

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206843Orig1s001, s003**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 206843

SUPPL # 001 & 003

HFD # 530

Trade Name DAKLNZA

Generic Name daclatasvir

Applicant Name Bristol-Myers Squibb Company

Approval Date, If Known 02/05/2016

### **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) SE5

b) 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:

c) Did the applicant request exclusivity?

YES  NO

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

(b) (4)

d) 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:

ALLY-1: study of DCV/SOF/RBV for 12 weeks in genotype 1 or 3, HCV infected subjects with recurrence of HCV after liver transplantation

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

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

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

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

ALLY-1: study of DCV/SOF/RBV for 12 weeks in HCV infected subjects

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

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

Investigation #1		!
		!
IND # 79,599	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

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

Investigation #1		!
		!
YES <input type="checkbox"/>		! NO <input type="checkbox"/>
Explain:		! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! 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:

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Name of person completing form: Sohail Mosaddegh

Title: Regulatory Project Manager

Date: 02/04/2016

Name of Office/Division Director signing form: Debra Birnkrant

Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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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.**  
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/s/  
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SOHAIL MOSADDEGH  
02/05/2016

DEBRA B BIRNKRANT  
02/05/2016

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 206843 BLA #	NDA Supplement # 001 & 003 BLA Supplement #	If NDA, Efficacy Supplement Type: SE5 <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: DAKLNIZA Established/Proper Name: daclatasvir Dosage Form: tablets		Applicant: Bristol-Myers Squibb Company Agent for Applicant (if applicable):
RPM: Sohail Mosaddegh		Division: DAVP
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b>For ALL 505(b)(2) applications, two months prior to EVERY action:</b></p> <ul style="list-style-type: none"> <li>• Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action 02/05/16</li> <li>• User Fee Goal Date is <u>02/05/16</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only):  
*(confirm chemical classification at time of approval)*

- |   |   |
|---|---|
| <input checked="" type="checkbox"/> Fast Track            | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

**(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)**

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

<b>Action Letters</b>	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) AP 02/05/16
<b>Labeling</b>	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included 2/3/16
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included 8/5/15
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included 2/3/16
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included 8/5/15
❖ Labels <b>(full color carton and immediate-container labels)</b> <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input type="checkbox"/> Included N/A
<ul style="list-style-type: none"> <li>• Proprietary Name               <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>• Review(s) <i>(indicate date(s))</i></li> </ul> </li> </ul>	N/A
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: 2/5/16, 9/28/15 DMEPA: 11/19/15 DMPP/PLT (DRISK): 1/21/16 OPDP: 1/21/16 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
<b>Administrative / Regulatory Documents</b>	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	Filing review/RPM memo: 9/25/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>This application is on the AIP                             <ul style="list-style-type: none"> <li>If yes, Center Director’s Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC</li> <li>If PeRC review not necessary, explain: <u>Expanded patient population, SE5</u></li> </ul>	N/A
❖ Breakthrough Therapy Designation	
<ul style="list-style-type: none"> <li>Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	Granted 04/08/14
<ul style="list-style-type: none"> <li>CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	03/19/14
<ul style="list-style-type: none"> <li>CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) ( <i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package</i> )	1/28/16, 1/8/16, 12/23/15, 12/17/15, 12/16/15, 12/7/15, 12/1/15, 11/22/15, 10/30/15, 10/23/15, 10/20/15 10/8/15, 10/8/15, 9/30/15, 9/29/15, 9/14/15 9/4/15
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	N/A
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	1/26/16
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	

<b>Clinical Reviews</b>	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) ( <i>indicate date for each review</i> )	1/27/16
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Page 72 of clinical review 1/27/16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	OSE/Pharmacovigilance Review consult 11/24/15
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	12/10/15
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	1/15/16, 12/21/15
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	1/20/16
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	1/12/16
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	1/27/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	9/22/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	Product quality review
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections ( <i>action must be taken prior to the re-evaluation date</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input checked="" type="checkbox"/> Not applicable

<b>Day of Approval Activities</b>	
<ul style="list-style-type: none"> <li>❖ For all 505(b)(2) applications:                             <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> </li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul> </li> </ul>	<input type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ For Breakthrough Therapy (BT) Designated drugs:                             <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul> </li> </ul>	<input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
<ul style="list-style-type: none"> <li>❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul> </li> </ul>	<input type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</li> </ul>	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter</li> </ul>	<input type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name</li> </ul>	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ Ensure Pediatric Record is accurate</li> </ul>	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ Send approval email within one business day to CDER-APPROVALS</li> </ul>	<input checked="" type="checkbox"/> Done

# Electronic Mail Correspondence – Information Request/Advice



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

---

**DATE:** January 28, 2016

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

**SPONSOR:** Bristol- Myers Squibb

**SUBJECT:** Labeling for sNDA 206843/S-001, S-002, S-003

---

Please see attached labeling comments/edits and submit revised labeling by 02/02/2016.

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

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

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/s/  
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SOHAIL MOSADDEGH  
01/28/2016

**From:** Mosaddegh, Sohail  
**To:** [marianne.frost@bms.com](mailto:marianne.frost@bms.com)  
**Subject:** DCV IR  
**Date:** Friday, January 08, 2016 3:02:00 PM

---

Hello:

please provide by Monday a table of all available SVR12 data from a 12 week duration of DCV/SOF/RBV in HCV GT1 subjects with Child Pugh C decompensated cirrhosis from clinical trial or early access programs. The 12 week window may include treatments between 11 and 13 weeks in duration.

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*

*Silver Spring, MD 20993-0002*

*Phone: (301) 796-4876*

*Fax: (301) 796-9883*

*Email: [Sohail.Mosaddegh@FDA.HHS.GOV](mailto:Sohail.Mosaddegh@FDA.HHS.GOV)*

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/s/  
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SOHAIL MOSADDEGH  
01/08/2016

# Electronic Mail Correspondence – Information Request/Advice



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

---

**DATE:** December 23, 2015

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

**SPONSOR:** Bristol- Myers Squibb

**SUBJECT:** Labeling for sNDA 206843/S-001, S-002, S-003

---

Please see attached labeling comments/edits and submit revised labeling by 01/08/2016.

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/  
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SOHAIL MOSADDEGH  
12/23/2015

**From:** Mosaddegh, Sohail  
**To:** [marianne.frost@bms.com](mailto:marianne.frost@bms.com)  
**Subject:** DCV sNDA 20684/s01 s/02 s/03 IR  
**Date:** Thursday, December 17, 2015 2:35:00 PM

---

Hello:

Please provide by Monday 12/21/2015 a table of the available SVR12 data from the ATU or other trial sources for GT3 cirrhotic subjects that received 12 weeks (or up to 13 weeks in total) of DCV/SOF/RBV. In the table please provide the SVR12 rate for the total overall of GT3 subjects with and without cirrhosis, including compensated and decompensated cirrhosis.

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](mailto:Sohail.Mosaddegh@FDA.HHS.GOV)*

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/s/  
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SOHAIL MOSADDEGH  
12/17/2015

**From:** Mosaddegh, Sohail  
**To:** [marianne.frost@bms.com](mailto:marianne.frost@bms.com)  
**Subject:** NDA 206483/s01 s/02 s/03 IR  
**Date:** Wednesday, December 16, 2015 2:18:00 PM

---

Please provide the following information from ALLY-1 by Friday 12/18/2015:

Provide by all study subjects and by genotype 1 subjects only:

- The mean and median RBV dose by Child Pugh Category and by baseline MELD score of < 15 and >=15
- Median time to RBV dose reduction and median time to RBV discontinuation by Child Pugh Category (A, B and C) and by pooled Child Pugh A and B only

Provide for Genotype 1 pooled by Child Pugh A and B only (consistent with labeling):

- The overall mean and median RBV dose for all subjects (GT1 Child Pugh A/B) and by baseline MELD score of < 15 and >=15 (GT1 Child Pugh A/B)
- Median time to RBV dose reduction and Median time to RBV discontinuation for all subjects (GT1 Child Pugh A/B) and by baseline MELD score of <15 and >= 15 (GT1 Child Pugh A/B)

*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](mailto:Sohail.Mosaddegh@FDA.HHS.GOV)*

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SOHAIL MOSADDEGH  
12/16/2015

**From:** Mosaddegh, Sohail  
**To:** [marianne.frost@bms.com](mailto:marianne.frost@bms.com)  
**Subject:** NDA 206843 s/01, s/02. s/03 comment in advance of telecon  
**Date:** Monday, December 07, 2015 4:02:00 PM

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We appreciate your responses in advance of our teleconference on December 8, 2015. With respect to screening for NS5A polymorphisms, the label will likely state testing HCV genotype 1a subjects with cirrhosis for the presence of virus with NS5A resistance-associated polymorphisms should be considered prior to initiation of treatment. According to labeling guidance and practices, this statement will be included as section 2.1: Testing Prior to Initiation. We are open to proposals to include the prevalence data and baseline NS5A polymorphisms and outcome data in section 12. Your proposal to only include screening for specific NS5A polymorphisms will be discussed further in detail during the teleconference. We look forward to a productive discussion tomorrow.

*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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SOHAIL MOSADDEGH  
12/07/2015

# Electronic Mail Correspondence – Information Request/Advice



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

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**DATE:** December 1, 2015

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

**SPONSOR:** Bristol- Myers Squibb

**SUBJECT:** Comments for sNDA 206843/S-001, S-002, S-003

---

## “Mid-Cycle” Communication Backgrounder for DAKLINZA (DCV) sNDA 001-003

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. 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, we may or may not be able to consider your response before we take an action on your application during this review cycle.

### **BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE**

#### 1. Substantive Review Issues

*Limited number of genotype 1 subjects with CPT-C cirrhosis and genotype 3 subjects with CPT-B and C:*

We appreciate the ALLY-1 trial was conducted in decompensated patients, a population currently in need of treatment options. The limited sample size of HCV genotype 1 CPT-A (11), CPT-B (n=24) and CPT-C (n=10) cirrhosis subjects in ALLY-1 presents challenges in the ability to grant labeling for all subpopulations. We conducted several analyses which pooled data from ALLY-1: CPT A and B cirrhotic cohort, ALLY-1: post-transplant F4 subgroup, and ALLY-2: compensated cirrhotic subgroup and conclude that the overall SVR12 rate was 92% (67/73), thus supporting dosing and administration for genotype 1 compensated cirrhotics (F4 and CPT-A) and CPT-B subjects. However, the limited sample size of GT1 CPT-C subjects from ALLY-1 and modest efficacy results [SVR12 50% (5/10)] are not sufficient to recommend a treatment regimen in labeling for these patients.

Accordingly, section 14: Clinical Trials will be revised to state, “Available data on subjects with Child Pugh class C cirrhosis are insufficient to provide recommendations; therefore, these results are not presented in table XX.” (b) (4)

(b) (4)  
As a result, section 2: Dosage and Administration will be limited to genotype 1: patients without cirrhosis, (b) (4) post-transplant patients (b) (4); Child-Pugh A and B and genotype 3 (b) (4) without compensated cirrhosis.

*Effect of baseline NS5A polymorphisms and SVR12 rates in GT1a subjects with cirrhosis*

The Division will be adding to Section 2 of the label a section on “Testing Prior to Initiation of DAKLINZA” to include language that recommends screening for the presence of NS5A polymorphisms at positions 28, 30, 31 or 93, prior to initiation of treatment with DAKLINZA in combination with sofosbuvir with or without ribavirin for patients with HCV GT1a infection and cirrhosis.

Based on a pooled analysis of the ALLY-1 and ALLY-2 trials (AI444215 and AI444216, respectively), SVR12 rates were lower among HCV GT1a infected subjects with HCV NS5A resistance-associated polymorphisms. Considering the four most critical DCV resistance-associated positions in NS5A (M28, Q30, L31 or Y93), and excluding subjects who received the 8-week treatment duration in ALLY-2, SVR12 rates were 13/17 (76%) and 142/149 (95%) for those with or without the DCV NS5A resistance-associated polymorphisms, respectively.

Subgroup analyses of the ALLY-1 and ALLY-2 trials are limited by the different treatments used (i.e., with or without RBV), and the relatively small sizes of key subgroups, but it appears that the impact of NS5A polymorphisms was restricted to HCV GT1a subjects with cirrhosis. Among pre-transplant HCV GT1a subjects with Child-Pugh A or B cirrhosis, SVR12 rates were 2/6 (33%) and 38/39 (97%) for those with or without a key DCV resistance-associated polymorphism, respectively. In other words, of the 5 virologic failure subjects with Child-Pugh A/B cirrhosis who received DCV/SOF ± RBV for 12 weeks, 4 of the 5 failures had virus with a key DCV resistance-associated polymorphism. In contrast, 9/9 (100%) HCV GT1a non-cirrhotic subjects with a key NS5A polymorphism achieved SVR12. No HCV GT1a subjects with Child-Pugh C cirrhosis had a polymorphism at any NS5A position that has even a minor association with DCV resistance. Furthermore, data from the Post-Transplant Cohort in ALLY-1 are insufficient to determine if resistance polymorphisms have an impact in this population, but we expect that, as in pre-transplant patients, NS5A polymorphisms would have a greater impact in those with more advanced liver disease post-transplant.

No subjects with NS5A Q30 polymorphisms experienced virologic failure, despite the fact that amino acid substitutions at this position were most common among subjects who experienced virologic failure. However, data are only available for a single subject with cirrhosis and a Q30 polymorphism, which may explain the lack of an association with

treatment outcome. Given that this position appears to be a critical DCV resistance-associated position in GT1a, we believe it should be included in the screening algorithm along with positions 28, 31 and 93.

There were resistance consequences of failure among subjects who had NS5A polymorphisms and experienced virologic failure in the ALLY-1 and ALLY-2 trials. Two of the four virologic failure subjects with baseline NS5A resistance-associated polymorphisms had additional treatment-emergent, resistance-associated substitutions in NS5A at the time of virologic failure, raising concerns that these subjects may not respond optimally to re-treatment with another NS5A inhibitor-containing regimen. Also, three of the four subjects had a treatment-emergent NS5B substitution possibly associated with sofosbuvir drug exposure (L159F, E237G or Q355H). The precise clinical impact of these NS5B substitutions is unclear, but this observation raises concerns that these subjects may have a viral population that also is not optimally sensitive to sofosbuvir.

We recognize this decision to recommend NS5A resistance screening for HCV GT1a patients with cirrhosis is based on an observation from a relatively small number of subjects. However, this observation is not entirely unexpected, as data from multiple other trials have demonstrated a clear impact of NS5A polymorphisms on treatment efficacy in the context of other DCV-containing regimens or HCV genotypes/subtypes. Ultimately, the Division believes that the strong signal of an impact of NS5A polymorphisms on treatment efficacy in this subgroup, as well as the limited DCV+SOF±RBV efficacy data for cirrhotic HCV GT1 infected patients in general, justifies this screening to reduce the risk and consequences of virologic failure.

Please be aware that if BMS does not accept this labeling approach the Division will need to reconsider whether the data from ALLY-1 and ALLY-2 are sufficient to support an indication for HCV GT1 infected patients with cirrhosis in general. The HCV treatment paradigm, even for patients with cirrhosis, is moving towards regimens with very high efficacy, yet insufficient data are available to identify a reasonably efficacious DCV+SOF-based regimen (e.g., with or without RBV, 12 weeks or longer) for cirrhotic patients with HCV GT1a and NS5A resistance-associated polymorphisms. At least two assays are now commercially available to detect and report NS5A resistance-associated polymorphisms in HCV GT1a. Finally, describing the information in Section 2-Dosage and Administration, rather than as a limitation of use in Section 1, may potentially allow for use of a DCV-containing regimen in HCV GT1a infected patients under certain circumstances or when alternative treatment options are not available.

Of note, discussions on the final presentation of the results from ALLY-1 and ALLY-2 in sections 12 and 14 are ongoing and additional labeling revisions are forthcoming.

## 2. Major Safety Concerns

- No major safety concerns identified at this time. Discussion regarding final presentation of safety data from ALLY-1 and ALLY-2 is ongoing.

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/  
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SOHAIL MOSADDEGH  
12/01/2015

# Electronic Mail Correspondence – Information Request/Advice



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

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**DATE:** November 22, 2015

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

**SPONSOR:** Bristol- Myers Squibb

**SUBJECT:** Clinical Pharmacology comments for sNDA 206843/S-001, S-002, S-003

---

- 1) For the AI444064 trial, the data analysis included a “completer” and an “evaluable population”. The completer population is proposed for inclusion in the daclatasvir USPI. Please clarify whether the main difference between the two populations was that only the completer population statistical analysis was conducted using paired comparisons for individual subjects.
- 2) For the AI444043 trial, please provide information on the following issues:
  - a. Please clarify why it was necessary to dilute lopinavir unknown samples reported as BLQ for the incurred sample reanalysis (ISR)?
  - b. For the lopinavir ISR results, numerous samples were reported as below the limit of quantification (BLQ). Similarly, for the darunavir ISR results, there were a few samples that were reported as below the limit of quantification (BLQ). Please provide additional information explaining the BLQ values since the enrolled subjects should have been receiving a stable HIV treatment regimen and the treatment regimens were not blinded.
  - c. For the following runs that were accepted, certain samples were listed as “deactivated”. Please provide further information as to why these samples were deactivated.
    - 9AGOF (darunavir): AGOF 283-288, 290, 299
    - 14AGOF (darunavir): AGOF 480, 487, 538- 539, 636-638, 672, 680-681, 694-698, 706-709
    - 2AGOF2 (lopinavir): AGOF 283-288, 290, 299
    - 4AGOF2 (lopinavir): AGOF 24, 76, 84-86,105-108, 160-161, 165, 203, 233-235, 241, 262, 280-282, 289, 291-298, 311, 362, 365-376, 378-385, 406-407, 409
    - 5AGOF2 (lopinavir): AGOF 76, 203, 241, 262, 362, 409
    - 12AGOF2 (lopinavir): AGOF 477, 480, 483,487-492
    - 14AGOF2 (lopinavir): AGOF 478-479, 481-482, 484, 487, 493
- 3) In the AI444093 trial, for run 6, both of the 4 ng/mL standards were excluded. Please clarify whether excluding the 4 ng/mL standards resulted in any changes in the concentration-

response model that was used for calibration curve fitting for run 6 from the one that was established during method validation (linear, 1/x<sup>2</sup>) that could potentially affect the reported concentrations.

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  
11/22/2015

**From:** Mosaddegh, Sohail  
**To:** "[Frost, Marianne](#)"  
**Subject:** RE: DCV, 206843 IR  
**Date:** Friday, October 30, 2015 3:25:00 PM

---

Hello:

In light of the Ally-1 trial data currently under review in the pretransplant decompensated and posttransplant populations with chronic hepatitis C infection, and the October 22, 2015 FDA Drug Safety Communication and regulatory actions based on postmarketing cases of serious liver injury reported with the use of two other hepatitis C direct-acting antivirals Viekira Pak and Technivie, we request a cumulative postmarketing hepatic safety assessment for daclatasvir and sofosbuvir-containing treatment regimens.

We acknowledge your recent hepatic safety reviews included in the daclatasvir NDA 206843. The requested cumulative assessment should include all cases (solicited and unsolicited) of worsening of hepatic decompensation, new onset decompensation, hepatic failure, transplant or death through October 15, 2015. Please summarize the data by categories of baseline liver status (a) patients with baseline decompensated liver disease or history of prior decompensation, (b) patients with baseline compensated liver disease and (c) patients where baseline liver status is unknown.

We acknowledge the limitations of the postmarketing data. However, you should attempt to provide the sufficient information to allow for a causality assessment. Please include the following in your response of hepatic decompensation/hepatic failure cases including fatal cases and cases leading to liver transplantation, and include summary tables, graphs or figures where appropriate:

- Time to onset
- Total bilirubin, direct bilirubin, AST, ALT, Serum creatinine, INR, albumin values at baseline, changes on treatment and posttreatment values
- Baseline CPT and MELD scores with change in scores on treatment and posttreatment displayed as summary shift tables
- If patient was listed for liver transplantation at the time of treatment initiation
- Any other pertinent information such as concomitant medications, comorbid conditions, diagnostic imaging studies, procedures

In addition, please provide narrative summaries for the cases. MedWatch reports may be acceptable if the appropriate information is included. For these cases please include baseline CPT and MELD scores with change in scores on treatment and posttreatment along with available liver biopsy data.

As an appendix please provide a table for all cases reported through October 15, 2015, and all narratives. We acknowledge you have submitted many of these narratives in other submissions, but for our comprehensive assessment the inclusion of all narratives in one submission will aid in our review.

Finally, please provide a benefit-risk assessment of hepatic safety with daclatasvir/sofosbuvir-containing treatment and your assessment regarding labeling.

Please submit a response to the above by 11/20/15.

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](mailto:Sohail.Mosaddegh@FDA.HHS.GOV)

---

**From:** Frost, Marianne [mailto:marianne.frost@bms.com]  
**Sent:** Wednesday, October 28, 2015 10:02 AM  
**To:** Mosaddegh, Sohail  
**Subject:** RE: DCV, 206843 IR

Hi Sohail,

The team met earlier this week and had a couple of questions below regarding the information request.

Thanks,

Marianne

- Are the postmarketing cases to be limited to unsolicited reports only (solicited reports would include those from the CUP/EAP studies)?
- Does the Division agree that MedWatch narratives of the fatal cases/or those meeting SAE's will fulfill the request for narratives?

---

**From:** Mosaddegh, Sohail [mailto:[Sohail.Mosaddegh@fda.hhs.gov](mailto:Sohail.Mosaddegh@fda.hhs.gov)]  
**Sent:** Friday, October 23, 2015 12:14 PM  
**To:** Frost, Marianne  
**Subject:** DCV, 206843 IR

Hello:

Please provide by 11/13/2015 a summary and your assessment of any postmarketing cases of hepatic decompensation and/or hepatic failure, including liver transplantation or fatal outcomes with use of DCV in combination with SOF, with or without RBV. Also provide narratives for fatal cases or those meeting SAE criteria for hepatic decompensation or failure.

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](mailto:Sohail.Mosaddegh@FDA.HHS.GOV)

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SOHAIL MOSADDEGH  
10/30/2015

**From:** Mosaddegh, Sohail  
**To:** [marianne.frost@bms.com](mailto:marianne.frost@bms.com)  
**Subject:** DCV, 206843 IR  
**Date:** Friday, October 23, 2015 12:13:00 PM

---

Hello:

Please provide by 11/13/2015 a summary and your assessment of any postmarketing cases of hepatic decompensation and/or hepatic failure, including liver transplantation or fatal outcomes with use of DCV in combination with SOF, with or without RBV. Also provide narratives for fatal cases or those meeting SAE criteria for hepatic decompensation or failure. 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](mailto:Sohail.Mosaddegh@FDA.HHS.GOV)*

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SOHAIL MOSADDEGH  
10/23/2015

**From:** Mosaddegh, Sohail  
**To:** [marianne.frost@bms.com](mailto:marianne.frost@bms.com)  
**Subject:** NDA 206843/s01- s03 IR  
**Date:** Tuesday, October 20, 2015 11:10:00 AM

---

1. It is our understanding that the latest resistance data from the long-term follow-up study, AI444046, were submitted in the original daclatasvir NDA submission. Please confirm.

2. In AI444216 (ALLY-2), four HCV/HIV coinfecting subjects were not on concomitant ART. Three of these four subjects had remarkably low plasma HIV-1 RNA levels throughout the study despite not being on ART (see table below). While it is possible that these subjects are "elite HIV controllers," please comment if you have any other information to explain these HIV-1 RNA results.

**Table: Plasma HIV-1 RNA levels in 4 subjects in AI444216 not on concomitant ART.**

USUBJID	HCV GT	HCV Treatment Visit	HIV-1 RNA (copies/mL)
AI444216-7-58	3A	PRE-TREATMENT	<40 TND
		PRE-TREATMENT	<40 TND
		Treatment Week 1	<40 TND
		Treatment Week 2	<40 TND
		Treatment Week 4	<40 TND
		Treatment Week 6	<40 TND
		Treatment Week 8	<40 TND
		Treatment Week 12	<40 TND
		Post-Treatment Week 4	<40 TND
		Post-Treatment Week 12	<40 TND
AI444216-13-15	1A	PRE-TREATMENT	312
		PRE-TREATMENT	98
		Treatment Week 1	92
		Treatment Week 2	<40 Detected
		Treatment Week 4	<40 Detected
		Treatment Week 6	<40 TND
		Treatment Week 8	<40 TND
		Post-Treatment Week 4	42
		Post-Treatment Week 12	<40 TND
AI444216-18-218	2A OR 2C	PRE-TREATMENT	<40 Detected
		PRE-TREATMENT	<40 Detected
		Treatment Week 1	<40 Detected
		Treatment Week 2	<40 TND
		Treatment Week 4	<40 TND
		Treatment Week 6	<40 TND
		Treatment Week 8	<40 TND
		Treatment Week 12	<40 TND
		Post-Treatment Week 4	<40 TND
		Post-Treatment Week 12	<40 Detected
AI444216-24-71	1B	PRE-TREATMENT	3813
		PRE-TREATMENT	1390
		Treatment Week 1	1694
		Treatment Week 2	4158
		Treatment Week 4	1883
		Treatment Week 6	1766

Treatment Week 8 2335  
Post-Treatment Week 4 3133  
Post-Treatment Week 12 3083  
Post-Treatment Week 24 3996

*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](mailto:Sohail.Mosaddegh@FDA.HHS.GOV)*

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/s/  
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SOHAIL MOSADDEGH  
10/20/2015

**From:** Mosaddegh, Sohail  
**To:** [marianne.frost@bms.com](mailto:marianne.frost@bms.com)  
**Subject:** BMS sNDAs IR for financial disclosure.  
**Date:** Thursday, October 08, 2015 2:08:00 PM

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Hello, we have the following IR for the Financial disclosure.

We recognize you have provided a financial disclosure document that provides the financial disclosure information for the sNDA 1-3; however, due to the table format, it is difficult to review and confirm the specific numbers of investigators overall. 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).

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  
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/s/  
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SOHAIL MOSADDEGH  
10/08/2015

**From:** Mosaddegh, Sohail  
**To:** [marianne.frost@bms.com](mailto:marianne.frost@bms.com)  
**Subject:** Inquiry regarding Interstitial Pneumonitis and DCV (IND 79599; NDA 206843)  
**Date:** Thursday, October 08, 2015 1:28:00 PM

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Hello, please see IR for IND 79599 and NDA 206843:

Please provide a complete summary of all cases of interstitial pneumonia and/or related pulmonary infiltrates with use of a DCV containing regimen. Please provide your overall assessment and any plans for changes to the DCV labeling in the US or in other countries.

Please also provide your interpretation of the lymphocyte stimulation testing with regards to its use for determining causality in the cases where it has been used.

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](mailto:Sohail.Mosaddegh@FDA.HHS.GOV)*

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/s/  
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SOHAIL MOSADDEGH  
10/08/2015



NDA 206843/S-003

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

Bristol-Myers Squibb Company  
Attention: Marianne Frost  
Director, Global Regulatory, Safety & Biometrics - US  
5 Research Parkway  
Wallingford, CT 06492

Dear Ms. Frost:

Please refer to your supplemental New Drug Application (sNDA) dated August 05, 2015, received August 05, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for DAKLNIZA (daclatasvir) tablets 30 and 60 mg.

We also refer to your amendments dated September 01, 2015, September 03, 2015, September 22, 2015, and September 25, 2015.

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**. Therefore, the user fee goal date is February 05, 2016.

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 January 12, 2016. 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](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

### **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:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, 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.

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/  
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DEBRA B BIRNKRANT  
09/30/2015

# Electronic Mail Correspondence – Information Request/Advice



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

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**DATE:** September 29, 2015

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

**SPONSOR:** Bristol- Myers Squibb

**SUBJECT:** Clinical Pharmacology comments for sNDA 206843/S-001, S-002, S-003

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- 1) For the trials listed below, please submit the method validation reports for the following analytes, including all the available addendums or amendments, plus long term stability data. The reports should also contain information indicating whether stability data was generated using freshly prepared stock solutions and calibration standards.
  - a. AI444064: daclatasvir, buprenorphine and norbuprenorphine
  - b. AI444093: daclatasvir
  - c. AI444043: daclatasvir, lopinavir, and darunavir
  
- 2) For the following trials, please submit both the bioanalytical reports and the method validation reports for respective analytes, including all the available addendums or amendments, plus long term stability data, for daclatasvir and dolutegravir. The method validation reports should also contain information indicating whether stability data was generated using freshly prepared stock solutions and calibration standards.
  - a. AI444273: daclatasvir and dolutegravir
  - b. AI444215 (ALLY-1): daclatasvir, sofosbuvir, and sofosbuvir metabolites (BMT-042794 [GS-331007] and BMT-175110 [GS-566500])
  - c. AI444216 (ALLY-2): daclatasvir, sofosbuvir, and sofosbuvir metabolites (BMT-042794 [GS-331007] and BMT-175110 [GS-566500])
  
- 3) For the analytes listed in comment #1 or comment #2, please provide information regarding both the temperature and duration of storage for the samples that were analyzed as part of the respective trials at each of the following locations: a) trial site, b) central laboratory or other storage facility (if applicable), and c) bioanalytical laboratory. Please also provide information regarding the total duration of storage from the time samples were drawn from subjects and processed to the time of analysis at the bioanalytical laboratory for these analytes.

- 4) For the AI444043 trial, the daclatasvir bioanalytical report includes Appendix F (a corrective action investigative report). Please provide a summary of the issue that was discussed and the final outcome of the discussions.
- 5) Please provide the DCV, SOF and SOF metabolites (BMT-042794 [GS-331007] and BMT-175110 [GS-566500]) concentration datasets from ALLY-1 and ALLY-2 or provide guidance to the reviewer on how to locate this information in the current submission.
- 6) For the AI444093, AI444064, AI444273, AI444043, AI444215 and AI444216 trials, please provide information regarding whether the formulations of daclatasvir, sofosbuvir or the concomitant medications that were administered are the U.S. marketed products.

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/  
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SOHAIL MOSADDEGH  
09/29/2015



NDA 206843/S-003

**ACKNOWLEDGMENT --  
PRIOR APPROVAL SUPPLEMENT**

Bristol-Myers Squibb Company  
Attention: Marianne Frost  
Director, Global Regulatory, Safety & Biometrics - US  
5 Research Parkway  
Wallingford, CT 06492

Dear Ms. Frost:

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

**NDA NUMBER:** 206843  
**SUPPLEMENT NUMBER:** 003  
**PRODUCT NAME:** DAKLNIZA (daclatasvir) tablets 30 and 60 mg  
**DATE OF SUBMISSION:** August 05, 2015  
**DATE OF RECEIPT:** August 05, 2015

This supplemental application proposes to expand the patient population to include the treatment of chronic hepatitis C virus infection in subjects with compensated or decompensated cirrhosis.

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 October 04, 2015, 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. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

**FDAAA TITLE VIII RESPONSIBILITIES**

You are also responsible for complying with the applicable provisions of sections 402(i) and (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).

**SUBMISSION REQUIREMENTS**

Cite the application number listed above 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, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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/  
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SOHAIL MOSADDEGH  
09/14/2015

**From:** Mosaddegh, Sohail  
**To:** [marianne.frost@bms.com](mailto:marianne.frost@bms.com)  
**Subject:** sNDA 206843/s-01, 02 & 03 labeling  
**Date:** Friday, September 04, 2015 1:58:00 PM

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Please submit a new label with the following revisions to Section 12.4 Microbiology:

- Remove all text and data pertaining to [REDACTED] (b) (4)

[REDACTED]

- Any tables [REDACTED] (b) (4)

[REDACTED]

- Please revise [REDACTED] (b) (4)

[REDACTED]

*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](mailto:Sohail.Mosaddegh@FDA.HHS.GOV)*

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/s/  
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SOHAIL MOSADDEGH  
09/04/2015



IND 121165

**GRANT –  
BREAKTHROUGH THERAPY DESIGNATION**

Bristol-Myers Squibb  
Attention: Marianne Frost  
Director, Global Regulatory Sciences –US  
5 Research Parkway  
Wallingford, CT 06492

Dear Ms. Frost:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for daclatasvir in combination with Sovaldi (sofosbuvir).

We also refer to your February 11, 2014, request for Breakthrough Therapy designation. We have reviewed your request and have determined that daclatasvir (b) (4)

[REDACTED] in combination with sofosbuvir for the treatment of genotype-1, chronic hepatitis C virus infection meets the criteria for Breakthrough Therapy designation. Therefore, we are only granting your request for Breakthrough Therapy designation for genotype 1 chronic hepatitis C virus infection. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of daclatasvir in combination with sofosbuvir for the treatment of genotype-1, chronic hepatitis C virus infection to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the draft *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.<sup>1</sup>

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Attachment 1 lists potential topics for discussion at this initial breakthrough therapy meeting.

<sup>1</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

Please refer to the *Guidance for Industry: Formal Meetings between FDA or Sponsors and Applicants*<sup>2</sup> for procedures on requesting a meeting. If you feel that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

If the Breakthrough Therapy designation for daclatasvir in combination with sofosbuvir for treatment of genotype-1, chronic hepatitis C virus infection is rescinded, submission of portions of the NDA or sNDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact 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

**Attachments:**

Attachment 1: Breakthrough Designated Product, Initial Multidisciplinary Comprehensive Meeting between FDA/Sponsor, Potential Topics for Discussion

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<sup>2</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

**Attachment 1: Breakthrough Designated Product**  
**Initial Multidisciplinary Comprehensive Meeting between FDA/Sponsor**  
**Potential Topics for Discussion**

**General/Regulatory:**

- Planned target date for NDA/BLA submission, including plans for rolling review
- Other indications in development
- Expanded access plans, including intent to communicate these plans publicly
- Plans to seek accelerated approval
- Regulatory status with non-U.S. regulatory agencies
- Plans to defer or waive studies or trials, including those to be conducted as postmarketing commitments/postmarketing requirements (PMC/PMRs)
- Rationale for proposed flexibility in study and trial design
- Plans for submission of a proprietary name request
- If a drug/device combination product, device development information and plan
- In-vitro diagnostic development plan with the Center for Device and Radiologic Health (CDRH)
- Target product profile for proposed indication
- Gantt chart of development timeline, including information on all areas noted below
- Proposed communication plan for periodic development program updates to the FDA, including timelines and content

**Clinical Activity and Data Analysis:**

- Existing and planned clinical sites and accrual data
- Efficacy
  - Status of all clinical studies and topline summary results
  - Preliminary evidence of proof of concept
  - Planned or completed clinical trials intended to support efficacy, including:
    - Overall study design, the population to be studied, trial size, proposed indications, endpoints, power, plans for interim analyses, plans for resizing of trials, Type I error control, and expected initiation/completion dates
    - Validity of the outcomes and endpoints. If using drug development tools, such as a patient reported outcomes or biomarkers, plans for the development and validation of the instrument, if appropriate.
- Safety
  - Potential safety issues from nonclinical studies/early clinical trials
  - Liver, kidney, cardiac, immune suppression, carcinogenicity, genotoxicity, and immunogenicity safety profile
  - Clinical trials safety monitoring plan for safety signals identified in nonclinical studies and early clinical trials, and for post-market drug safety and surveillance (pharmacovigilance)
    - Proposed size of safety population
    - Plan or need for long-term safety studies

- Pre-approval
- Post-approval
- Plans to mitigate/minimize risk, proposed Risk Evaluation and Mitigation Strategy (REMS)
- Specific Populations
  - Dose, study design, efficacy endpoints, size and composition of population, additional safety trials, for populations such as:
    - Geriatrics
    - Pediatrics
    - Hepatically/Renally Impaired
  - Proposed pediatric development plan with outlines/synopses of additional studies.

#### **Clinical Pharmacology and Pharmacokinetics:**

- Justification for all dose selections, including number of doses, dose intervals, etc
- Clinical pharmacology, pharmacodynamics, and pharmacokinetics studies: completed, ongoing, planned, and requests for deferral, such as:
- Immunogenicity
- Dosing
  - Single ascending dose
  - Multiple ascending dose
  - Dose response study
- Food-effect
- Drug-drug interactions (DDI)
- Thorough QT/QTc
- Organ impairment
- Pharmacogenomics
- Plans for an in vivo bridging trial of the formulation studied in the clinical development program to the to-be-marketed formulation
- Plans for conducting population pharmacokinetics, exposure-response modeling/simulation analyses
- Plans to describe dose modifications in labeling based on DDI, age, organ impairment, etc.
- 

#### **Nonclinical Pharmacology, Pharmacokinetics, and Toxicology**

- Nonclinical studies completed, ongoing, and planned, including, the number and sex of animals per dose, doses, route of administration, toxicities, duration of study and study results. For studies planned timelines for initiation and submission of study reports. Examples of such studies include:

- Subacute and chronic toxicology
- Gene toxicology
- Reproductive toxicology
- Carcinogenicity studies
- Animal models of disease and PK parameters associated with efficacy

- Evidence of mechanism of action
- Safety pharmacology, where appropriate
- Disease specific animal models

### **Chemistry, Manufacturing, and Controls:**

- Drug product:
  - Dosage form
  - Formulation description
  - Administration instructions, delivery systems (e.g. vials, pre-filled syringes, etc.)  
proposed draft packaging, and disposal instructions
  - Critical quality attributes
  - Control and stability strategies
  - Proposed shelf life and required stability studies
- Drug substance:
  - Characterization
  - Critical quality attributes
  - Control and stability strategies
  - Proposed shelf life or retest period and required stability studies
- Proposed commercial processes:
  - Manufacturing process, in process controls, scale-up plans
  - Comparison of proposed commercial manufacturing processes to clinical manufacturing processes
  - Physico-chemical comparability of lots used in clinical studies and commercial lots or a plan to establish analytical comparability
  - Current manufacturing site(s) and proposed commercial site(s), if different, registration numbers, readiness, and manufacturing timelines
  - Current release and stability testing site(s) and proposed commercial testing site(s), if different
  - Anticipated market demand at launch
- Proposed validation approaches:
  - Drug substance and drug product manufacturing process
  - Microbial control and sterility assurance
  - Viral clearance
  - Analytical methods

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/s/  
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DEBRA B BIRNKRANT  
04/08/2014

**CDER Medical Policy Council Brief  
Breakthrough Therapy Designation  
Division of Antiviral Products  
March 28, 2014**

**Summary Box**

1. IND 121,165
2. Bristol-Myers Squibb
3. Daclatasvir (DCV) in combination with sofosbuvir (SOVALDI™)
4. Indication: Treatment of Chronic Hepatitis C
5. Daclatasvir in combination with other direct acting antivirals (DAAs) is intended to treat a serious or life-threatening disease or condition.
6. The preliminary clinical evidence indicates that the drug combination of DCV/SOF may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints (safety and efficacy).

**1. Brief description of the drug**

DCV is a direct acting antiviral (DAA) being developed for the treatment of chronic hepatitis C virus (HCV) infection. DCV is an HCV NS5A replication complex inhibitor (also referred to as an "NS5A inhibitor"). Currently, no NS5A replication complex inhibitors are approved. DCV has picomolar activity against several HCV genotypes and subtypes, including genotypes 1a, 1b, 2 and 3 for which this Breakthrough Therapy Designation request applies. This Breakthrough request is specific to the combination regimen of DCV and sofosbuvir (SOF, Sovaldi™, marketed by Gilead) a uridine nucleotide analog inhibitor of HCV NS5B RNA-dependent RNA polymerase. SOF has nanomolar antiviral activity against HCV genotypes 1 through 6. SOF is approved for treatment of chronic hepatitis C infection as a component of a combination antiviral treatment regimen (with pegylated interferon and ribavirin, or with ribavirin). SOF efficacy was established in subjects with HCV genotype-1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection.

BMS is applying for Breakthrough Therapy Designation for DCV when used in combination with SOF based on the phase 2 data from trial AI444040 (further detailed in section 6) for treatment of genotype 1 (b) (4) HCV infection. DAVP agrees that the combination of DCV + SOF meets the standards for Breakthrough Therapy Designation for genotype 1. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

## 2. Brief description of the disease and intended population

Approximately 3.2 million people in the United States and 170 million worldwide have chronic HCV infection, which can lead to cirrhosis and hepatocellular carcinoma. Chronic hepatitis C is currently the most common reason for liver transplantation in the United States. A recent CDC analysis of death certificate data found that HCV-attributable deaths increased significantly between 1999 and 2007. CDC estimates that there were 15,106 deaths caused by HCV in 2007. HCV now surpasses HIV as a cause of death in the United States. Cirrhosis is the 12<sup>th</sup> leading cause of death in the US, but 4<sup>th</sup> among those ages 45 to 54 years old.<sup>1</sup> The Division considers chronic HCV infection a serious and life-threatening condition.

At least seven different HCV genotypes have been identified, numbered 1 to 7, with further breakdown into subtypes (e.g., genotype 1 subtypes 1a and 1b). In the United States, genotype 1 is the most common (70 to 80 percent; of which 75% is 1a, 25% is 1b), followed by genotypes 2 and 3. The remaining genotypes occur uncommonly in the United States, but may predominate in other parts of the world.

The primary objective of anti-HCV treatment is the achievement of a sustained virologic response (SVR), typically defined as unquantifiable HCV RNA 12 weeks following the cessation of treatment (i.e., "SVR12"). SVR12 is generally considered a "virologic cure". Because of the numerous and potentially serious and life-threatening toxicities associated with interferon including neuropsychiatric, autoimmune, bone marrow suppression, ischemic and infectious disorders, plus the teratogenicity and anemia associated with RBV, the push remains to develop interferon - and RBV-free oral direct-acting antiviral (DAA) treatment regimens that are effective with high SVR rates (>90%) and acceptable safety profiles. Collaborative HCV Treatment Guidelines developed by AASLD and IDSA were recently published online (<http://www.hcvguidelines.org>) and are planned to remain in online format only due to the rapid evolution of HCV treatment and management to allow for real-time updates.

The current standard-of-care treatment for HCV genotype 1 infection in patients eligible for interferon is a combination of pegylated interferon alpha (PegIFN), RBV, and the recently approved NS5B polymerase inhibitor, sofosbuvir (SOF, Sovaldi™) administered for 12 weeks. Sofosbuvir + PegIFN/RBV has an overall SVR rate of 90%, but a lower SVR rate in patients with HCV genotype subtype 1b (82%) compared to genotype subtype 1a (92%), and a lower SVR rate in subjects with cirrhosis (80%). The current treatment guidelines no longer recommend boceprevir or telaprevir (both are NS3/4A protease inhibitors) + PegIFN/RBV for treatment of genotype 1 HCV. Additionally, the recently approved protease inhibitor, simeprevir, in combination with PegIFN/RBV is recommended only as an alternate therapy for genotype 1 HCV.

Importantly, a significant proportion of HCV-infected patients are believed to be intolerant to or ineligible (based on comorbidities or age) to use interferon-based therapies. Sofosbuvir, in combination

with ribavirin (without interferon) for 24 weeks duration was approved for treatment of genotype 1 patients who are ineligible for interferon-based therapy. The SVR12 response rates for this regimen in subjects coinfecting with HIV is 76%. The treatment guidelines recommend the DAA oral combination of sofosbuvir + simeprevir with or without ribavirin for 12 weeks in genotype 1 patients. This recommendation is based on published data from the phase 2 COSMOS study where SVR rates in genotype 1 subjects treated with sofosbuvir + simeprevir with or without RBV for 12 weeks were between 93-100%. Of note, the treatment combination of sofosbuvir + simeprevir with or without RBV is not included in the dosage and administration or clinical trials section of either drug label.

Because of the limitations of interferon-based and ribavirin-containing regimens, there has been great interest in the development of all oral, interferon-free, ribavirin-free regimens consisting of combinations of multiple classes of HCV DAAs. After several years of development and optimization, several interferon-free, combination HCV DAA regimens being developed by various pharmaceutical sponsors have now completed Phase 3 clinical trials, with NDAs either submitted or in preparation. It is widely anticipated that at least some of these regimens will have substantially improved efficacy (or, in some populations have similar efficacy in the case of SOF/PegIFN/RBV) over the available therapy, particularly for HCV genotype 1, with short treatment durations. Most importantly, because these regimens do not require the use of interferon, they are expected to have a substantially improved safety and tolerability profiles compared to the currently recommended regimens, and will be available to patients who cannot use interferon-based therapies.

**3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area**

The Sponsor is relying on sustained virologic response or SVR12 (described in #2 above) as the efficacy endpoint to support their request for Breakthrough Therapy Designation and this endpoint is also used in the Sponsor’s clinical trials. SVR12 is accepted by the Division as a clinically significant endpoint for chronic HCV treatment trials. This is a surrogate endpoint known to predict clinical benefit, as achievement of SVR has been associated with reduced all-cause mortality, and liver-related morbidity and mortality.

**4. Brief description of available therapies (if any)**

The following table provides a brief summary of available therapies specifically for treatment of genotype 1, 2, and 3 HCV. Please note that all regimens contain pegylated interferon and ribavirin (PegIFN/RBV), except for SOF/RBV indicated for HCV genotype 1 infected subjects ineligible for a PegIFN/RBV containing regimen, and for HCV genotypes 2 and 3.

Treatment Regimen	Duration	Approved Indication	SVR rates
Sofosbuvir/PegIFN/RBV	12 weeks	GT1	GT1 Overall: 89%* 1a: 92% 1b: 82%

Sofosbuvir/RBV	12 weeks	GT2	Tx-naïve: 93-97% Tx-experienced: 82- 90%
Sofosbuvir/RBV	24 weeks	GT1 ineligible for PR	GT1 Overall: 66% - 76%
Sofosbuvir/RBV	24 weeks	GT3	Tx-naïve: 93% Tx-experienced: 77%
Simeprevir/PegIFN/RBV	24-48 weeks	GT1	Tx-naïve: 80% Tx- experienced†:53%- 79%
Telaprevir/PegIFN/RBV	24-48 weeks (Response Guided Therapy)	GT1	Tx-naïve: 74-79% Tx- experienced†:32%- 86%
Boceprevir/PegIFN/RBV	28-48 weeks (Response Guided Therapy)	GT1	Tx-naïve: 63% Tx-experienced†: 38%-59%

GT=genotype

\*Treatment-naïve subjects. FDA analysis based on baseline predictive factors of PR based regimens predicts SVR rates of 71-78% in treatment-experienced GT1 subjects.

† Treatment-experienced SVR range includes data from prior null responders (historically more difficult to treat and with the lower end of SVR rates), prior partial responders, and prior relapsers.

**5. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation**

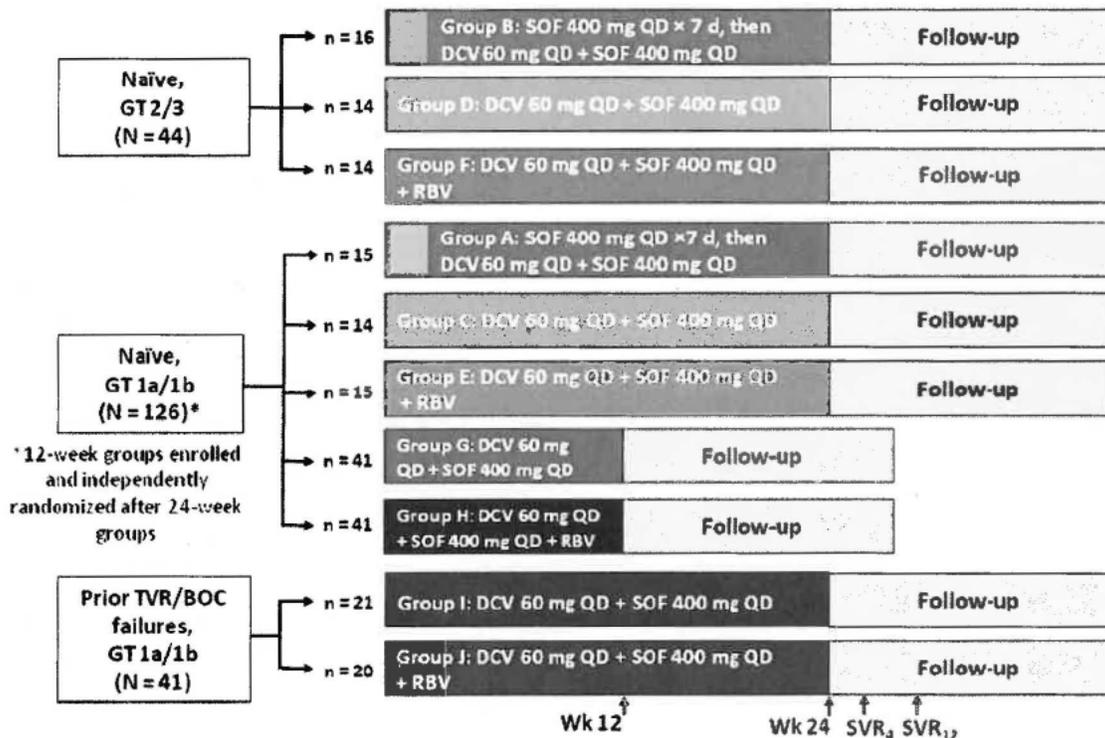
The following table provides a summary of all other HCV drug regimens that have received breakthrough therapy designations.

Sponsor	DAA Combination	BT Designation	Date
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(b) (4)			

## 6. Description of preliminary clinical evidence

Data from a phase 2 trial A1444040 is provided to support the request for Breakthrough Designation. In brief, A1444040 evaluated DCV + SOF ± RBV in treatment-naïve subjects with HCV genotype 1, 2 or 3 infection, and in HCV genotype 1 subjects who previously failed a telaprevir (TVR) or boceprevir (BOC) based regimen (TVR and BOC are NS3/4A protease inhibitors). Of particular interest, the DCV + SOF ± RBV regimen is a potentially valuable treatment option for patients who failed prior TVR- or BOC-based treatment because resistance to NS3/4A protease inhibitors would not confer cross-resistance to DCV or SOF. Subjects with baseline cirrhosis were excluded; however 15.2% (32/211) of subjects in this trial had F3-F4 (n=2) or F4 (n=30) liver fibrosis measured by baseline Fibrotest analysis. The trial was comprised of 10 treatment groups which differed by HCV genotype, treatment duration (12 or 24 weeks), the inclusion or not of RBV, or if treatment-naïve or prior TVR or BOC + pegIFN/RBV treatment-failure (see Figure 1).

Figure 1.: A1444040 Study Design



Abbreviations: BOC, boceprevir; d, days; DCV, daclatasvir; GT, genotype; QD, once daily; RBV, ribavirin; SOF, sofosbuvir; SVR<sub>12</sub>, sustained virologic response for 12 weeks after the last dose of study drug; SVR<sub>4</sub>, sustained virologic response for 4 weeks after the last dose of study drug; TVR, telaprevir; Wk, week.

Overall, the efficacy results from this trial showed that the combination of DCV + SOF ± RBV in treatment-naïve subjects with HCV genotype 1, 2 or 3 were high (>90% SVR12). Only 1 true virologic failure was observed (genotype 3 subject) among the 211 subjects treated in this trial. The SVR results achieved in treatment-naïve subjects were independent of use of RBV, IL-28B host genotype, HCV genotype or subtype and were similar for both the 12 and 24 week treatment durations (12W evaluated in genotype 1 only, groups G and H). Importantly, the DCV + SOF ± RBV regimen was effective in genotype 1 subjects who previously failed treatment with TVR or BOC, who currently have no established treatment options. The following table provides the baseline characteristics and pooled efficacy results from the treatment groups.

Efficacy Results from A1444040. (Note: Data are pooled for regimens dosed with or without RBV. All treatment durations were 24 weeks except for 81 of the 126 treatment-naïve, GT1 subjects who received 12 weeks).

Total (N=211)			
<b>Baseline characteristics associated with lower efficacy reported with other regimens (n, %)</b>			
Age, ≥ 65 years	12 (5.7)		
Race, Black/African American	26 (12.3)		
HCV RNA, ≥ 800,000 IU/mL	169 (80.1)		
METAVIR score >F3 (Fibrotest)	32 (15.2)		
IL-28B non-CC	150 (71.1)		
<b>HCV Genotype</b>			
1a	132 (62.6)		
1b	35 (16.6)		
2	26 (12.3)		
3	18 (8.5)		
<b>Virologic Endpoints % (Responder /N) Modified ITT analysis</b>			
	<b>Treatment-naïve Subjects with GT-1</b>	<b>Treatment-naïve Subjects with GT-2/-3</b>	<b>TVR/BOC Failures with GT-1</b>
	<b>DCV/SOF ± RBV N = 126</b>	<b>DCV/SOF ± RBV N = 44 all N = 26 GT-2 N = 18 GT-3</b>	<b>DCV/SOF ± RBV N = 41</b>
SVR12	124 <sup>a</sup> (98.4)	40 (90.9) all 24 (92.3) GT-2 16 (88.9) GT-3	40 (97.6)

<sup>a</sup> The one GT-1a subject who relapsed is a likely re-infection, since the viral sequences at relapse were different from those at baseline and absence of DCV/SOF resistance detected in the virus at relapse.

The overall efficacy results for the genotype 1 subjects are impressive for this treatment regimen, both for treatment-naïve and treatment-experienced, in particular, for prior TVR or BOC failures. Although a few interferon-free treatment regimens for HCV genotype 1 patients are available and described in current HCV treatment guidelines, only a 24-week SOF + RBV regimen is specifically described in FDA-approved prescribing information. The evidence for SOF + RBV efficacy in HCV genotype 1 subjects is

from treatment-naïve subjects coinfecting with HIV-1 who were treated for 24 weeks and had an SVR rate of 87/114 (76%), and a relapse rate of 22%. Efficacy data from AI444040 indicate that DCV + SOF ± RBV has significantly improved efficacy over SOF + RBV in HCV genotype 1 subjects, and likely only requires 12 weeks of treatment duration and no ribavirin for certain patient populations. The DCV + SOF ± RBV regimen demonstrated SVR rates of 98% in the treatment-experienced, protease inhibitor (TVR and BOC) failure population, a population not included in current labeling for any approved HCV agent.

In the treatment-naïve genotype 2 and 3 subjects, the overall numbers treated with DCV + SOF are small and all subjects were treated with 24 weeks duration. The SVR rates for the DCV + SOF 24 week regimen (approximately 90%) was similar to the approved SOF + RBV regimen for 12 weeks in genotype 2 subjects, and SOF + RBV for 24 weeks in genotype 3 subjects. Therefore, substantial improvement over existing therapies is not evident for the DCV + SOF regimen compared to the SOF + RBV regimen in genotype 2 and 3 subjects. Lastly, data in a cell culture model show DCV has ~10- to >1,000-fold reduced activity against HCV genotype 2 and 3 compared to HCV genotype 1a and 1b.

Overall, the DCV + SOF ± RBV combination was well tolerated. There were no deaths and 7% of subjects reported SAEs. Two subjects had an AE leading to discontinuation and both subjects achieved SVR. The most common AEs were fatigue, headache and nausea. Grade 1 and 2 hemoglobin abnormalities were numerically higher in groups that received RBV compared to those without RBV. Five patients had their RBV dose reduced due to anemia. As of November 2013, >5,600 subjects have received a DCV-containing regimen. Overall, the all-oral DCV containing regimens have improved safety and tolerability compared to the approved regimens for patients with genotype 1 HCV (all contain PegIFN/RBV or RBV).

## **7. Division's recommendation and rationale**

In conclusion, the Breakthrough Designation for DCV in combination with SOF, an all oral, interferon-free treatment regimen for genotype 1 treatment-naïve and treatment-experienced subjects is supported by the following:

1. DCV has a novel mechanism of action that represents a previously untargeted pathway. Currently, there are no other approved NS5A replication complex inhibitors.
2. The overall SVR rate of >97% was achieved in genotype 1 HCV patients who were treatment-naïve and who had failed prior treatment with a TVR or BOC + PegIFN/RBV regimen
3. The all-oral combination provides a simple once-daily treatment regimen with low pill burden
4. The safety profile of DCV/SOF is promising. It avoids the serious toxicities of IFN such as significant cytopenias, flu-like syndromes, mood disorders and depression. And, for some populations the regimen may also be RBV-free, avoiding anemia and the potential for teratogenicity (avoidance of pregnancy for both males and females during treatment and for 6 months post-administration).

Based on the data available, DAVP believes that DCV in combination with SOF meets the definition of Breakthrough Therapy for the treatment of chronic hepatitis C in genotype 1 treatment-naïve and prior

treatment-experienced patients including those who failed a protease inhibitor based regimen as outlined in Section 903 of the Food and Drug Administration Safety and Innovation Act, and recommends DCV in combination with SOF be given the specified Breakthrough Therapy Designation.

[REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]  
[REDACTED]

**8. Division's next steps and sponsor's plan for future development**

The Division plans to work with the Sponsor to fully review and provide guidance for their planned development program for the combination of DCV and SOF.

**9. References**

1. Deaths. Preliminary Data for 2007. National Vital Statistics Report 2009: 58.

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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.**  
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/s/  
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03/19/2014

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