Preliminary Response: From a technical standpoint, providing cross reference information under List of References is not an acceptable approach.

Sponsors options of cross referencing information submitted to another application would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

1. To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), and (5) the submission identification (e.g., submission serial number, volume number, electronic folder, and file name) of the referenced document. Hyperlinks to those documents are optional, but could be of help to reviewers, if provided.
2. To use the second option (cross application links), both applications would need to be in

eCTD format and reside on the same server which is the case, for both NDAs. The applications need to include the appropriate prefix in the href links (e.g. nda, ind,). Also, when cross application links are used, it's strongly recommended that a cross reference document be placed in m1.4.4, in case any of the links don't work and in the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference" and application number (e.g. Cross Ref to nda123456). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application and the application that is being referenced.

Prior to using cross application linking in an application, it is recommended that the sponsor submits an "eCTD cross application links" sample to ensure successful use of cross application links.

To submit an eCTD cross application link sample, sponsors would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. Please refer to the Sample Process web page which is located at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

Question 17: Anticipating the approval of the PSPs for DCV and ASV prior to submission of the NDA for DCV, does FDA agree that the approved PSPs should be provided in Module 1.9 of the DCV NDA and that these will satisfy the need to discuss the pediatric development of DCV in the DCV NDA?

DAVP's Preliminary Response: Yes, the approved PSPs may satisfy the need to discuss the pediatric development in the respective NDAs. The approved PSPs must be submitted as part of the NDA in Module 1.9 to satisfy the requirement.

IND (b) (4) **ASV Questions**
Chemistry, Manufacturing, and Controls (CMC)

(b) (4)

IND 79599
IND (b) (4)

Preliminary Meeting Comments

(b) (4)

IND 79599

IND (b) (4)

Preliminary Meeting Comments

(b) (4)

3.0 Additional FDA Comments
IND 79599 DCV Additional Comments

Biopharmaceutics Comments

We have the following comments regarding the biopharmaceutics information (not limited to) that should be provided in your NDA.

1. Dissolution acceptance criterion: For the selection of the dissolution acceptance criterion of your product, the following points should be consider
 - a. The in vitro dissolution profiles should encompass the timeframe over which at least 80% of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.
 - b. The proposed dissolution acceptance criterion should have the capability to reject for batches with inadequate performance (e.g. reject aberrant batches or reject batches that are not bioequivalent)
 - c. The dissolution profile data from the bio-batches (clinical & PK) and registration stability batches should be used for the setting of the dissolution acceptance criterion (i.e., specification-sampling time points and specification value).
 - d. The dissolution acceptance criterion should be set in a way to ensure consistent performance from lot to lot and this criterion should not allow the release of any lots with dissolution profiles outside those that were tested clinically.

Note that the acceptability of the proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data.

IND (b) (4) **ASV Additional Comments**

(b) (4)

IND 79599
IND (b) (4)

Preliminary Meeting Comments

(b) (4)



Additional Clinical Pharmacology comments for daclatasvir and asunaprevir NDAs

1. Please specify whether the bioanalytical information that will be included at the time of the initial NDA submission for all clinical trials that will be used to support the proposed labels for daclatasvir and asunaprevir will include all the items outlined in the draft Guidance for Industry, Bioanalytical Method Validation, September 2013, section IX (Appendix), Tables 1 to 4, including long term stability data and information on the storage temperature and the duration of storage at each site (e.g. trial site, secondary storage sites, the bioanalytical laboratory) that pharmacokinetic samples were stored at. This information should be available for daclatasvir, asunaprevir, sofosbuvir and any concomitant medications that were evaluated.

2. In the Summary of Biopharmaceutical Studies and Associated Analytical Methods, please include a table that lists the specific daclatasvir and asunaprevir formulations that were administered for each of the clinical trials that will be submitted for the daclatasvir and asunaprevir NDAs. The information should be categorized by the phase of the clinical development program (e.g. trials where the Phase 1 formulation was administered, etc). Please also include summaries of the relative bioavailability data linking the different daclatasvir or asunaprevir formulations.
3. For the drug interactions trials that will be submitted for the daclatasvir and asunaprevir NDAs, in the Summary of Clinical Pharmacology Studies, please specify whether any of the concomitant medications were evaluated using a non U.S. marketed formulation and provide information regarding the difference in bioavailability from the U.S. marketed formulation.

Additional eSub Team comments for daclatasvir and asunaprevir NDAs

From a technical standpoint (not content related) the proposed format for the draft TOCs for both NDAs are acceptable. Please see additional comments below.

- FDA FORM 3674 should reside under m1.2 cover letter section with a clear leaf title
- Providing Table of Contents in 2.1 is not necessary in the eCTD structure.
- It is acceptable and preferred to provide a single heading node in m.3 (i.e. a single m3.2.S, m3.2.P and m3.2.p.4 section) with attribute of "ALL" and differentiating documents with clear and concise leaf titles that indicates the file's true content, instead of providing separate heading nodes for each strength (e.g. 3.2.P Drug Product - 30 mg tablet; 3.2.P Drug Product - 60 mg tablet)
- Do not provide placeholders for sections that will not be submitted (e.g. 4.2.3.7.2 Immunotoxicity - Not Applicable). Placeholders are only allowed when submitting ANDAs
- Study Tagging Files (STF) are required for submissions to the FDA when providing study information in modules 4 and 5, with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF including case report forms (crfs). Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008), located at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissions/Requirements/ElectronicSubmissions/UCM163560.pdf>
- Regarding use of the m5-3-7 heading element, FDA doesn't use module 5.3.7 CRFs. Instead, case report forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form". Do not use 5.3.7 as a heading element in the index.xml
- To submit PADER descriptive portion (only) in eCTD format, it should be provided as a single pdf file with bookmarks, table of contents and hyperlinks in the eCTD section,

m5.3.6. Please ensure that the leaf title of the report includes the reporting period, since each report is for a specific time period and it also helps when the leaf title follows a standard format, so reviewers can quickly differentiate one report from another.

- The descriptive portion of the Periodic ADE Report in module 5.3.6 should not contain the 3500A forms, but instead, at the end of the summary, it should specify how the 3500A forms were submitted. For example, you would reference that the 3500A forms were submitted in Paper to AERS or the 3500A forms were sent in E2B XML format via the Electronic Submissions Gateway. For Steps to Submitting ICSRs Electronically in the XML Format, please visit:
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115914.htm>
- If you submit the 3500A forms in paper, it's recommended that you provide the date of the submission, address shipped to, as well as any other pertinent information.

Below is the address for the 3500A paper submissions:

FDA/Central Document Room
Attn: AERS 3500A Reports Production
5901-B Ammendale Rd.
Beltsville, MD. 20705-1266

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our December 26, 2013, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements of Prescribing Information* website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents , and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

ATTACHEMENT 2

Question 1: Does FDA agree to accept additional stability data within 30 days of submission of the DCV NDA without impacting the review clock of the application?

DAVP's Preliminary Response: Yes, we concur with the plan to submit 12 months of long-term data in the initial submission (including 5°C, 25°C/60%RH, and 30°/75%RH conditions), with an 18-month update within 30 days. We confirm that this schedule would not alter the review clock for the application.

BMS Clarification/Question: To be clear, we interpret this to mean that in the scenario of a rolling submission it would be acceptable to submit such data within 30 days of the “Original Application” which starts the review clock. If this interpretation is not accurate we would like DAVP to clarify.

Question 10: Does FDA agree with the proposal and timeline as presented in Module 2 of the draft Table of Contents for the DCV NDA in Appendix 10 for rolling submissions to the DCV NDA?

DAVP's Preliminary Response: We acknowledge your request to roll-in sections of Module 2, however, the Agency would prefer to receive data that will assist in making the review process more efficient. Prior to submitting your formal request to the IND, we strongly recommend you consider including additional sections of your NDA in your rolling review proposal. For example, we would accept the following:

- a. Module 3 as follows:
 - entire drug substance section
 - entire drug product section, except the 18-month stability update that will be submitted within 30 days of receipt of the application.
- b. Module 4 - The entire module
- c. Module 5 - Completed clinical study reports with any available associated completed datasets

(Additional DAVP comments re rolling submission format not included)

BMS Clarification/Question: We would like to clarify our current plan for a rolling submission for these 2 NDAs, which was not clear in the background document. We would propose submitting completed Modules 3 and 4 together by the end of February for each application. These would be accompanied by the relevant Quality and Nonclinical summaries provided in Module 2 and any necessary components for Module 1. Should the summaries in Module 2 reference any Clinical Study Reports (CSRs), we would then include those CSRs in Module 5 without accompanying datasets/CRFs. The full component of datasets and CRFs for these CSRs would be provided in the “Original Application” submission.

We will submit this plan to the INDs but any feedback on this proposal Friday would be appreciated.

Question 16: Does FDA agree with BMS' proposal for managing cross referencing between the DCV and ASV NDAs?

DAVP's Preliminary Response: From a technical standpoint, providing cross reference information under List of References is not an acceptable approach.

Sponsors options of cross referencing information submitted to another application would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

(Additional DAVP comments re cross referencing options not included.)

BMS Clarification/Question: Since the time of the submission of the background document for this meeting we have come to the conclusion that in order to facilitate the review of each NDA we will provide all reports cited in an application, even though they may also reside in the other NDA. In other words, there will be no need to cross reference between applications since each application will stand on its own having all referenced documents contained within it. Is this acceptable?

ATTACHEMENT 3

7 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MAMMAH S BORBOR
02/28/2014

DEBRA B BIRNKRANT
02/28/2014



IND 79599
IND [REDACTED] (b) (4)

MEETING MINUTES

Bristol-Myers Squibb
Attention: Charles D. Wolleben, PhD
Group Director, Global Regulatory Sciences- US
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Wolleben:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMS-650032 (asunaprevir) and BMS-790052 (daclatasvir).

We also refer to the meeting between representatives of your firm and the FDA on February 27, 2012. The purpose of the meeting was to discuss the Phase 3 development program for the DUAL and QUAD regimens for the treatment of patients with chronic hepatitis C with unmet medical needs.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Elizabeth Thompson, M.S., Regulatory Project Manager, at (301) 796-0824 or via email at elizabeth.thompson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: February 27, 2012; 11:00 am EST
Meeting Location: White Oak, Bldg 22, Room 1315

Application Numbers: 79599 and (b) (4)
Product Names: BMS-790052 (DCV) and BMS-650032 (ASV)
Indication: treatment of chronic hepatitis C infection
Sponsor/Applicant Name: Bristol-Myers Squibb

FDA ATTENDEES

Division of Antiviral Products (DAVP)

1. Elizabeth Thompson, M.S., Regulatory Project Manager
2. Rob Kosko, Pharm.D., M.P.H., Regulatory Project Manager
3. Karen Winestock, Chief Project Management Staff
4. Kimberly Struble, Pharm.D., Clinical Team Leader
5. Linda Lewis, M.D., Clinical Team Leader
6. Wendy Carter, D.O., Clinical Reviewer
7. Patrick Harrington, Ph.D., Clinical Virology Reviewer
8. Lisa Naeger, Ph.D., Clinical Virology Reviewer
9. Lalji Mishra, Ph.D., Clinical Virology Reviewer
10. Jules O'Rear, Ph.D., Clinical Virology Team Leader
11. Debbie Birnkrant, M.D., Division Director
12. Jeff Murray, M.D., M.P.H., Deputy Division Director

Office of New Drug Quality Assessment II

13. Steve Miller, Ph.D., CMC Lead

Office of Clinical Pharmacology

14. Jianmeng Chen, Ph.D., Staff Fellow
15. Stanley Au, Ph.D., Clinical Pharmacology Reviewer
16. Shirley Seo, Pharm.D., Acting Clinical Pharmacology Team Leader
17. Jeff Florian, Ph.D., Pharmacometrics Reviewer

Office of Biostatistics

18. Wen Zeng, Ph.D., Statistics Reviewer
19. Fraser Smith, Ph.D., Acting Statistics Team Leader

SPONSOR ATTENDEES

1. Steven Schnittman, MD, VP Global Development Lead - HCV, Global Clinical Research GCR)
2. Douglas Manion, MD, VP Development, Neuroscience, Virology and Japan, GCR
3. Eric Hughes, MD, PhD, Group Director, GCR – Virology
4. Patricia Mendez, MD, Director, GCR – Virology
5. Dessislava Dimitrova, MD, Global Medical Director, Medical Safety Assessment, Global Pharmacovigilance and Epidemiology
6. Alaa Ahmad, PhD, Director, Discovery Medicine Clinical Pharmacology (DMCP) - Clinical Pharmacology
7. Timothy Eley, PhD, Associate Director, DMCP - Clinical Pharmacology
8. David Gardiner, MD, Director, Discovery Medicine – Virology
9. Richard Bertz, PhD, Executive Director, DMCP - Virology
10. Min Gao, PhD, Research Fellow, Research & Development – Virology (by phone)
11. Fiona McPhee, DPhil, Senior Principal Scientist, Research & Development – Virology
12. Andrew Damokosh, PhD, Director, Global Biometric Sciences (GBS)
13. Thomas Kelleher, PhD, Group Director, GBS, Neuroscience & Virology
14. Theodora Salcedo, PhD, Principal Scientist, Drug Safety Evaluation (DSE) – Toxicology (by phone)
15. Prashant Deshpande, PhD, Associate Director, Chemical Development (by phone)
16. Stephanie Danetz, Associate Director, Project Planning Management (by phone)
17. Margo Heath-Chiozzi, MD, Vice President, Global Regulatory & Safety Sciences (GRSS) – Virology
18. Joan Fung-Tomc, PhD, Director, GRSS- Virology
19. Charles Wolleben, PhD, Group Director, GRSS-US
20. Joseph Lamendola, PhD, VP, U.S. Regulatory Sciences and Regulatory Relations & Policy
21. Chirag Patel, PhD, Manager, Global Regulatory Coordination, GRSS

1.0 BACKGROUND

A Type C clinical meeting was held on July 7, 2011 on the DUAL (DCV/ASV) and QUAD (DCV/ASV/pegIFN/RBV) development programs. The background package for this meeting contained Phase 2 data and proposed Phase 3 plans. The Division requested additional data/information before making final decisions on several of the questions from this background package. On December 16, 2011, Bristol-Myers Squibb (BMS) requested an End of Phase 2 meeting with the Division to further discuss their proposed Phase 3 program for the DUAL/QUAD regimens. The DUAL program includes the treatment-naïve patient population. In addition, the DUAL/QUAD program targets the following patient groups with unmet medical needs:

- null/partial responders
- intolerant/ineligible-naïves

The Division granted the meeting on December 27, 2011 and provided preliminary comments on February 24, 2012.

2. DISCUSSION

Below are the questions from the sponsor, Division preliminary responses, and the meeting discussion.

Question 1a: Should BMS and FDA reach alignment on the specifics of protocol AI447029 prior to or during the EOP2 QUAD/DUAL meeting, and the final protocol is included in the combination IND submission, can FDA waive the 30-day wait after receipt of the combination IND to initiate study AI447029?

DAVP Response:

We agree to consider your request upon submission of the combination IND submission. If the 30-day wait period is waived, we will provide you notification of this decision in the acknowledgement letter for your combination IND. The decision to waive the 30 day wait period will be based on the extent of changes from the previously reviewed protocol. If you have any changes to what FDA has previously reviewed in protocol AI447029, please clearly highlight the changes for our review. If there are any CMC changes to the drug products that are being introduced for study AI447029, submit information that supports patient safety as soon as available (e.g., a preIND submission).

Discussion:

The Division provided clarification regarding the 30-day waiver for the combination IND submission. The Division stated that for the protocol for the QUAD regimen (AI447029), if changes are clearly highlighted, it may be possible to waive the 30-day wait. Because of the expected protocol design changes for the DUAL regimen (AI447028), if BMS submitted the DUAL/QUAD protocols together, the Division would not be able to grant a 30-day waiver. The Division stated that BMS could submit the QUAD protocol with the request for a waiver and then subsequently submit the formal DUAL protocol to the combination IND. This would allow the QUAD Phase 3 program to initiate while the DUAL protocol is under re-design and review.

BMS also stated that there would be no new CMC information regarding the ASV (b) (4) (b) (4) or the DCV tablets in the combination IND.

Question 1b: Does FDA agree that given similar magnitude in the in vitro activity of DCV and ASV against GT-1 and GT-4, and assuming similar efficacy for the DUAL/QUAD regimens in GT-1 (-1b) and GT-4 null/partial responders (GT-4 being 10% maximum of the experienced patients in studies AI447028 and AI447029), this could lead to a labeled indication for (b) (4) patients in the DUAL/QUAD United States package inserts (USPIs)?

DAVP Response:

We disagree that the planned amount of data from your Phase 3 program will be adequate to justify an indication for HCV (b) (4)

(b) (4)
(b) (4)



Question 2a: Does FDA agree with the study design outlined in the draft protocol for the Phase 3 DUAL study AI447028 designed to evaluate treatment-experienced (null/partial responders) and treatment-naïve patients (including the

subpopulations mentioned above who are ineligible-naïve or intolerant to pegIFN α /RBV)?

DAVP Response:

In general, the protocol design of AI447028 for both treatment-experienced and treatment-naïve subjects is acceptable. The definitions for the intolerant and ineligible-naïve populations are acceptable for this phase 3 trial. It is important to note that labeling for these sub-populations will be a review issue and unless there are inconsistent results from these subpopulations, the indication is likely to be generalized to the broader genotype 1b population.

One disadvantage of the single arm trial design is the lack of comparative safety data. We recommend you consider whether an immediate treatment versus deferred treatment design might be feasible as this type of design would provide some comparative safety data. Maintaining the blind and minimizing the potential for placebo arm drop out would need to be addressed in the trial design.

Statistics:

- For treatment-naïve genotype HCV-1b subjects, due to the SVR₂₄ rates of 71% in BOC and 79% in TVR, it does not seem to be valid to compare SVR₁₂ of the treatment-naïve cohort to 59% SVR₁₂ rate even for INF free regimen proposed here for the hypothesis of treatment-naïve group with the single arm design in AI447028. Please clarify your rationale and why you anticipate a lower SVR rate in treatment-naïve subjects than you observed in null responders.
- In study AI447029 (QUAD for genotypes 1a, 1b and 4), the lower bound of SVR for the hypothesis test of null/partial responders was selected as 70%, while 59% was selected for study AI447028 (DUAL for genotypes 1b and 4) for the same null/partial population. Please clarify your rationale for selecting these response rates.
- Also, the lower bound of SVR for the hypothesis test may be changed due to the proportions of P/R null and partial responders in the P/R null/partial responder cohort. Please consider to have at least ~50% representation of P/R null responders in both AI447028 and AI447029 to support an indication for this more challenging to treat group.

Additional recommendations on the AI447028 study design are included at the end of this letter. Please also note the Division's response to Question 1b.

Discussion:

BMS presented slide 4, noting a randomized placebo group was incorporated into the treatment-naïve arm (12 weeks) of the DUAL (AI447028) protocol based on the Division's recommendation for an immediate versus deferred treatment design to obtain some comparative safety data. The placebo subjects, after 12 weeks, would be treated for the full 24 weeks with the DUAL regimen in a rollover study. The Division asked how this arm will be blinded, and when the timing of the NDA would occur. BMS stated that the study will be blinded (including all HCV RNA results) up to week 12, and then it will be unblinded afterwards. BMS expects to begin this study in late June 2012 (after SVR4 data are available from AI447011) and noted that

dosing in Phase 3 for the DUAL regimen has already begun in Japan. BMS also stated they prefer labeling for both regimens and plan to simultaneously submit the NDAs. Because the data to support the NDAs will not be available until the third quarter of 2013, the time line for submitting the NDA submissions is not currently available.

In addressing the statistical comments, BMS stated that the SVR12 rates used in the two protocols were estimates to provide context and that there was no formal hypothesis testing or sample size calculation. The power listed on the slide 5 came from the simulation given the sample size and target SVR12 rates, and the sample size was driven primarily by the ICH Guidance for safety numbers. The target SVR12 rates were selected based on what was deemed "clinically meaningful" differences compared to currently available treatment options for the populations and regimens being studied.

The Division questioned the SVR12 rate (69%) and the lower bound of the 95% CI (59%) used in the protocol AI447028 in treatment-naïve cohort. Because the SVR24 rate was 79% with 95% CI [71.8%, 85.4%] for telaprevir for treatment-naïve 1b subpopulation, and if BMS only expected 69% SVR12 rate, then the proposed single arm design of AI447028 for this population is questionable. The language in the submitted protocol has to be changed in order to be consistent with the primary efficacy analysis and to support the claim for a win for the treatment-naïve cohort in the proposed single arm trial design. BMS stated that their proposal was contextual and that the DUAL regimen offers the advantage of a PR sparing regimen. The Division noted potential advantages of DUAL over PR-contained regimen, and the final SVR rate assessment would be a review issue by considering the balance of risk/benefit of DUAL regimen. BMS agreed to revise the statistical language in the protocol to provide clarity and consistency.

Question 2b: Does FDA agree to the proposed review, finalization of protocol AI447028 and timing for dosing first patient in study AI447028 after the final protocol has been submitted to the combination IND?

DAVP Response:

While proof-of-concept SVR data with the DUAL regimen with the higher 600 mg BID ASV dose level has been demonstrated in both Japanese and U.S./E.U. study populations, the US population infected with HCV genotype 1b has not been evaluated with the ASV 200 mg BID dose level. There is insufficient information at this time to predict that the DUAL regimen with the reduced ASV dose level will have comparable efficacy in Japanese and non-Japanese HCV genotype 1b infected populations. Therefore, we agree with your plan to review SVR4 data from all patients and all available SVR12 data from the expansion cohort for the DUAL regimen in study AI447011 prior to enrollment of AI447028. However, these data should be submitted as a top line executive summary for review and you should allow for adequate time for response prior to initiation of AI447028.

Discussion:

BMS summarized the timing of receipt of SVR4 data from the AI447011 DUAL expansion cohorts in relation to initiating the Phase 3 DUAL trial AI447028. They stated that they plan to begin ex-U.S. enrollment of AI447028 once they have obtained and internally

reviewed SVR4 data from the AI447011 DUAL expansion cohorts, and to begin U.S. enrollment once they have submitted the SVR4 data to the Division and received feedback.

BMS gave additional clarification regarding the timing and amount of data to be submitted from the AI447011 DUAL expansion cohorts. They stated that 18 subjects in the BID ASV arm and 20 subjects in the QD ASV arm, all HCV genotype 1b P/R null responders, will have available SVR4 data by mid July 2012. The Division asked what countries are represented in these data, and BMS responded that approximately $\geq 50\%$ are from Europe (all France), without providing precise data on the number of subjects to be from U.S. The Division requested that the SVR4 data submitted from these subjects also be summarized by study site: U.S. vs. non-U.S. BMS asked how long the Division would need to review SVR4 data. The Division replied approximately 2 weeks.

Question 3a: Does FDA agree that the high and sustained antiviral activity observed with the QUAD regimen (including the HCV RNA undetectability or $< \text{LOQ}$ from all 41 null responders from the expansion cohort in study AI447011) supports the proposal to include partial responders in the Phase 3 QUAD study without the need to include a comparator?

DAVP Response:

We agree that the data supports inclusion of partial responders in your proposed single armed trial without a comparator.

Discussion:

No discussion occurred

Question 3b: Does FDA agree that the available SVR12 and SVR24 concordance data on the QUAD and DUAL support the use of SVR12 as the primary endpoint for the phase 3 trials with these 2 regimens?

DAVP Response:

Yes, we agree that SVR12 may be the primary endpoint for your proposed phase 3 trials.

We have the following requests regarding the SVR12 and SVR24 concordance analysis summarized on pages 28-29:

- a. Please clarify the HCV RNA cutoffs used for your SVR12 and SVR24 concordance analysis. The footnote about the one subject with discordant results appears to contradict the footnote stating that SVR results were based on $< \text{LLOQ}$ ($< 25 \text{ IU/mL}$).
- b. Please provide a listing of each subject with HCV RNA $< \text{LLOQ}$ detected at the Follow-up Week 12 or Follow-up Week 24 visits, and in this listing report all subsequent follow-up results that are available for each subject. This analysis is needed to validate the use of HCV RNA $< 25 \text{ IU/mL}$ (i.e., $< \text{LLOQ}$, detected or not

detected) as the cutoff for SVR determinations. Also with this listing, please confirm the HCV RNA assay and vendor used for all of the results.

- c. In the final Phase 3 protocols, study reports, datasets, and other future submissions, it is critical that you use more precise and consistent language to describe low level HCV RNA results that are near the assay limits. The inconsistent and ambiguous terminology used in Table 1.2.1.2 and the associated summary make it difficult to interpret the data. Please do not use terms such as “<LOD” since HCV RNA levels below the assay limit of detection can still be detected to some extent. HCV RNA levels should be reported using terminology that is consistent with recommendations in FDA-approved assay package inserts. For example, HCV RNA levels that are not detected should be reported as “HCV RNA not detected”, “target not detected”, or “<(LLOQ value) not detected”. HCV RNA levels that are detected but <LLOQ should be reported as “<(LLOQ value) detected”.

Discussion:

BMS agreed with the recommendations for use of precise terminology to allow for accurate interpretation of the data. BMS confirmed that the Roche COBAS® TaqMan® HCV 2.0 quantitative HCV RNA assay will be used for their Phase 3 trials, and that (b) (4) laboratories will remain the vendor carrying out these analyses. Low level HCV RNA results will be reported either as “HCV RNA Not Detected” for target not detected results, or “<25 IU/mL HCV RNA detected” for results that are detected but <LLOQ. The Division noted that the raw data BMS has previously submitted has been clear in distinguishing these results, whereas the summary reports have not always used consistent language.

Question 3c: Does FDA agree that both SVR12 (primary endpoint) (b) (4) (b) (4) can be included in the USPI?

DAVP Response:

(b) (4) (b) (4) (b) (4)
(b) (4) The primary endpoint for regulatory action is SVR12. (b) (4)
(b) (4)
(b) (4) The primary endpoint of SVR12 will be (b) (4)
included in the USPI but at this time, (b) (4)
(b) (4)

Of note, under PDUFA V, FDA may allow a limited number of application components to be submitted no later than 30 calendar days after the original application submission. Examples of these components are updated stability data or final audited report of a preclinical study. Other major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.

Discussion:

BMS stated that the USPI will be used by other Health Authorities where (b) (4) data currently remains the primary endpoint. BMS agrees that no additional data will be submitted during the course of the NDA review. BMS stated that because they are global, they are trying to meet the needs of all Health Authorities. They are committed to SVR12 as the primary efficacy endpoint

(b) (4)

Question 4: Does FDA agree that the QUAD/DUAL NDA could consist of the following?

- **Safety/efficacy from > 1,200 subjects on DUAL or QUAD therapies at the indicated dose or higher and who have been treated with DUAL/QUAD for at least 24 weeks:**
 - **350 GT-1 (to 390 GT-1/-4) null/partial responders treated with QUAD, who have reached SVR12**
 - **200 GT-1b (to 220 GT-1b/-4) null/partial responders treated with DUAL, who have reached SVR12**
 - **200 GT-1b treatment-naive subjects treated with DUAL, who have reached SVR12**
 - **At least 75 (of the 225) subjects from 1 of the 3 targeted GT-1b intolerant/ineligible-naive groups (i.e., subjects with a history of anemia or neutropenia, depression, compensated advanced fibrosis/cirrhosis with thrombocytopenia) treated with DUAL, who have reached SVR12**
 - **200 GT-1b subjects treated with DUAL (Phase 3 Japanese study AI447026), ~ 50 GT-1/-4 subjects treated with QUAD (retreatment study AI444026) and ~ 160 subjects from the Phase 2 studies (AI447011, AI447017)**
- **Safety from ~ 800 subjects treated with DCV + pegIFN α /RBV for at least 24 weeks (not including subjects in the ongoing comparative Phase 3 trials AI444042 and AI444052)**

• (b) (4)

DAVP Response:

In general, your safety database proposal appears adequate for the DUAL and QUAD treatment regimens. However, please also refer to our previous comments regarding genotype 4 subjects for both the DUAL and QUAD regimens and the need for adequate characterization of the regimens for the various genotype 4 common subtypes. Our preference is for you to submit all available safety and SVR12 data from the other 2 lagging cohorts of intolerant/ineligible subjects with the original application.

Additional recommendations on the AI447028 and AI447029 study designs are included at the end of this letter. Please also note the Division's response to Question 1b.

Discussion:

BMS presented slide 6 regarding their safety database for the DUAL/QUAD NDAs. The Division stated that based on this slide there was concern that insufficient U.S. data would be submitted for the DUAL regimen NDA. BMS stated that they plan to have 15% U.S. representation in AI447028, noting that HCV genotype 1b is relatively less common in the U.S. compared to Europe. The Division stated that we were concerned that they might not have enough data from U.S. subjects in AI447028 if there is a lag of enrollment of U.S. subjects in this trial. BMS emphasized that there will be U.S. subject data for the DUAL included in the NDA, again noting the planned 15% U.S. representation and, at minimum, 475 subjects' data from AI447028 are planned for submission with the NDA.

Question 5: Does FDA have any comments on the target indication in the DCV + ASV (b) (4) based on the proposed NDA package outlined in Section 1.2 for:

5a) DCV + ASV + pegIFN α /RBV (i.e., QUAD)?

5b) DCV + ASV (i.e., DUAL)

DAVP Response:

We acknowledge your proposed target indications for the QUAD and DUAL regimens (b) (4). As you are aware, the final indication is a review issue. A phase 4 study may be requested to evaluate the DUAL compared to QUAD regimen to address this issue if it remains unclear.

Discussion:

No discussion occurred.

Question 5c: Does FDA have any comments on any other sections of the DCV + ASV (b) (4) (provided as Appendix 1 of this briefing document)?

DAVP Response:

We encourage you to review Section 12.4 Microbiology of the boceprevir and telaprevir labels. We anticipate similar information and levels of detail will be appropriate for labeling of other HCV DAAs.

Discussion:

No discussion occurred.

Question 5d: Does FDA agree that if the clinical experience with DUAL includes ~ 80 - 100 subjects 65 years of age and older with population pharmacokinetic (PPK) data, this may provide sufficient experience among the elderly to include such information in the Geriatric Use section of the USPI?

DAVP Response:

The inclusion of population pharmacokinetic (PPK) data for geriatric subjects 65 years of age and older will be a review issue. In general, a sample size of 80 to 100 subjects is sufficient to

provide information to include in section 8 and section 12.3 on age related differences for asunaprevir and daclatasvir.

Discussion:

No discussion occurred.

Question 6a: Does FDA agree that it is appropriate to have commercial presentations of DCV and ASV as single-products (b) (4)?

DAVP Response:

We agree with your plan to have commercial presentations of DCV and ASV as single-products (b) (4) presentation. We recommend that the stability data on the two individual products include a presentation (b) (4) (b) (4)

Discussion:

BMS stated they plan to have 12 month stability data for the three NDAs and that they will also provide stability data for the individual DCV and ASV products in (b) (4) packaging. BMS brought examples of the ASV (b) (4) (b) (4)

Question 6b: Does FDA agree the (b) (4) dose of each agent (i.e., 60 mg QD DCV tablets (b) (4) (b) (4)?

DAVP Response:

Yes, we agree.

Discussion:

No discussion occurred.

Question 6c: Does FDA agree that to support the individual-product (b) (4) (b) (4)

Question 6d: Does FDA agree that submission of 2 NDAs (one for DCV and one for ASV) would support the QUAD/DUAL registration?

DAVP Response to Q 6c/d:

Based on the information you provided on page 6 of the briefing package, you will need to submit an NDA for DCV and an NDA for ASV to support the presentation of the single DAAs individually, (b) (4) The Division will need to discuss the USPI presentations with other FDA counterparts prior to providing further recommendations.

Discussion:

No discussion occurred.

Question 7a: Does FDA have any comments on the updated Resistance Monitoring Plan?

DAVP Response:

Please refer to the following recent communications:

- 1/11/2012: Recommendations on the BMS resistance monitoring plan submitted 12/29/2011 (IND (b) (4) eCTD 236)
- 1/23/2012: Updated resistance analysis dataset template
- 1/27/2012: Additional feedback regarding the submission of electronic resistance datasets

Discussion:

No discussion occurred.

Question 7b: Is FDA in agreement with the proposed plan for BL testing in Phase 3 trials?

DAVP Response:

We agree with your plans to characterize baseline sequences for all treated subjects in DUAL, QUAD and DAA + Peg-IFN α /RBV Phase 3 trials, but only for treatment failure subjects receiving Peg-IFN λ -based regimens. However, depending on emerging information we may revisit the need to conduct additional baseline sequence analyses for subjects receiving Peg IFN λ -based regimens, and therefore request you collect and archive baseline samples from all subjects in these trials.

Discussion:

No discussion occurred.

Question 8a: Based on the observation that ASV

(b) (4)

(b) (4)

(b) (4) **does FDA agree with BMS' plan to administer the BMS QUAD therapy to subjects who have detectable TVR/BOC-resistant variants in the retreatment study AI444026?**

Question 8b: Based on the observation that the 2-DAA/pegIFN α combination suppresses the emergence of DAA-resistant variants in GT-1a-NS5AQ30R/L31M replicons, does FDA agree with the BMS plan to administer the BMS QUAD therapy to subjects who have detectable DCV-resistant variants in the retreatment study AI444026?

DAVP Response to Q 8a/b:

For AI444026 Amendment 02 (submitted 1/30/2012, IND (b) (4) eCTD 245), we are concerned about the potential resistance-related implications of failing treatment with a QUAD regimen, and request you enroll prior boceprevir or telaprevir treatment failure subjects in a more

conservative manner.

(b) (4)

(b) (4)

For this initial proof-of-concept retreatment study, please plan to explore the efficacy impact of (a) prior treatment response to boceprevir, telaprevir or DCV (e.g., breakthrough, nonresponse, relapse), (b) time since boceprevir, telaprevir or DCV exposure, and (c) the detection of minority NS3/4A protease inhibitor or NS5A inhibitor resistant viral populations (as appropriate based on treatment history). For (c) we recommend using an assay that can detect variants comprising 5-10% (or lower) of the total population. If possible, please also extrapolate from HCV RNA data to characterize the absolute quantity of drug resistant virus at the time of prior treatment failure and at the time of re-treatment.

Given the complexities of the protocol for retreatment subjects who previously failed a DAA + P/R regimen, BMS may want to consider a stand alone protocol for this study.

Discussion:

(b) (4)

Question 9: Does FDA agree with the clinical pharmacology plan as outlined in Section 5.2.1 of the briefing document to support the registration of the QUAD/DUAL regimens?

DAVP Response:

The clinical pharmacology team requests a separate meeting to discuss your clinical pharmacology plan. In particular, we would like to discuss the following issues:

- The rationale for not conducting future drug-drug interaction trials or repeating previously conducted drug-drug interaction trials (for example with medications such as midazolam or oral contraceptives) with the combination of asunaprevir and daclatasvir requires further discussion. The submission of a table outlining the respective drug-drug interaction profiles and available drug-drug interaction PK data for asunaprevir and daclatasvir would be useful in facilitating this discussion.
- Conducting additional hepatic and renal impairment trials with the combination of asunaprevir and daclatasvir.
- Conducting or repeating drug-drug interaction, hepatic and renal impairment trials with the combination of asunaprevir and daclatasvir that include administering the new Phase 3 asunaprevir capsules.

Based upon the clinical pharmacology trials that have been conducted and the proposed clinical pharmacology trials, DAVP has the following comments and recommendations:

1) Please clarify the rationale for conducting the renal impairment trial as a postmarketing trial. This information will be important as part of the initial NDA submission to determine if dosage adjustments are needed for asunaprevir when administered in combination with daclatasvir in renally impaired hepatitis C infected (HCV) patients.

2) For asunaprevir

(b) (4)

(b) (4)

3) For both asunaprevir and daclatasvir, please clarify if data is available evaluating their ability to induce CYP1A2, CYP2B6, or CYP3A using the change in mRNA expression as an endpoint. Based on the draft FDA February 2012 guidance to industry on drug interaction studies, if mRNA information is not available, DAVP recommends conducting additional in vitro studies using the change in mRNA expression as an endpoint for both asunaprevir and daclatasvir.

4) Based on the potential for asunaprevir

(b) (4)
(b) (4)

•

(b) (4)
For all other coadministered antiretroviral medications that will be permitted, we recommend conducting dedicated drug-drug interaction trials to determine if dosage adjustments are needed for either asunaprevir (or daclatasvir if both are coadministered) or the antiretroviral medications.

- DAVP recommends conducting the following additional drug-drug interaction trials with the following medications:
 - Opioid dependence: buprenorphine
 - Immunosuppressants: cyclosporine and tacrolimus

Discussion:

BMS clarified that ASV

(b) (4)
(b) (4)

BMS provided the following discussion regarding the clinical pharmacology plan, including conducting clinical pharmacology trials with a combination of both asunaprevir and daclatasvir:

- BMS will consider conducting drug-drug interaction trials evaluating a combination of both asunaprevir and daclatasvir and the following medications: a) oral contraceptives, and b) digoxin as a P-gp substrate, and c) methadone.
- A (b) (4) drug-drug interaction trial will be conducted as a post-marketing trial.
- The renal impairment trial will be rescheduled so that the data can be included as part of the NDA submission.
- BMS believes the hepatic and renal impairment trials evaluating both asunaprevir and daclatasvir are not necessary. BMS also confirmed that the DUAL and QUAD regimens will not be recommended for use (b) (4)
- BMS noted that instead of the ASV/DCV combination, they plan to study DCV in combination with (b) (4) compound (with or without ribavirin) for use in HCV/HIV coinfecting subjects and the transplant population.
- BMS also stated that the combination of DCV and peginterferon-lambda will be planned for use in (b) (4)
- In response to Clinical Pharmacology additional comment #14 for the proposed Phase 3 DUAL/QUAD trials, BMS responded that collecting a 12 hour sample for asunaprevir and daclatasvir and a 24 hour sample for daclatasvir in order to obtain more accurate estimates of C_{min} and $AUC_{(0-\tau)}$ was not logistically feasible. BMS clarified that the purpose of collecting intensive sampling in a subset of subjects in the Phase 3 trials was

to obtain additional pharmacokinetic information for the new Phase 3 formulation and the proposed intensive sampling schedule would provide information on the absorption phase of the PK profile for the new Phase 3 formulation. The Division responded that if collecting the additional samples was not feasible, the existing intensive sampling schedule for the Phase 3 trials was acceptable.

BMS stated they would put together a submission discussing their clinical pharmacology plan, including responses to the Division's preliminary comments for review. BMS would follow-up to determine if a separate clinical pharmacology meeting would be required.

The Division referred BMS to the draft guidance on unmarketed drugs that are used in combination that includes a recommendation that trials evaluating intrinsic factors should evaluate a combination of both medications and also stated that PBPK modeling could be explored as a method to obtain drug-drug interaction information on the combination. BMS stated that PBPK modeling was being conducted but did not provide specific details.

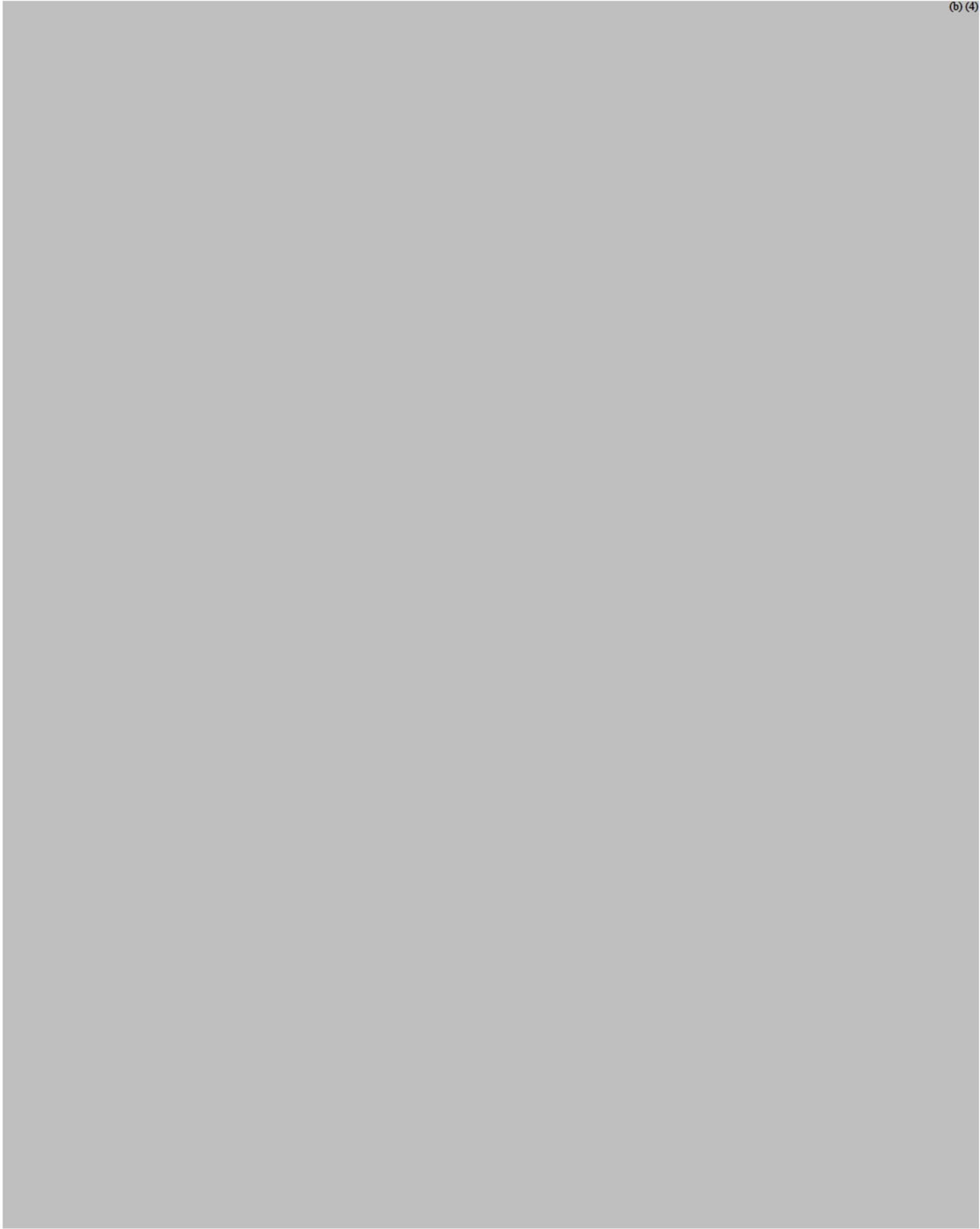
BMS acknowledged the Hepatitis C community advisory board drug-drug interaction statement, specifically the need for interaction trials with oral contraceptives, methadone and buprenorphine. BMS intends to respond to this statement.

Question 10: Does FDA agree that the dose for ASV for Phase 3 in DUAL/QUAD regimens is 100 mg BID of the (b) (4) without regard to meals?

DAVP Response:

The proposed asunaprevir dosage regimen of 100 mg twice daily with or without meals as part of the Dual/Quad regimens in the Phase 3 trials may be acceptable. However, please clarify the following issues:





Question 12a: Does FDA agree to preliminarily grant a waiver for children < 3 years of age being treated with QUAD/DUAL regimens, as was done with DCV + pegIFNa/RBV?

Question 12b: Does FDA agree to defer the start of the safety/efficacy studies (Studies 5 & 6) with the QUAD/DUAL regimens until the doses of DCV and ASV have been determined in children (Studies 1 & 3)?

DAVP Response to Q12a/b:

Similar to our discussions during the EOP2 meetings for NS5A and Lambda, we appreciate your efforts in planning your pediatric program and we expect to continue ongoing discussions regarding the pediatric plan based on the data provided from the adult development plans. We agree with the proposal for a waiver in children under age 3 years. We agree to your plan to defer the start of the safety and efficacy studies with QUAD/DUAL until the appropriate DCV and ASV doses have been determined for children. As we have discussed previously, additional adult data will help further guide the ongoing development of the pediatric plan.

Discussion:

No discussion occurred.

ADDITIONAL COMMENT

Please be prepared to discuss with us during the EOP2 meeting your plans for an early access/treatment IND program for populations with unmet medical needs who could benefit from the DUAL and QUAD regimens.

Discussion:

BMS stated that their first priority is to develop and understand these drug products for the broad unmet need population and that there is a learning curve for other populations that could benefit from these regimens. BMS would need to determine what other patient populations to consider and what drugs and drug combinations should be evaluated based on the emerging data. BMS will continue to focus on the currently proposed broad unmet need population now, but will consider early access/treatment IND programs for other populations early next year. BMS also agreed to continue to consider providing drug products to individual patients with specific medical needs on a case-by-case basis.

COMMENTS FOR THE PHASE 3 PROTOCOLS

CLINICAL

Comments Regarding AI447028 and AI447029:

1. Clarification of the language for the inclusion criteria defining chronic hepatitis C infection is needed so that it is consistent with the liver biopsy requirements for the trials. In protocol AI447028, inclusion criterion 2a should reflect the need for liver biopsy unless the subject is known to be cirrhotic, which is consistent with inclusion criterion 2g. This same clarification is needed for protocol AI447029.
2. Please provide your rationale for use of the 14.6 kPa cut-point to determine cirrhotic versus non-cirrhotic changes and any supportive correlating liver biopsy data.
3. Use of ESAs or G-CSFs should be recorded on the CRFs and will need to be included in the analysis datasets for an NDA.

Comments Regarding AI447028:

4. The protocol titles read as if only Peg-IFN α -2a treatment history will be considered; if incorrect, we recommend changing the protocol titles or clarifying the inclusion criteria to avoid confusion. Also, the title of the protocol should include enrollment of genotype 4 subjects.

CLINICAL VIROLOGY

Comments Regarding AI447028 and AI447029:

5. Please clarify in the inclusion/exclusion criteria how DAA exposure history will be considered for P/R treatment-experienced or P/R-intolerant/ineligible subjects. Based on the protocol synopses we assume that any prior HCV DAA exposure is exclusionary, but this is not clearly described in the bodies of the protocols.
6. We agree with your plan to use the HCV RNA assay LLOQ as the cutoff for primary efficacy and futility assessments. However, to avoid confusion, please do not define "HCV RNA detectable" as " \geq LLOQ."
7. While we agree with your virologic futility rules, for analysis purposes we consider any on-treatment HCV RNA changes from $<$ LLOQ to confirmed \geq LLOQ as indicative of virologic breakthrough (in addition to $\geq 1 \log_{10}$ increases from nadir).

Comments Regarding AI447028:

8. Please comment on the planned proportion of study subjects from U.S. and non-U.S. study sites. A sufficient number of U.S. study subjects should be included to assess efficacy for U.S. genotype 1b infected subjects, and to conduct a comparative analysis of efficacy according to geographic location.
9. Please plan to collect and report antiviral activity and efficacy results from subjects who receive P/R add-on rescue therapy, as the results may be informative for clinical practice.
10. Please plan to retrospectively confirm the accuracy of the VERSANT HCV genotype 2.0 assay for identification of HCV genotype 1b subjects, relative to phylogenetic analysis of NS3 and NS5A sequences obtained at baseline for resistance analysis purposes. Similar analyses should be conducted for HCV genotype 4 subtypes.

Comments Regarding AI447029:

11. Please plan to collect and report antiviral activity and efficacy results from subjects who discontinue P/R but continue on DUAL therapy, as the results may be informative for clinical practice.

CLINICAL PHARMACOLOGY

Comments Regarding AI447028 and AI447029:

12. DAVP recommends including the following information in section 3.4 of the trial protocols (the specific language should be similar to the information included in the AI443014 protocol):
 - Because asunaprevir (b) (4)
(b) (4)
 - Because both asunaprevir and daclatasvir (DCV, BMS-790052) can inhibit P-gp and the magnitude of their potential additive effect is unknown, please include a statement that all P-gp substrates should be used with caution at the lowest efficacious dose with appropriate monitoring.
13. In section 4.1, Table 4.1, please include a footnote for both the asunaprevir (b) (4) formulation and the daclatasvir tablet formulation indicating that both formulations are the Phase 3 formulations.

14. For the intensive pharmacokinetic sampling on day 14, DAVP recommends obtaining a 12 hour sample for asunaprevir and daclatasvir and a 24 hour sample for daclatasvir in order to obtain more accurate estimates of C_{\min} and $AUC_{(0-\tau)}$.
15. For the day 14 intensive sampling, please clarify whether C_{\min} (defined as the trough observed plasma concentration) is the lowest concentration during the dosing interval (12 hours for asunaprevir or 24 hours for daclatasvir) or the concentration immediately before the next dose of medication.

STATISTICS

Comments Regarding AI447028 and AI447029:

16. Sensitivity analyses for both studies AI447028 and AI447029: A range of sensitivity analyses should be performed to demonstrate that the primary analysis is robust to discontinuation and noncompliance. All patients who discontinue the investigational drug before trial completion should be followed and assessed the same way as other patients. Sensitivity analyses for patients who discontinued from the trial before the end of the scheduled follow-up period or who had missing HCV RNA values at the end of the scheduled follow-up period should include:
 - Their last observation carried forward (LOCF) (while still on randomized treatment). If the response is not observed at the scheduled end of treatment then they should be considered to be treatment failures.
 - HCV RNA results on the last non-missing post-treatment week rather than the last on-treatment HCV RNA to estimate the week 12 follow-up HCV RNA result. For example, if there is no HCV RNA sample at week 60, the week 48 HCV RNA is negative, and the week 52 HCV RNA is positive, the patient should be counted as not having an SVR. If all post-treatment HCV RNA values are missing, then their LOCF (while still on randomized treatment) should be used; if their response is missing at the scheduled end of treatment then they should be considered to be treatment failures.
 - The SVR for patients who had undetectable HCV RNA at their scheduled end of treatment visit with no post-treatment HCV RNA data by assuming they were non-informatively censored. These patients should be imputed to have the same probability of undetectable viral load as the patients with post-treatment HCV RNA data who had undetectable HCV at their scheduled end-of-treatment visit.
 - Other sensitivity analyses treating a percentage of discontinuations, different reasons for discontinuation, or late discontinuations as successes.

3.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

4.0 ACTION ITEMS

- BMS will amend statistical language in protocol AI447028 (DUAL)
- BMS will respond to clinical pharmacology comments provided in the DAVP's preliminary meeting response letter dated February 24, 2012. BMS stated they would request a meeting to further discuss if warranted.

5.0 ATTACHMENTS AND HANDOUTS

- The following handout was presented by BMS at the meeting

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

/s/

DEBRA B BIRNKRANT
03/05/2012



IND 79,599

MEETING MINUTES

Bristol-Myers Squibb Company
Attention: Joan C. Fung-Tome, Ph.D., ABMM
Director, Global Regulatory Sciences
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Fung-Tome:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMS-790052.

We also refer to the meeting between representatives of your firm and the FDA on July 6, 2011. The purpose of the meeting was to discuss the Phase 3 core program for BMS-790052, which specifically evaluates BMS-790052 added-on to pegylated interferon-alfa/ribavirin for treatment of chronic hepatitis C (CHC) in treatment-naive patients.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Robert G. Kosko, Jr., Pharm.D., M.P.H., regulatory project manager, at (301) 796-3979 or the Division's main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2

Meeting Date and Time: July 6, 2011; 12:30-2:00 PM EST
Meeting Location: White Oak Building 22, Conference Room: 1419

Application Number: IND 79,599
Product Name: BMS-790052
Indication: Treatment of chronic hepatitis C
Sponsor/Applicant Name: Bristol-Myers Squibb Company

Meeting Recorder: Robert G. Kosko, Jr., Pharm.D., M.P.H.

FDA ATTENDEES

1. Edward Cox, M.D., M.P.H., Office of Antimicrobial Products (OAP) Director
2. David Roeder, Associate Director of Regulatory Affairs, OAP
3. Debra Birnkrant, M.D., Director, Division of Antiviral Products (DAVP)
4. Jeffrey Murray, M.D., MPH, Deputy Director, DAVP
5. Kimberly Struble, Pharm.D., Clinical Team Leader, DAVP
6. Linda Lewis, M.D., Clinical Team Leader, DAVP
7. Wendy Carter, D.O., Medical Officer, DAVP
8. Sarah Connelly, M.D., Medical Officer, DAVP
9. Hanan Ghantous, Ph.D., DABT, Pharmacology/Toxicology Team Leader, DAVP
10. Laine Peyton Myers, Ph.D., Pharmacologist, DAVP
11. Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
12. Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
13. Pravin Jadhav, Ph.D., Pharmacometrics Team Leader
14. Jeffry Florian, Ph.D., Pharmacometrics Reviewer
15. Shashi Amur, Ph.D., Pharmacogenomics Reviewer
16. Jules O'Rear, Ph.D., Virology Team Leader, DAVP
17. Lalji Mishra, Ph.D., Virology Reviewer, DAVP
18. Patrick Harrington, Ph.D., Virology Reviewer, DAVP
19. Lisa Naeger, Ph.D., Virology Reviewer, DAVP
20. Fraser Smith, Ph.D., Acting, Statistics Team Leader
21. Wen Zeng, Ph.D., Statistics Reviewer
22. George Lunn, Ph.D., Chemistry Manufacturing and Controls Reviewer
23. Karen Winestock, Chief, Project Management Staff, DAVP
24. Robert Kosko, PharmD, M.P.H., Regulatory Project Manager, DAVP

SPONSOR ATTENDEES

1. Steven Schnittman, M.D., Vice President, Global Development Lead - HCV Antiviral Agents
2. Eric Hughes, MD, Ph.D., Group Director, Global Clinical Research (GCR) - Virology

3. Philip Yin, M.D., Director, GCR - Virology
4. Dessislava Dimitrova, M.D., Global Medical Director, Medical Safety Assessment, Global Pharmacovigilance and Epidemiology
5. Marc Bifano, M.S., Associate Director, Discovery Medicine Clinical Pharmacology (DMCP) - Clinical Pharmacology
6. Richard Bertz, Ph.D., Executive Director, DMCP - Virology
7. Fiona McPhee, D.Phil., Senior Principal Scientist, R&D - Virology
8. Theodora Salcedo, Ph.D., Principal Scientist, Drug Safety Evaluation (DSE) – Toxicology
9. Andrew Damokosh, Ph.D., Director, Global Biometric Sciences
10. Thomas Kelleher, Ph.D., Group Director, Global Biometric Sciences, Neuroscience & Virology
11. Stephanie Danetz, Associate Director, Project Planning Management
12. Carolyn Seyss, Pharm.D., Director and Team Leader, Virology & Transplant Promotion Integrity
13. Margo Heath-Chiozzi, M.D., Vice President, Global Regulatory Sciences (GRS) – Virology
14. Charles Wolleben, Ph.D., Group Director, Regulatory Liaison & Strategy, GRS-Virology
15. Joan Fung-Tomc, Ph.D., Director, GRS

1. BACKGROUND

Bristol-Myers Squibb Company (BMS) is developing BMS-790052, an NS5A inhibitor, for the treatment of hepatitis C virus (HCV) infection. On May 6, 2011, BMS requested a meeting to discuss the Phase 3 core program for BMS-790052, which specifically evaluates BMS-790052 added-on to pegylated interferon-alfa/ribavirin for treatment of chronic hepatitis C (CHC) in treatment-naïve patients. In addition, BMS plans to develop BMS-790052 as combination therapy with their NS3/NS4A and NS5B small molecule inhibitors for the treatment of HCV infection. BMS submitted their meeting package on May 27, 2011. The Division provided BMS with preliminary responses to these questions on July 1, 2011. After review of the preliminary comments, BMS requested the discussion at the July 6, 2011 meeting focus on questions #1, #2a, #5, #6, #17, additional comment #1 and additional comment #5.

Questions submitted by BMS in their May 27, 2011 meeting package are in **bold**, the Division's July 1, 2011 preliminary responses are in *italics*, and discussions during the July 6, 2011 meeting are in regular font.

2. DISCUSSION

BMS began by thanking the Division for the preliminary comments and stated they will submit an official response to all preliminary comments to IND 79,599.

Question 1: Does FDA agree with the study design, as outlined in the protocol synopses, for the following registrational studies:

– [REDACTED] (b) (4)

– **AI444042 (NS5A + pegIFN α /RBV vs pegIFN α /RBV)**

FDA Response:

AI444042

The recent FDA approvals of VICTRELIS® (boceprevir) on May 13, 2011, and INCIVEK® (telaprevir) on May 23, 2011, for the treatment, in combination with peginterferon and ribavirin (pegIFN α /RBV), of compensated chronic hepatitis C infection (CHC) genotype 1 have changed the standard of care for this disease condition in the U.S. We are aware that these new products are becoming available and rapidly being distributed to pharmacies in the U.S. With the availability of these products, a comparator regimen consisting of pegIFN α /RBV alone appears to provide suboptimal treatment, exposing some patients to repeated courses of peginterferon-alfa and ribavirin, and may lead informed patients to decline participation in the trial in order to receive one of the new drugs. Therefore, your proposed study design for AI444042 is not acceptable.

[REDACTED] (b) (4)

(b) (4)



Question 5: Does FDA agree with the study design, as outlined in the protocol synopsis, for the long-term follow-up study AI444046?

FDA Response: *The design of AI444046 is consistent with the HCV guidance and is acceptable. We recommend subjects, who have a diagnosis of cirrhosis regardless of AFP levels, undergo liver ultrasound every 6-12 months to assess for HCC. Additional comments may be provided after review of the full protocol.*

Please exclude the subjects from the final analysis, who did not enroll or enrolled but did not meet eligibility criteria. Analysis results should be robust to study. Every effort should be made to follow every subject for the whole study to avoid early discontinuation before the end of the study. The consent form should ask for permission to contact subjects who prematurely withdraw from the follow-up study at the scheduled end of follow-up in order to determine their final status. One sensitivity analysis could treat subjects who enrolled and discontinued from the long-term study before having an event as having an event at the time of discontinuation.

BMS stated they agree with the preliminary comments concerning this question and no additional discussions are warranted at this time.

Question 6: Does FDA agree that data from Phase 1 and 2 studies of BMS-790052 support the BMS plan to determine baseline sequence only for subjects who experience viral rebound or breakthrough in Phase 3 studies with BMS-790052 + pegIFN α /RBV?

FDA Response: *We do not agree with your plan to determine baseline NS5A sequence only for subjects who experience viral rebound or breakthrough in Phase 3 studies with BMS-790052 + pegIFN α /RBV as sufficient data have not been provided to assess the impact of baseline polymorphisms corresponding to known BMS-790052 resistance-associated substitutions. Please determine the baseline genotype for all subjects and their IL28B genotype. Provide a summary of the frequency of known and newly identified (in Phase 3) BMS-790052 resistance-associated substitutions at baseline.*

Please identify polymorphisms that were observed in isolates from 2 subjects in study AI444004 and their impact on BMS-790052 resistance.

BMS stated that they have analyzed over 900 baseline sequences and found 7% of isolates contain baseline polymorphisms corresponding to NS5A resistance-associated substitutions.

With respect to analysis of baseline sequences, the Division stated their concerns about potential differences between genotype/subtypes based upon geographic differences which might impact response. The Division asked BMS to conduct a phylogenetic analysis of NS5A amino acid sequence for genotype 1a and for genotype 1b comparing US and other geographically distinct isolates. Are these intermingled or distinct groups? Also, of interest, does the 7% baseline polymorphisms corresponding to NS5A resistance-associated substitutions hold true for the U.S. both in terms of overall percentage in each genotype 1 subtype and with respect to relative proportions of each polymorphism?

BMS stated that they have conducted a phylogenetic analysis of genotype 1b and these were mostly intermingled. They will conduct an analysis of genotype 1a.

Question 17a: Does FDA agree with the integrated pediatric plan for NS5A as outlined in Table 1.4B and in Appendix 4 of the background document?

Question 17b: Does FDA agree to a waiver for development of BMS' HCV regimens (as outlined in Table 1.4B) in children < 3 years of age?

Question 17c: Does FDA agree to defer

- the NS5A pediatric PK study (NS5A + pegIFN α /RBV) until end-of- Phase 3 in adults to allow development of a pediatric formulation, availability of juvenile rat toxicology data, and more comprehensive safety/efficacy data in adults?
- the safety/efficacy studies (as outlined in Table 1.4B) until the doses of NS5A, NS3 and pegIFN λ have been determined in the pediatric PK studies?

FDA Response: *FDA appreciates your efforts in planning your pediatric development program. However, additional adult efficacy and safety data are needed from multiple development programs prior to providing advice on the specifics of the pediatric plan. However, we also encourage you to consider obtaining some pediatric data earlier than your proposal of the end-of-Phase 3 in adults (e.g. enrolling the pediatric PK study prior to the end of Phase 3). We expect to have ongoing discussions with you regarding the pediatric development plan based on the data provided from the adult development plans. We do agree with a waiver for children < 3 years of age. However, a final determination can only be made during the review of your NDA submission. Please submit your request with the application. To ensure your request is complete, please consult the Guidance for Industry Document entitled, “How to Comply with the Pediatric Research Equity Act.”*

BMS stated they concur with the Division’s preliminary comments to obtain pediatric data prior to the end of Phase 3.

(b) (4)
(b) (4)

The Division stated they were pleased BMS planned to conduct pediatric PK trials earlier in the development process and not wait until after all the adult Phase 3 data were completed.

(b) (4)
(b) (4)

Additional Comments

Clinical

1. *Because of the change in paradigm for the “standard of care” regimen for treatment of genotype-1 HCV infected patients, please provide your plan for the retreatment trial, AI444026 and your plan for use of this data in support of a NDA.*

BMS stated that patients who fail will be a well-defined population and will be offered the QUAD treatment. (b) (4)

(b) (4) The Division expressed concern for the amount of data that will be obtained. BMS responded that the main intent of AI444026 is to provide access for patients and if enough data are obtained, (b) (4) This will be a review issue.

Clinical Pharmacology

5. *In addition to the atazanavir/ritonavir-BMS-790052 drug-drug interaction trial, in order to provide more information on whether potential dosage adjustments are necessary with use of HIV-1 protease inhibitors and BMS-790052, DAVP recommends that additional drug-drug interaction trials be conducted with the other protease inhibitor regimens that will be permitted as concomitant medications in the Phase 3 trials for HIV-1 and Hepatitis C coinfecting subjects. In particular, darunavir/ritonavir and lopinavir/ritonavir in combination with BMS-790052 should be evaluated.*

BMS stated data are pending for a drug-drug interaction trial evaluating the use of BMS-790052 with atazanavir/ritonavir. Based on the in vivo and in vitro data obtained to date, BMS believes that there is adequate characterization of the drug-drug interaction potential between BMS-790052 and protease inhibitors and additional drug-drug interaction trials are not necessary. In support of this statement, the following information was provided:

1. In the drug-drug interaction trial evaluating the use of BMS-790052 with atazanavir/ritonavir, BMS reports that a two fold increase in BMS-790052 exposure was observed. Subsequently, BMS is proposing to adjust the BMS-790052 dosage regimen to 30 mg once daily when administered in combination with ritonavir boosted protease inhibitors.
2. No clinically significant change in midazolam exposure in the drug-drug interaction trial evaluating the effect of BMS-790052 on midazolam was observed.
3. Trough concentrations for both HIV antivirals and BMS-790052 will be collected in the Phase 3 trial.
4. The CYP 3A inhibitory effects for ritonavir boosted protease inhibitors are primarily ritonavir mediated.
5. BMS-790052 did not inhibit any other CYPs in vitro nor induced any CYPs in vitro.

BMS further stated that the BMS-790052 dose response relationship allows for flexibility in dosing regardless of the changes in BMS-790052 exposure and either the trial reports or a reference would be submitted for the relevant trials, including the report for the BMS-790052-atazanavir/ritonavir drug-drug interaction trial.

In response, the Division stated that the relevant materials would be reviewed, and follow up comments will be provided to BMS.

Additional Discussion

BMS confirmed all carcinogenicity studies will be available for submission in February 2014.

The Division requested that consent forms be included when final protocols are submitted. BMS agreed to comply with this request.

The Division also inquired about recruitment of minorities in their trials and our preference for BMS to not solely focus on recruitment into single-arm trial, but to work to enroll minority subjects into the randomized controlled Phase 3 trial(s). BMS stated they were focusing their efforts on their Phase 3 trials and will be employing a vendor for minority recruitment. The Division asked BMS to submit an outline of all efforts for minority recruitment. BMS agreed to do so.

3. DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues required further discussion at this time.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit official response to meeting preliminary comments	BMS	N/A
Submit a proposal for sensitivity analyses when developing final protocols	BMS	N/A
Conduct a phylogenetic analysis of NS5A amino acid sequence for genotype 1a comparing US and other geographically distinct isolates	BMS	N/A

Submit a PIP for review and comment	BMS	October 2011
Submit either the trial reports or a reference for the relevant dose response relationship trials, including the report for the BMS-790052-atazanavir/ ritonavir drug-drug interaction trial	BMS	N/A
Submit an outline of all efforts for minority recruitment	BMS	N/A

6.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts for this meeting.

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

/s/

DEBRA B BIRNKRANT
07/21/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 79,599

Bristol-Myers Squibb Company
Attention: Joan Fung-Tomc, Ph.D.,
Director, Global Regulatory Sciences
P.O. Box 5100
Wallingford, CT 06492-7660

Dear Dr. Fung-Tomc:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMS-790052.

We also refer to the meeting between representatives of your firm and the FDA on December 2, 2008. The purpose of this meeting was to discuss the design of your Phase 2 studies.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Robert G. Kosko, Jr., Pharm.D., M.P.H., regulatory project manager, at (301) 796-3979.

Sincerely,

{See appended electronic signature page}

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

Enclosures - Meeting Minutes

The Division's November 26, 2008 facsimile
Original slides submitted by BMS on November 20, 2008 (SDN 55)
Revised slides submitted by BMS on December 2, 2008

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 2, 2008
TIME: 11:00 AM-12:00 PM
LOCATION: WO Bldg. 22, Rm. 1419
APPLICATION: IND 79,599
DRUG NAME: BMS-790052
TYPE OF MEETING: Type B, End-of-Phase 1

MEETING RECORDER: Robert G. Kosko, Jr.

FDA ATTENDEES: (All attendees from DAVP)

- | | |
|---|---|
| 1. Debra Birnkrant, M.D. | Director |
| 2. Jeffrey Murray, M.D., M.P.H. | Deputy Director |
| 3. Kendall Marcus, M.D. | Deputy Director for Safety |
| 4. Kimberly Struble, Pharm.D. | Clinical Team Leader |
| 5. Scott Proestel, M.D. | Clinical Team Leader |
| 6. Regina Alivisatos, M.D. | Clinical Reviewer |
| 7. Yodit Belew, M.D. | Clinical Reviewer |
| 8. Wendy Carter, D.O. | Clinical Reviewer |
| 9. Kirk Chan-Tack, M.D. | Clinical Reviewer |
| 10. Sarah Connelly, M.D. | Clinical Reviewer (via phone) |
| 11. Russell Fleischer, P.A., M.P.H. | Clinical Reviewer (via phone) |
| 12. Charu Mullick, M.D. | Clinical Reviewer (via phone) |
| 13. Andreas Piki, M.D. | Clinical Reviewer |
| 14. Alan Shapiro, M.D. | Clinical Reviewer |
| 15. Hanan Ghantous, Ph.D. | Pharmacology/Toxicology Team Leader |
| 16. Peyton Myers, Ph.D. | Pharmacology/Toxicology Reviewer |
| 17. Julian O'Rear, Ph.D. | Virology Team Leader |
| 18. Lalji Mishra, Ph.D. | Virology Reviewer |
| 19. Kellie Reynolds, Pharm.D. | Clinical Pharmacology Deputy Director (via phone) |
| 20. Stanley Au, Ph.D. | Clinical Pharmacology Reviewer (via phone) |
| 21. Sarah Robertson, Pharm.D. | Clinical Pharmacology Reviewer |
| 22. Jenny Zheng, Ph.D. | Clinical Pharmacology Reviewer |
| 23. George Lunn, Ph.D. | Chemistry, Manufacturing, and Controls Reviewer |
| 24. Fraser Smith, Ph.D. | Biometrics Reviewer |
| 25. Pravin Jadhav, Ph.D. | Pharmacometrics Reviewer |
| 26. Lauren Neal | Pharmacometrics Reviewer |
| 27. Karen Winestock | Chief, Project Management Staff |
| 28. Robert Kosko, Jr., Pharm.D., M.P.H. | Regulatory Project Manager |
| 29. Rashmi Kalla, Pharm.D. | Regulatory Project Manager |

EXTERNAL CONSTITUENT ATTENDEES: (All attendees from BMS)

- | | |
|--|---|
| 1. Robert Hindes, M.D. | Group Director, GCR-Virology |
| 2. Juan Carlos Lopez-Talavera, M.D., Ph.D. | Executive Director, GCR-Virology |
| 3. Douglass Manion, M.D. | Vice President, GCR-Virology & Neuroscience |
| 4. Richard Nettles, M.D. | Medical Director, DMCP-Virology |
| 5. Dennis Grasela, Pharm.D., Ph.D. | Executive Director, DMCP-Virology |
| 6. Claudio Pasquinelli, M.D., Ph.D. | Group Medical Director, DMCP-Virology |
| 7. Richard Bertz, Ph.D. | Group Director, DMCP-Virology |
| 8. Marc Bifano | Associate Director, DMCP-Virology |
| 9. Min Gao, Ph.D. | Senior Principle Scientist, R&D-Virology |
| 10. Fiona McPhee, Ph.D. | Group Leader, R&D-Virology |
| 11. Theodora Salcedo, Ph.D. | Senior Research Investigator II, DSE-Toxicology |
| 12. Robert Lange, Ph.D. | Senior Research Investigator, DSE-Toxicology |
| 13. Marc Davies, Ph.D. | Director, DSE-Toxicology |
| 14. Alexandra Thiry, Ph.D. | Associate Director, GBS-Virology |
| 15. Anne Cross, Ph.D. | Group Director, GBS-Virology |
| 16. Margo Heath-Chiozzi, M.D. | Vice President, GRS-Virology & Oncology |
| 17. Joan Fung-Tomc, Ph.D. | Director, GRS |
| 18. Janet Roome | Associate Director, Project Planning & Management |

BACKGROUND:

Bristol-Myers Squibb Company (BMS) is developing BMS-790052, an NS5A inhibitor, for the treatment of hepatitis C virus (HCV). On September 9, 2008, BMS requested a meeting to discuss proposed plans for Phase 2 studies evaluating BMS-790052 in combination with pegylated interferon (pegINF)/ribavirin. In addition, BMS plans to develop BMS-790052 as combination therapy with their NS3/NS4A and NS5B small molecules for the treatment of HCV. BMS submitted their meeting package on October 8, 2008 and an updated list of questions on October 10, 2008. The Division provided BMS with preliminary responses to these questions on November 26, 2008. Finalized slides were provided by BMS for the meeting on December 2, 2008. After reviewing the Division's preliminary comments, BMS decided to limit the discussion to their questions 4, 6, 7, and the Division's general comment.

Questions submitted by BMS are in **bold**, the Division's facsimiled comments are in *italics*, and discussions during the December 2, 2008 meeting are in regular font.

MEETING OBJECTIVES:

The following objectives were presented by BMS in their meeting package:

- To summarize the non-clinical toxicity findings with BMS-790052, in particular those studies conducted since the original IND application, and to reiterate (as previously outlined in the pIND # (b)(4) background document) the non-clinical

studies that will be done to support combination studies of BMS-790052 with standard of care (SOC) or with NS3 inhibitor BMS-650032.

- To share with FDA, preliminary safety, pharmacokinetic (PK) and anti-viral activity results from the Single Ascending Dose studies and early doses from the Multiple Ascending Dose studies for BMS-790052, and how these results direct our plans for the development of this molecule.
- To seek FDA's input on the design (e.g., subject population, study endpoints) and timing of the Phase 2b studies for BMS-790052 + SOC in treatment-naïve and non-responder subjects. Analysis of key data from the Phase 2b studies will influence the design of BMS' Phase 3 studies.
- To share with FDA preliminary results from ongoing Phase 1 studies with BMS-650032 (NS3 target) and seek FDA input on the proposed early studies with BMS-790052 + BMS-650032. With multiple anti-HCV agents in development, BMS' HCV program aims to explore antiviral combinations to potentially replace SOC.

The following objectives were presented by BMS on the day of the meeting:

- Achieve alignment on obtaining early safety and antiviral activity for the naïve Phase 2a study with standard-of-care (SOC).
- Achieve alignment on similar design for Phase 2b Non Responder (treatment experienced) study with SOC.
- Acknowledge that compensated cirrhotics will be included in Phase 2b and Phase 3.
- Achieve alignment on dosing duration for NS5A + NS3 antiviral drug-drug interaction study in healthy volunteers.
- Seek FDA input on necessity of Phase 2a SOC study for NS3 and NS5B or just antivirals with new MOA.

DISCUSSION POINTS:

1. Does FDA agree that, based on 1) the potency and observed antiviral activity of BMS-790052, and 2) external data (telaprevir) demonstrating the efficacy of a direct anti-viral + SOC in a non-responder population,¹ that the Phase 2b study with BMS-790052 + SOC in non-responders could be started at the same time as the Phase 2b study in treatment-naïve subjects with this regimen?

(General comments regarding add-on to SOC in the treatment-naïve population provided by the Division address this question.)

Initiating the proposed Phase 2b trials based on 14-day monotherapy studies with five patients per dose cohort is premature at this time. Additionally, preliminary safety and activity data with BMS-790052 in combination with pegINF and ribavirin is lacking. The proposed Phase 2b study design is complex and attempts to evaluate multiple doses and treatment durations along with a SOC lead-in strategy. As designed the study may not provide the necessary supportive data for Phase 3 studies.

Prior to initiation of a Phase 2b trial, we recommend you conduct a smaller Phase 2a study evaluating a few doses in combination with pegINF and ribavirin for 48 weeks. Interim data from this Phase 2a study could be used to design a Phase 2b study. The Phase 2b study could include additional duration and lead-in strategies. For example, the Week 12 on-treatment data could be used to design a Phase 2b study. With this additional data, you may consider initiating studies in treatment-naïve and treatment-experienced patients simultaneously.

As stated, discussions regarding Phase 2b studies are premature at this time; however, we recognize the need to adequately plan for later stage development and are providing the following recommendations for future Phase 2b and 3 studies.

We recognize the utility of evaluating shorter durations of SOC for genotype 1 treatment-naïve subjects and recommend these strategies be evaluated in Phase 2 and confirmed, if appropriate, in Phase 3. However, based on the currently available data, we disagree with shortening the standard length of therapy in genotype 1 treatment-naïve subjects to less than 24 weeks. We recommend evaluating a treatment strategy which allows subjects who reach RVR and maintain a suppressed HCV RNA level at Week 12 (extended RVR) to receive 24 weeks of therapy and those who do not attain extended RVR receive 48 weeks of therapy. Phase 2b and Phase 3 studies should include 48-week treatment regimens.

(b) (4)

(b) (4)

A Phase 2b study should allow for a direct comparison between treatment arms with respect to dose, strategy and duration. For each dose, a strategy (with and without lead-in SOC) and duration with an equivalent comparator would provide the most meaningful comparisons to help in making decisions regarding the design of a Phase 3 program.

Please provide your rationale and supporting data to justify the proposed SOC lead-in strategy.

The study design issue comments from the naïve population are applicable to treatment-experienced patients.

During the meeting, BMS presented a new Phase 2a study and a revised Phase 2b study for hepatitis C treatment naïve patients. See pages 3 and 4 of the 12/2/08 slides.

The Division found the Phase 2A plan acceptable but they informed BMS that data from all dosing cohorts will be needed to support initiation of the Phase 2b study.

2. If non-responder studies are required to follow treatment-naïve studies, would FDA agree an indication in treatment-naïve for BMS-790052 + SOC can be based on acceptable results from one Phase 3 study adequately powered to show superiority to SOC and one supporting Phase 2b study in this population?

While designing Phase 2 and 3 studies to support a NDA submission, please consider the following safety data base recommendations. In general, we recommend approximately 1000-1500 subjects from Phase 1-3 exposed to the to-be-marketed dose and duration of the drug. Please note the dose choice for treatment naïve and treatment-experienced patients will also be an important factor in determining the size of the safety database. If additional safety issues arise a larger safety database may be required.

3. Does FDA agree the non-responder studies can include relapsers and that this group should be analyzed separately from the non-responder (null + partial) populations?

Subjects who relapse may be included; however, all populations need to be clearly defined and analyzed separately. Please consider that adequate numbers of subjects for each group will be needed to reach meaningful endpoints.

4. Does the FDA agree with a) the proposed design of the Phase 2 treatment-naïve study? and b) the proposed design of the Phase 2 non-responder study?

Refer to general comments regarding add-on to SOC in the treatment-naïve population provided by the Division under Question 1.

BMS began by describing the design of their Phase 2a study. The Division commented enrollment of subjects with genotype 1a and 1b should be represented and requested that efforts be made to ensure adequate representation of minority populations and females in all phases of development. In response to a BMS question regarding SVR data, the Division stated some SVR 12 and SVR 24 data from the Phase 2a study is needed prior to initiation of Phase 3.

BMS then discussed their Phase 2b study design. Clarification was provided by BMS that the four arms using the NS5A inhibitor would not supply subjects for the fifth study arm using the NS5A inhibitor. The fifth arm will enroll subjects for 48 weeks. The lead-in SOC strategy proposed for 2 of the arms is still being internally decided by BMS. A decision on use of a lead-in strategy will be made in the near future. Also, the Division advised that subjects obtaining extended RVR (eRVR) should be continued on study drug for 24 weeks instead of being stopped at 12 weeks. The Division agreed data from the Phase 2a study would support simultaneous studies in treatment-naïve and treatment-experienced populations.

The Division requested BMS provide available SVR 12 and SVR 24 data before initiating Phase 3.

5a. Does FDA agree that subjects in the BMS-790052 + SOC Phase 2b studies who do not achieve EVR and/or have detectable HCV RNA at the EOT should be discontinued from

the study, and that these patients may be considered treatment failures for primary efficacy analysis?

Yes, subjects should be discontinued from study. Please ensure subjects are evaluated for safety 30 days after discontinuation. We also agree that these subjects may be considered treatment failures for primary efficacy analysis.

5b. Does FDA consider that similar rules (as in Question 5a) also apply for Phase 3 add-on to SOC studies?

Yes, as above.

6a. Does FDA agree with BMS' proposed plans to exclude cirrhotics from Phase 2b studies, but allow compensated cirrhotics (b) (4) to participate in Phase 3 studies?

DAVP strongly recommends BMS consider inclusion of subjects with compensated cirrhosis in both Phase 2 and 3 studies. Both efficacy and safety data from Phase 2 in subjects with compensated cirrhosis will be important for design of Phase 3 studies. We do not agree with the proposed (b) (4) in Phase 3 studies. You may choose to stratify based on this criterion. We recommend you enrich the study population with subjects with compensated cirrhosis.

BMS revised their proposal to include compensated cirrhotics in Phase 2b and 3 studies with limited enrollment (b) (4). The plans to include compensated cirrhotics are in line with other antivirals in development for HCV and represents the prevalence in the patient population.

The Division accepted the revised proposal presented by the sponsor.

6b. If FDA requires baseline liver biopsies, would a liver biopsy within 2 years prior to screening be sufficient?

For treatment-naïve subjects, a liver biopsy within 2 years of screening is sufficient. For treatment-experienced subjects, a biopsy within 2 years may not be necessary if a documented history of biopsy and an adequate treatment history are available.

7. Does FDA agree with the proposed timing and study design (7-day single agent followed by 14-day antiviral combinations) for the DDI studies in healthy volunteers?

In general, the design and timing of the DDI study appears appropriate. However, given that the purpose of the study is to derive PK and preliminary safety data, it is not necessary that healthy subjects be exposed to 14 days of co-administration. Seven days of combined treatment is likely sufficient to characterize any potential DDI (unless one of the drugs is suspected to be a metabolic inducer). Further comments will be provided upon receipt of a full protocol complete with doses.

BMS proposed to maintain the current design to address not only potential for pharmacokinetic interaction but also safety interaction. The safety interaction of the two combined agents would be evaluated after 14 days.

The Division accepted the proposal that was presented by the sponsor.

8. Does FDA agree with the proposed timing and the proposed design for the antiviral combination Phase 2a POC study in HCV-1 treatment-naïve patients?

The proposed timing for the antiviral combination Phase 2a POC study is premature. DAVP recommends that some Phase 2b efficacy and safety data should be available for both drugs prior to initiation of combination therapies. As currently proposed, the combination POC study would be started prior to the Phase 2b + SOC study of treatment-naïve subjects for BMS-650032. Additionally the target of a (b) (4) log HCV RNA reduction for treatment-naïve subjects with combination therapy is not adequate. Please provide a rationale for this target. Additional comments will be provided after Phase 2a data are available from both products.

ADDITIONAL DISCUSSION AND QUESTIONS:

- BMS asked the Division about the combination of two small molecules and the data required to initiate studies. DAVP agrees a pilot study for this combination of BMS-790052 and BMS-650032 may be conducted in null responders after multiple dose proof-of-concept data from both small molecules is submitted and evaluated by the Division.
- For treatment-naïve subjects and partial responder/relapse subjects, the Division recommends each single agent be evaluated in combination with SOC prior to the evaluation of the combination of products alone, or the combination of small molecules plus pegINF with or without ribavirin.
- Dr. O'Rear requested BMS submit resistance data and data on the persistence of resistant virus prior to Phase 3 for each of the individual products.

-  (b) (4)

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- FDA will determine and provide feedback to BMS concerning whether a new IND application is required for the two molecule combination studies.

ACTION ITEMS:

- BMS will provide follow-up to the additional comments and requests from the November 26, 2008 facsimile that were not previously addressed.
- BMS will provide the Division with a polymorphism analysis for the NS5A gene as requested by the virology team leader.

ATTACHMENTS/HANDOUTS:

Attachment A- The Division's November 26, 2008 facsimile

Attachment B- Original slides submitted by BMS on November 20, 2008 (SDN 55)

Attachment C- Revised slides submitted by BMS on December 2, 2008 (Officially, December 8, 2008)



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: November 26, 2008

To: Joan Fong-Tomc, Ph.D.

From: Robert G. Kosko, Jr., Pharm.D.,
M.P.H.

Company: Bristol-Myers Squibb

Title: Regulatory Project Manager, HFD-
530

Fax number: 203-657-6063

Fax number: 301-796-9883

Phone number: 203-677-3817

Phone number: 301-796-3979

Subject: Preliminary response to end-of-phase 1 meeting questions

Total number of pages including cover: 6

Comments:

Document to be mailed:

YES

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: 79,599

Drug: BMS-790052

Date: November 26, 2008

To: Joan Fung-Tomc, Ph.D.

Sponsor: Bristol-Myers Squibb

From: Robert G. Kosko, Jr., Pharm.D., M.P.H. Regulatory Project Manager

Concur: Debra Birnkrant, M.D., Director
Jeffrey Murray, M.D., M.P.H., Deputy Director
Wendy Carter, D.O., Acting Clinical Team Leader
Hanan Ghantous, Ph.D., Non-clinical Team Leader
Anita Bigger, Ph.D., Non-clinical Team Leader
Peyton Myers, Ph.D., Non-clinical Reviewer
Julian O'Rear, Ph.D., Virology Team Leader
Lalji Mishra, Ph.D., Virology Reviewer
Kellie Reynolds, Pharm.D., Clinical Pharmacology Deputy Director
Sarah Robertson, Pharm.D., Clinical Pharmacology Reviewer

Subject: Preliminary response to end-of-phase 1 meeting questions

Please reference your submissions dated October 10, 2008 and November 20, 2008. The following are *preliminary* comments being conveyed on behalf of the Division with regards to the questions submitted with your end-of-phase 1 meeting background materials. The following comments provide a framework to focus the meeting discussion. As BMS-790052 is still early in development, additional comments and recommendations will be provided during development of your drug as an add-on to standard-of-care (SOC) and for combination with BMS-650032.

Add-on to SOC in the treatment-naïve population

Initiating the proposed Phase 2b trials based on 14-day monotherapy studies with five patients per dose cohort is premature at this time. Additionally, preliminary safety and activity data with BMS-790052 in combination with pegINF and ribavirin is lacking. The proposed Phase 2b study design is complex and attempts to evaluate multiple doses and treatment durations along with a SOC lead-in strategy. As designed the study may not provide the necessary supportive data for Phase 3 studies.

Prior to initiation of a Phase 2b trial, we recommend you conduct a smaller Phase 2a study evaluating a few doses in combination with pegINF and ribavirin for 48 weeks. Interim data from this Phase 2a study could be used to design a Phase 2b study. The Phase 2b study could include additional duration and lead-in strategies. For example, the Week 12 on-treatment data could be used to design a Phase 2b study. With this additional data, you may consider initiating studies in treatment-naïve and treatment-experienced patients simultaneously.

As stated, discussions regarding Phase 2b studies are premature at this time; however, we recognize the need to adequately plan for later stage development and are providing the following recommendations for future Phase 2b and 3 studies.

We recognize the utility of evaluating shorter durations of SOC for genotype 1 treatment-naïve subjects and recommend these strategies be evaluated in Phase 2 and confirmed, if appropriate, in Phase 3. However, based on the currently available data, we disagree with (b) (4)

(b) (4) We recommend evaluating a treatment strategy which allows subjects who reach RVR and maintain a suppressed HCV RNA level at Week 12 (extended RVR) to receive 24 weeks of therapy and those who do not attain extended RVR receive 48 weeks of therapy. Phase 2b and Phase 3 studies should include 48-week treatment regimens. We do not agree with your proposal to (b) (4)

A Phase 2b study should allow for a direct comparison between treatment arms with respect to dose, strategy and duration. For each dose, a strategy (with and without lead-in SOC) and duration with an equivalent comparator would provide the most meaningful comparisons to help in making decisions regarding the design of a Phase 3 program.

Please provide your rationale and supporting data to justify the proposed SOC lead-in strategy.

The study design issue comments from the naïve population are applicable to treatment-experienced patients.

In addition we have the following responses to your questions as outlined in the background document.

Question 5a: Does FDA agree that subjects in the BMS-790052 + SOC Phase 2b studies who do not achieve EVR and/or have detectable HCV RNA at the EOT should be discontinued from the study, and that these patients may be considered treatment

failures for primary efficacy analysis?

Yes, subjects should be discontinued from study. Please ensure subjects are evaluated for safety 30 days after discontinuation. We also agree that these subjects may be considered treatment failures for primary efficacy analysis.

Question 5b: Does FDA consider that similar rules (as in Question 5a) also apply for Phase 3 add-on to SOC studies?

Yes, as above.

Question 6a: Does FDA agree with BMS' proposed plans to exclude cirrhotics from Phase 2b studies, but allow compensated cirrhotics ^{(b) (4)} to participate in Phase 3 studies?

DAVP strongly recommends BMS consider inclusion of subjects with compensated cirrhosis in both Phase 2 and 3 studies. Both efficacy and safety data from Phase 2 in subjects with compensated cirrhosis will be important for design of Phase 3 studies. We do not agree with the proposed ^{(b) (4)} in Phase 3 studies. You may choose to stratify based on this criterion. We recommend you enrich the study population with subjects with compensated cirrhosis.

Question 6b: If FDA requires baseline liver biopsies, would a liver biopsy within 2 years prior to screening be sufficient?

For treatment-naïve subjects, a liver biopsy within 2 years of screening is sufficient. For treatment-experienced subjects, a biopsy within 2 years may not be necessary if a documented history of biopsy and an adequate treatment history are available.

Question 7: Does FDA agree with the proposed timing and study design (7-day single agent followed by 14-day antiviral combinations) for the DDI studies in healthy volunteers?

In general, the design and timing of the DDI study appears appropriate. However, given that the purpose of the study is to derive PK and preliminary safety data, it is not necessary that healthy subjects be exposed to 14 days of co-administration. Seven days of combined treatment is likely sufficient to characterize any potential DDI (unless one of the drugs is suspected to be a metabolic inducer). Further comments will be provided upon receipt of a full protocol complete with doses.

Question 8: Does FDA agree with the proposed timing and the proposed design for the antiviral combination Phase 2a POC study in HCV-1 treatment-naïve patients?

The proposed timing for the antiviral combination Phase 2a POC study is premature. DAVP recommends that some Phase 2b efficacy and safety data should be available for both drugs prior to initiation of combination therapies. As currently proposed, the combination POC study would be started prior to the Phase 2b + SOC study of treatment-naïve subjects for BMS-650032.

Additionally the target of a (b) (4) HCV RNA reduction for treatment-naïve subjects with combination therapy is not adequate. Please provide a rationale for this target. Additional comments will be provided after Phase 2a data are available from both products.

Question 2: If non-responder studies are required to follow treatment-naïve studies, would FDA agree an indication in treatment-naïve for BMS-790052 + SOC can be based on acceptable results from one Phase 3 study adequately powered to show superiority to SOC and one supporting Phase 2b study in this population?

While designing Phase 2 and 3 studies to support a NDA submission, please consider the following safety data base recommendations. In general, we recommend approximately 1000-1500 subjects from Phase 1-3 exposed to the to-be-marketed dose and duration of the drug. Please note the dose choice for treatment naïve and treatment-experienced patients will also be an important factor in determining the size of the safety database. If additional safety issues arise a larger safety database may be required.

Question 3: Does FDA agree the non-responder studies can include relapsers and that this group should be analyzed separately from the non-responder (null + partial) populations?

Subjects who relapse may be included; however, all populations need to be clearly defined and analyzed separately. Please consider that adequate numbers of subjects for each group will be needed to reach meaningful endpoints.

The following comments are being conveyed on behalf of the Pharmacology and Toxicology review team:

1. (b) (4)
2. Prior to beginning long-term clinical trials with BMS-790052 or BMS-650032, please submit your nonclinical studies that will support the dose and duration of the clinical trial for review.
3. Also, prior to proceeding with your short-term (< 1 month) combination trial (BMS-790052 combined with BMS-650032), please submit your nonclinical studies that support the dose and duration for review
4. If you plan (b) (4) chronic dosing in a combination trial, the 90-day nonclinical bridging study should be submitted prior to beginning the clinical trial for review.

The following comment is being conveyed on behalf of the Clinical Virology review team:

5. Please provide available information on the persistence of BMS-790052 resistant virus.

We look forward to a productive meeting and continued development for BMS-790052 and BMS-650032.

We are providing this above information via telephone facsimile for your convenience.
THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.
Please feel free to contact me at 301-796-3979 if you have any questions regarding the contents of this transmission.

Robert G. Kosko, Jr., Pharm.D., M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

32 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Linked Applications

Sponsor Name

Drug Name / Subject

IND 79599

BRISTOL MYERS
SQUIBB CO

BMS 790052

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

/s/

Robert G Kosko Jr
12/24/2008

DEBRA B BIRNKRANT
12/29/2008

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 206844
NDA 206843

LATE-CYCLE MEETING MINUTES

Bristol-Myers Squibb Company
Attention: Charles D. Wolleben, PhD
Group Director, Global Regulatory Sciences - US
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Wolleben:

Please refer to your New Drug Applications (NDAs) dated March 31, 2014, received March 31, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for asunaprevir (b) (4) and daclatasvir tablets 30 and 60 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 22, 2014.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Sohail Mosaddegh, PharmD, Regulatory Project Manager, at (301) 796-4876 or (301) 796-1500.

Sincerely yours,

{See appended electronic signature page}

Kim Struble, PharmD
Clinical Team Lead
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: September 22, 2014 1:00 pm to 3:00 pm
Meeting Location: 10903 New Hampshire Ave., Bldg. 22, Room 1419, Silver Spring MD 20993

Application Number: NDA 206843 & 206844
Product Name: asunaprevir & daclatasvir
Applicant Name: Bristol-Myers Squibb Company

Meeting Chair: Kim Struble, PharmD
Meeting Recorder: Sohail Mosaddegh, PharmD

FDA ATTENDEES

1. Edward M Cox, MD, MPH, Director, Office of Antimicrobial Products
2. Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
3. Jeffrey Murray, MD, MPH, Deputy Director, DAVP
4. Dave Roeder, Associate Director Regulatory Affairs, Office of Antimicrobial Products
5. Kim Struble, PharmD, Medical Team Lead, DAVP
6. Wendy Carter, DO, Medical Officer, DAVP
7. Chih-Ying (Natasha) Chen, PhD, Visiting Scientist/Epidemiologist, Division of Epidemiology
8. Donald Langan, Pharmacy Student, DRISK
9. Fang Li, PhD, Pharmacometrics Reviewer, Office of Clinical Pharmacology
10. Jamie Wilkins Parker, PharmD, Division of Risk Management (DRISK)
11. Julian O'Rear, PhD, Virology Team Lead, DAVP
12. Karen Winestock, Chief, Project Management Staff, DAVP
13. Lalji Mishra, PhD, Virology Reviewer, DAVP
14. Naomi S. Redd, PharmD, Drug Risk Management Analyst, Office of Medication Error Prevention and Risk Management
15. Patrick Harrington, PhD, Virology Reviewer, DAVP
16. Sandra Suarez, PhD, Biopharmaceutics Reviewer, Office of New Drug Quality Assessment
17. Sohail Mosaddegh, PharmD, Regulatory Project Manager, DAVP
18. Wen Zeng, PhD, Statistician, Division of Biometrics

FDA ATTENDEES BY PHONE

19. Debra Boxwell, Safety Evaluator, Division of Pharmacovigilance
20. Karen Dowdy, Patient Labeling Reviewer, Division of Medical Policy Programs
21. Kemi Asante, PharmD, Senior Regulatory Review Officer, Office of Prescription Drug Promotion

22. Monica Calderon, PharmD, Safety Evaluator, Division of Medication Error Prevention and Analysis
23. Peyton Myers, PhD, Pharmacologist/Toxicologist, DAVP
24. Stephen Miller, PhD, CMC-Lead, Office Of New Drug Quality Assessment

EASTERN RESEARCH GROUP ATTENDEES

25. Christopher Sese, Independent Assessor

APPLICANT ATTENDEES

26. Math Hukkelhoven, Sr. VP, Global Regulatory, Safety and Biometrics (GRSB)
27. Doug Manion, Head Specialty Development and interim Head Global Pharmacovigilance and Epidemiology (GPV&E)
28. Steven Schnittman, VP Global Development Lead - HCV, Global Clinical Research (GCR)
29. Eric Hughes, Executive Director, GCR
30. Stephanie Noviello, Group Director, GCR - Virology
31. Debra Feldman, VP, GPV&E
32. Claire Jurkowski, Medical Director, GPV&E
33. Tushar Garimella, Associate Director, Clinical Pharmacology and Pharmacometrics
34. Timothy Eley, Director, Clinical Pharmacology and Pharmacometrics
35. Frank LaCreta, Executive Director, Clinical Pharmacology and Pharmacometrics
36. Beatrice Anduze-Faris, Group Director, Viral Hepatitis Lead, US Medical
37. Theodora Salcedo, Associate Director , DSE - Toxicology
38. Margo Heath-Chiozzi, VP, GRSB, Virology
39. Thomas Kelleher, Group Director, GRSB, Virology
40. Andrew Damokosh, Director, GRSB
41. Joan Fung-Tomc, Group Director, GRSB - Virology
42. Charles Wolleben, Group Director, GRSB - US
43. Chirag Patel, Manager, Global Regulatory Strategy Management, GRSB
44. Megan Wind-Rotolo, Principal Scientist, Clinical Biomarkers Virology
45. (b) (4)

APPLICANT ATTENDEES BY PHONE

(b) (4)

BACKGROUND

NDA 206844 was submitted on March 31, 2014 for asunaprevir, (b) (4).
NDA 206843 was submitted on March 31, 2014 for daclatasvir, 30 & 60 mg tablets.

Proposed indication: Treatment of Chronic Hepatitis C Infection

PDUFA goal date: November 30, 2014

FDA issued a Background Package in preparation for this meeting on September 10, 2014.

DISCUSSION

1. LCM Agenda

- Introductory Comments – 5 minutes (Sohail Mosaddegh /Kimberly Struble)
 - Welcome, Introduction, Ground rules, Objectives of the meeting
- Discussion of Substantive Safety Review Issues – 40 minutes (All)
 - Update from BMS and FDA expert consultations
- Information Requests – 20 minutes
- Discussion of Upcoming Advisory Committee Meeting – 30 minutes (All)
 - Review of potential AC discussion topics
 - Coordination of AC backgrounders and presentations
- Major Labeling Issues – 10 minutes (All)
 - BMS proposal for Warning/Precaution: Hepatotoxicity
- PMR/PMC – 5 minutes (Kimberly Struble)
 - PREA – PMRs
 - Other PMR/PMC dependent on outcome of AC and recommendations.
 - Consideration for trials needed to further define risks or optimize use of ASV/DCV. Additional pharmacogenomics evaluations
- Review Plans–5 minutes (Sohail Mosaddegh/Kimberly Struble)
 - Await feedback from AC meeting
 - Continue with labeling review and discussions
 - Await inspection reports
- Wrap Up/Action Items – 5 minutes (Sohail Mosaddegh)

2. Introductory Comments

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans and our objectives for the remainder of the review. The discussion during the meeting was guided by the attached slides which were provided by BMS and addressed the substantive review issues.

3. Discussion of Substantive Review Issues

Following introductions BMS provided a top line summary of the assessment of hepatic effects, pyrexia, and eosinophilia conducted in collaboration with Drs. (b) (4). This presentation concluded with a presentation of a Venn diagram which illustrated the overlap of pyrexia, eosinophilia and increased ALT. FDA appreciated the value of representing these findings in such a graphic and commented that it would be helpful to have the same graphic broken down by Japanese and non-Japanese patients.

Drs. (b) (4) stated their perspectives regarding the issue of the observed hepatic effects:

- ALT reaching 10X ULN is a reasonable level to advise discontinuation of therapy.
- Eosinophilia with or without pyrexia was an observation but was not useful parameter(s) for monitoring as it was not predictive of hepatic injury. Peripheral and/or hepatic eosinophils in the setting of hepatic necrosis have been reported to be associated with a more favorable

patient outcome. Moreover, there was only 1 patient with a mild rash (referring to patient who also had pyrexia, eosinophilia and grade 2 elevated ALT), and no DRESS observed in the BMS HCV clinical programs. Dr. (b) (4) indicated that there was no evidence of a hypersensitivity reaction. There also appears to be no immune memory when patients are rechallenged, as some subjects had drug restarted or improved while continued on therapy.

- There was no obvious reason why eosinophilia and pyrexia were more apparent in Japanese subjects; however, genetic, environmental, or cultural factors could be involved.
- ALT elevations seem to be the most clinically relevant parameter to monitor.

In order to show the impact of baseline factors on the potential of developing ALT elevations BMS presented the results of a logistic regression model. Three different ALT elevation definitions, ALT >3x ULN, ALT >5x ULN and ALT >3x nadir concurrent with ALT >2xULN, were analyzed separately to illustrate the impact on effects of each dependent variable in the logistic regression model, including age group, gender, BMI categories, treatment by country interaction and treatment by cirrhosis status interaction. It was noted that in the BMS Phase 3 trials, subjects with baseline ALT up to 5x ULN were enrolled. A higher proportion of patients with baseline ALT 3-5x ULN were enrolled in the Japanese trial than in the non-Japanese global trials. It was noted that the ALT determinations in Japan were done at local labs which may have different values for the ULN, some of which are lower than the ULN values from the central lab (which tested the global trials).

FDA agreed that using incident elevations of ALTs expressed in factors of ULN during therapy may be more relevant for clinical monitoring purposes, while looking at factors of nadir values may be more relevant to compare populations for analyses. Both FDA and BMS expressed difficulty in defining the most clinically relevant definition of ALT elevations for this treatment population, including what is considered normal ALT levels. FDA recommended that BMS make a proposal regarding their final analysis plan for the logistic regression regarding what may be the most useful parameters to evaluate, in order to reach alignment with the Agency before the Advisory Committee. FDA expressed a concern regarding the possibility of the risk of missing hepatic dysfunction by monitoring the ALT/bilirubin infrequently and that labeling should provide for timely interruption of therapy before liver impairment, while also ensuring that treatment is not discontinued inappropriately.

FDA confirmed that the subject in Japanese study AI447026 who experienced elevated LFTs, with pyrexia and eosinophilia and biopsy proven drug induced liver injury triggered the heightened level of concern for the Agency.

BMS inquired if, following the information discussed above, the Agency's perspective regarding the hepatic effects had changed since the Mid-Cycle meeting when they were characterized as significant safety issues that may affect approvability of the application. FDA stated that the Agency management reviews have not yet been conducted but confirmed that the the information and discussion with the hepatologists and DILI experts were helpful. However, FDA is seeking feedback from the Advisory Committee to evaluate the totality of the data and risk/benefit. FDA generally agreed with BMS' current position that the concern is about ASV, not DCV.

With regard to preparation for the Advisory Committee, BMS informed the Agency that they are intending to reflect the daclatasvir/sofosbuvir Phase 2 study AI444040 (daclatasvir in combination with sofosbuvir with and without ribavirin) in their Advisory Committee background document and present it as a Phase 2 study supporting the activity and safety of daclatasvir with other agents. FDA stated that this study should be represented only as part of the safety discussion. BMS committed to share the next version of the draft presentation to their next mock panel with the Division for feedback by October 03, 2014.

FDA asked Dr. Pooradad to give a clinician's perspective of the hepatic safety issues. Dr. Pooradad stated that elevations of transaminases are not new to clinicians treating HCV infected patients and he was not concerned with the ability of clinicians who treat HCV to adequately monitor patients undergoing therapy. He acknowledged, however, that less experienced health care providers may start to use DAAs and that labeling and guidance should be simple and clear. He suggested that threshold could be considered as absolute ALT values versus multiples of ULN. He also suggested that 10xULN may be a good threshold for enhanced monitoring and, not for drug discontinuation in some cases. Any upward trend of liver enzymes should warrant more frequent monitoring (every two weeks) and higher ALT numbers may need weekly monitoring.

FDA noted that BMS should not emphasize the message that patients who discontinued therapy for ALT elevations still reached SVR.

4. Discussion of Upcoming Advisory Committee Meeting

BMS asked if an Advisory Committee was necessary versus having a very concerted effort with experts to resolve the issue of labeling for these products. Dr. Cox stated that given the nature of the issue and the fact that there is a pre-marketing case of drug induced liver injury (biopsy proven), it is important to have a public discussion and feedback on the topic. FDA will continue as planned to conduct an Advisory Committee on Nov 17. The topics for the Advisory Committee will include:

- A focus on Phase 3 studies mainly (with mention of the Phase 2 studies, as needed)
- A discussion around ALT elevations with and without bilirubin elevations, and discontinuations (FDA is likely to ask the advisory panel about eosinophilia and pyrexia)
- A discussion of role of ASV in the hepatic effects compared to DCV
- How to identify at-risk patients who need enhanced monitoring, or to whom treatment would be deemed as not appropriate.
- Discussions regarding monitoring schedule and discontinuation criteria
- Is race a factor (Japanese vs non-Japanese patients)?
- Vote question to solicit committee interpretation of the data and risk/benefit assessment for approvability.

In addition BMS was advised that it may be helpful to dedicate some time early in the Advisory Committee presentation to a general discussion of Drug-Induced Liver Injury. FDA indicated that we are still in process of finalizing the panel.

5. REMS or Other Risk Management Actions

FDA asked BMS's to provide a summary of the planned post-marketing surveillance in Japan. BMS presented the 6-month program as well as the Post Marketing Surveillance study in 3,000 patients over 30 months in the context of the Japan postmarketing regulations. FDA asked for more information about the educational materials provided to health care providers in Japan such as letters, mandatory training, etc. FDA recommended BMS make presentation at the Advisory Committee about their proposal for postmarketing plans. This should include the following:

- Any additional pharmacogenomics assessments
- Other efforts to further characterize the mechanism of the liver injury, specifically analyses of HLA genotype in additional studies. Dr. ^{(b) (4)} noted that beyond pharmacogenomic assessments it would be difficult to further characterize the mechanism of liver injury nonclinically; especially the mechanism of increased frequency in Japanese subjects, and such work would likely not lead to a definitive characterization.
- Post-marketing communication plan (such as a DHCP letter, Journal Ads, etc.) to providers and/or patients
- Potential role of HCV-TARGET in collecting data for post-marketing commitments
- Enhanced pharmacovigilance plan (including targeted questionnaires, outside adjudication of the events, PBRER).

6. Major Labeling Issues

See Discussion of Substantive Review Issues above

7. Review Plans

BMS and FDA agreed to a follow up teleconference before October 15, 2014 so BMS can:

- Present a more detailed post marketing plan
- Address suggestions about enhanced PV plans
- Discuss HCV target database, and pharmacogenomics work

Final labeling and non PREA PMRs/PMCs are dependent on outcome of AC and recommendations.

8. Wrap-up and Action Items

BMS will:

- Prepare pyrexia/eosinophilia/ALT Venn diagram for Japanese and non-Japanese patients.
- Provide a proposal regarding the most useful parameters to evaluate for the multivariate logistic regression model so there can be alignment with the Agency on what will be presented during the Advisory Committee discussion
- Provide FDA, by October 03, 2014, with the next version of the draft presentation for the next mock Advisory Committee panel
- Provide a copy of the current targeted hepatic event questionnaires used by GPVE

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader and therefore, this meeting did not address the final regulatory decision for the application.

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BMS and DAVP MEETING ATTENDEES

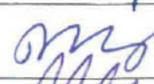
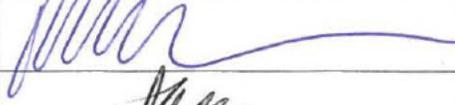
Date: 09/22/2014 **Time:** 1:00 pm – 3:00 pm

Place: WO Bldg.22, room 1419

Firm: BMS LCM NDA 206843/206844

NAME	SIGNATURE	REPRESENTING
Andrew Damokosh, Director, GRSB	(b) (4)	BMS
Beatrice Anduze-Faris, US Medical Virology Lead, US Medical	(b) (4)	BMS
Charles Wolleben, Group Director, GRSB - US	(b) (4)	BMS
Chirag Patel, Manager, Global Regulatory Strategy Management, GRSB	(b) (4)	BMS
Claire Jurkowski, Medical Director, GPV&E	(b) (4)	BMS
Debra Feldman, VP, GPV&E	(b) (4)	BMS
Doug Manion, Head Specialty Development and interim Head Global Pharmacovigilance and Epidemiology (GPV&E)	(b) (4)	BMS
Eric Hughes, Executive Director, GCR	(b) (4)	BMS
Frank LaCreta, Executive Director, Clinical Pharmacology and Pharmacometrics	(b) (4)	BMS
Fred Poordad, Texas Liver Institute (by phone)	(b) (4)	BMS
	(b) (4)	
Joan Fung-Tome, Group Director, GRSB - Virology	(b) (4)	BMS
Margo Heath-Chiozzi, VP, GRSB, Virology	(b) (4)	BMS
Mark Arnold, Executive Director, Analytical & Bioanalytical Development	(b) (4)	BMS
Math Hukkelhoven, Sr. VP, Global Regulatory, Safety and Biometrics (GRSB)	(b) (4)	BMS
Megan Wind-Rotolo, Principle Scientist, Exploratory Clin&Translational Research	(b) (4)	BMS
	(b) (4)	
Stephanie Noviello, Director, GCR - Virology	(b) (4)	BMS
Steven Schnittman, VP Global Development Lead - HCV, Global Clinical Research (GCR)	(b) (4)	BMS
Theodora Salcedo, Senior Principal Scientist, DSE - Toxicology	(b) (4)	BMS
Thomas Kelleher, Group Director, GRSB, Virology	(b) (4)	BMS
Timothy Eley, Director, Clinical Pharmacology and Pharmacometrics	(b) (4)	BMS
Tushar Garimella, Associate Director, Clinical Pharmacology and Pharmacometrics	(b) (4)	BMS
	(b) (4)	
	(b) (4)	
	(b) (4)	

Chih-Ying (Natasha) Chen, PhD, Visiting Scientist/Epidemiologist, Division of Epidemiology	Via phone	
Christopher Sese, Independent Assessor (Eastern Research Group)	<i>Christopher A. Sese</i>	ERG
Dave Roeder, Associate Director Regulatory Affairs, Office of Antimicrobial Products	<i>D Roeder</i>	FDA
Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)	<i>Debra Birnkrant</i>	FDA
Debra Boxwell, Safety Evaluator, Divisions of Pharmacovigilance	Via Phone	
Edward M Cox, MD, MPH, Director, Office of Antimicrobial Products	<i>Edward M Cox</i>	FDA
Fang Li, PhD, Pharmacometrics Reviewer, Office of Clinical Pharmacology	<i>Fang Li</i>	FDA
Hanan Ghantous, PhD, DABT, Pharmacology/ Toxicology Team Lead	Via Phone	
Jeff Florian, PhD, Acting Team Leader, Division of Pharmacometrics		
Jeffrey Murray, MD, MPH, Deputy Director, DAVP	<i>Jeffrey Murray</i>	FDA
John Farley, MD, Deputy Director, Office of Antimicrobial Products		
Julian O'Rear, PhD, Virology Team Lead, DAVP	<i>Julian O'Rear</i>	DAVP
Karen Dowdy, Patient Labeling Reviewer, Division of Medical Policy Programs	Via phone	
Karen Winestock, Chief, Project Management Staff, DAVP	<i>Karen Winestock</i>	DAVP
Kemi Asante, PharmD. Senior Regulatory Review Officer, Office of Prescription Drug Promotion	Via phone	
Kim Struble, PharmD, Medical Team Lead, DAVP	<i>Kim Struble</i>	DAVP
Lalji Mishra, PhD, Virology Reviewer, DAVP	<i>Lalji Mishra</i>	DAVP
Monica Calderon, PharmD, Safety Evaluator, Division of Medication Error Prevention and Analysis	Via phone	
Naomi S. Redd, PharmD, Drug Risk Management Analyst, Office of Medication Error Prevention and Risk Management	Via phone	
Patrick Harrington, PhD, Virology Reviewer, DAVP	<i>Patrick Harrington</i>	
Peyton Myers, PhD, Pharmacologist/Toxicologist, DAVP	Via Phone	
Rajiv Agarwal, PhD, Product Quality reviewer, Office Of New Drug Quality Assessment		
Sandra Suarez, PhD, Biopharmaceutics reviewer, Office Of New Drug Quality Assessment	Via Phone	

Sohail Mosaddegh, PharmD, Regulatory Project Manager, DAVP		VVA
Stephen Miller, PhD, CMC-Lead, Office Of New Drug Quality Assessment	Via phone	
Wen Zeng, PhD, Statistician, Division of Biometric		FDA
Wendy Carter, DO, Medical Officer, DAVP		FDA
Jamie Williams Parker, PharmD Team leader, DRISK		DRISK
Donald Langan, Pharmacy Student DRISK		DRISK

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/s/

KIMBERLY A STRUBLE
10/17/2014



NDA 206844
NDA 206843

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Bristol-Myers Squibb Company
Attention: Charles D. Wolleben, PhD
Group Director, Global Regulatory Sciences - US
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Wolleben:

Please refer to your New Drug Applications (NDAs) dated March 31, 2014, received March 31, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for asunaprevir [REDACTED] (b) (4) and daclatasvir tablets 30 and 60 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 22, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Sohail Mosaddegh, PharmD, Regulatory Project Manager, at (301) 796-4876 or (301) 796-1500.

Sincerely yours,

{See appended electronic signature page}

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

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: September 22, 2014 1 PM to 3 PM
Meeting Location: 10903 New Hampshire Avenue, Building 22, Room 1419. Silver Spring MD 20993

Application Number: NDA 206843 & 206844
Product Name: asunaprevir & daclatasvir
Indication: Treatment of Chronic Hepatitis C Infection
Applicant Name: Bristol-Myers Squibb Company

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

During initial review hepatotoxicity (dose-related liver toxicity and liver toxicity associated with eosinophilia) was identified as a primary safety issue. An initial presentation of a case of pyrexia, peripheral eosinophilia and significant biopsy proven liver toxicity with eosinophils occurred during a phase 3 trial conducted in Japan. Subsequent FDA analysis of pyrexia and eosinophilia was based on a broader exploration of any subjects who reported an AE of pyrexia and elevation of eosinophils from laboratory results. Based on the additional eosinophilia/pyrexia with and without liver involvement findings and the overall hepatic safety analyses, FDA decided to pursue expert opinion through internal FDA consultation as well as through an Advisory Committee Meeting.

DISCIPLINE REVIEW LETTERS

No Discipline Review Letters have been issued to date.

SUBSTANTIVE REVIEW ISSUES

The following substantive review issues have been identified to date:

- Hepatotoxicity
- Eosinophilia with and without pyrexia and with and without liver involvement.
- Baseline NS5A L31F/I/M/V and Y93H polymorphisms reduced the efficacy of the ASV/DCV regimen in HCV genotype 1b infected subjects. Screening for the presence of these polymorphisms is recommended and alternative therapy should be considered for patients with NS5A L31F/I/M/V or Y93H.

ADVISORY COMMITTEE MEETING

An advisory committee meeting is planned for November 17, 2014.

Date AC briefing packages due: BMS briefing package is due October 15, 2014.

Potential discussion topics for AC Meeting are as follows:

- Comments regarding the safety profile of asunaprevir and daclatasvir (ASV/DCV) focusing on (1) hepatotoxicity specifically increases in ALT/AST with and without increases in total bilirubin and (2) eosinophilia with and without pyrexia and with and without increases in ALT. Comments regarding if the above safety findings are one clinical issue or potentially an immune component as a separate presentation. Race as a potential risk factor for these observed events.
- Comments on whether there are additional measures to improve hepatic safety and eosinophilia with or without liver involvement, e.g. laboratory monitoring and schedule. Are there “at risk patients who need enhanced monitoring or for whom use of ASV/DCV should not be recommended?”
- Vote question – considering potential risks and benefits does the available data support approval of ASV/DCV for treatment of chronic hepatitis C in patients with genotype 1b and ASV/DCV/pegylated interferon /ribavirin for treatment of chronic hepatitis C in patients with genotype 1 and 4?

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (Sohail Mosaddegh /Kimberly Struble)
 - a. Welcome, Introduction, Ground rules, Objectives of the meeting
2. Discussion of Substantive Safety Review Issues – 40 minutes (All)
 - a. Update from BMS and FDA expert consultations

3. Information Requests – 20 minutes
4. Discussion of Upcoming Advisory Committee Meeting – 30 minutes (All)
 - a. Review of potential AC discussion topics
 - b. Coordination of AC backgrounders and presentations
5. Major Labeling Issues – 10 minutes (All)
 - a. BMS proposal for Warning/Precaution: Hepatotoxicity
6. PMR/PMC – 5 minutes (Kimberly Struble)
 - a. PREA – PMRs
 - b. Other PMR/PMC dependent on outcome of AC and recommendations.
 - i. Consideration for trials needed to further define risks or optimize use of ASV/DCV. Additional pharmacogenomics evaluations
7. Review Plans–5 minutes (Sohail Mosaddegh/Kimberly Struble)
 - a. Await feedback from AC meeting
 - b. Continue with labeling review and discussions
 - c. Await inspection reports
8. Wrap Up/Action Items – 5 minutes (Sohail Mosaddegh)

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/s/

DEBRA B BIRNKRANT
09/10/2014