CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204671Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 204671 SUPPL # HFD # 530

Trade Name SOVALDI

Generic Name sofosbuvir

Applicant Name Gilead Sciences, Inc.

Approval Date, If Known December 6, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☒ NO ☐

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

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5 Years

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

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

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 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"):

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 # YES ☐ ! NO ☐
! Explain:

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

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

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

YES ☐ NO ☐

If yes, explain:

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Name of person completing form: Linda C. Onaga, MPH
Title: Regulatory Project Manager
Date: November 12, 2013

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

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

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

/s/

SOHAIL MOSADDEGH
12/06/2013

DEBRA B BIRNKRANT
12/06/2013

Debarment Certification

Gilead Sciences, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application (NDA 204-671, sofosbuvir).

[See appended electronic signature]

Andrew Cheng, MD, PhD
SVP, HIV Therapeutics & Development Operations
Gilead Sciences, Inc.

133-Debarment Certification

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (yyyy-MM-dd hh:mm)
Andrew Cheng	R&D eSigned	2013-02-20 19:17

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 204671 BLA #	NDA Supplement # 0 BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: sofosbuvir Established/Proper Name: Sovaldi Dosage Form: oral tablet		Applicant: Gilead Sciences Inc Agent for Applicant (if applicable):
RPM: Sohail Mosaddegh		Division: Division of Antiviral Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(For additional information regarding 505(b)(2)s, please refer to http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/RegulatoryAffairsTeam/ucm027499.htm)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

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.

❖ Actions	
• Proposed action • User Fee Goal Date is 12/08/13	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (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., nrew listed drug, patent certification revised).

❖ 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 http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): Type 1

☒ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☒ Breakthrough Therapy designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ 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

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

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Information Advisory

[3] 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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☐ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[4]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 12/06/2013
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	12/06/2013
• Original applicant-proposed labeling	04/08/2013
• Example of class labeling, if applicable	N/A

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	12/06/2013
• Original applicant-proposed labeling	04/08/2013
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	12/06/2013
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Acceptable letter: 11/07/2013 Name Review: 11/06/2013 Verified
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 06/07/2013 (PLR format) ☒ DMEPA 09/24/2013 ☒ DMPP/PLT (DRISK) 11/26/2013 ☒ OPDP (DDMAC) 11/26/2013 ☒ SEALD 11/29/2013 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	RPM filing review 06/07/2013
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included 12/06/2013
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 09/11/2013 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	4/15/2013, 4/25/2013, 5/9/2013, 6/5/2013, 6/7/2013, 6/11/2013, 6/14/2013, 6/21/2013, 7/9/2013, , 7/12/2013, 7/15/2013, 7/24/2013, 8/5/2013, 8/7/2013, 8/8/2013, 8/20/2013, 8/20/2013, 8/20/2013, 8/21/2013, 8/27/2013, 8/29/2013, 9/3/2013, 9/4/2013, 9/6/2013, 9/6/2013, 9/12/2013, 9/27/2013, 10/3/2013, 10/4/2013, 10/8/2013, 10/9/2013, 10/11/2013, 10/16/2013, 10/17/2013, 10/18/2013, 10/21/2013, 10/21/2013, 10/22/2013, 10/29/2013, 10/29/2013, 11/7/2013, 11/8/2013, 11/15/2013, 11/18/2013, 11/19/2013, 11/19/2013, 11/20/2013, 11/21/2013 ,11/25/2013, 11/25/2013, 11/25/2013, 11/26/2013, 12/2/2013, 12/4/2013
❖ Internal memoranda, telecons, etc.	09/20/2013. 09/22/2013. 09/26/2013, 10/08/2013
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 03/14/2013
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 10/17/2012 (type C), 10/11/2012 (CMC EOP2), 06/05/2012, 08/11/2011
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	Mid Cycle meeting: 07/17/2013 Late Cycle meeting 10/10/2013
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	10/25/2013
• 48-hour alert or minutes, if available *(do not include transcript)*	48 hour minutes attached

Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 12/06/2013
Division Director Summary Review *(indicate date for each review)*	☐ None 11/27/2013
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 12/11/2013, 11/08/2013
PMR/PMC Development Templates *(indicate total number)*	☐ None 16
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	N/A
• Clinical review(s) *(indicate date for each review)*	11/20/2013, 09/06/2013 Filing review 05/08/2013
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Clinical Review (pg 19) 09/06/2013
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested Review: 08/21/2013 Letters: 10/29/2013, 10/21/2013, 10/21/2013, 09/06/2013, 08/20/2013
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None 11/20/2013, 11/19/2013, 11/19/2013, 09/06/2013, 09/06/2013 Filing review: 05/08/2013
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 11/21/2013, 11/20/2013, 09/06/2013 Filing review: 05/10/2013

[6] Filing reviews should be filed with the discipline reviews.

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11/22/2013, 09/05/2013 Filing Review: 05/10/2013
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 09/06/2013
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 11/20/2013, 11/20/2013, 09/06/2013 Filing review: 05/09/2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 12/02/2013
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 11/19/2013, 09/05/2013, Filing review: 05/09/2013 Biopharmaceutics: 11/05/2013, 08/30/2013 Filing review: 05/08/2013
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 07/11/2013 Filing review: 06/03/2013
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	05/09/2013 (see CMC labeling review, page 11 of 23)
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 11/22/2013 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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/s/

SOHAIL MOSADDEGH
12/11/2013

From: Mosaddegh, Sohail
To: shalini.gidwani@gilead.com
Subject: 204671 - container labeling
Date: Monday, November 25, 2013 12:06:00 PM

Please relocate the net quantity (i.e. 28 tablets) away from the strength statement (i.e. 400 mg) on the container labels to avoid confusion between the two numbers (next to NDC number for example).
thanks

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

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/s/

SOHAIL MOSADDEGH
11/25/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **November 21, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Subject: **NDA 204671 PMR/PMCs**

Please reference your new drug application for sofosbuvir. The following comments are being conveyed on behalf of the review team for your application.

Please find attached the Division' proposed list of post marketing requirements and commitments for NDA 204671.

Please review, comment, and provide your response no later than 4:00PM EST (1:00 PM PST) on November 22, 2013.

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

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

Recommended Postmarketing Requirements include:

1. Evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of sofosbuvir as a component of an antiviral treatment regimen in pediatric subjects 3 through 17 years of age with chronic hepatitis C. (b) (4)

Final Protocol Submission:	MM/YY
Study Completion:	MM/YY
Final Report Submission:	(b) (4)

2. Collect and analyze long-term safety data for subjects enrolled in the pediatric sofosbuvir PK, safety and efficacy trial(s). Data collected should include at least 3 years of follow-up in order to characterize the (b) (4) long-term safety of sofosbuvir in pediatric subjects, including growth assessment, sexual maturation and characterization of sofosbuvir resistance-associated substitutions in viral isolates from subjects failing therapy.

Final Protocol Submission:	MM/YY
Study Completion:	MM/YY
Final Report Submission:	MM/YY

3. Submit the final study report and datasets including next generation sequencing for the ongoing trial P7977-2025 in order to identify treatment-emergent substitutions and to obtain additional safety and efficacy data in this population with hepatocellular carcinoma meeting Milan criteria awaiting liver transplantation.

Final Protocol Submission:	MM/YY
Study Completion:	MM/YY
Final Report Submission:	MM/YY

4. Submit the final study report and datasets for the ongoing trial GS-US-334-0154, entitled, "A Phase 2b, Open-Label Study of 200 mg or 400 mg Sofosbuvir + RBV for 24 Weeks in Genotype 1 or 3 HCV-Infected Subjects with Renal Insufficiency", in order to provide dosing recommendations for chronic hepatitis C patients with severely impaired renal function.

Final Protocol Submission:	MM/YY
Study Completion:	MM/YY
Final Report Submission:	MM/YY

5. Submit the final study report and datasets for the ongoing trial GS-US-334-0154, entitled, "A Phase 2b, Open-Label Study of 200 mg or 400 mg Sofosbuvir + RBV for 24 Weeks in Genotype 1 or 3 HCV-Infected Subjects with Renal Insufficiency", in order to provide dosing recommendations for chronic hepatitis C patients with ESRD.

Final Protocol Submission:	MM/YY
Study Completion:	MM/YY
Final Report Submission:	MM/YY

6. Submit the final study reports for the 2 year carcinogenicity studies.

Final Protocol Submission:	MM/YY

Study Completion: MM/YY
Final Report Submission: MM/YY

7. Determine the phenotypic susceptibility of sofosbuvir against:

HCV replicons	Substitution
Genotype 1a	L159F L159F + L320F LI59F + C316N C316N, H, and F L320F, S282R, and L320F + S282R D61G D61G + N62H, D and N
Genotype 1b	L159F L159F+L320F L159F+C316N C316N, H, and F E440G
Genotype 2b	L159F L159F+L320F L159F+C316N
Genotype 3a	L159F L159F+L320F L159F+C316N K211R V321A P540L T542A

Final Protocol Submission: MM/YY
Study Completion: MM/YY
Final Report Submission: MM/YY

Postmarketing Commitments

8. Submit the final study report and datasets for the ongoing trial GS-US-334-0133 (VALENCE), entitled, "A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of GS-7977 + Ribavirin for 12 Weeks in Treatment Naïve and Treatment Experienced Subjects with Chronic Genotype 2 or 3 HCV Infection".

Final Protocol Submission: MM/YY
Study Completion: MM/YY
Final Report Submission: MM/YY

9. Submit the final study report and datasets for the ongoing trial GS-US-334-0123 (PHOTON-1), entitled, "A Phase 3, Open-label Study to Investigate the Efficacy and Safety of GS-7977 plus Ribavirin in Chronic Genotype 1, 2 and 3 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co-infected Subjects".

Final Protocol Submission: MM/YY
Study Completion: MM/YY

Final Report Submission: MM/YY

10. Submit the final study report and datasets for the ongoing trial GS-US-334-0109, entitled, "An Open-Label Study of GS-7977 + Ribavirin with or without Peginterferon Alfa-2a in Subjects with Chronic HCV Infection who Participated in Prior Gilead HCV Studies".

Final Protocol Submission: MM/YY
Study Completion: MM/YY
Final Report Submission: MM/YY

11. Submit the final study report and datasets for the ongoing trial GS-US-334-0153, entitled, "A Phase 3B Randomized, Open-Label, Multi-Center Trial Assessing Sofosbuvir + Ribavirin for 16 or 24 Weeks and Sofosbuvir + Pegylated Interferon + Ribavirin for 12 Weeks in Subjects with Genotype 2 or 3 Chronic HCV Infection".

Final Protocol Submission: MM/YY
Study Completion: MM/YY
Final Report Submission: MM/YY

12. Submit the final study report and datasets for the ongoing trial GS-US-334-0126, entitled, "A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of GS-7977 and Ribavirin for 24 weeks in Subjects with Recurrent Chronic HCV Post Liver Transplant".

Final Protocol Submission: MM/YY
Study Completion: MM/YY
Final Report Submission: MM/YY

13. Submit the final study report and datasets for the ongoing trial GS-US-334-0125, entitled, "A Phase 2, Multicenter, Open-Label, Randomized Study to Investigate the Safety and Efficacy of GS-7977 and Ribavirin Administered for 48 weeks in Patients Infected with Chronic HCV with Cirrhosis and Portal Hypertension with or without Liver Decompensation".

Final Protocol Submission: MM/YY
Study Completion: MM/YY
Final Report Submission: MM/YY

14. Submit an interim study report from the ongoing trial GS-US-248-0122, entitled, "A Long Term Follow-up Registry for Subjects Who Achieve a Sustained Virologic Response to Treatment in Gilead-Sponsored Trials in Subjects with Chronic Hepatitis C Infection", with the three year follow-up data from: P7977-1231 (FISSION), GS-US-334-0107 (POSITRON), GS-US-334-0108 (FUSION), GS-US-334-0110 (NEUTRINO), GS-US-334-0133 (VALENCE), GS-US-334-0123 (PHOTON-1).

Final Protocol Submission: MM/YY
Study Completion: MM/YY
Final Report Submission: MM/YY

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/s/

LINDA C ONAGA
11/21/2013

MEMORANDUM of TELECONFERENCE

MEETING DATE: November 20, 2013
TIME: 12:30 PM, EST
LOCATION: WO 22, Room 3201
APPLICATION: NDA 204671
DRUG NAME: Sovaldi (sofosbuvir)
SPONSOR: Gilead
TYPE OF MEETING: Proprietary Name

FDA ATTENDEES:

Morgan Walker, Acting Team Leader, DMEPA
Todd Bridges, Acting Deputy Director, DMEPA
Danyal Chaudhry, Safety Regulatory Project Manager

SPONSOR ATTENDEES:

Dr. David Pizzuti, VP, Regulatory Affairs
Dr. John McHuthison, Senior VP, Liver Disease Therapeutics
Kevin Young, Exec VP, Commercial
Joe Steele, VP, Commercial Strategy
Gretchen Stroud, Senior Director, Trademarks
Shalini Gidwani , Associate Director, Regulatory affairs

MEETING OBJECTIVES:

FDA requested the teleconference to inform Gilead of acceptability of their primary proprietary name, "Sovaldi".

DISCUSSION:

FDA informed Gilead that their name, "Sovaldi" has been found acceptable. FDA advised Gilead to work with the Division of Anti-Viral Prodcucts to update the label and labeling with their proprietary name.

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/s/

AZEEM D CHAUDHRY
11/20/2013

*****For Internal Use Only*****

Denied Proprietary Name: Sovaldi

IND 106739; NDA 204671

Sponsor: Gilead Sciences, Inc.

Sponsor Teleconference August 7, 2013, 1:00 PM Location: WO. 22, Rm 5201

Purpose of Sponsor Requested Teleconference:

Gilead requesting teleconference after proprietary name "Sovaldi" denied under IND 106739 (NME Program NDA 204671 in-house for review) to discuss next steps for name submission

Discussion & Agreements:

Gilead inquired about the process and methodology that the FDA uses to evaluate proprietary name requests and FDA communicated that information regarding processes used to evaluate name requests is available at the FDA homepage.

FDA stated that Gilead could submit an alternate proprietary name for review to their application along with other names for a preliminary evaluation, however if additional names are submitted for review, the originally proposed name would no longer be reviewed for consideration. FDA further clarified that an alternate name submitted can be withdrawn at any time and the original name can be re-submitted for review. FDA stated that it evaluates and communicates with sponsors regarding a proposed proprietary name that after submission is being evaluated.

Gilead made reference to a communication from 7/25/13 regarding their proposed proprietary name. FDA will respond to the communication as appropriate and clarified to Gilead that it will only communicate review findings that are specific to their application.

Meeting Participants:

FDA:

Morgan Walker, PharmD, MBA, Reviewer, Division of Medication Error Prevention and Analysis

Jamie Wilkins Parker, PharmD, Team Leader, Division of Medication Error Prevention and Analysis

Danyal Chaudhry: Safety Regulatory Health Project Manager, Office of Surveillance & Epidemiology

Gilead Sciences, Inc:
Dr. David Pizzuti, Vice-President, Regulatory Affairs
Joe Steele, Vice-President, Commercial Strategy
Dr. Bittoo Kanwar, Clinical Team
Patrick Lamy, Senior Director, Commercial Strategy
Shalini Gidwani, Associate Director, Regulatory Affairs

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/s/

AZEEM D CHAUDHRY
11/20/2013

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Denied Proprietary Name: Sovaldi

NDA 204671

Sponsor: Gilead Sciences, Inc.

Sponsor Teleconference August 27, 2013, 11:30 AM Location: WO. 22, Rm 3266

Purpose of FDA Requested Teleconference:

To discuss Gilead's communications from July 25 and August 15, 2013 regarding their proprietary name request.

Discussion & Agreements:

FDA stated that Gilead's communications appeared to be a request for re-consideration of Gilead's originally proposed proprietary name and that Gilead should formally submit this re-consideration request to their NDA indicating their choice of the preferred name. Gilead agreed to formally submit the re-consideration request by Friday, August, 30, 2013.

Meeting Participants:

FDA:

Morgan Walker, PharmD, MBA, Reviewer, Division of Medication Error Prevention and Analysis

Jamie Wilkins Parker, PharmD, Team Leader, Division of Medication Error Prevention and Analysis

Danyal Chaudhry: Safety Regulatory Health Project Manager, Office of Surveillance & Epidemiology

Gilead Sciences, Inc:

Dr. David Pizzuti, VP, Regulatory Affairs
Dr. Tobias Peschel, VP, Drug Safety and Public Health
Dr. Mani Subramanian, VP, Liver Disease Therapeutic affairs
Joe Steele, VP, Commercial Strategy
Shalini Gidwani, Associate Director, Regulatory affairs

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/s/

AZEEM D CHAUDHRY
11/20/2013

MEMORANDUM OF TELECONFERENCE

Teleconference Date: October 29, 2013

Application Number: NDA 204671
Product Name: sofosbuvir
Sponsor/Applicant Name: Gilead Sciences, Inc.

Subject: Manufacturing Testing Site Gilead Foster City

FDA Participants :

1. Edward Cox, MD, MPH, OAP
2. Debra Birnkrant, MD, DAVP
3. Tara Gooen, Branch Chief, OC/OMPQ/DGMPA
4. David Doleski, BS, Director, Division of Good Manufacturing Practice Assessment (DGMPA)
5. Mahesh Ramanadham, PharmD., M.B.A., OC/OMPQ
6. Krishnakali Ghosh, MSc., PhD, OC/ OMPQ
7. Rapti Madurawe, PhD ONDQA
8. Stephen Miller, PhD, ONDQA
9. Sohail Mosaddegh, PharmD, Regulatory Project Manager, DAVP
10. George Lunn, PhD, ONDQA
11. Sarah Connelly, MD, DAVP
12. Poonam Mishra, MD, DAVP
13. Linda Onaga, MPH, Regulatory Project Manager, DAVP
14. Karen Winestock, DAVP
15. Stephanie Yao, FDA Press Office

Sponsor/Applicant Participants

1. Norbert Bischofberger, Ph.D., Executive Vice President, Research and Development
2. Taiyin Yang, Ph.D., Senior Vice President, Pharmaceutical Development and Manufacturing
3. John McHutchison, MD, Senior Vice President, Liver Disease Therapeutics
4. Reza Oliyai, PhD, Vice President, Pharmaceutical Development and Manufacturing
5. David Pizzuti, MD, Vice President, Regulatory Affairs
6. Gary Visor, Vice President, Analytical Operations
7. Tammis Matzinger, Senior Director, QA
8. Shalini Gidwani, M.Sc, RAC, Associate Director, Regulatory Affairs

1.0 BACKGROUND

Foster City – Testing Site

The Agency and Gilead Sciences discussed inspectional issues identified at Foster City facility site. The Agency sent Gilead two options to support an approval recommendation from the Office of Manufacturing and Product Quality (OMPQ). A conference call has been scheduled with Gilead for October 29, 2013 to discuss the options listed below. OMPQ would prefer Option 1, but will like to provide an opportunity to Gilead Sciences to present any alternate proposals that would also be acceptable to FDA. The following two options will be proposed:

Option 1 (Facility Withdrawal as Quality Control Testing Lab) Performed prior to action date:

A. Remove Gilead Foster City as a testing site for Drug Substance and Drug Product release and stability testing operations from the application via an amendment to NDA 204671. Transfer stability studies along with API and final product testing responsibilities to a CGMP compliant testing lab already listed in the application (b) (4) Gilead may continue to perform the final product release for Sofosbuvir. Also, submit a list of manufactured batches intended for distribution with lot numbers, sizes of the lots, and projected ability to meet market demand with those lots to FDA by November 15, 2013.

Post-Marketing:

Using an independent, expert third party, evaluate the commercial batches tested for release and stability at Gilead Foster City as described in Option 2. Submit the evaluation report to FDA by December 8, 2013. This report must be received at least 1 day prior to distribution. A copy of the report must be maintained at Gilead Foster City for future on-site inspections.

Option 2: Post-Marketing:

1. Gilead will retain an independent, expert party that will, prior to the distribution of each batch, review all records for all testing operations at Gilead Foster City. The expert will review all raw data and equipment audit trails, logbooks and usage logs, out of specification investigations, invalidated test results and retest plans, equipment failures, maintenance and calibrations records, QC testing data (raw data, chromatograms, print outs and calculations) and:

    A. Certify that, based upon the expert's review of all data derived from all manufacturing and testing sites, no deviations occurred during the testing of the batch that, in the expert's professional opinion, would, during its labeled expiration period, adversely affect the safety, identity, strength, quality, or purity of the batch or cause the batch to fail to meet any and all applicable approved specifications established in its application; **or**

    B. If the expert is unable to make the certification described in subparagraph A above, deliver a written report to Gilead, explaining the expert's reasons for not certifying the batch, which report shall include:

- List and description of unexplained discrepancies, adequacy of investigations and a scientific analyses of laboratory tests failures with appropriate root cause determinations and timely corrective actions
- Justification for the specific basis for invalidating test results, retesting products or testing of new samples when indicated
- Assessment on the effect of unexplained discrepancies on the safety, identity, strength, quality, or purity of the batch the QA/QC has failed to address during review of batch records/test results
- Determination of batch disposition

Additionally, review and certify all testing data associated with the ongoing stability studies for Sofosbuvir and ensure that the stability studies are conducted in a timely manner under CGMP regulations. Review the adequacy of the corrective actions associated with the stability program. Gilead shall not release batches for market distribution until one day after this independent, expert certification is received. Gilead may ship product for further processing or holding under quarantine.

Gilead shall provide summary results of the expert's reports on a quarterly basis to FDA/CDER/OC/OMPQ following approval. Copies of reports should be maintained at the Foster City facility and be made immediately available upon request. Activities for this option will continue until receipt of the Field Management Directive-145 (Establishment Inspection Reports) for the FDA inspections ending on 04/26/2013 and 10/09/2013.

2.0 DISCUSSION

Gilead received the Agency's comments and agreed to option number 1. Gilead will remove Foster City as a testing site in the application. However, Gilead did not agree that option 1 should be a post-marketing item.

Gilead identified (b) (4) as the testing site for all the commercial batches of sofosbuvir. Since there is duplication of manufacturing sites in the application, Gilead believed that the post-marketing requirement is not necessary.

Gilead will provide the API lot number, maturation, testing information for drug substance and drug product, batch and testing information.

Gilead confirmed that the entire stability program was done at cGMP laboratories which are listed in the NDA. Gilead transferred the stability program from Foster City to (b) (4) in the June/July 2013 timeframe, which was prior to the Foster City inspection for this application.

The Agency request a document from Gilead identifying the functions of each manufacturing facility listed in the application, including what type of tests were conducted at each facility.

Gilead inquired about the impact of Foster City on ongoing and future applications. The Agency recommended a telecon with the Divisions to discuss these issues and its impact on future applications. Prior to the telecom Gilead should include an overall assessment that addresses the issues raised in this application.

(b) (4)

3.0 ACTION ITEMS:

Gilead:

1. Submit a letter confirming the drug substance and drug product is not stored or tested at Gilead Foster City.
2. Submit a letter removing Foster City as a testing site.
3. Submit a list of drug product lots intended for commercial distribution
4. Submit draft launch plans for sofosbuvir without the use of drug substance from (b) (4)
5. Submit release and testing site for all lots intended for commercial distribution.

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/s/

LINDA C ONAGA
11/20/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: **204671**

Drug: **Sofosbuvir**

Date: **November 19, 2013**

To: **Shalini Gidwani, MSc, RAC**
Associate Director, Regulatory Affairs

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, Regulatory Project Manager**

Subject: **NDA Labeling Comments**

The attached Microsoft WORD Document was sent to the Sponsor on November 12, 2013 and incorporated labeling for NDA 204671.

Please respond by 4:00 PM EST (1:00 PM PST) on November 21, 2013.

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

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

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

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/s/

LINDA C ONAGA
11/19/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **November 19, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Concur: **Poonam Mishra, MD, Clinical Reviewer**
Sarah Connelly, MD, Cross Discipline Team Lead

Subject: **NDA 204671**

Please reference your new drug application for sofosbuvir. The following comments are being conveyed on behalf of the review team for your application.

Clinical:

1. 1. Please provide clinical narrative for Subject # 1961-8812 in GS-US-334-0123 (PHOTON-1) with an investigator-reported AE of pancreatitis considered related to study drug.

2. Please comment on the increased incidence of "Asthenia" reported in trial GS-US-334-0133 (VALENCE).

3. Please comment on the increased frequency of cough and dizziness observed in SOF+RBV 24 Weeks treatment groups (Group 2 and 3) in trial GS-US-334-0123 (PHOTON-1).

4. Please provide data on the number of subjects who have received 48 weeks of SOF+RBV in pre-transplant trial P7977-2025, and provide safety information to justify the 48 week duration proposed in the label.

Please provide your response no later than noon EST on November 20, 2013.

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

_____

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

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/s/

LINDA C ONAGA
11/19/2013

MEMORANDUM OF TELECONFERENCE

Teleconference Date: September 27, 2013

Application Number: NDA 204671
Product Name: sofosbuvir
Sponsor/Applicant Name: Gilead Sciences, Inc.

Subject: Submission of VALENCE and PHOTON-1 Phase 3 data to support new treatment regimen in genotype 1 and 3 HCV infection

FDA Participants :

1. Edward Cox, MD, MPH, Director, Office of Antimicrobial Products
2. Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
3. Jeffrey Murray, MD, MPH, Deputy Director, DAVP
4. Poonam Mishra, MD, Clinical Reviewer
5. Sarah Connelly, MD, CDTL
6. Jeffry Florian, PhD, Pharmacometrics Reviewer
7. Karen Qi, PhD, Statistical Reviewer
8. Wen Zeng, PhD, Secondary Statistical Reviewer
9. Greg Soon, PhD, Statistical Team Lead
10. Dionne Price, PhD, Acting Division Director, DBIV
11. John Lazor, PhD, Director, DCPIV
12. Kim Struble, PharmD, Clinical Team Lead
13. Karen Winestock, CPMS
14. Yaning Wang, PhD, Pharmacometric Team Lead
15. Christopher Ellis, PhD. Acting Pharmacology Toxicology Team Lad
16. Lisa Naeger, PhD, Virology Reviewer
17. Jules O'Rear, PhD, Virology Team Lead
18. Michael Pacanowski, PharmD MPH, Associate Director for Genomics and Targeted Therapy
19. Sarah Dorff, PhD, Pharmacogenomics Reviewer

Sponsor/Applicant Participants

1. John McHutchison, MD, Senior Vice President, Liver Disease Therapeutics
2. Neby Bekele, PhD, Senior Director, Biostatistics
3. Diana Brainard, MD, Senior Director, Clinical Research LDTA
4. Shalini Gidwani, MSc, RAC, Associate Director, Regulatory Affairs
5. William T. Symonds, Pharm D, Project Team Lead/Vice President, Clinical Research LDTA
6. Mani Subramanian, MD, Vice President, Liver Disease Therapeutics
7. Paul Tomkins, PhD, Senior Director, Regulatory Affairs

1.0 BACKGROUND:

The Agency requested a teleconference with Gilead to discuss evidence to support effectiveness of sofosbuvir plus pegylated interferon and ribavirin (PEG/RBV) in HCV genotype 1 prior PEG/RBV non-responders, and to discuss data on a longer sofosbuvir/ribavirin treatment regimen in genotype 1 and 3 HCV-infected patients. VALENCE (GS-US-334-0133) was a Phase 3, multicenter, randomized, double-blind placebo-controlled trial initially designed to investigate the efficacy and safety of sofosbuvir plus ribavirin for 12 weeks in treatment naïve and treatment experienced patients with chronic hepatitis 2 or 3 infection. Emerging data led to a protocol amendment to extend the sofosbuvir plus ribavirin treatment duration to 24 weeks in all eligible genotype 3 HCV-infected subjects. PHOTON-1 is a Phase 3, open-label trial to investigate the efficacy and safety of sofosbuvir plus ribavirin in chronic genotype 1, 2, and 3 hepatitis C virus and human immunodeficiency virus co-infection.

2.0 DISCUSSION:

Genotype 1 HCV Prior PEG/RBV non-responders

Gilead agreed with the Agency's analysis on treating genotype 1 prior PEG/RBV non-responders, although their modeling approach differs from the Agency. The Agency confirmed this analysis did not include prior HCV protease inhibitor (PI) non-responders, as data on this subgroup are very limited. Gilead will provide the Agency with their modeling approach and prepare a slide for the Advisory Committee presentation on this topic.

At the time of the teleconference, Gilead did not have data available from prior PEG/RBV non-responders administered SOF+PEG/RBV in the -0109 trial. However, on-treatment data and early SVR data in a subset of subjects would be available by the late cycle meeting on October 10, 2013. Gilead will provide this data prior to the LCM meeting to the Agency. In addition, Gilead will add genotype 3 modeling information back in their AC briefing book and add one slide to the presentation for genotype 1 prior PEG/RBV non-responders.

VALENCE and PHOTON-1

The Agency acknowledged receipt of the Gilead's abstracts on sofosbuvir, which will be presented at AASLD in early November. VALENCE trial supports a longer (24 week) sofosbuvir plus ribavirin treatment regimen in genotype 3 patients and PHOTON-1 supports a sofosbuvir plus ribavirin regimen (24 weeks) in genotype 1 patients who are unable to take interferon. Based on this information, the Agency requested all available VALENCE and PHOTON-1 data to be submitted. The submission should include interim study reports, raw data, some derived datasets, topline safety data, and clinical investigator information. Additionally, Gilead was instructed to submit a breakthrough therapy designation request for sofosbuvir in combination with ribavirin for the treatment of chronic genotype 1, 2, and 3 HCV patients.

The NEUTRINO trial currently supports a shorter duration in genotype 3 patients; however there was a high relapse rate in this trial. The preliminary 24 week data from VALENCE shows better treatment outcomes and lower relapse rates. The Agency will present VALENCE information at

the AC but not PHOTON-1 data because the AC members have not been screened to discuss the co-infection trial.

Gilead will provide submission timelines for the two trials to the Agency by Monday, September 30, 2013.

3.0 ACTION ITEMS:

Gilead:

1. Submission of VALENCE interim study data and clinical investigator information
2. Submission of PHOTON-1 interim study data
3. Submission of BT Designation Request for sofosbuvir in combination with ribavirin
4. Submission of modeling analyses to support SOF+PEG/RBV use in genotype 1 prior PEG/RBV non-responders

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/s/

LINDA C ONAGA
11/19/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: **204671**

Drug: **Sofosbuvir**

Date: **November 15, 2013**

To: **Shalini Gidwani, MSc, RAC**
Associate Director, Regulatory Affairs

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, Regulatory Project Manager**

Subject: **NDA Labeling Comments**

The attached Microsoft WORD Document was sent to the Sponsor on November 12, 2013 and incorporated labeling for NDA 204671.

DMEPA has the following comment regarding the carton and container labeling for this application:

1. Relocate the dosage form "Tablets" to appear on the same line next to the active ingredient "sofosbuvir" as follows:

   (sofosbuvir) Tablets
   400 mg

Please respond by 9:00 AM EST (6:00 AM PST) on November 18, 2013.

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

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

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/s/

LINDA C ONAGA
11/15/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: **204671**

Drug: **Sofosbuvir**

Date: **November 8, 2013**

To: **Shalini Gidwani, MSc, RAC**
Associate Director, Regulatory Affairs

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, Regulatory Project Manager**

Subject: **NDA Labeling Comments**

The attached Microsoft WORD Document was sent to the Sponsor on November 8, 2013 and incorporated labeling comments for NDA 204671.

Please respond by 3:00 PM EST (12:00 PM PST) on November 12, 2013.

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

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

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

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/s/

LINDA C ONAGA
11/08/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 204671

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

ATTENTION: Shalini Gidwani, M.Sc., R.A.C.
Associate Director, Regulatory Affairs

Dear Ms. Gidwani:

Please refer to your New Drug Application (NDA) dated April 6, 2013, and received April 8, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Sofosbuvir Tablets, 400 mg.

We also refer to your correspondence dated August 15, 2013, received August 16, 2013, requesting review of your proposed proprietary name, (b) (4) We have completed our review of the proposed proprietary name (b) (4) and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your August 16, 2013, submission are altered, the name must be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Linda Onaga at (301) 796-0759.

Sincerely,

{See appended electronic signature page}

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

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/s/

AZEEM D CHAUDHRY
11/07/2013

CAROL A HOLQUIST
11/07/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **October 22, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Concur: **Poonam Mishra, MD, Clinical Reviewer**
Jenny Zheng, PhD, Clinical Pharmacology Reviewer
Shirley Seo, PhD, Clinical Pharmacology Team Lead
Sarah Connelly, MD, Cross Discipline Team Lead

Subject: **NDA 204671**

Please reference your NDA submission for sofosbuvir. The following comments are being conveyed on behalf of the review team for your application.

VALENCE (GS-US-334-0133)

1. Study GS-US-334-0133 is a non-IND study conducted in Europe. Sponsors using foreign clinical studies not conducted under an IND must comply with 21 CFR 312.120. Please submit all information needed to comply with 21 CFR 312.120. You may refer to the March 2012 Guidance, *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND, Frequently Asked Questions.*

2. Please submit narratives for serious adverse events and discontinuations due to adverse events.

PHOTON-1 (GS-US-334-0123)

1. Please submit narratives for serious adverse events and discontinuations due to adverse events.

2. We request submission of PK datasets. If the datasets are not currently available, please provide a timeline for their completion.

Please provide your response 4:00PM EST on October 30, 2013.

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

_____

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

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/s/

LINDA C ONAGA
10/22/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **October 18, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Concur: **Poonam Mishra, MD, Clinical Reviewer**
Lisa Naeger, PhD, Virology Reviewer
Jules O'Rear, PhD, Virology Team Lead
Sarah Connelly, MD, Cross Discipline Team Lead

Subject: **NDA 204671**

Please reference your new drug application for sofosbuvir. The following comments are being conveyed on behalf of the review team for your application.

Clinical:

1. Please provide a comprehensive summary focused on cardiovascular events observed in each of the VALENCE and PHOTON-1 trials. Please include details on any serious adverse events, Grade 3 or 4 AEs or AEs leading to treatment discontinuations.

2. Please provide the hemoglobin values at the time of cardiac events of palpitations and tachycardia noted in the Table 8 of the FDA background package and in the VALENCE and PHOTON-1 trials.

Please provide your response no later than 12:00 PM EST on October 21, 2013.

Virology:

1. Please provide the baseline resistance data and response data for subjects in Study GS-US-334-0109.

Please provide your response no later than November 5, 2013.

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

_____

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

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/s/

LINDA C ONAGA
10/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204671

WITHDRAWAL -
BREAKTHROUGH THERAPY REQUEST

Gilead Sciences, Inc.
Attention: Shalini Gidwani, MSc, RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Gidwani:

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

We acknowledge receipt on October 3, 2013, of your October 1, 2013, request for breakthrough therapy designation submitted under section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) for sofosbuvir in combination with ribavirin for the treatment of genotypes 1, 2, and 3 chronic hepatitis C virus infection. (b) (4)

.

If you have any questions, call me, at (301) 3796-0759 or the Division mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

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

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/s/

DEBRA B BIRNKRANT
10/17/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **October 16, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Concur: **Poonam Mishra, MD, Clinical Reviewer**
Karen Qi, PhD, Statistician
Wen Zeng, PhD, Statistician
Sarah Connelly, MD, Cross Discipline Team Lead

Subject: **NDA 204671**

Please reference your submission dated October 10, 2013. The following comments are being conveyed on behalf of the review team for your application.

1) Please populate and resubmit the PHOTON-1 DM domain with ACTARM and ACTARMCD to differentiate 12 week versus 24 week treatment arms. The ARM, ARMCD, ACTARM, ACTARMCD structure in the VALENCE study was a good representation of that trial. We suggest a similar approach for PHOTON-1. If there is an alternative approach that would give us confidence as to which subjects in the SDTM dataset were assigned to 12 week versus 24 week arms, we would be open to considering it (e.g., verify that all subjects in EX received the treatments they were supposed to and no more or less, we could use EX to determine the arms). We need to have something clear to which we can refer in order to ensure traceability in our safety analyses.

2) The AE datasets for VALENCE and PHOTON-1 do not include treatment emergent flag (AETEAE). Please either confirm that all AEs included in VALENCE and PHOTON-1 datasets are treatment emergent as is suggested on the CSR or provide the AETEAE flag in the AE domains.

3) Please confirm if creatine kinase and lipase labs were performed for the VALENCE or PHOTON-1 trials. If they were performed, please submit that information in the LB domains.

4) In the AEACN (action taken on AE) variable only one of the code values is used from the code list submitted. Without the actual codes, it is impossible to link the AE to what happened with regards to drug or dose adjustment. The following codes should be used for both VALENCE and PHOTON-1 AE domain datasets. If there are truly multiple, we suggest using a supplemental dataset to contain additional codes. The codes listed in the define file submission include:

ACN, Reference Name (ACN)	
Code Value	**Code Text**
DOSE INCREASED	Dose Increased
DOSE NOT CHANGED	Dose Not Changed
DOSE REDUCED	Dose Reduced
DRUG INTERRUPTED	Drug Interrupted
DRUG WITHDRAWN	Drug Withdrawn
NOT APPLICABLE	Not Applicable
UNKNOWN	Unknown
MULTIPLE	MULTIPLE

5) In VALENCE, there were 25 treated subjects whose dates of discontinuation from study in ADEFFOUT.XPT differed from the discontinuation dates in DS.XPT (see below list of subjects). Please clarify.

Obs	USUBJID	Disc study date in ADDEFFOUT.XPT	Disc study date in /DS.XPT
1	GS-US-334-0133-0475-2259	2013-07-16	07/02/13
2	GS-US-334-0133-1043-2152	2013-07-02	06/20/13
3	GS-US-334-0133-1065-2246	2013-04-28	03/12/13
4	GS-US-334-0133-1081-2180	2013-08-30	08/20/13
5	GS-US-334-0133-1081-2327	2013-05-08	03/12/13
6	GS-US-334-0133-1082-2281	2013-07-24	07/10/13
7	GS-US-334-0133-1088-2145	2013-07-18	06/26/13
8	GS-US-334-0133-1088-2273	2013-03-28	03/27/13
9	GS-US-334-0133-1242-2265	2013-05-31	03/08/13
10	GS-US-334-0133-2012-2239	2013-08-19	07/11/13
11	GS-US-334-0133-2012-2243	2013-07-12	07/03/13
12	GS-US-334-0133-2055-2092	2013-01-14	01/07/13

13	GS-US-334-0133-2188-2319	2013-08-05	07/23/13
14	GS-US-334-0133-3974-2140	2013-07-01	06/17/13
15	GS-US-334-0133-4361-2135	2013-07-18	06/20/13
16	GS-US-334-0133-4991-2035	2013-06-25	06/10/13
17	GS-US-334-0133-4991-2055	2013-09-10	06/06/13
18	GS-US-334-0133-5294-2029	.	11/20/12
19	GS-US-334-0133-5528-2353	2013-04-18	03/14/13
20	GS-US-334-0133-6818-2153	2013-07-11	06/21/13
21	GS-US-334-0133-6819-2364	2013-02-07	02/06/13
22	GS-US-334-0133-6821-2312	2013-03-06	03/01/13
23	GS-US-334-0133-6828-2075	2013-04-05	03/06/13
24	GS-US-334-0133-6831-2053	2013-08-09	07/29/13
25	GS-US-334-0133-6831-2086	2013-06-27	06/13/13

Please provide your response 4:00PM EST on October 17, 2013.

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

_____

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

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/s/

LINDA C ONAGA
10/16/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **October 11, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Concur: **Antoine El Hage, PhD, Office of Scientific Investigations**
Sarah Connelly, MD, Cross Discipline Team Lead

Subject: **NDA 204671**

Please reference your submission dated October 9, 2013. The following comment is being conveyed on behalf of the review team for your application.

To date, Gilead has had two sites audited, Dr. Riina Salupere (site #6816) and Professor Stefan Zeuzem (site #1081). To further support the reliability of the data submitted to the NDA for VALENCE, we are requesting that Gilead conduct audits of three additional randomly selected sites. These audit reports should contain summaries for each of the three sites, including the number of subject records reviewed, the number of subjects enrolled, randomized, completed, discontinued, and a brief listing of significant findings.

Please provide your response to the above questions by October 25, 2013.

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

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

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/s/

LINDA C ONAGA
10/11/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: **204671**

Drug: **Sofosbuvir**

Date: **October 9, 2013**

To: **Shalini Gidwani, MSc, RAC**
Associate Director, Regulatory Affairs

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, Regulatory Project Manager**

Subject: **NDA Labeling Comments**

The attached Microsoft WORD Document was sent to the Sponsor on October 9, 2013 and incorporated labeling comments for NDA 204671.

Please respond by October 29, 2013.

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

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

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/s/

LINDA C ONAGA
10/09/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **October 8, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Concur: **Poonam Mishra, MD, Clinical Reviewer**
Sarah Connelly, MD, Cross Discipline Team Lead
Jeffry Florian, PhD, Pharmacometrics Reviewer
Stephen Miller, PhD, CMC Lead
Krishna Ghosh, PhD, Office of Compliance

Subject: **NDA 204671**

Please reference your NDA. The following comment is being conveyed on behalf of the review team for your application.

GS-US-334-0109:

1. We request additional data from your ongoing roll-over trial (GS-US-334-0109) for genotype 1 prior P/R-nonresponders. Specifically, we request an update on the end of treatment outcome of the 59 subjects who completed 12 weeks of SOF + PEG + RBV (e.g., what percentage of these subjects had HCV RNA target not detected at the end of treatment?). Also, please provide an updated version of Table 3 that includes all genotype 1 subjects who enrolled into GS-US-334-0109, sorted by study identification number and treatment regimen. In addition, please provide a summary of any genotype 1 subjects from GS-US-334-0109 who have experienced virologic breakthrough. Finally, of the genotype 1 subjects enrolled in GS-US-3340-0109, please summarize how many of the subjects were classified as treatment failures from a previous regimen versus subjects who stopped treatment due to discontinuation of the study arm.

CMC/OC:

2. The Division received your submission dated October 7, 2013 with updates on the (b) (4) manufacturing site. We request that Gilead be prepared to discuss your draft launch plans for sofosbuvir without the use of API from (b) (4) at the upcoming late cycle meeting with the Agency.

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

_____

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

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/s/

LINDA C ONAGA
10/08/2013

Benton, Sandra J

From:	Benton, Sandra J
Sent:	Monday, October 07, 2013 2:54 PM
To:	Sherman, Rachel E; Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Horn, Pamela; Birnkrant, Debra B
Cc:	Onaga, Linda; Mishra, Poonam; Connelly, Sarah; Murray, Jeffrey S; Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis
Subject:	RE: Medical Policy Council – Breakthrough Therapy Designation - IND 106739

As the Council agrees with DAVP's recommendation to grant Gilead Sciences' breakthrough therapy designation request and does not believe a Council discussion is needed, a meeting will not be scheduled.

Thank you!

Sandy Benton
Senior Policy Analyst
CDER/Office of Medical Policy
301-796-1042
sandra.benton@fda.hhs.gov

From: Benton, Sandra J
Sent: Friday, October 04, 2013 2:14 PM
To: Sherman, Rachel E; Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Horn, Pamela; Birnkrant, Debra B
Cc: Onaga, Linda; Mishra, Poonam; Connelly, Sarah; Murray, Jeffrey S; Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis
Subject: FW: Medical Policy Council – Breakthrough Therapy Designation - IND 106739
Importance: High

Folks –

A minor correction was made to Section 4 of DAVP's background. There are only 3 drugs that has received BT designation. Please refer to this version.

I've resent the industry submission.

Sorry for any confusion.

Sandy
301-796-1042

<< File: NDA 204671 Breakthrough Therapy Designation Request.Updated.doc >> << File: NDA 204671 BTDR.PDF >>

From:	Benton, Sandra J
Sent:	Friday, October 04, 2013 2:01 PM
To:	Sherman, Rachel E; Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Horn, Pamela; Birnkrant, Debra B
Cc:	Onaga, Linda; Mishra, Lalji; Connelly, Sarah; Murray, Jeffrey S; Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis

Subject: Medical Policy Council – Breakthrough Therapy Designation - IND 106739
Importance: High

Hi! DAVP has received a breakthrough therapy designation request and has asked that it be expedited.

It is from Gilead Sciences Inc. for its NDA 204671 and IND 106739 for sofosbuvir for the treatment of chronic hepatitis C infection.

DAVP requested that Gilead Sciences submit this breakthrough therapy request and recommends that it be granted. Attached is DAVP's background on the breakthrough therapy designation with its rationale for granting the request.

Would you please review DAVP's recommendation and let me know by noon on Monday, October 7 if –

- You agree with DAVP's recommendation to grant this breakthrough therapy request and you do not believe a Council discussion is needed.
- You agree with DAVP's recommendation to grant this breakthrough therapy request. However, you would like a Council discussion regarding any questions you have.
- You disagree with DAVP's recommendation to grant this breakthrough therapy request.

If the Council agrees with bullet 1, a discussion on this breakthrough therapy request will not be scheduled.

Please let me know if you have any questions. Thank you.

Sandy Benton
Senior Policy Analyst
CDER/Office of Medical Policy
301-796-1042
sandra.benton@fda.hhs.gov

<< File: NDA 204671 BG for BTDR Final.doc >> << File: NDA 204671 BTDR.PDF >>

CDER Medical Policy Council Brief
Breakthrough Therapy Designation
Division of Antiviral Products
[MPC Meeting]

Summary Box

1. NDA 204671, IND 106739
2. Company: Gilead Sciences, Inc.
3. Drug Name: Sofosbuvir
4. Indication: Treatment of Chronic Hepatitis C Infection
5. Sofosbuvir, in combination with ribavirin +/- interferon, is intended to treat a serious or life-threatening disease or condition.
6. The preliminary clinical evidence indicates that this drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints (safety and efficacy).

1. Brief description of the drug

Sofosbuvir (SOF) is a nucleotide NS5B RNA-dependent RNA polymerase inhibitor currently under priority NDA review for treatment of chronic HCV infection. The PDUFA V goal date is December 8, 2013. SOF is a once-daily pill with the potential to advance HCV therapy by providing an effective, all oral treatment regimen with a more favorable safety profile than currently approved therapies for the treatment of chronic HCV infection. Fast track designation was granted on August 11, 2010. Breakthrough therapy designation was granted for SOF combined with ledipasvir (LDV, HCV NS5A inhibitor) on July 22, 2013.

2. Brief description of the disease, intended population, and currently available therapies

Approximately 3.2 million people in the United States 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. The Division considers chronic HCV infection a serious and life-threatening condition.

At least six different HCV genotypes have been identified, numbered 1 to 6, 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; mostly subtype 1a), 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". The current standard-of-care treatment for HCV genotype 1 infection is a combination of pegylated interferon alpha (Peg-IFNα), RBV, and one of two recently approved HCV NS3 protease inhibitors (boceprevir or telaprevir) administered for 24 to 48 weeks depending on the specific drug regimen and patient population. These regimens are associated with favorable efficacy (65-75% SVR12 rates) in treatment-naïve patients without the severe liver complications of HCV infection, but have lower efficacy in certain difficult-to-treat populations, for example those with cirrhosis. The regimens are difficult to administer (Peg-IFNα is given as a weekly injection, boceprevir and telaprevir are given 3 times daily with food restrictions and pill burdens of up to 24 pills per day) and are poorly tolerated in many patients, as each drug is associated with numerous serious and life-threatening toxicities including neuropsychiatric, autoimmune, ischemic and infectious disorders (Peg-IFNα), teratogenicity (RBV), anemia (RBV, telaprevir, boceprevir), bone marrow suppression (Peg-IFNα, RBV) and severe rash (telaprevir-boxed warning). Furthermore, like many other HCV direct-acting antivirals (DAAs), boceprevir and telaprevir have relatively narrow genotype-specificity, and therefore are not approved for the treatment of non-genotype 1 HCV. Current standard-of-care for non-genotype 1 HCV infection is a 24- to 48-week duration of Peg-IFNα/RBV, which has limited efficacy in certain populations. Importantly, a significant proportion of HCV-infected patients are believed to be intolerant or ineligible (based on comorbidities or age) to use interferon-based therapies and these patients currently have no viable antiviral treatment options.

Because of the limitations of interferon-based therapies, there has been great interest in the development of all oral, interferon-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 are now being studied in Phase 3 clinical trials. It is widely anticipated that at least some of these regimens will have substantially improved efficacy over the current standard-of-care, particularly for HCV genotype 1, with treatment duration possibly as short as 12 weeks. Most importantly, because these regimens do not require the use of interferon, they are expected to have a substantially improved safety and tolerability profile compared to the current standard-of-care 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 a breakthrough therapy designation, and this endpoint is also used in the Sponsor's pivotal 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 any drugs being studied for the same indication that received breakthrough therapy designation

Three breakthrough therapy designations were recently granted for interferon-sparing all oral HCV treatment regimens. The first was for Bristol Myers Squibb's all oral DAA combination of daclatasvir (DCV), asunaprevir (ASV) and BMS-791325 (325) for the treatment of genotype 1 treatment-naïve chronic HCV-infected patients. DCV is an NS5A replication complex inhibitor, ASV is a selective inhibitor of HCV NS3 protease and BMS-791325 is a selective non-nucleoside NS5B polymerase inhibitor of the hepatitis C virus. The second was for AbbVie's all oral DAA combination of ABT-450/r (ritonavir-boosted HCV NS3/4A protease inhibitor), ABT-267 (HCV NS5A inhibitor) and ABT-333 (non-nucleoside HCV NS5B-palm polymerase inhibitor). The third was for Gilead's fixed-dose combination of SOF, the subject of this current Breakthrough Therapy Designation Request, (nucleotide analog HCV NS5B inhibitor) and ledipasvir (GS-5885, HCV NS5A inhibitor).

5. Description of preliminary clinical evidence

Preliminary Clinical Evidence for SOF+RBV Supports the Treatment of HCV Genotype 1 Infection

Clinical evidence available to date suggests SOF+RBV for 24 weeks duration may represent an improvement versus the current standard of care for the treatment of HCV genotype 1 infected patients:

- SOF+RBV provides a treatment option for patients unable or unwilling to take an interferon-based regimen
- SOF+RBV is simpler to take due to low pill burden
- SOF+RBV has an improved safety profile based on available data

The primary clinical data supporting the use of SOF+RBV for 24 weeks for the treatment of HCV genotype 1 infection is derived from GS-US-334-0123 (PHOTON-1). Note, this regimen does not include interferon (IFN). PHOTON-1 is a Phase 3 trial evaluating SOF+RBV for the treatment of HCV genotypes 1-3 in HCV/HIV-coinfected subjects, a historically more difficult to treat population, including subjects with compensated cirrhosis. Treatment durations are 12 or 24 weeks, depending on HCV genotype and treatment history.

In PHOTON-1, SOF+RBV was studied for 24 weeks in 114 HIV/HCV genotype 1 treatment-naïve subjects (Table 1). Out of these 114 subjects, 87 (76%) have achieved a sustained virologic response 12 weeks after treatment (SVR12) with this IFN-free regimen.

Table 1. Preliminary Efficacy Results in HCV Genotype 1 Treatment-naïve Subjects with HCV/HIV-1 Co-infection in Study GS-US-334-0123

	SOF+RBV 24 Weeks
SVR4, n/N (%)	92/114 (81)
SVR12, n/N (%)	87/114 (76)
Virologic Failure, n/N (%)	26/114 (23)
Relapse	25/114 (22)
On-treatment virologic failure	1/114 (<1)
Other, n/N (%)	2/114 (2)

Source: NDA 204671 Breakthrough Designation Request

Phase 2 data from the SPARE trial (NIAID 11-I-0258) and the re-treatment arm of Study P2938-0721 (QUANTUM) further support the results obtained in PHOTON-1 with SVR12 response rates of 68% and 66% in genotype 1 HCV-infected patients who are not co-infected with HIV, and who were treated with SOF+RBV for 24 weeks, respectively.

These Phase 2 and 3 data demonstrate HCV genotype 1 treatment-naïve SVR rates between 66 and 76% following SOF+RBV for 24 weeks, which is similar to the current HCV genotype 1 standard of care of a PI (boceprevir or telaprevir) plus PEG/RBV with SVR rates between 66% and 75%, after 24-48 weeks of therapy. The current SOF NDA contains Phase 3 single-arm data on SOF+RBV+PEG in 292 HCV genotype 1 treatment-naïve subjects (GS-US-334-0110, NEUTRINO), where 261 (89%) achieved SVR12, a higher rate than observed with the currently approved therapies. Although the SOF+RBV 24 duration has lower SVR rates than observed in NEUTRINO, this SOF+RBV regimen offers an all oral, interferon-free, low pill burden option to HCV genotype 1 patients who may be unable to take interferon.

Preliminary Clinical Evidence for SOF + RBV Supports the Treatment of HCV Genotypes 2 and 3 Infection

HCV Genotype 2 Infection

Clinical evidence available to date suggests SOF+RBV for 12 weeks duration may represent a substantial improvement versus the current standard of care for the treatment of genotype 2 HCV-infected patients:

- SOF+RBV is more efficacious
- SOF+RBV provides an interferon-free regimen
- SOF+RBV is simpler to take due to low-pill burden
- SOF+RBV has an improved safety profile based on available data

The primary clinical data supporting the use of SOF+RBV for 12 weeks for the treatment of genotype 2 HCV infection is derived from three registrational Phase 3 trials.

- P7977-1231 (FISSION) evaluated SOF+RBV treatment for 12 weeks in treatment-naïve subjects

- GS-US-334-0107 (POSITRON) evaluated SOF+RBV for 12 weeks in subjects who were interferon intolerant, ineligible, or unwilling to take interferon
- GS-US-334-0108 (FUSION) evaluated SOF+RBV for 12 or 16 weeks in treatment-experienced subjects

	FISSION		POSITRON		FUSION	
	SOF+RBV 12 weeks	PEG/RBV 24 weeks	SOF+RBV 12 weeks	Placebo	SOF+RBV 12 weeks	SOF+RBV 16 weeks
HCV Genotype 2						
SVR12	95% (69/73)	78% (52/67)	93% (101/109)	0 (0/34)	82% (32/39)	89% (31/35)
Relapse Rate	5% (4/73)	15% (9/62)	5% (5/107)	n/a	18% (7/39)	11% (4/35)

Source: NDA 204671 data obtained from AC Backgrounder

GS-US-334-0133 (VALENCE) is a Phase 3 non-IND European trial evaluating SOF+RBV for the treatment of HCV genotypes 2 or 3 infection in treatment-naïve or treatment-experienced subjects, including patients with compensated cirrhosis, with treatment durations of 12 or 24 weeks, depending on HCV genotype. In VALENCE, SOF+RBV was studied for 12 weeks in 73 HCV genotype 2 subjects. Out of these 73 subjects, 68 (93%) have achieved SVR12 (Table 2). These data support the prior registrational Phase 3 trial results.

Collectively, these HCV genotype 2 subjects had high SVR rates and were treated with an all oral regimen for 12 weeks. These data contrast with the current HCV genotype 2 standard of care treatment of PEG/RBV for 24 weeks, with SVR rates of 78% observed in FISSION.

HCV Genotype 3 Infection

Clinical evidence available to date suggests SOF+RBV for 24 weeks duration may represent a substantial improvement versus the current standard of care for the treatment of genotype 3 HCV-infected patients:

- SOF+RBV is more efficacious
- SOF+RBV provides an interferon-free regimen.
- SOF+RBV is simpler to take due to low-pill burden
- SOF+RBV has an improved safety profile based on available data

The primary clinical data supporting the use of SOF+RBV for 24 weeks for the treatment of HCV genotype 3 infection is derived from GS-US-334-0133 (VALENCE). In VALENCE, SOF+RBV was studied for 24 weeks in 250 HCV genotype 3 treatment-naïve and treatment-experienced subjects (Table 2). Out of these 250 subjects, 217 (87%) have achieved SVR four weeks after treatment (SVR4).

Table 2. Preliminary Efficacy Results in Study GS-US-334-0133

Subjects, n/N (%)	GT 2 12 weeks N=73	GT3 12 weeks N=11	GT 3 24 weeks N=250
SVR4	68/73 (93)	5/11 (46)	217/250 (87)
SVR12	68/73 (93)	3/11 (27)	Pending
Virologic Failure	5/73 (7)	6/11 (55)	30/250 (12)
Relapse	5/73 (7)	6/11 (55)	30/250 (12)
On-treatment virologic failure	0	0	0
Other	0	2/11 (18)	3/250 (1)

GT = genotype
Source: NDA 204671 Breakthrough Designation Request

Table 3 provides preliminary SVR4 data according to prior treatment experience and cirrhosis status. SVR12 data for Study GS-US-334-0133 will be provided to FDA October 9, 2013.

Table 3. Preliminary SVR12 (Gentoype 2) and SVR4 (Genotype 3) Results by Subgroup in Study GS-US-334-0133

Subjects, n/N (%)	GT 2 12 weeks N=73	GT 3 24 weeks N=250
Overall	68/73 (93)	217/250 (87)
Treatment-naïve	31/32 (97)	98/105 (93)
Non-cirrhotic	29/30 (97)	86/92 (93)
Cirrhotic	2/2 (100)	12/13 (92)
Treatment-experienced	37/41 (90)	119/145 (82)
Non-cirrhotic	30/33 (91)	88/100 (88)
Cirrhotic	7/8 (88)	31/45 (69)

GT = genotype
Source: NDA 204671 Breakthrough Designation Request

These HCV genotype 3 subjects had high SVR rates and were treated with an all oral regimen for 24 weeks. These data contrast with the current genotype 3 HCV standard of care of PEG/RBV for 24 weeks, with SVR rates of 63% observed in the FISSION treatment-naïve trial. Note, retreatment with PEG/RBV in patients who failed prior PEG/RBV treatment is not recommended by the AASLD Practice Guidelines[1].

Sofosbuvir Safety Assessment

With respect to safety, the absence of PEG from the regimen diminishes concerns about autoimmune diseases, retinal disease, and other adverse events. The safety database for SOF is >1600 and >350 subjects for ≥12 weeks and ≥ 24 weeks duration, respectively.

[1] Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49 (4):1335-74.

From the NDA 204671 clinical review, the most common SOF+RBV treatment-emergent adverse events reported in the registrational trials (>10%) include: fatigue, headache, nausea, insomnia, anemia, irritability, diarrhea and cough. Serious adverse events occurred in <4%, and <2% discontinued due to an adverse event.

6. Division's recommendation and rationale

In conclusion, the breakthrough therapy designation for SOF as part of a SOF+RBV all oral, interferon-free regimen is supported by the following:

1. SOF has a novel mechanism of action that represents a previously untargeted pathway. Currently there are no other approved NS5B inhibitors.
2. The Phase 3 PHOTON-1 SVR12 and Phase 2 SPARE and QUANTUM data provide evidence of similar efficacy in HCV genotype 1 subjects compared to the currently available standard of care, and a treatment option for patients unable to receive interferon.
3. The Phase 3 FISSION, POSITRON, FUSION and VALENCE data provide evidence of an improvement in efficacy in both HCV genotype 2 and genotype 3 compared to the currently available standard of care, and a treatment option for patients unable to receive interferon.
4. The SOF+RBV all oral regimen provides a simpler treatment regimen than currently available.
5. The safety profile of SOF is promising. The regimen is interferon-free providing an improved safety profile and no injections.

Based on the data presented, DAVP believes SOF meets the definition of a breakthrough therapy for the treatment of genotypes 1, 2 and 3 chronic hepatitis C patients as outlined in Section 903 of the Food and Drug Administration Safety and Innovation Act and recommends SOF be given a breakthrough therapy designation.

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

The Division plans to work with the Sponsor to review the VALENCE and PHOTON-1 data during this current priority NDA review cycle to be able to recommend a more potent regimen with fewer relapses in HCV genotype 3 patients who would receive 24 weeks of the combination, and to provide a treatment regimen for HCV genotype 1 patients who may be unable to receive interferon-containing treatment.

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/s/

SANDRA J BENTON
10/08/2013

DEBRA B BIRNKRANT
10/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204671

ACKNOWLEDGE -
BREAKTHROUGH THERAPY REQUEST

Gilead Sciences, Inc.
Attention: Shalini Gidwani, MSc, RAC
Associate Director, Regulatory Affairs
333 Lakeside Dr.
Foster City, CA 94404

Dear Ms. Gidwani:

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

We acknowledge receipt on October 3, 2013, of your October 3, 2013, request for Breakthrough Therapy designation submitted under section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) for the treatment of genotype 1, 2 and 3 chronic hepatitis C infection. We are reviewing your request and will respond to you within 60 days of the receipt date. We will contact you if we have any questions or require additional information.

If you have any questions, call me at (301) 796-0759 or the Division mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

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

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/s/

LINDA C ONAGA
10/04/2013

Informational Center Director Briefing Minutes
September 19, 2013 11:00 a.m. to 12:00 p.m.

Topic: Sofosbuvir

CDER Staff Contact: Debra Birnkrant, Director, Division of Antiviral Products (DAVP)

CDER Executive Operations Staff Contact: Arlethia Royster

Invitees: Janet Woodcock, John Jenkins, Edward Cox, David Roeder, John Farley, Debra Birnkrant, Jeffrey Murray, Sarah Connelly, Mary Singer, Poonam Mishra, Adam Sherwat, Damon Deming, Julian O'Rear, Stephen Miller, Rapti Madurawe, Linda Onaga, Victoria Tyson, Hanan Ghantous, Karen Winestock, Elizabeth Thompson, George Lunn, Fuqiang Liu, Krishnakali Ghosh, Mahesh Ramanadham, Christopher Leptak, Michael Pacanowski, Guoxing Soon, Tara Gooen, Don Henry, David Doleski, Dionne Price, Fraser Smith, Yanming Yin, Janice Lansita, Christopher Ellis, Jeffry Florian, Vipul Dholakia, Lisa LaVange, Minerva Hughes, Carmelo Rosa, Alicia Mozzachio, Lawrence Yu

Background: The purpose of this briefing was to inform the Center Director of the current status of Gilead's sofosbuvir, a NME NDA application for the treatment of hepatitis C virus.

Summary of Discussion:

- Sofosbuvir in combination with ribavirin provides the first interferon-free regimen for the treatment of chronic hepatitis C in adults with genotype 2 or 3 infection and in combination with pegylated interferon and ribavirin provides improved efficacy and shorter duration of treatment in adults with genotype 1 or 4 infection.
- An Advisory Committee meeting has been scheduled for October 25, 2013.
- Eight out of the twelve total facilities for sofosbuvir have been found acceptable.
- (b) (4) manufactures over (b) (4) of the drug substance for sofosbuvir. CDER OC plans to issue an Import Alert for (b) (4) based on the EDQM inspectional findings due to finding related to GMP regulations and data integrity issues. EDQM had identified approximately 18 categories of GMP manufacturing documents that were falsified.
- Gilead Foster City is the major test site for sofosbuvir. Due to CMC issues found during the first cycle review for NDAs for (b) (4) Gilead Foster City is currently being recommended for a Warning Letter by the district which is under evaluation by CDER OC. The pre-approval inspection for sofosbuvir will begin on 9/23/13 at Gilead Foster City.
- Approval of the sofosbuvir NDA is based on the withdrawal of (b) (4) as a drug substance manufacturer and a determination that Gilead Foster City has an acceptable cGMP status.

Informational Center Director Briefing Minutes
September 19, 2013 11:00 a.m. to 12:00 p.m.

Topic: Sofosbuvir

Action Item:

- Office of Compliance will schedule a follow-up briefing with Dr. Woodcock to provide an update on the inspection findings.

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/s/

LINDA C ONAGA
09/26/2013

MEMORANDUM OF TELECONFERENCE

Teleconference Date: August 20, 2013

Application Number: NDA 204671
Product Name: sofosbuvir
Sponsor/Applicant Name: Gilead Sciences, Inc.

Subject: (b) (4) Manufacturing Site

FDA Participants
1. Edward Cox, MD, MPH, OAP
2. Debra Birnkrant, MD, DAVP
3. Jeffrey Murray, MD, MPH, DAVP
4. David Roeder, OAP
5. Mahesh Ramanadham, PharmD., M.B.A., OC/OMPQ
6. Krishnakali Ghosh, MSc., PhD, OC/ OMPQ
7. Robert Wittorf, PharmD, OC/OMPQ
8. Stephen Miller, PhD, ONDQA
9. Minerva Hughes, PhD, ONDQA
10. George Lunn, PhD, ONDQA
11. Sarah Connelly, MD, DAVP
12. Poonam Mishra, MD, DAVP
13. Hanan Ghantous, PhD, DAVP
14. Karen Winestock, DAVp
15. Wendy Carter, Acting Medical Team Leader, DAVP

Sponsor/Applicant Participants
1. Norbert Bischofberger, Ph.D., Executive Vice President, Research and Development
2. Taiyin Yang, Ph.D., Senior Vice President, Pharmaceutical Development and Manufacturing
3. John McHutchison, MD, Senior Vice President, Liver Disease Therapeutics
4. William T. Symonds, Pharm D, Project Team Lead/Vice President, Clinical Research LDTA
5. David Pizzuti, MD, Vice President, Regulatory Affairs
6. Matt Coulomb, Vice President, Chemical Manufacturing
7. Gary Visor, Vice President, Analytical Operations
8. Valerie Brown, Senior Director, QA
9. Shalini Gidwani, Associate Director, Regulatory Affairs

1.0 BACKGROUND:

The FDA requested this informal telephone conference to inform Gilead of their preliminary assessment of the (b) (4) manufacturing site located in (b) (4)

2.0 DISCUSSION:

The Agency informed Gilead Sciences that the Office of Compliance has begun a partnership with their foreign partners when evaluating manufacturing sites. The Agency has received the EDQM report for the (b) (4) site and the Agency's initial evaluation is concerning. However, the Agency's review is ongoing. The Agency's evaluation of a site is usually based upon an FDA inspection, but foreign inspection results may impact FDA's evaluation. The Agency noted that any site that is non-compliant with current good manufacturing practices (CGMP) could affect the approvability of a pending application. The Agency asked whether Gilead was aware of the findings at this site and if, there were any other facilities listed in the NDA performing the same work as (b) (4)

Gilead confirmed that they are aware of the EDQM report and that they had reviewed the entire report. They stated that they have been working with (b) (4) for the past 18 months to get the facility into compliance. In November 2012, the site began changing their procedures and processes. However, he EDQM inspection occurred in (b) (4) when the site was still trying to get into compliance with CGMPs. Gilead attributed the problems to two to three problematic employees at the site. They further stated that two additional for-cause inspections had been conducted after the EDQM inspection and both inspections were said to have positive outcomes. Gilead was confident that the (b) (4) site had corrected their GRMP issues.

Gilead also noted that the additional API sites have similar processes, but the (b) (4) site provides (b) (4) of the capacity of sofosbuvir. It would take Gilead approximately 18 months to replace the site, if it needed to be removed from the application.

Gilead asked whether the Agency planned to provide additional feedback if the Agency determines the site is not operating under CGMPs. Gilead noted that the Agency's inspection of the site had been postponed and asked whether Gilead could provide additional information to address the Agency's concerns.

The Agency stated that the feedback provided today was based upon the importance of the application currently under review. The next feedback will occur when the Agency takes action on the application.

Gilead asked whether they could discuss the Gilead Foster City, California inspection issues, but the Agency stated that the issues at this site could not be discussed during this meeting.

3.0 ACTION ITEMS:

- Gilead needs to decide whether to keep or withdraw the (b) (4) manufacturing site from the application.

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/s/

KAREN D WINESTOCK
09/24/2013

PeRC PREA Subcommittee Meeting Minutes
September 11, 2013

PeRC Members Attending:
Lynne Yao
Hari Cheryl Sachs
Karen Davis-Bruno
Rosemary Addy
Patricia Dinndorf
Tom Smith
Shrikant Pagay
Ethan Hausman
Peter Starke
Wiley Chambers
Lily Mulugeta
Daiva Shetty
Andrew Mulberg
Andrew Mosholder
Martha Nguyen
Dianne Murphy
Susan McCune
Gregory Reaman
Kevin Drudys
Dionna Green
Renan Bonnel
Jane Inglese

Guests Attending:
Nichella Simms (PMHS)
Erica Radden (PMHS)
Courtney Suggs (OCP)
Gilbert Burckart (OCP)
Donna Snyder (PMHS)
Senait Alemu (OCP)
Lei Nie (DBIV)
William Boyd (DTOP)
Lois Almoza (DTOP)
Elizabeth O'Shaughnessy (OAP)
Carmen DeBellas (OAP)
Karen Winestock (DAVP)
Linda Onaga (DAVP)
Yodit Belew (OAP)
Sarah Connelly (DAVP)
Poonam Mishra (DAVP)
Kathy Robie Suh (DHP)

Agenda

10:15 NDA 204671 Sofosbuvir Partial Waiver/Deferral/Plan

(b) (4)

Sofosbuvir Partial Waiver/Deferral/Plan

- NDA 204671 seeks marketing approval for sofosbuvir for treatment, in combination with other agents, of chronic hepatitis C (CHC) in adults.
- The application was submitted on April 8, 2013, and has a PDUFA goal date of December 8, 2013.
- The application triggers PREA as directed to a new active ingredient.
- A waiver is being requested for pediatric patients aged birth to less than three years because studies are impossible or highly impractical.
- *Division justification for waiver*: No systematic surveillance of chronic HCV infection among pediatric patients is available, making an accurate assessment of prevalence and severity in this age group difficult. The primary mode of HCV transmission to children is via vertical transmission. Rate of vertical transmission is estimated to be about 5%, but may be increased in the presence of HIV infection. Infants infected by vertical transmission have a high rate of spontaneous resolution approaching 25% to 40%. Most have spontaneous resolution by 24 months of age, but some may have spontaneous resolution as late as 7 years after vertical infection. Severe manifestations or complications of infection are unusual in infants and young children, and pediatric hepatologists acknowledge a lack of consensus regarding when to begin treatment in pediatric patients. Based on these data and current practice guidelines, a waiver for children less than 3 years of age is deemed appropriate.
- A deferral is being requested for pediatric patients aged 3 to less than 18 years because adult studies have been completed and the product is ready for approval.
- The sponsor plans to conduct the following clinical studies:

(b) (4)

- The Division is in general agreement with the sponsor's current proposal to satisfy PREA requirements.

- *PeRC Recommendations:*
  - The PeRC agreed with the Division to grant a partial waiver in pediatric patients aged birth to less than 3 years because studies are impossible or highly impractical.

- The PeRC agreed with the Division to grant a deferral for pediatric patients aged 3 to 18 years because the product is ready for approval in adults. The PeRC agreed to the proposed timelines for the deferred studies.

- Additional Items and Comments
  - The PeRC recommends that the Division identify any specific safety signals from the adult studies and incorporate any safety signals identified into the protocol for the pediatric studies.

(b) (4)

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/s/

JANE E INGLESE
09/22/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **September 12, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Concur: **Chris Ellis, PhD, Pharmacology Toxicology Reviewer**
Hanan Ghantous, PhD, DABT, Pharmacology Toxicology Team Lead
Eric Donaldson, PhD, Virology Reviewer
Lisa Naeger, PhD, Virology Reviewer
Jules O'Rear, PhD, Virology Team Lead
Poonam Mishra, MD, Clinical Reviewer
Sarah Connelly, MD, Cross Discipline Team Lead

Subject: **NDA 204671**

Please reference your NDA. The following comment is being conveyed on behalf of the review team for your application.

Clinical Virology:

1. Please submit the NGS data including fastq files, frequency tables and the resistance analysis tables for the 5 breakthrough/non-responder subjects in the pretransplant study P7977-2025. Please submit the fastq files on a hard drive or DVD.
2. Please provide the SOF phenotypic data from the 5 breakthrough/non-responder subjects (0773-7712, 1249-7720, 0451-7732, 0585-7751, 0773-7734) in study P7977-2025.
3. Substitutions T84S+A150T+E202D emerged in one subject who experience on-treatment failure. Substitution E341D was a treatment emergent substitution that developed in 13 subjects infected with GT3a HCV in two clinical trials (P7977-1231, n=10; GS-US-334-0107, n=3) and it was only found in subjects who relapsed. The L159F substitution emerged in 6 subjects with GT3a and is a previously identified NS5B substitution (Tong X et al., 2012). The L159F and E341D emerged together in one GT3a infected subject. Therefore, we are requesting they be characterized in combination in phenotypic assays to determine if they contribute to decreased SOF susceptibility.

a. Please assess the phenotypic susceptibility of substitutions T84S, E202D, and T84S+A150T+E202D.
b. Please assess the phenotypic susceptibility of substitution E341D.
c. Please also assess the phenotypic susceptibility of the combination of substitutions L159F+E341D.

Clinical Virology Labeling Comments:

1. Please provide median EC50 values of SOF in the Antiviral Activity section of the label.

Antiviral Activity
In HCV replicon assays, the EC_{50} values of sofosbuvir against full-length replicons from genotype 1a, 1b, 2a, 3a and 4a, and chimeric 1b replicons encoding NS5B from genotype 2b, 5a or 6a ranged from 0.014 to 0.11 μM. [Comment to sponsor: Provide medians and ranges in the following sentence.] The median EC_{50} value of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates was ? μM for genotype 1a (N=67), for genotype 1b (N=29), ? μM for genotype 2 (N=15) and ? μM for genotype 3a (N=106).

Pharmacology Toxicology Labeling Comments:

1. We acknowledge receipt of your recent response (sequence #0021) to the Agency's labeling comment that describes your position with regards to including rat cardiac toxicity findings in section 13.2 of the sofosbuvir label. Although we agree that sofosbuvir poses less risk then BMS-986094, it is our contention that the rat 7-day study data with GS-9851 suggest that the cardiac toxicity findings are a direct test-article related effect, since also observed in three surviving females not exhibiting clear dose-limiting effects. Therefore, we maintain our position that communicating this potential heart risk in the product label is important (refer to draft 13.2 label below). We also recommend that you consider conducting a short duration rat toxicology study with sofosbuvir at dose levels up to 2000 mg/kg to determine its contribution to the heart degeneration and inflammation observed with GS-9851. This study could not only more clearly define drug-related exposure multiples (based on heart findings) but, if indeed contributing to heart toxicity, further characterize this toxicity by including treatment-free groups (to evaluate reversibility) and additional study endpoints (*e.g.*, circulating biomarkers of cardiac toxicity, heart specific sofosbuvir and related metabolite concentrations).

13.2 Animal Toxicology and/or Pharmacology
Heart degeneration and inflammation were observed in rats following GS-9851 (a stereoisomeric mixture containing approximately 50% sofosbuvir) doses of 2000 mg/kg/day for up to 5 days. At this dose, estimated AUC exposure to the sofosbuvir-derived predominant circulating metabolite GS-331007 (b) (4) *. No heart degeneration or inflammation was observed in rats following sofosbuvir doses of up to 500 mg/kg/day for 6 months.* (b) (4) *In dogs and mice, heart degeneration and inflammation* (b) (4) *not* (b) (4) *observed following sofosbuvir doses of up to 500 and 1000 mg/kg/day for 9 and 3 months, respectively, the highest doses tested.* (b) (4)

Please provide your response to the above questions by September 18, 2013.

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

_____

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

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/s/

LINDA C ONAGA
09/12/2013

From: Shalini Gidwani
To: Onaga, Linda
Subject: RE: NDA 204671 Clarification question
Date: Tuesday, September 03, 2013 4:17:19 PM

Hi Linda,

In response to the 2 questions you raised please see responses below in red:

For Study P7977-1910, Cohort 3, was the ATV/r dose 300 mg/100 mg instead of 400 mg/100 mg once daily?

For study P7977-1910, Cohort 3, Prior to Study entry the ATR/r dose was 300/100mg. During the treatment period (Day 1-7), ATV/r dose was 400 mg/100 mg once daily.

(b) (4)

Please let me know if you have further questions.
Thanks
Shalini

From: Onaga, Linda [mailto:Linda.Onaga@fda.hhs.gov]
Sent: Tuesday, September 03, 2013 7:13 AM
To: Shalini Gidwani
Subject: NDA 204671 Clarification question

Good Morning Shalini,

Please find below a clarification question for NDA 204671.

(b) (4)

Linda

Linda C. Onaga, MPH
Regulatory Project Manager
Division of Antiviral Products (DAVP)
FDA/CDER/OND/OAP
White Oak Complex, Bldg 22, Rm 6321
10903 New Hampshire Ave.
Silver Spring, MD 20993
Ph: 301.796.0759
Fax: 301.796.9883

Email: linda.onaga@fda.hhs.gov

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/s/

LINDA C ONAGA
09/06/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **September 4, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Concur: **Lisa Naeger, PhD, Virology Reviewer**
Jules O'Rear, PhD, Virology Team Lead
Poonam Mishra, MD, Clinical Reviewer
Sarah Connelly, MD, Cross Discipline Team Lead

Subject: **NDA 204671**

Please reference your NDA. The following comment is being conveyed on behalf of the review team for your application.

Please provide your explanation for why the 5 patients in the pretransplant study P7977-2025 experienced breakthrough or had a slower response including possible drug-drug interactions, PK issues, resistance emergence other than S282T, etc.

In addition, please provide the posttransplantation virologic response rates and relapse rates by genotype.

Please provide your response to the above questions by September 6, 2013.

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

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

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/s/

LINDA C ONAGA
09/04/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **September 3, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Concur: **Poonam Mishra, MD, Clinical Reviewer**
Sarah Connelly, MD, Cross Discipline Team Lead

Subject: **NDA 204671**

Please reference your NDA. The following comments are being conveyed on behalf of the review team for your application.

Clinical:

1. Please provide information regarding cirrhosis determination in pivotal Phase 3 trials. Specifically, please provide the number of subjects in whom cirrhosis determination was based on histology (liver biopsy) and those in whom it was based on non-invasive tests including the numbers in each category (e.g. Fibroscan, FibroTest and APRI).

Please provide your response to the above questions by September 4, 2013.

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

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

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/s/

LINDA C ONAGA
09/03/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **August 29, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Concur: **Jenny Zheng, PhD, Clinical Pharmacology Reviewer**
Shirley Seo, PhD, Clinical Pharmacology Team Lead
Poonam Mishra, MD, Clinical Reviewer
Sarah Connelly, MD, Cross Discipline Team Lead

Subject: **NDA 204671**

Please reference your NDA. The following comments are being conveyed on behalf of the review team for your application.

Clinical and Clinical Pharmacology:

1. Please submit your assessment of adverse events of hypersensitivity in sofosbuvir clinical development plan.

2. We have some reservations on the use of cyclosporine (CsA) in combination with SOF, because CsA increased SOF AUC by about 4.5-fold and no human safety data are available from the NDA submission to support the combined use of CsA and SOF. The only data you have provided to support the combined use are safety margins calculated based on animal data. Please provide one or both of the following pieces of information to support your claim of no clinically significant effect of CsA on SOF exposures:

    a. Any available safety and PK data from the ongoing post-transplant study where SOF and CsA are coadministered
    b. Any safety data with SOF exposure that reaches the level observed when SOF was coadministered with CsA.

Please provide your response to the above questions by August 30, 2013.

Clinical Pharmacology Labeling Comments:

1. Please revise Table 1 to make it clear that treatment duration is for the entire treatment regimen because the durations for PEG and RBV in their respective labels are different from what we recommend for use with SOF. In addition, for Genotypes 2 and 3, the recommended RBV dose is also different from the RBV label, but dose reduction for moderate renal impairment should be made according to the RBV label. Please add a footnote (or some other denotation) to make this dosing concept clear in Dosing and Administration.

2. In Table 5:
   a. Tipranavir/ritonavir should be included because it is a potent P-gp inducer; [redacted] (b) (4)

3. For Section 12.3 Pharmcokinetics: Absorption, you indicated " [redacted] (b) (4) results from Study P2938-0212 and P7977-0523 indicated that the exposures of SOF and GS-331007 in HCV-infected subjects are similar to healthy subjects. The difference between population PK results and the results from Study P2938-0212 could be caused by the coadministration of RBV.

5. [redacted] (b) (4) (b) (4) drugs that have no significant DDI effect should be listed in text

   Please respond to the Clinical Pharmacology Labeling Comments by September 6, 2013.

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

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

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/s/

LINDA C ONAGA
08/29/2013

ELECTRONIC MAIL

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

DATE: August 21, 2013

TO: Shalini Gidwani, M.Sc, RAC,
Associate Director, Regulatory Affairs

SPONSOR: Gilead Sciences, Inc.

SUBJECT: NDA 204671 – Full Prescribing Information section

Please refer to your new drug application (NDA) for sofosbuvir for the treatment of chronic hepatitis C. The nonclinical review team has identified the following issue regarding the "Nonclinical Toxicology" section of the labeling:

- Given the potential for a class-associated effect of significant clinical concern, we recommend communicating the non-clinical cardiac toxicity findings in the labeling. Therefore, please provide draft 13.2 labeling to the Agency that includes the cardiac toxicity findings observed in the rat 7-day repeat-dose toxicology study with GS-9851.

We are providing this above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0834 if you have any questions regarding the contents of this transmission.

Karen Winestock, CPMS
Division of Antiviral Products

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/s/

KAREN D WINESTOCK
08/21/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204671

METHODS VALIDATION MATERIALS RECEIVED

Gilead Sciences Inc.
Attention: Shalini Gidwani
333 Lakeside Drive
Foster City, CA 94404
FAX: (650) 522-5489

Dear Shalini Gidwani:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sofosbuvir tablets, 400 mg and to our July 3, 2013, letter requesting sample materials for methods validation testing.

We acknowledge receipt on August 16, 2013, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

MICHAEL L TREHY
08/20/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204671 **INFORMATION REQUEST**

Gilead Sciences, Inc.
Attention: Shalini Gidwani, M.Sc, RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Gidwani:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sofosbuvir, 400 mg tablets.

We are reviewing the Product Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. FDA respectfully disagrees with your conclusion that the proposed QC dissolution method over discriminates at early time points and recommends a dissolution acceptance criterion of Q = (b) (4) at 15 minutes. We acknowledge the relative bioavailability data submitted for finished tablets manufactured using Form I and Form II drug substance in Study GS-US-334-0131; however, these data are insufficient to support the conclusion that the two formulations are bioequivalent by current FDA standards. Moreover, (b) (4) appropriate controls should be implemented to assure that the dissolution performance of future drug product (b) (4) lots is consistent with the observed performance of the (b) (4) product used in the pivotal clinical studies. It is not the general practice to establish quality controls that account for future unknown process or analytical variability. From FDA's perspective, a mean dissolution of (b) (4) at 15 minutes adequately supports an acceptance criterion of Q = (b) (4) at 15 minutes and already accounts for reasonable process and analytical variability. Provide a revised drug product specification table reflecting a change in the dissolution acceptance criterion from Q = (b) (4) minutes to Q = (b) (4) at 15 minutes on or before August 14, 2013.

2. For the following drug substance batches, supply all available release and stability analytical results and indicate the site where each result was obtained. This should include data obtained by the original manufacturer, data obtained by the analysis of incoming batches by the drug product manufacturer, and data obtained at other sites. If any of these batch numbers refers to a combination of 2 batches please supply the data for each individual batch.

40409003
40410001
40409002
GS-7977(5)/P-36-12001
GS-7977(7)-6-12001
GS-7977(5)-6-12002
GS-7977(6)-6-12001/2 and
GS-7977(6)-6-12002/1

3. For each drug substance release, acceptance, or stability test result related to point #2, provide details of the analytical methods that were used if they are different from the methods described in the NDA application.

4. For each drug substance and drug product release and stability test result that you have submitted in your NDA, as amended, please indicate the testing site at which this information was obtained. Please note that this request is not limited to the drug substance lots that are listed above.

In order to meet the internal and external goal dates for this NDA, we urge you to expedite your responses and to err on the side of completeness when preparing the documents. Please supply the test results and site information requested in points 2 and 4 above as soon as possible, and the information described in point 3 by August 23, 2013.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

RAPTI D MADURAWE
08/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204671

REQUEST FOR METHODS VALIDATION MATERIALS

Gilead Sciences
Attention: Shalini Gidwani
333 Lakeside Drive
Foster City, CA 94404

Dear Shalini Gidwani:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sofosbuvir Tablets, 400 mg.

We will be performing methods validation studies on Sofosbuvir Tablets, 400 mg, as described in NDA 204671.

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

Method, current version

(b) (4) Identification, assay, and degradation product content of Sofosbuvir tablets

(b) (4) Dissolution of Sofosbuvir tablets

Samples and Reference Standards

(b) (4)

4 bottles of Sofosbuvir tablets, 400 mg per tablet, 28 tablets per bottle

Equipment

(b) (4)

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

Forward these materials via express or overnight mail to:

Shipping address before August 16, 2013

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
1114 Market Street, Room 1002
St. Louis, MO 63101

Our laboratory is moving. No shipments from August 17th to August 30th.

Shipping address after September 2nd, 2013 is provided below.

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

MICHAEL L TREHY
08/05/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204671

MID-CYCLE COMMUNICATION

Gilead Sciences, Inc.
Attention: Shalini Gidwani, MSc, RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Gidwani:

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

We also refer to the teleconference between representatives of your firm and the FDA on July 17, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Linda Onaga, Regulatory Project Manager at (301) 796-0759 or the Division mainline at (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

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: July 17, 2013

Application Number: 204671
Product Name: sofosbuvir
Proposed Indication: [TRADENAME] is indicated in combination with other agents for the treatment of chronic hepatitis C (CHC) in adults
Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Sarah Connelly, MD, CDTL
Meeting Recorder: Linda Onaga, MPH, RPM

FDA ATTENDEES

1. Debra Birnkrant, MD, Director, DAVP
2. David Roeder, MS, ADRA, OAP
3. Sarah Connelly, MD, CDTL, DAVP
4. Poonam Mishra, MD, Clinical Reviewer, DAVP
5. Kimberly Struble, Pharm D, Clinical Team Lead, DAVP
6. Mahesh Ramanadham, Pharm D, MBA, RPh, Team Lead (acting), Office of Compliance
7. Stephen Miller, PhD, CMC Lead
8. Jeffry Florian, PhD, Pharmacometrics Reviewer
9. Wen Zeng, PhD, Biometrics Reviewer, DAVP
10. Karen Qi, PhD, Biometrics Reviewer, DAVP
11. Mary Singer, MD, Clinical Team Lead, DAVP
12. Adam Sherwat, MD, Clinical Reviewer, DAVP
13. Damon Deming, PhD, Virology Reviewer, DAVP
14. Victoria Tyson, Regulatory Project Manager, DAVP
15. Nina Mani, PhD, Regulatory Project Manager, DAVP
16. Karen Winestock, Chief, Project Management Staff, DAVP
17. Linda Onaga, MPH, Regulatory Project Manager, DAVP
18. Kimberly Taylor, Operations Research Analyst, CDER

EASTERN RESEARCH GROUP ATTENDEES

19. Patrick Zhou

APPLICANT ATTENDEES

1. John McHutchinson, MD Senior Vice President, Liver Disease Therapeutics
2. Neby Bekele, PhD, Senior Director, Biostatistics

3. Diana Brainard, MD Senior Director, Clinical Research Liver Disease Therapeutics
4. Brian Kearney, Pharm D, Senior Director, Clinical Pharmacology
5. Shalini Gidwani, MSc, RAC, Associate Director, Regulatory Affairs
6. Hongmei Mo, PhD, Director, Clinical Virology
7. Reza Oliyai, PhD, Vice President, Pharmaceutical Manufacturing and Development
8. William T. Symonds, Pharm D, Project Team Lead/Vice President, Clinical Research Liver Disease Therapeutics
9. Chin Tay, PhD DABT, Associate Director, Drug Safety Evaluation
10. Paul Tomkins, PhD Senior Director, Regulatory Affairs

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

There are no significant issues at this time.

3.0 INFORMATION REQUESTS

The following topics were discussed:

Chemistry, Manufacturing, and Controls:

1. Gilead acknowledged receipt of the CMC and CMC Biopharmaceutics information request on July 12, 2013.
2. Inspections for manufacturing sites submitted in the new drug application (NDA) package for sofosbuvir are ongoing.
3. (b) (4) inspections of Foster City manufacturing site conducted under (b) (4) NDAs were comprehensive GMP inspections. The outcome of these inspections may affect other pending Gilead products including sofosbuvir.

Statistics:

4. Analyses are ongoing to evaluate 16 week duration both in GT3 HCV patients and in GT2 HCV patients with poor baseline predictors such as cirrhosis and prior treatment experience.
5. Analyses are ongoing to evaluate differences in GT1a and 1b HCV patients.

6. Discussions are ongoing to account for misclassified patients in P7977-1231 and GS-US-334-0108.

Clinical:

7. Internal discussions are ongoing regarding regulatory implications of proposed broader indication (for sofosbuvir use) - "in combination with other agents."
8. Few subjects with genotype 5 (N=1) and genotype 6 (N=6) were included in the clinical trials. Discussions are ongoing whether available data on genotypes 5 and 6 is sufficient for dosing recommendations.
9. Regarding proposed indication in pre-transplant population, at the present time we believe an indication should specify the subpopulation studied which was patients with HCC meeting Milan criteria and awaiting liver transplantation. Discussions regarding how best to communicate the available information in the Prescribing Information (PI) are ongoing.
10. Available efficacy and safety data in HIV/HCV coinfected subjects (N=31) is limited and may preclude an indication in this special population.
11. Comprehensive safety review of the cardiac events and elevated creatine kinase (CK) events is ongoing.
12. There is a need to identify any subgroups of genotype 2 patient population which might potentially benefit from extended treatment duration of 16 weeks of sofosbuvir and ribavirin. We do acknowledge the small numbers, but improved SVR trends in GT2 treatment-expereinced (mainly prior non responders) and GT 2 patients with cirrhosis and non-CC IL28B genotype look promising and needs to be explored further.
13. We might recommend including all grades in the treatment-emergent adverse event table in the PI (b) (4)

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns/risk management issues at this time.

5.0 ADVISORY COMMITTEE MEETING

The Advisory Committee Meeting for sofosbuvir will be on October 25, 2013. The time and location have not been determined at this time. The Agency will update Gilead with this information once it is confirmed.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

Labeling and PMR/PMC information will be sent to Gilead on or before September 12, 2013.

The Division will hold a Late-Cycle meeting with Gilead to discuss any potential application deficiencies, the advisory committee meeting topics for discussion, labeling and any outstanding information requests.

Gilead will receive the Late Cycle meeting package via the secure email account on or before October 4, 2013. The late cycle meeting with Gilead is tentatively scheduled for October 10, 2013 from 3-4:30 pm.

The Action date for this application is December 8, 2013.

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/s/

DEBRA B BIRNKRANT
07/24/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **July 15, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Concur: **Jenny Zheng, PhD, Clinical Pharmacology Reviewer**
Su-Young Choi, PhD, Clinical Pharmacology Reviewer
Shirley Seo, PhD, Clinical Pharmacology Team Lead
Poonam Mishra, MD, Clinical Reviewer
Sarah Connelly, MD, Cross Discipline Team Lead

Subject: **NDA 204671**

Please reference your NDA. The following comments are being conveyed on behalf of the review team for your application.

1. The mass balance study shows that at least 76% of administered drug was recovered from urine, indicating that at least 76% of administered drug is absorbed from the GI tract. The result suggests P-gp/BCRP inhibition should not increase sofosbuvir concentrations by more than 31.5% (up to 100% absorption). However, the cyclosporine drug interaction study with sofosbuvir demonstrated that cyclosporine increased sofosbuvir AUC by approximately 4-fold, increased GS-566500 AUC by approximately 3-fold, with no increase in GS-331007 exposures. These results are not likely to be soley explained by P-gp/BCRP inhibition. Do you have any data to suggest that cyclosporine may affect the conversion of sofosbuvir to GS-331007 and/or the active triphosphate?

2. You have indicated that renal excretion is not a significant pathway for elimination of sofosbuvir and GS-566500. Although sofosbuvir and GS-566500 account for only <4% of the excreted dose, the renal clearance (CLr) value for SOF is comparable to GS-331007. Because absolute bioavailability was not determined, it is difficult to estimate the percentage of the total clearance (CLt) that is due to CLr. If SOF is substantially converted to metabolites in epithelial cells in the GI tract and during first pass, then CLr

of SOF could account for a significant portion of its CLt, since a large majority of the parent drug would not be bioavailable and thus not subject to renal excretion. In the renal impairment study, plotting AUCs of sofosbuvir and GS-566500 versus CLcr identified significant negative correlations, which implied that renal excretion could be an important pathway for elimination of sofosbuvir and GS-566500. Please indicate if you have any data to suggest what other mechanisms could be involved in increasing the exposure of sofosbuvir and GS-566500 in the setting of decreased renal function, other than reduced renal clearance.

3. In the thorough QT study, an increase in sofosbuvir dose from 400 mg to 1200 mg dose resulted in near dose proportional increases in sofosbuvir and GS-331007 AUCs, which is consistent with the low affinity and high capacity hydrolase nucleotide phosphorylation involvement in the metabolism of sofosbuvir. However, the cyclosporine drug interaction study with sofosbuvir shows that cyclosporine increased concentrations of sofosbuvir and GS-566500, but not GS-331007. In addition, the hepatic impairment study also shows that concentrations of sofosbuvir and GS-566500, but not GS-331007, increased in subjects with hepatic impairment. Please provide rationale for this observed inconsistency.

4. Single dose sofosbuvir (in healthy volunteer, Study GS-US-334-0131) reduced raltegravir Cmax and AUC by 43% and 27%, respectively; similar to the effects of efavirenz (36%↓ AUC and Cmax) and rifampin (38% ↓ for AUC and 40% ↓Cmax and 61% ↓ Cmin) on raltegravir; no dose adjustment is recommended for efavirenz because efficacy data support the combination use without dose adjustment. However, doubling the standard raltegravir dose is recommended when raltegravir is combined with rifampin. Because sofosbuvir is only administered as a single dose in the study, the maximum interacting effect may not be achieved, and it is possible that a dose increase of raltegravir may be needed when coadministered with sofosbuvir. However, the multiple dose sofosbuvir drug interaction study (in HIV/HCV co-infected patients, Study P7977-1910) with raltegravir showed there was a trend of <u>increased</u> raltegravir concentrations when coadministered with multiple doses of sofosbuvir. Because there were only 4 subjects in the study, it is not clear if the discordant results are due to single dose v.s. multiple dose of sofosbuvir, different populations, or inconclusive results from the multiple dose study due to low subject numbers. For this issue, please provide:

    a. your interpretation of these results
    b. your plan for presenting these data in the label
    c. your proposed dose recommendations in the label (taking into account your interpretation above and knowledge of raltegravir dosing recommendations with concomitant administration of drugs with a similar magnitude of interaction)

5. In your proposed labeling and in the summary of clinical pharmacology, you stated that (b) (4)

[redacted] (b) (4)

6. Please provide additional information on the enzyme(s) responsible for the conversion of GS606965 to GS331007, including the results of supportive in vitro studies (if applicable).

7. For study reports PC-PSI-7851-09-0009 and PC-PSI-7977-09-0011, please provide detailed information on the following.

    a. Experimental methods- each concentration of SOF, its metabolites, and the positive controls tested in these studies.
    b. Experimental methods- assay conditions including preparation of stock solutions, buffer, time of pre-incubation and incubation, method of reaction termination, and sample analysis methods
    c. Data analysis method- calculation methods for the determination of CYP isoform activities (i.e. rates of metabolite production) and IC_{50}.
    d. Results- CYP isoform activities at each concentration of SOF, its metabolites, and positive controls as graphs and/or table.

8. For study report AD-334-2013, please provide detailed information of the results (UGT activities at each concentration of SOF, its metabolites, and a positive control as graphs and/or tables).

Please provide your response by July 29, 2013.

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

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

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/s/

LINDA C ONAGA
07/15/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204671

INFORMATION REQUEST

Gilead Sciences, Inc.
Attention: Shalini Gidwani, M.Sc., RAC
Associate Director, Regulatory Affairs
334 Lakeside Dr.
Foster City, CA 94404

Dear Ms. Gidwani:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sofosbuvir, 400 mg tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by July 23, 2013, in order to continue our evaluation of your NDA.

1. We recommend the following revisions to the drug substance specification: Revise "Particle Size" to include "NMT (b) (4) wt% retained on a (b) (4) µm screen" from your current proposal of NMT (b) (4) In the NDA submission we do not find sufficient information to set the acceptance criterion for drug substance particles above (b) (4) µm in size. Accordingly, propose and justify an acceptance criterion for % level of particles retained on a (b) (4) µm screen.

2. We agree with the proposed acceptance criteria of NMT (b) (4) for the genotoxic impurity (b) (4) in the specification for (b) (4) (b) (4) As changes are likely over product lifecycle, in order to ensure detectability and continued minimization of the risk of this genotoxic impurity above acceptable levels in the drug substance, we recommend that (b) (4) be listed as a specified impurity in the specification for (b) (4)

3. In general, a drug substance's intrinsic dissolution rate correlates with the apparent dissolution of the drug product since the same solid state properties influence both dynamic processes (i.e., slow rate translates to slow dissolution). However, the characterization information on the major drug substance polymorphs (b) (4) indicates (b) (4) and the apparent dissolution of the finished tablets using your proposed dissolution method. Provide a scientific explanation for why (b) (4)

4. Describe any experiments that you have carried out to assess the [(b) (4)] of sofosbuvir in the drug product. Has the [(b) (4)] been observed to change on stability? Provide a risk assessment of the potential for change in [(b) (4)] during manufacture of the tablets or on storage.

5. Your proposed dissolution acceptance criterion of Q = [(b) (4)] minutes is not supported by the data and is not acceptable. The product performance data using the proposed method (USP 2, 50 mM potassium phosphate buffer at pH 6.8, 75 rpm) suggest that 15 minutes is a more appropriate sampling time point for routine quality control testing. Provide a revised drug product specification table reflecting a change in the dissolution acceptance criterion from Q = [(b) (4)] to Q = [(b) (4)] at 15 minutes.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

RAPTI D MADURAWE
07/12/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **July 9, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Concur: **Poonam Mishra, MD, Clinical Reviewer**
Sarah Connelly, MD, Cross Discipline Team Lead

Subject: **NDA 204671**

Please reference your NDA. The following comment is being conveyed on behalf of the review team for your application.

Please provide the reason why serum creatine kinase measurements were evaluated in only two of the four pivotal Phase 3 trials submitted in the NDA.

Please provide your response by July 15, 2013.

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

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

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LINDA C ONAGA
07/09/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **June 21, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Concur: **Karen Qi, PhD, Biometrics Reviewer**
Wen Zeng, PhD, Secondary Biometrics Reviewer
Poonam Mishra, MD, Clinical Reviewer
Sarah Connelly, MD, Cross Discipline Team Lead

Subject: **NDA 204671**

Please reference your NDA. The following initial comments are being conveyed on behalf of the review team for your application.

There seem to be more ALT values listed in LAB.XPT at some visits than what were reported in the study reports. The follow lists are some examples. Please clarify.

1. In Study 1231, the following ALT values at Week 24 were available in LAB.XPT but not included in Table 9-7.

USUBJID	Lab day	ALT value
P7977-1231-1001-310102	169	19
P7977-1231-1002-310418	176	15
P7977-1231-1009-310098	175	18
P7977-1231-1012-310290	173	21
P7977-1231-1019-310267	179	35
P7977-1231-1029-310550	169	21
P7977-1231-1035-310293	169	91
P7977-1231-1038-310207	174	50
P7977-1231-1054-310407	173	38
P7977-1231-1054-310458	174	24
P7977-1231-1079-310016	176	39

P7977-1231-1081-310551	178	35
P7977-1231-1083-310467	176	48
P7977-1231-1088-310276	175	27
P7977-1231-1091-310316	172	80
P7977-1231-1172-310594	175	16
P7977-1231-1188-310525	169	31
P7977-1231-1197-310628	166	23
P7977-1231-1216-310471	168	17
P7977-1231-1231-310372	175	21
P7977-1231-1235-310526	167	37
P7977-1231-1235-310529	167	44
P7977-1231-1235-310562	167	29
P7977-1231-1241-310259	169	109
P7977-1231-1252-310533	173	15
P7977-1231-1252-310542	173	13
P7977-1231-1252-310543	174	59

2. In Study 107, the following ALT values at Week 12 were available in LAB.XPT but not included in Table 9-7.

USUBJID	Lab day	ALT value
GS-US-334-0107-0057-7260	88	20
GS-US-334-0107-0452-7469	91	39
GS-US-334-0107-0535-7281	85	35
GS-US-334-0107-0535-7301	88	24
GS-US-334-0107-0773-7326	86	36
GS-US-334-0107-1119-7442	91	75
GS-US-334-0107-1516-7377	90	23
GS-US-334-0107-2130-7355	93	22
GS-US-334-0107-4238-7275	89	45
GS-US-334-0107-5586-7321	91	34
GS-US-334-0107-6074-7410	92	20

3. In Study 107, the following ALT values at 4 weeks after treatment were available in LAB.XPT but not included in Table 9-7.

USUBJID	Lab day	ALT value
GS-US-334-0107-0057-7212	131	16
GS-US-334-0107-0057-7224	118	12
GS-US-334-0107-0331-7394	120	31
GS-US-334-0107-0380-7220	153	30
GS-US-334-0107-0380-7234	115	37
GS-US-334-0107-0451-7424	117	16
GS-US-334-0107-0452-7459	115	21
GS-US-334-0107-0529-7328	118	28
GS-US-334-0107-1069-7371	119	28
GS-US-334-0107-1516-7412	132	83

GS-US-334-0107-2074-7397	119	22
GS-US-334-0107-2191-7406	122	33
GS-US-334-0107-2689-7247	116	10
GS-US-334-0107-4139-7272	117	14
GS-US-334-0107-4139-7282	118	70
GS-US-334-0107-4139-7318	119	13
GS-US-334-0107-5369-7403	120	13
GS-US-334-0107-5498-7435	123	18
GS-US-334-0107-5518-7253	114	12
GS-US-334-0107-5518-7254	114	70
GS-US-334-0107-5518-7386	118	15
GS-US-334-0107-5665-7202	134	11

4. In Study 108, the following ALT values at 4 weeks after treatment were available in LAB.XPT but not included in Table 9-7.

USUBJID	dyaltfw4	saltfw4
GS-US-334-0108-0380-1524	115	38
GS-US-334-0108-0451-1546	113	53
GS-US-334-0108-0518-1568	145	15
GS-US-334-0108-0530-1404	116	100
GS-US-334-0108-0530-1419	143	47
GS-US-334-0108-2493-1421	153	16
GS-US-334-0108-2493-1422	147	40
GS-US-334-0108-2493-1429	147	96
GS-US-334-0108-3060-1497	113	139
GS-US-334-0108-4238-1508	113	49
GS-US-334-0108-4262-1506	144	21
GS-US-334-0108-4434-1447	144	31
GS-US-334-0108-5367-1498	114	114
GS-US-334-0108-5369-1536	113	18
GS-US-334-0108-5369-1592	146	33
GS-US-334-0108-5852-1502	113	99
GS-US-334-0108-6214-1448	112	37
GS-US-334-0108-6833-1467	115	19

5. In Study 110, the following ALT values at 4 weeks after treatment were available in LAB.XPT but not included in Table 9-8.

USUBJID	Lab day	ALT value
GS-US-334-0110-0057-6543	116	19
GS-US-334-0110-0380-6670	121	22
GS-US-334-0110-0407-6483	115	18
GS-US-334-0110-0521-6706	117	13
GS-US-334-0110-0530-6412	120	68
GS-US-334-0110-0532-6587	128	14
GS-US-334-0110-0532-6672	120	29

GS-US-334-0110-0532-6720	120	41
GS-US-334-0110-0535-6441	118	406
GS-US-334-0110-1055-6565	113	25
GS-US-334-0110-1516-6589	119	13
GS-US-334-0110-1536-6514	118	36
GS-US-334-0110-1543-6512	115	142
GS-US-334-0110-1543-6573	116	106
GS-US-334-0110-1543-6666	115	18
GS-US-334-0110-1603-6465	121	84
GS-US-334-0110-1668-6506	125	33
GS-US-334-0110-2130-6630	130	13
GS-US-334-0110-2130-6650	124	11
GS-US-334-0110-2493-6453	120	16
GS-US-334-0110-2689-6428	116	19
GS-US-334-0110-2689-6534	116	8
GS-US-334-0110-3060-6417	120	130
GS-US-334-0110-3060-6614	126	37
GS-US-334-0110-3996-6607	115	19
GS-US-334-0110-4238-6712	116	92
GS-US-334-0110-4262-6430	116	9
GS-US-334-0110-4262-6466	120	21
GS-US-334-0110-4262-6522	117	23
GS-US-334-0110-4262-6572	117	24
GS-US-334-0110-4262-6703	118	91
GS-US-334-0110-4262-6715	141	34
GS-US-334-0110-4262-6728	116	19
GS-US-334-0110-4434-6634	123	35
GS-US-334-0110-5369-6553	117	14
GS-US-334-0110-5369-6554	116	16
GS-US-334-0110-5498-6540	116	15
GS-US-334-0110-5498-6544	116	15
GS-US-334-0110-5518-6426	117	24
GS-US-334-0110-5586-6468	117	18
GS-US-334-0110-5586-6473	115	31
GS-US-334-0110-5665-6445	117	44
GS-US-334-0110-5665-6496	119	10
GS-US-334-0110-6834-6410	71	13
GS-US-334-0110-6840-6549	117	25
GS-US-334-0110-6840-6597	115	151
GS-US-334-0110-6840-6632	117	170

Please provide your response by July 12, 2013.

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

_____

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

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/s/

LINDA C ONAGA
06/21/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **June 14, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Sohail Mosaddegh, PharmD**

Concur: **Poonam Mishra, MD, Clinical Reviewer**
Sarah Connelly, MD, Cross Discipline Team Lead

Subject: **NDA 204671**

Please reference your NDA. The following initial comments are being conveyed on behalf of the review team for your application.

1. Please provide follow-up information on subject # 1031-310130 (Study P7977-1231) with increased creatine phosphokinase leading to discontinuation of study drugs. Specifically, what was the final diagnosis on this subject? Please provide additional relevant information such as past medical history, concomitant medications and laboratory data including but not limited to serum creatinine values. Also provide reports of any additional diagnostic testing done for the definitive diagnosis.

2. Please provide an assessment of the observed finding of increased creatine kinase levels. Please provide safety data on the primary safety population as well as the secondary safety population, including special HCV populations and subjects enrolled in Other Studies and Individual Investigator/Compassionate Use programs as described in your NDA submission. Please include relevant case narratives with pertinent information such as past medical history, concomitant medications and laboratory data including serum creatinine values.

3. Please provide the laboratory data on subject # 0535-7281 (Study GS-US-334-0107) with muscle spasms.

4. Please provide a high level comprehensive safety summary on muscle-related adverse events.

Please provide your response by June 28, 2013.

We are providing this above information via telephone facsimile for your convenience. Please feel free to contact Linda Onaga, MPH at 301-796-0759 if you have any questions regarding the contents of this transmission.

Sincerely,

{See appended electronic signature page}

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

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/s/

SOHAIL MOSADDEGH
06/14/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **June 10, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Concur: **George Lunn, PhD, CMC Reviewer**
Fuqiang Liu, PhD, CMC Reviewer
Steve Miller, PhD, CMC Lead
Poonam Mishra, MD, Clinical Reviewer
Sarah Connelly, MD, Cross Discipline Team Lead

Subject: **NDA 204671**

Please reference your NDA. The following initial comments are being conveyed on behalf of the review team for your application.

Drug Substance

1. We recommend the following revisions to the drug substance specification:

   a. Per ICH Q3A guidance, revise "unspecified impurity" to (b) (4) from your current proposal of (b) (4)

   b. Include (b) (4) in your drug substance specification as it is used in (b) (4) (b) (4) of the drug substance manufacturing process.

2. Provide (b) (4) study data for the (b) (4) of drug substance. This data is currently not listed in the Elucidation of Structure (3.2.S.3.1).

3. Table 8 in Section 3.2.S.2.6 (page 29) lists an impurity identified as (b) (4) Clarify if this is accurately listed or if it is (b) (4)

4. On page 13 of 3.2.S.7.1, you claimed drug substance storage condition of "store below 30 ºC", [redacted]

5. We are currently reviewing your proposed starting materials. Regarding controls of your proposed starting materials and intermediates, we have the following recommendations:

   a. For the specification of [redacted], revise [redacted] impurity" to [redacted] from your current proposal of NMT [redacted] as [redacted] is [redacted] from the drug substance.

   b. For the specification of [redacted]

      i. You proposed NMT [redacted] for [redacted] impurity", but you mentioned acceptance level of NMT [redacted] in 3.2.S.2.6. Please reconcile.

      ii. Include an acceptance criterion of NMT [redacted] for [redacted] as indicated in 3.2.S.2.6.

   c. For intermediates [redacted] propose and justify appropriate acceptance criterion for [redacted] impurity."

6. In the Amendment of 5/21/13 you describe the various [redacted] methods that have been used to test the drug substance. However, it is not clear to us which method was used to test which batch. Please indicate which method was used to test each batch of the drug substance listed in section S.4.4, Table 1.

Drug Product

7. A complete description of the commercial scale drug substance and drug product manufacturing processes is required and should include process parameters. Therefore, include a master batch record and/or a detailed manufacturing process description in section S.2.2 (drug substance) and P.3.3 (drug product) of the application. Notification of all changes including changes to process parameters should be provided in accordance with 21CFR 314.70. The Agency recognizes that changes to low criticality process parameters can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation. Separate unexecuted Master Batch Records or detailed manufacturing process descriptions should be provided for commercial scale batches of tablets as manufactured by [redacted] and Gilead Cork.

8. The drug product should comply with USP <467> for residual solvents. To satisfy this requirement, provide a formal analysis of the residual solvent limits for the drug substance and excipients.

9. We note that there are no tests for the [redacted] of the drug product. [redacted]

10. With regards to the container-closure system,

    a. We note that a variety of container-closure system components have been used for the primary stability batches of drug product. Please provide manufacturer names and part numbers for the components that you intend to use for commercial batches. Please describe the change control strategy you will use if you wish to employ a container-closure system component that has not been used for one of the primary stability batches. This should include a side by side comparison of the container-closure system, dimensions and properties (head space, moisture permeation, etc) that affect stability, to show that the proposed container-closure system provides equivalent protection to the container closure system used for the primary stability batches.

    b. Please provide a Letter of Authorization to refer to a DMF for the polyester coil.

    c. Please provide more details for the bottle described as (b) (4) used for primary stability batch DC1204B1.

    d. Batch 12SB003R uses a (b) (4) CR closure (b) (4) from Top Seal. Is this covered by one of your referenced Letters of Authorization?

11. Please provide a methods validation package consisting of a list of samples that could be supplied and links to the various methods.

12. In the Amendment of 5/21/13 you describe the various dissolution methods that have been used to test the 400 mg tablets. However, it is not clear to us which method was used for which batch. Please indicate which dissolution method was used to test each batch of 400 mg tablets manufactured from (b) (4) drug substance (as listed, for example, in Table 4 in 3.2.P.5.4).

13. Tablet Batch 12SB001R appears to (b) (4) Please comment.

14. In Section P.2.2, page 25, you describe the dissolution of Lot FYA-5206-40 made from (b) (4) drug substance. Also in P.2.1, page 11, Table 6 you refer to (b) (4) drug substance Lot 1254-51-1. Please indicate how you quantitatively determined that these batches of drug substance were (b) (4) Provide the relative amounts of (b) (4) and (b) (4) in drug substance batches FYA-5206-40 and 1254-51-1? What are the relative amounts of (b) (4) and (b) (4) in the batches of drug substance used to manufacture the batches of drug product in P.5.4, Table 4 on page 9.

Please provide your response by June 21, 2013.

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

_____

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

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/s/

LINDA C ONAGA
06/11/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204671

FILING COMMUNICATION

Gilead Sciences, Inc.
Attention: Shalini Gidwani, MSc, RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Gidwani:

Please refer to your New Drug Application (NDA) dated April 6, 2013, received April 8, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for sofosbuvir 400 mg tablet.

We also refer to your amendments dated April 8, 2013, May 1, 2013, May 3, 2013, and May 21, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm. Therefore, the user fee goal date is December 8, 2013.

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 September 8, 2013. In addition, the planned date for our internal mid-cycle review meeting is July 8, 2013. We are 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.

We request that you submit the following information:

1. In the NDA Safety Update Report, please include narratives for all cases of completed suicide, suicide attempt, and suicidal ideation in the sofosbuvir clinical development program through the Safety Update Report cutoff date. Also include your assessment of this safety issue.

2. We acknowledge your proposal for reduced microbiological testing, in particular the elimination of microbial limits testing at product release and annual stability batch testing but not the primary stability batches. While the elimination of microbial limits testing at release may be acceptable, based on the development history of the drug product consistently meeting the microbial burden acceptance criteria, we request that you include microbial limits testing in your commitment to annual batch testing where a single, initial time point would suffice. Please provide a microbial limits specification for the yearly testing commitment and reference to the testing method which should comply with USP <61> and <62> or the equivalent, as previously cited.

3. FDA encourages sponsors to submit a pharmacovigilance plan designed to detect new safety risks and to further evaluate identified safety risks with sofosbuvir following market approval. The pharmacovigilance plan can be included in Module 5 of the Electronic Common Technical Document (eCTD). Currently, submission of a pharmacovigilance plan is voluntary and is not subject to specific regulatory or statutory requirements.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Highlights of Prescribing Information –

    a. Please remove the space between the product title and the initial US approval line The Initial US approval must be directly under the TRADENAME.

    b. The indication statement must identify the established pharmacologic class. Please update accordingly.

    c. Please remove bullet 4 under Use in Specific Populations. The absence of information about (b) (4) should not be included under this heading.

2. Full Prescribing Information –

    a. The indication statement must identify the established pharmacologic class. Please update accordingly.

    b. Please confirm if the patient information is a separate document. If it is, please add the manufacture information after section 17 of the Full Prescribing Information.

    c. Please include the findings from the formal ECG study (thorough QT study) performed in healthy volunteers, Protocol P7977-0613 entitled "A Single Dose, Randomized, Blinded, Placebo and Positive Controlled, Four Period Cross Over Study to Investigate the Effect of PSI 7977 at a Projected Therapeutic and Supratherapeutic Dose on the QT/QTc Interval in Healthy Volunteer", in section 12 Clinical Pharmacology.

We request that you resubmit labeling that addresses these issues by June 21, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

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

If you have any questions, call Linda C. Onaga, Regulatory Project Manager, at (301) 796-0759 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

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/s/

DEBRA B BIRNKRANT
06/07/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **June 5, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Concur: **Poonam Mishra, MD, Clinical Reviewer**
Sarah Connelly, MD, Cross Discipline Team Lead

Subject: **NDA 204671**

Please reference your NDA. The following initial comments are being conveyed on behalf of the review team for your application.

1. Please provide additional information on Subject# 2074 - 7350 (Case Number: 2012-0061503; Study GS-US-334-0107) who died 47 days after the last dose of study drug. Specifically, provide any available results for echocardiograms done prior to enrollment in the trial and the echocardiogram done after completion of study treatment (i.e. prior to aortic valve replacement). Also obtain and provide the copy of the autopsy/coroner's report.

2. As you might be aware, the clinical development of one of the direct acting antiviral agents, a nucleotide polymerase (NS5B) inhibitor in development for the treatment of hepatitis C, was stopped due to concerns of a serious safety issue related to cardiac toxicity. Since sofosbuvir (GS-7977) belongs to the same drug class although structurally different, we would like you to provide an integrated safety summary focused on cardiovascular events. Please provide safety data on the primary safety population as well as the secondary safety population, including special HCV populations and subjects enrolled in Other Studies and Individual Investigator/Compassionate Use programs as described in your NDA submission. Please include relevant case narratives as well.

3. Please also provide a high level safety summary on gastrointestinal and renal adverse events, including relevant case narratives.

   Please provide your response by June 25, 2013.

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

_____

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

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/s/

LINDA C ONAGA
06/05/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **May 9, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Concur: **Poonam Mishra, MD, Clinical Reviewer**
Sarah Connelly, MD, CDTL
George Lunn, PhD, Product Quality Reviewer
Fuqiang Liu, PhD, Product Quality Reviewer
Stephen Miller, Product Quality Team Lead

Subject: **NDA 204671**

Please reference your NDA. The following initial comments for are being conveyed on behalf of the review team for your application.

Clinical:

1. Be aware of for future submissions the following issue: There were inconsistent values for LBTESTCD within LBTEST in FISSION study. For example: for LBTEST = Creatinine Clearance there were two different LBTESTCD (CRCLCG and CRCLCKD), two different methods, and two different units. There should have been a unique LBTEST for each LBTESTCD.

CMC

2. In light of ORA observations that were communicated to Gilead, Foster City CA in the FDA form 483 dated April 26, 2013, clarify if different analytical procedures, or different versions of analytical procedures, than those submitted in this application were used for the NDA release and primary stability data. Please provide a detailed summary of the differences and include bridging data where appropriate.

Please respond to the FDA CMC correspondence by June 7, 2013.

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

_____

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

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/s/

LINDA C ONAGA
05/09/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **204671**

Drug: **sofosbuvir**

Date: **April 24, 2013**

To: **Shalini Gidwani, MSc, RAC Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

From: **Linda C. Onaga, MPH**

Concur: **Eric Donaldson, PhD, Clinical Virology Reviewer**
Jules O'Rear, PhD, Clinical Virology Team Lead

Subject: **NDA 204671**

Please reference your NDA. The following initial comments for are being conveyed on behalf of the review team for your application.

Please provide the Unique Subject Identifiers (USUBJID) for all of the Next Generation Sequencing files submitted for studies p2938-0721, p7977-0221, P7977-0422, P7977-0724, P7977-0523, P7977-1231, GS-US-334-0107, GS-US-334-0108, and GS-US-334-0110. We recommend doing this by adding USUBJID as column 1 to the filemap.xpt file for each study. Please provide these modified tables by **May 1, 2013.**

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

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

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/s/

LINDA C ONAGA
04/25/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204671

NDA ACKNOWLEDGMENT

Gilead Sciences, Inc.
Attention: Shalini Gidwani, M.Sc., RAC
Associate Director, Regulatory Affairs
334 Lakeside Dr.
Foster City, CA 94404

Dear Ms. Gidwani:

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

Name of Drug Product: sofosbuvir, 400 mg tablets

Date of Application: April 6, 2013

Date of Receipt: April 8, 2013

Our Reference Number: NDA 204671

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 June 7, 2013, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.
If you have any questions, call Linda C. Onaga, Regulatory Project Manager, at (301) 796-0759 or the Division mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

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

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/s/

LINDA C ONAGA
04/15/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106739

MEETING MINUTES

Gilead Sciences, Inc.
Attention: Shalini Gidwani, MSc, RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Gidwani:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sofosbuvir (GS-7977).

We also refer to the meeting between representatives of your firm and the FDA on March 14, 2013. The purpose of the meeting was to discuss the contents of a complete NDA package for sofosbuvir.

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

If you have any questions, call Linda C. Onaga, MPH, Regulatory Project Manager at (301) 796-0759 or the Division mainline at (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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	pre-NDA
Meeting Date and Time:	March 14, 2013
Meeting Location:	FDA White Oak Campus 10903 New Hampshire Ave Bldg 22 RM 1315 Silver Spring, MD 20903
Application Number:	106739
Product Name:	sofosbuvir
Proposed Indication:	[TRADENAME] is indicated for the treatment of chronic hepatitis C (CHC) in adults, in combination with ribavirin for patients with genotype 2 or 3 infection; and in combination with ribavirin and pegylated interferon for patients with genotype 1, 4, 5 or 6 infection.
Sponsor/Applicant Name:	Gilead Sciences, Inc.
Meeting Chair:	Debra Birnkrant, M.D.
Meeting Recorder:	Linda C. Onaga, M.P.H.

FDA ATTENDEES (* participated via telephone)

David Roeder, MS*	ADRA, OAP
Debra Birnkrant, M.D.	Director, DAVP
Kendall Marcus, M.D.	Deputy Director for Safety, DAVP
Kimberly Struble, Pharm.D.	Clinical Team Lead, DAVP
Linda Lewis, M.D.*	Clinical Team Lead, DAVP
Mary Singer, M.D.	Clinical Team Lead, DAVP
Sarah Connelly, M.D.	Clinical Reviewer, DAVP
Poonam Mishra, M.D.	Clinical Reviewer, DAVP
Julian O'Rear, Ph.D.	Virology Team Lead, DAVP
Lisa Naeger, Ph.D.	Virology Reviewer, DAVP
Eric Donaldson, Ph.D.	Virology Reviewer, DAVP
Shirley Seo, Ph.D.	Clinical Pharmacology Team Leader, DCP4
Jenny Zheng, Ph.D.	Clinical Pharmacology Reviewer
Jeffry Florian, Ph.D.	Pharmacometrics Reviewer
Chris Ellis, Ph.D.	Acting Pharmacology and Toxicology Team Lead, DAVP
Stephen Miller, Ph.D.	CMC Lead, ONDQA
Fraser Smith, Ph.D.	Biometrics Reviewer
Karen Qi, Ph.D.	Biometrics Reviewer

Wen Zeng, Ph.D.*	Biometrics Reviewer
Katherine Schumann, M.S.	Acting Chief, Project Management Staff
Linda Onaga, M.P.H.	Regulatory Project Manager, DAVP
Kyong Hyon, CDR	Safety Regulatory Project Manager, DAVP
Alfred Sorbello, M.D.*	DPVII/OSE
Kendra Worthy, Pharm.D.*	Team Lead, DRISK
Kim Taylor*	OPA/FDA
Morgan Walker, Pharm.D.*	DMEPA/OSE
Patrick Harrington, Ph.D.*	Virology Reviewer, DAVP
Islam Younis, Ph.D.*	Clinical Pharmacology Team Leader, DCP4
Ruben Ayala, Pharm.D.*	Clinical Pharmacology Reviewer

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou	Independent Assessor

SPONSOR ATTENDEES

John McHutchinson, M.D.	Senior Vice President, Liver Disease Therapeutics
William T. Symonds, Pharm.D.	Vice President, Clinical Research Liver Disease Therapeutics
Mani Subramanian, M.D.	Vice President, Clinical Research Liver Disease Therapeutics
Diana Brainard, M.D.	Senior Director, Clinical Research Liver Disease Therapeutics
Neby Bekele, Ph.D.	Senior Director, Biostatistics
Brian Kearney, Pharm.D.	Senior Director, Clinical Research, Clinical Pharmacology
Michael Miller, Ph.D.	Senior Director, Clinical Virology
Evguenia Svarovskaia, Ph.D.	Senior Research Scientist I, Clinical Virology
Paul Tomkins, Ph.D.	Senior Director, Regulatory Affairs
Shalini Gidwani, MSc, RAC	Associate Director, Regulatory Affairs

1.0 BACKGROUND

Gilead Sciences, Inc. (Gilead) is developing sofosbuvir (GS-7977), a direct-acting antiviral agent for the treatment of chronic hepatitis C (CHC) infection in genotypes 1, 2, 3, 4, 5, and 6. On October 17, 2012, representatives from Gilead met with the Division of Antiviral Products (Division) in a type C meeting to discuss the strategy related to the format and content of the New Drug Application (NDA) for sofosbuvir. Due to the lack of top line data from all phase 3 trials, the Division could not reach full agreement on all aspects related to the submission of an NDA for sofosbuvir. The Division inquired about Gilead's plans to request a pre-NDA meeting, since sofosbuvir is a new molecular entity and would be subject to "The Program" under PDUFA V. During this meeting, Gilead informed the Division that they would not request a pre-NDA meeting for this application because a pre-NDA meeting did not fit into their expedited timeline of a mid-April 2013 NDA submission.

On February 1, 2013, Gilead provided emerging data from two phase 3 clinical trials, plans to modify ongoing studies, and submission of a new protocol to the Division. In addition, Gilead informed the Division that the treatment duration for genotype 3, treatment-experienced patients would be extended from 12 weeks to 16 weeks based on this new information. In light of the new information and change to treatment duration, the Division advised Gilead to request a pre-NDA meeting for this application.

The primary purposes of this pre-NDA meeting are:

1. To seek agreement with the Agency on key aspects related to the content and format of the application.

2. To seek agreement on key phase 3 data and discuss with the Agency the proposed indication for sofosbuvir, specifically for genotype 3 subjects.

2. DISCUSSION

After introductions, Dr. Debra Birnkrant provided opening comments on Gilead's development program for sofosbuvir, including optimizing the genotype 2 treatment-experienced and genotype 3 treatment sustained virologic response (SVR) rates, post-marketing clinical trial studies, and additional clinical trials for special populations. Gilead agreed with the comments and noted more work is required with the sofosbuvir clinical development program.

Gilead proposed that the meeting focus on the Agency's preliminary comments I, III, IV, V, and VII. Gilead will respond to FDA Additional Comments II, VI, VIII, and IX in writing.

To convey the discussion points from this meeting, the preliminary FDA comments are in *italics* and discussion points in regular text.

2.1. Additional FDA Comments

I. Potential review and Advisory Committee topics

A. Optimal HCV GT2 and GT3 duration

We request your assessment for why SOF/RBV x 16 weeks is or is not supported for HCV GT2 treatment-experienced subjects and GT3 treatment-naïve subjects based on the following:

1. ***HCV GT2 treatment-experienced population, SOF/RBV-12 versus -16 weeks***
   GS-US-334-0108 demonstrates a numerical trend toward improved SVR12 rates with longer SOF/RBV duration, particularly in certain subgroups (e.g., cirrhosis, prior nonresponse); however, small subgroup sample size is acknowledged.

   Discussion: (Slides 3-5)

   Gilead presented summary data supporting 12-week treatment duration for genotype 2 treatment-naïve and treatment-experienced HCV-infected patients. Their rationale for the 12-week duration is based on the high response rates in genotype 2 across multiple trials, overlapping confidence intervals, and small numbers in subgroups such as cirrhosis which therefore affect the differences observed. Gilead stated that they were cautious about over interpreting results given the small numbers across the subgroups. Therefore, Gilead has no plans to change the 12 week treatment duration for all genotype 2 patients in the proposed label.

   The Agency advised Gilead to provide their justification for the 12 week regimen in genotype 2 treatment-experienced patients with their original NDA submission. In addition, this proposed treatment duration maybe a topic for discussion at the FDA Advisory Committee Meeting. The Agency also recognizes that the subgroups have small numbers and will review the data during the NDA review cycle.

2. ***HCV GT3 treatment-naïve population, SOF/RBV-12 versus -16 weeks***
   HCV GT3 SVR rates are improved with longer treatment duration in GS-US-334 0108, the only pivotal trial where different durations were explored. These data, combined with the approximately 40% relapse rate in the treatment-naïve trials, strongly suggest a longer GT3 treatment duration would be beneficial in all GT3 subjects.

   Discussion: (Slides 6 - 7)

   Gilead agreed with the Agency's recommendation that longer treatment duration (16 weeks) would be more beneficial for all genotype 3 treatment-naïve and treatment-experienced HCV-infected patients. Gilead confirmed the longer duration for genotype 3 treatment-naïve and treatment-experienced patients will be proposed in

the NDA package for sofosbuvir. In addition, the NDA package will include a rationale and modeling data supporting a genotype 3 treatment-naïve 16 week treatment duration.

B. Future HCV GT2 and GT3 development

Further optimizing treatment duration and/or the contribution of pegylated interferon in GT2 treatment-experienced and all GT3 patients will likely be an Advisory Committee topic for discussion. We believe you have the opportunity to begin addressing these questions now in the context of a phase 4 clinical trial.

Discussion: (Slide 8-9)

Gilead presented the ongoing trials using sofosbuvir plus ribavirin and with/without pegylated interferon. The treatment duration in the VALENCE trial (GS-US-334-0133) was extended for genotype 3 subjects from 12 to 24 weeks and the majority of subjects enrolled in this European based study are treatment-experienced. LONESTAR2 (GS-US-334-0151) is currently enrolling, but there has been difficulty enrolling additional subjects into the trial. For the Open Label Access Study (GS-US-334-0139), Gilead incorporated Agency comments regarding expanding access to sofosbuvir for subjects who have no other treatment options and will provide this information in writing to the Agency. It was agreed that the Agency and Gilead would have a follow-up teleconference to continue discussion on expanded access of sofosbuvir to severely ill patients.

For GS-US-334-0109, the open label protocol for prior Gilead-sponsored trial participants, Gilead received the Agency's comments and will respond in writing. The Agency inquired about the possibility of designing a randomized clinical trial to answer some of the questions related to treatment duration and regimen (with or without pegylated interferon) for the harder to treat populations (e.g. genotype 3, prior sofosbuvir relapsers). Gilead stated that a randomized clinical trial with a pegylated interferon-containing arm may be more difficult if enrolling previous sofosbuvir trial participants since many of the genotype 2 and 3 subjects enrolled in the sofosbuvir development program are interferon ineligible or unwilling or have other co-morbidities.

The Agency also inquired about the possibility of having a separate clinical trial to retreat prior sofosbuvir-failure patients with sofosbuvir plus ribavirin and with/or without pegylated interferon for 12 or 24 weeks, particularly since development of NS5B resistance does not appear to be a major concern. Gilead replied that the definition of relapse is important. Re-treating a patient with another 12 weeks of sofosbuvir plus ribavirin versus an initial treatment of the same regimen for a longer duration would be more beneficial since the longer duration may decrease the likelihood of relapse. FDA advised that a second follow-on study answering the question of optimal treatment duration is desirable.

Gilead will internally discuss a future trial in sofosbuvir-failure patients and come back to the Agency with a proposal.

The Agency informed Gilead that this future genotype 2 and 3 development may be a topic for discussion at the Advisory Committee meeting. The Agency stressed the importance of knowing the development program now for the long-term cohesive plan.

Additional Advisory Committee Discussion:

Gilead inquired about the specificity of the indications to be included in the labeling for this NDA, as they struggle with what content will be in the label and what healthcare providers will do in practice. (b) (4) (b) (4) (b) (4) The Agency responded that this issue will also be a topic for discussion during the NDA review and the Advisory Committee meeting.

The Agency expressed concern on the amount of information including emerging data made public by Gilead and its impact on the Advisory Committee meeting and the regulatory decision making. Regulatory decisions are based on data and information submitted and reviewed by the Agency. Therefore if the data were not formally submitted with the original NDA submission, then it will be extremely difficult for the Agency to discuss the data at an Advisory Committee meeting. The Agency would like to avoid additional discussion at this public meeting on data that were not reviewed by the Agency.

Gilead inquired about whether other topics would be discussed at the Advisory Committee meeting. The Agency responded that other potential topics could include discussion of the use of pegylated interferon, treatment duration, safety, post-marketing studies, bridging and modeling data, and special populations. Gilead will be notified of the topics for the Advisory committee meeting well in advance of the meeting. The goal of the Advisory Committee meeting is to obtain advice from experts on this important drug. This meeting also provides a chance for the public to comment on this drug during the review cycle.

III. SVR24 data to be included at the time of NDA submission.

The pre-NDA background document noted anticipated dates for complete pivotal trial SVR24 data. Please provide the amount of SVR24 data for each trial to be included with the NDA submission.

Discussion: (Slide 10)

Gilead will provide all available SVR24 data with the original NDA submission, including all subjects from POSITRON and the SOF/RBV x 12-week arm in FISSION. Gilead will not provide SVR24 data with the original submission for the FUSION, NEUTRINO and

the PEG/RBV x 24-weeks arm in FISSION trials because enrollment occurred rapidly and the last study visits dates are during the NDA review cycle.

IV. Transplant and decompensated cirrhosis populations.

Please comment if P7977-2025 data is planned for labeling. In addition, please provide the current trial status of GS-US-334-0125 and GS-US-334-0126.

Discussion: (Slides 11-19)

Gilead will request labeling for transplant and (b) (4) populations in the NDA submission; however, there are challenges of how and where to describe the data in the label. P7977-2025 enrollment is complete across 16 sites; 28 transplants have occurred out of 61 enrolled subjects. Gilead noted that more than half of the relapses occurred at one site in Spain. Study investigators for this clinical trial will conduct additional discussion with the Spanish site investigator and perform additional data analyses to see what occurred. The Agency noted that there appeared to be several relapsers and recommended that Gilead do a phylogenetic analysis of the baseline isolates from these subjects.

According to Gilead, the data generated from this study yielded impressive results, which (b) (4) Gilead has received interest from the investigators to publish the current results in a prominent journal in the summer of 2013.

The decompensated liver disease trial, GS-US-334-0125, is enrolling. A recent protocol amendment extended sofosbuvir + ribavirin treatment duration to 48 weeks. The post-liver transplant trial, GS-US-334-0126, should finish by the end of May 2013. Gilead noted that the majority of subjects were undetectable by Week 3. At this time, expanding the treatment duration in this trial would be difficult. Their rationale is based on the avoidance of over exposure of the treatment therapy in individuals who have chronic HCV infection and a new liver. Gilead would like to answer the question on whether 24 weeks is sufficient before extending treatment duration.

Discussion on labeling for the pre-liver transplant population will be done in the context of the NDA review. Gilead will submit P7977-2025 synoptic reports for each subject with the NDA submission and subject narratives would not be available. The Agency requested Gilead provide these narratives with the initial NDA submission. The narratives would be helpful for the review and potentially labeling. In any event, narratives would be requested during the NDA review; so Gilead should start preparing and ideally submit with the initial NDA.

V. Renal dosing

The P7977-0915 clinical study report indicates that for primary circulating metabolite, GS-331007, AUC_{0-24} was 54%, 64%, and 193% higher in subjects with mild, moderate, and severe renal impairment compared with subjects with normal renal function, respectively. The Cmax values were 28%, 10%, and 34% higher in subjects with mild, moderate, and

severe renal impairment, respectively. In subjects with ESRD, relative to subjects with normal renal function, the GS-331007 AUC_{0-24} and Cmax values were 162% and 10% greater when sofosbuvir was dosed 1 hour prior to hemodialysis compared with 404% and 80% higher when sofosbuvir was administered after hemodialysis. You conclude SOF 400 mg is not recommended for use in subjects with severe renal impairment or ESRD because there is no clinical safety data available to support these GS-331007 levels, and a sofosbuvir dose reduction to lower metabolite exposures may not result in adequate exposures of sofosbuvir and its active anabolite at the site of action.

We request further discussion to explore SOF dosing in severe renal impairment.

Discussion: (Slide 20)

Gilead provided clarification on the Agency's comment regarding P7977-0915 clinical study report and presented the predicted steady-state exposure values of sofosbuvir and its metabolite GS-331007 in HCV-subjects with renal impairment. Gilead is committed to doing an additional trial in HCV-infected subjects with severe renal impairment and will work with the Agency to design the trial.

VII. Virology – Next Generation Sequencing Agreement on NGS

Thank you for providing the mock dataset for the Quantum phase 2 study. We have analyzed a portion of the data submitted and compared our results to those provided by you in the DEEPFRQ.xpt file. We noted important differences that likely resulted from the different approaches used to do these analyses:

A. *We detected cross-contamination of samples. For example, GT1a NS5B was consistently found in GT3a samples. For the most part these sequences did not interfere with an appropriate assembly but could be a problem for genotypes and subtypes that are more closely related. Please comment on how this cross-contamination may have occurred and provide a strategy for reducing the potential impact of cross-contaminated samples.*

Discussion:

Gilead agreed that contaminating sequences were present at less than 1% in several samples and agreed to check with their contractors to reduce this cross contamination that was likely an artifact of barcoding. They indicated that since this is below 1% that it is below the agreed upon threshold, but agreed to look in future samples.

B. *The filtering criteria used by the different algorithms employed for assembly provided significantly different results. For example, in subject 20038, we used two independent assembly algorithms (with different filtering criteria) and both of these identified an R374W substitution in two of the three W+4 sequence runs. This substitution was reported at a frequency of greater than 99% by both of these algorithms, but was not reported at any*

frequency in the results provided by Gilead. Please provide an explanation for this discrepancy.

Discussion:

Gilead provided an explanation for this discrepancy by stating that the population based changes were reported in a different table. They asked if these types of substitutions should be reported in the frequency table.

The Agency requested Gilead report all substitutions that occur at a frequency of 1% or greater as compared to the reference sequence in the frequency table. Do not report frequencies for wild type amino acids. Gilead agreed to do this, stating that it would be a change to the current rules for population sequencing.

C. *Filtering/mapping/variant calling criteria will be an important consideration for NGS data submissions. Please provide the detailed parameters used by your algorithm for filtering and mapping reads and calling variants. For example, in our initial analysis, we used the following parameters:*

1. *Filtering*
    i. *Reads were trimmed by quality score using the modified-Mott trimming algorithm with a limit of 0.05*
    ii. *The maximum number of ambiguities allowed per read after trimming the ends: 2*
    iii. *Reads of 15 or less in length were discarded*
2. *Mapping*
    i. *Mismatch cost: 2*
    ii. *Insertion cost: 3*
    iii. *Deletion cost: 3*
    iv. *Length fraction of read required for mapping: 0.5*
    v. *Similarity fraction: 0.85*
    vi.
3. *Variant detection*
    i. *Quality was assessed in a neighborhood of 5 nucleotides flanking the SNP*
    ii. *Reads with 2 or more mismatches or gaps were ignored for variant calling*
    iii. *Any reads with an average quality Phred score below 15 in the neighborhood where ignored for variant calling*
    iv. *Reads containing the variant must have quality Phred scores equal to or greater than 20*
    v. *Minimum coverage was set to 500*
    vi. *Frequency was set to 1%*

vii. *The variant was required to be present in reads from both to the forward and reverse directions*

Discussion:

Gilead agreed that these criteria will be important for interpretation of results and indicated that they use pyromap and did not provide these details with the mock dataset. They also indicated that the parameters they use are much different than those reported here, and indicated that they used much less stringent criteria for calling variants for the purpose of finding as much variation as possible. They agreed to submit the cut offs used for filtering, trimming, mapping and calling variants.

The Agency commented on the different assembly and mapping algorithms which have provided enormous differences in mapping and indicated that having these parameters will be useful for comparing results.

D. *We recommend a minimum targeted coverage of 5000. However, we recognize that some samples with lower viral loads may not produce assemblies at this level of coverage. Please identify samples that did not reach this level of coverage.*

Discussion:

Gilead responded that they are shooting for coverage of 10,000 at each position and indicated that they will provide a coverage table indicating the exact coverage of each position for each sequence run. However, they also indicated that it is impossible to get this coverage in some regions and indicated that they will continue to report substitutions that occur in low frequency regions in the frequency table. These will be reported as values not flags.

The Agency agreed that this would be sufficient but warned that substitutions that occur in low frequency regions will be interpreted with caution. This will be particularly true if there is disagreement on coverage levels between mapping algorithms.

E. *Frequency table modifications. Please do not provide the frequency of the wild type amino acid in the frequency table. In the example below, rows colored yellow should not be reported:*

STUDYID	SUBID	NGSPL	VISIT	AVISIT	ISOLDTC	ISOLID	AAPOS	AAREF	AASUB	TCOV	VCOV	PERCENT
P2938-0721	20038	Illumina MiSeq	BASELINE/DAY1			AB442474	11	I	V	19756	3078	15.58
P2938-0721	20038	Illumina MiSeq	BASELINE/DAY1			AB442474	11	I	I	19756	16625	84.15
P2938-0721	20038	Illumina MiSeq	BASELINE/DAY1			AB442474	113	S	G	6928	101	1.45
P2938-0721	20038	Illumina MiSeq	BASELINE/DAY1			AB442474	113	S	S	6928	6819	98.42
P2938-0721	20038	Illumina MiSeq	BASELINE/DAY1			AB442474	116	I	V	7002	943	13.46
P2938-0721	20038	Illumina MiSeq	BASELINE/DAY1			AB442474	116	I	I	7002	6028	86.08
P2938-0721	20038	Illumina MiSeq	BASELINE/DAY1			AB442474	250	R	K	11808	487	4.12
P2938-0721	20038	Illumina MiSeq	BASELINE/DAY1			AB442474	250	R	R	11808	11286	95.57
P2938-0721	20038	Illumina MiSeq	BASELINE/DAY1			AB442474	282	S	S	11711	11557	98.68

Discussion:

Gilead agreed to report all amino acid differences from baseline that occur at or above 1% and to not report the wild type amino acid frequency in the frequency table.

F. *Please provide the summary tables previously agreed upon, including the frequency table, the table presenting a high-level summary of the predominant substitutions, and the table containing the consensus sequences for each NGS sequence run in the same format used for population-based sequencing applying two filtering levels: 1) only show amino acids with a frequency greater than or equal to 0.2, and 2) only show amino acids present at a frequency equal to or greater than 0.05. Blank cells should be used when there is no change from baseline.*

Discussion:

(b) (4)

G. *Submission of Data to DAVP*

Currently, NGS data must be submitted via a portable hard drive to the division, following the procedure used to submit the mock data. However, please prepare these data using these suggestions:

1. *Only fasta and fastq files should be submitted on the hard drive.*

   Discussion:

   Gilead agreed to submit only the fasta and fastq sequences on the external hard drive

2. *Summary tables and protocols should be submitted with the original NDA submission through the electronic gateway.*

   Discussion:

Gilead agreed to submit summary tables and protocols with the original NDA submission through the electronic gateway in Module 5.3.5.4.

3. *You are welcome to submit fasta alignment files, but we do not have the capacity at this time to analyze alignment files in this format. Assemblies should be submitted in the ACE, SAM or BAM format if you would like these considered in the review process. Alternatively, the fasta sequences used to generate the assemblies can be submitted in fasta format.*

Discussion:

Gilead agreed to submit fasta sequences for their alignments where they will remove the dashes that represent gaps in the alignment (or placeholders for the alignment).

The Agency currently does both *de novo* assemblies and mapping to a reference, using two independent algorithms. It was agreed that Gilead could provide the fasta sequences that could then be realigned to the reference. However, for it was re-iterated that if the sponsor would like the alignments reviewed as they created them, then these would have to be submitted in the in the ACE, SAM or BAM format.

4. *Please rename all sequence files to reflect the Study ID, the Subject ID and the Visit. For example:*

For study: P2938-0721 Subject: 20038 Visit: BASELINE/DAY1

The fastq file was: ms2017019-wgc001243.fastq
Please rename to: p2938-0721-20038.BL.fastq

If you resequence a particular sample at a given timepoint, distinguish these by numbers:

p2938-0721-20038.W+4-1.fastq
p2938-0721-20038.W+4-2.fastq

Discussion:

Gilead agreed to rename the sequence files with the Study ID, the Subject ID and the accession number that is unique to each sample as the visit was too long in some cases. These will be reported in the FILEMAP file.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

The following agreements were reached at this pre-NDA meeting:

1. A complete new drug application for sofosbuvir will be submitted on April 15, 2013.
2. There will be no late submissions for this NDA submission.
3. The Agency will receive only the next generation sequencing raw data on a separate external hard drive, mailed to the Central Document Room on the same day as the submission of the original NDA for sofosbuvir.
4. Gilead will submit all NGS summary tables and protocols with the original NDA submission via the electronic gateway.
5. The sofosbuvir NDA will have an Advisory Committee Meeting.
6. The meeting minutes from the October 17, 2012 Type C teleconference and the March 14, 2013 pre-NDA meeting will serve as an agreement between Gilead Sciences and the Agency as to what constitutes a complete NDA package for sofosbuvir.

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

- A preliminary discussion on the need for REMS was held and it was concluded that the original application for sofosbuvir will not have a REMS.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. Gilead stated they will submit a complete application and therefore, there are no agreements for late submission of application components.

4.0 PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver,

if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

5.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.

- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[*see Warnings and Precautions (5.2)*]".

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

6.0 MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

7.0 ISSUES REQUIRING FURTHER DISCUSSION

The Agency and Gilead Sciences will have additional discussion on the expanded access program for sofosbuvir.

8.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Confirm the that the cutoff of 1% is adequate for the NGS datasets*	FDA	
Discussion on expanded access program with the Division	FDA and Gilead	

* The Agency provided post meeting comments regarding cutoff percentage for NGS datasets on March 18, 2013

6.0 ATTACHMENTS AND HANDOUTS

Please see attached.

Type B Pre-NDA Meeting
Sofosbuvir Tablets

Gilead Sciences, Inc.
14 March 2013

Today's Agenda

1. To seek agreement with the Agency on key aspects related to the content and format of the application.

2. To seek agreement on key phase 3 data and discuss with the Agency the proposed indication for sofosbuvir, specifically for genotype 3 subjects.

3. Additional points raised in 12March2013 email.

I.A. Optimal HCV GT2 and GT3 duration

1. **HCV GT2 treatment-experienced patients, SOF/RBV– 12 versus 16 weeks**

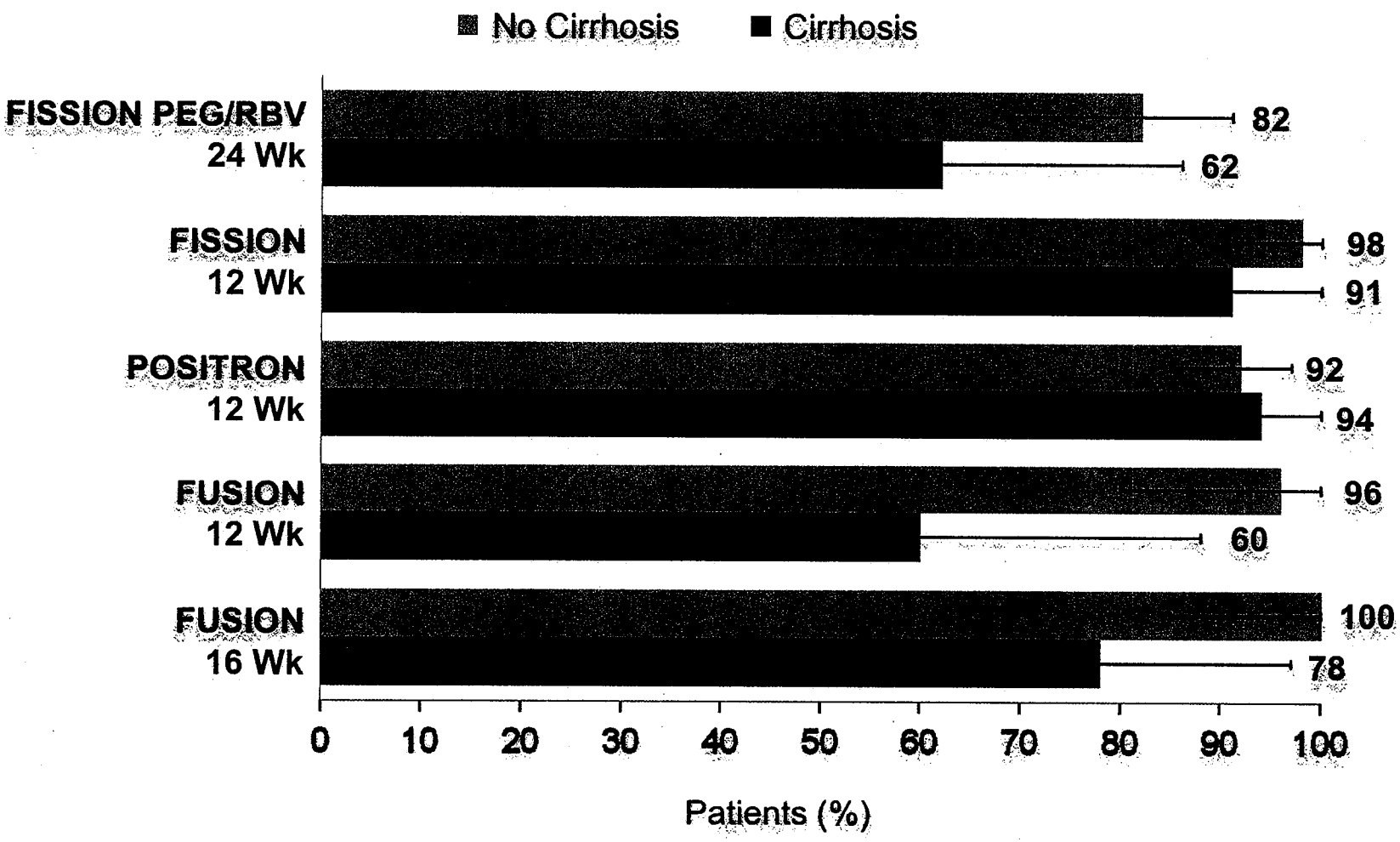
   Response: We believe the appropriate treatment duration for genotype 2 HCV-infected patients is 12 weeks:

   - **High response rates in GT2 across studies**
   - **Overlapping confidence intervals**
   - **Differences in subgroups impacted by small numbers**

SVR12 in GT2 Subjects by Subgroup

n/N (%)	Treatment Naive	IFN Unable	Treatment Experienced	
	SOF+RBV 12 Weeks	SOF+RBV 12 Weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks
Overall SVR12	68/70 (97)	101/109 (93)	31/36 (86)	30/32 (94)
95% CI	90-100%	86-97%	71-95%	79-99%
No Cirrhosis	58/59 (98)	85/92 (92)	25/26 (96)	23/23 (100)
Cirrhosis	10/11 (91)	16/17 (94)	6/10 (60)	7/9 (78)
Male	42/43 (98)	59/64 (92)	18/23 (78)	20/22 (91)
Female	26/27 (96)	42/45 (93)	13/13 (100)	10/10 (100)
<50 years	22/22 (100)	27/29 (93)	5/6 (83)	3/4 (75)
≥50 years	46/48 (96)	74/80 (93)	26/30 (87)	27/28 (96)
HCV RNA <800,000 IU/mL	23/23 (100)	26/28 (93)	8/9 (89)	2/2 (100)
HCV RNA ≥800,000 IU/mL	45/47 (96)	75/81 (93)	23/27 (85)	28/30 (93)
BMI <30	50/50 (100)	61/66 (92)	23/25 (92)	15/16 (94)
BMI ≥30	18/20 (90)	40/43 (93)	8/11 (73)	15/16 (94)

SOF+RBV in GT 2 by Cirrhosis Status



I.A. Optimal HCV GT2 and GT3 duration

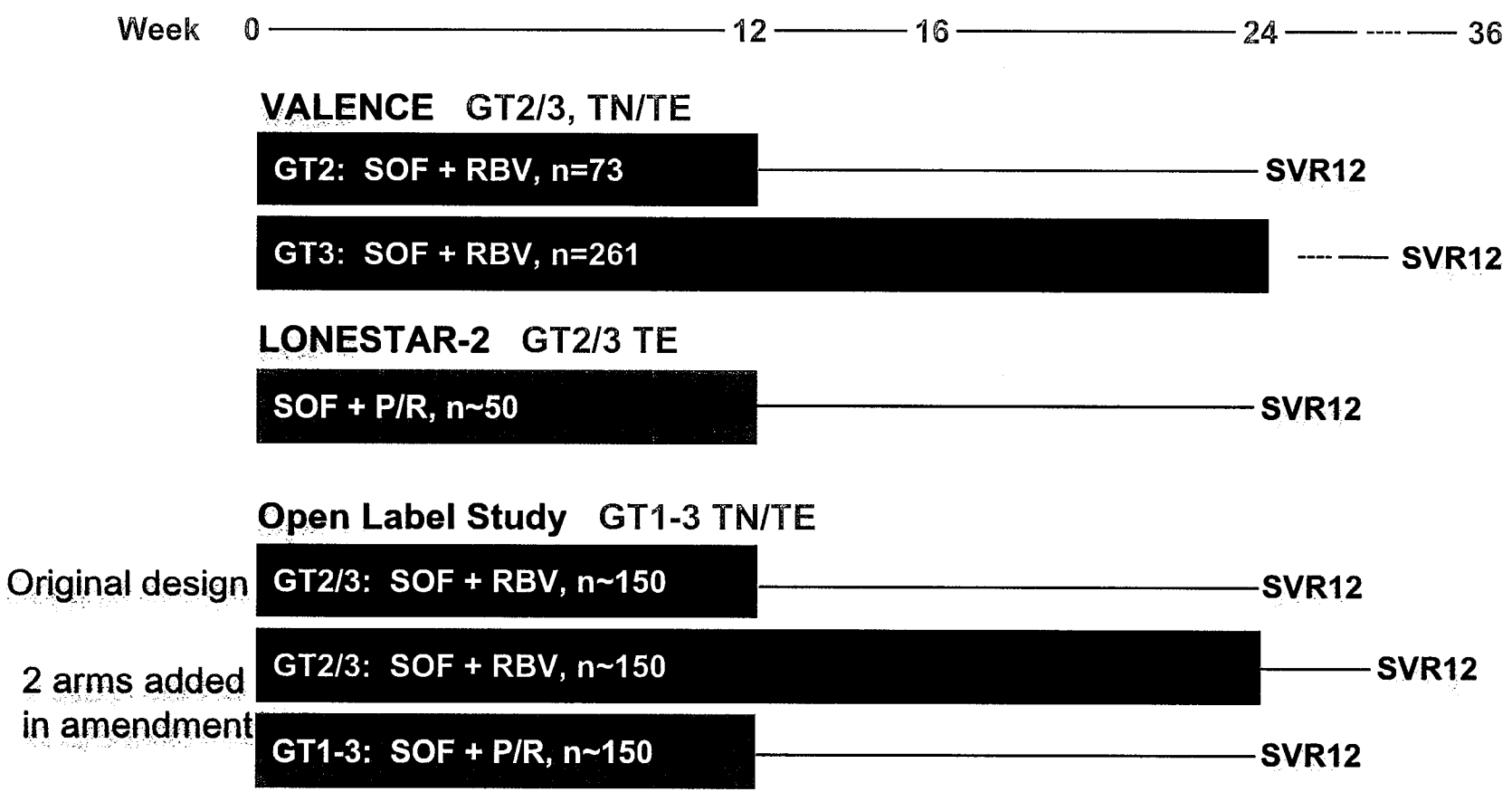
2. HCV GT3 treatment-naïve population, SOF/RBV-12 versus -16 weeks.

   Response: We agree that 16 weeks would be beneficial in all GT3 patients.

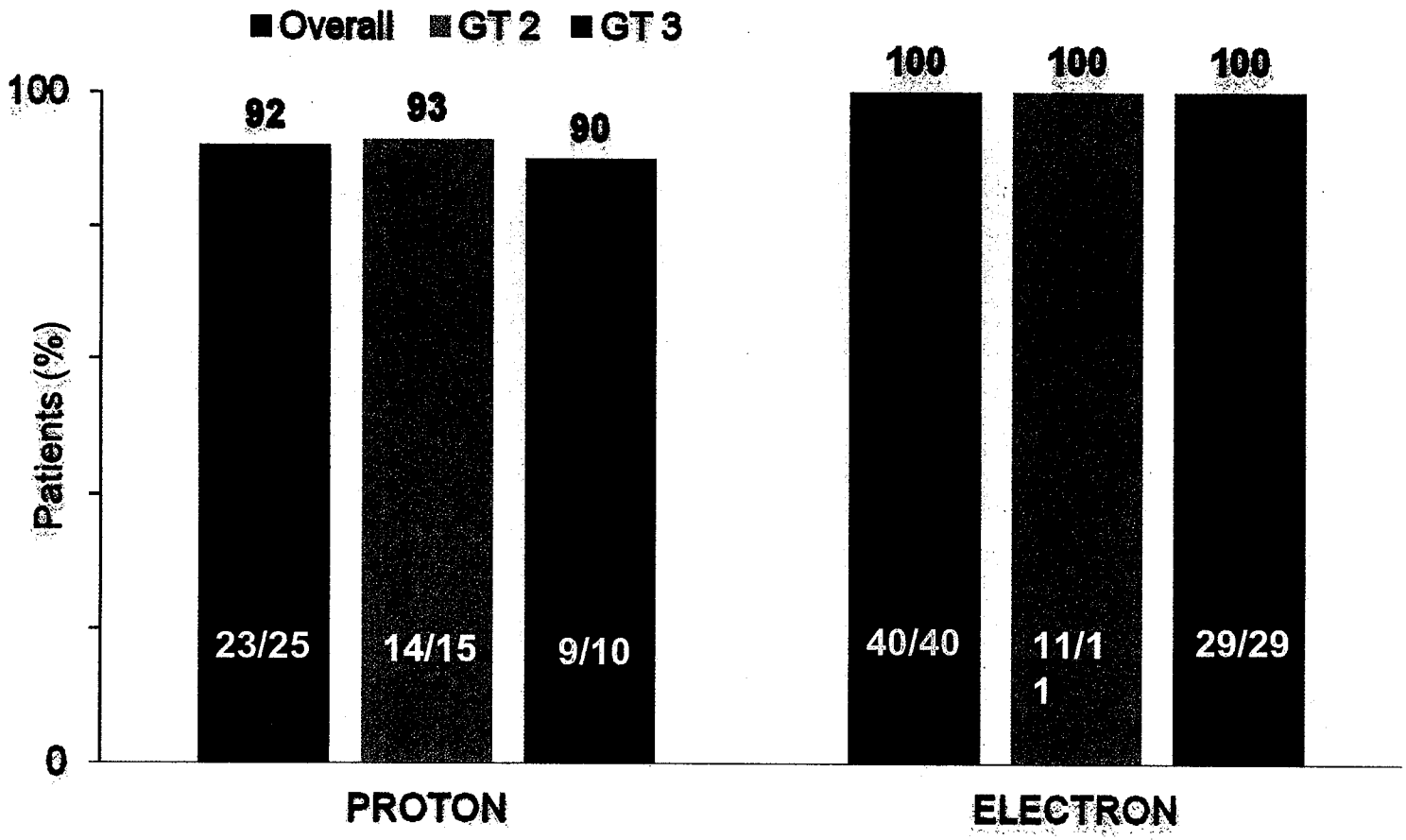
Bridging Analysis (Interaction Model)

FISSION/FUSION BAYESIAN MODEL III GT 3 SUBJECTS	SVR12 (95% Credible Set) rate for estimated from the FUSION Data using Bayesian Model	Actual SVR12 rate
FISSION SOF subjects	55.80% (48.91%,62.59%)	55.70%
FISSION PEG Subjects	62.54% (55.69%,68.96%)	62.50%
FUSION 12 WKs Subjects	29.64% (19.45%,40.56%)	29.70%
FUSION 16 WKs Subjects	62.89% (49.97%,72.95%)	61.90%
FISSION 16 WKS (Gamma=1.25)	81.91% (63.72%,93.06%)	
FISSION 16 WKS (Gamma=1.00)	78.16% (61.84%, 89.45%)	
FISSION 16 WKS (Gamma=0.75)	73.51% (59.56%,84.29%)	
FISSION 16 WKS (Gamma=0.50)	68.01% (56.92%,77.47%)	
FISSION 16 WKS (Gamma=0.25)	61.96% (53.73%, 69.53%)	
FISSION 16 WKS (Gamma=0.00)	55.80% (48.91%,62.59%)	

I.B. Ongoing/Future HCV GT2 and GT3 Development



SOF+RBV+PEG in GT2/3: Phase 2 Data



No virologic failures

Includes 4 regimens with varying durations of Peg-IFN

III. SVR24 data to be included at the time of NDA submission.

Study	SVR24 Data Available
POSITRON	Included in 2.7.3
FISSION SOF+RBV x 12 wks	Included in 2.7.3
FISSION P/R x 24 wks	09 April 2013
FUSION	03 May 2013
NEUTRINO	12 April 2013

- SVR24 data will be provided in final study reports

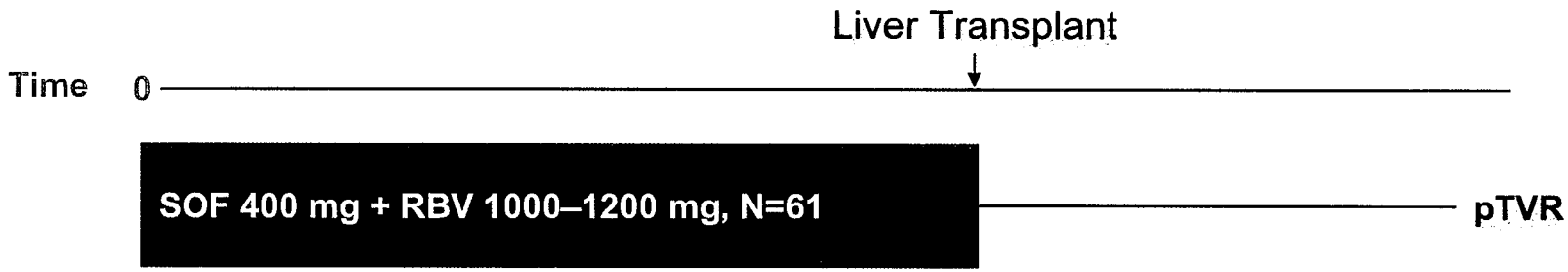
IV. Transplant [redacted] populations

- [redacted]

Response: Yes, based upon the following:

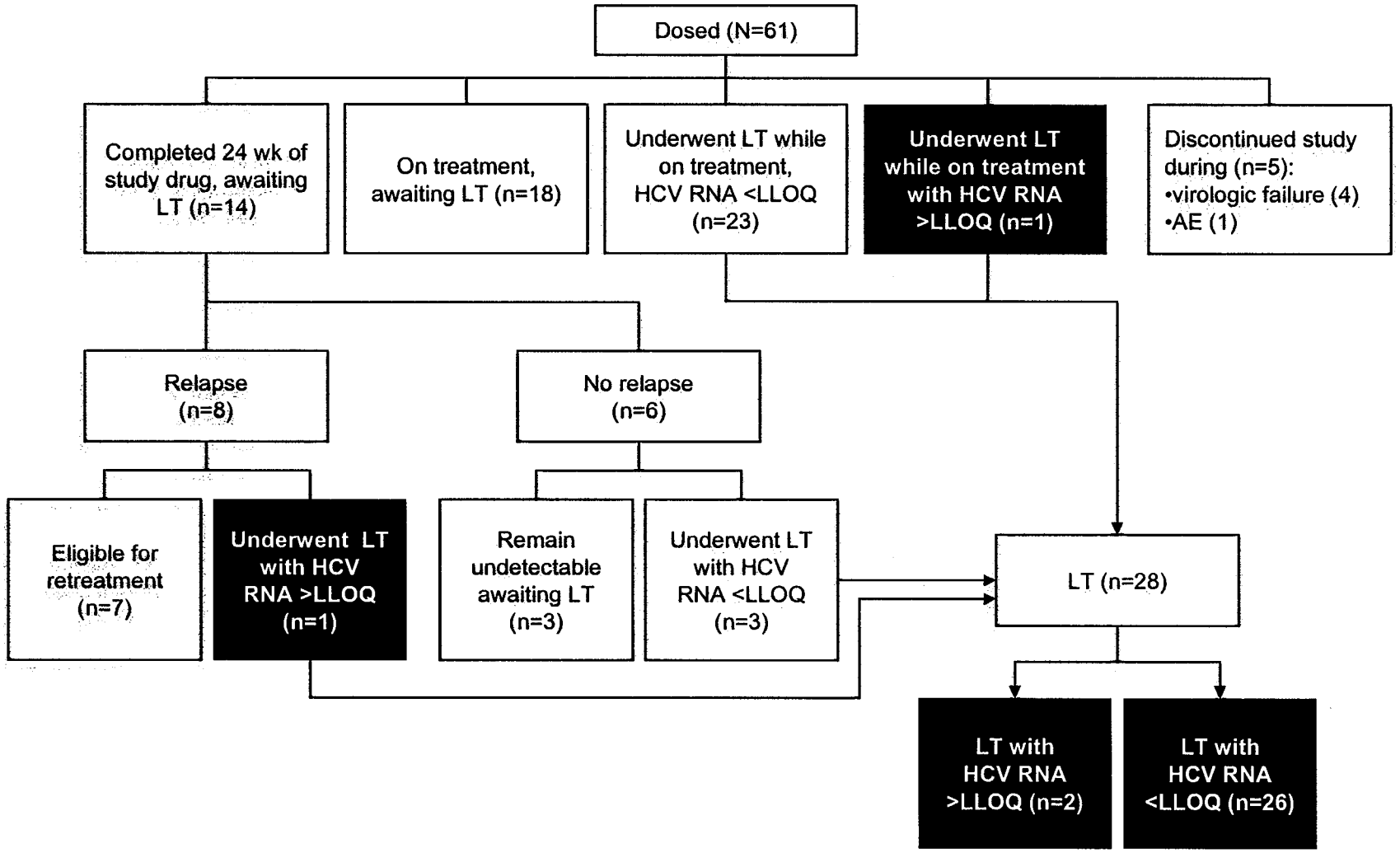
- High unmet medical need in this population
- Favorable safety and tolerability profile in this population
- Preliminary data suggesting that of those who are HCV RNA <LLOQ at time of transplant, approximately 2/3 remain HCV RNA <LLOQ 12 weeks post transplant.

Pre-Liver Transplant Pilot Study



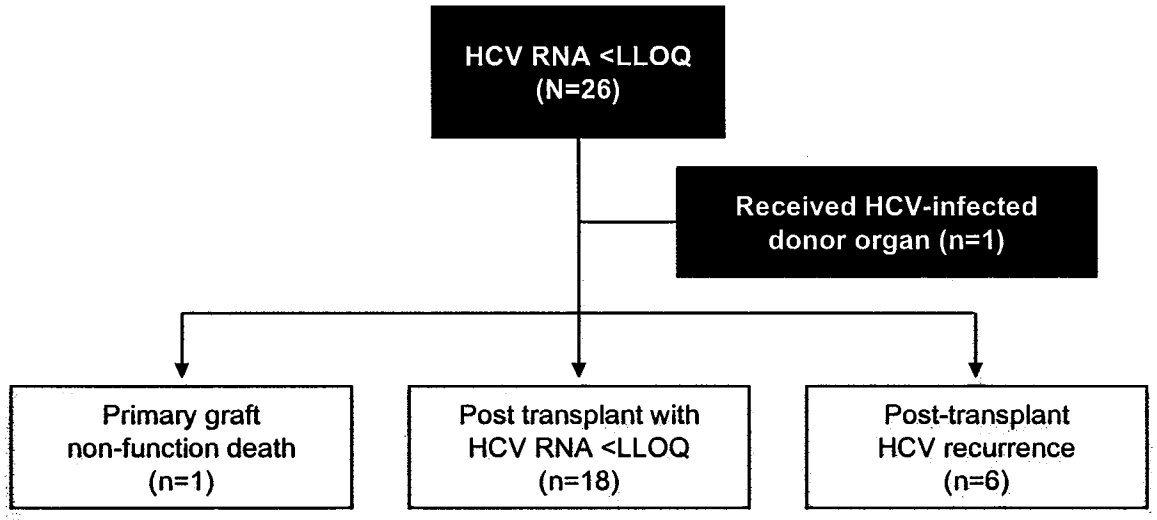
- Objective: prevention of HCV recurrence following OLT
  - Post-transplant virologic response (pTVR) at Wk 12
- Study criteria
  - Meeting MILAN criteria undergoing LT for HCC 2° to HCV
    - MELD <22 and HCC-weighted MELD ≥22
  - Child-Pugh-Turcotte score ≤7
- Enrollment: Complete across 16 sites (including Spain)
  - 28 transplants to date

Patient Disposition (Received ≥1 Dose)



LLOQ, lower limit of quantification; LT, liver transplantation.

Post-Transplant Patient Disposition

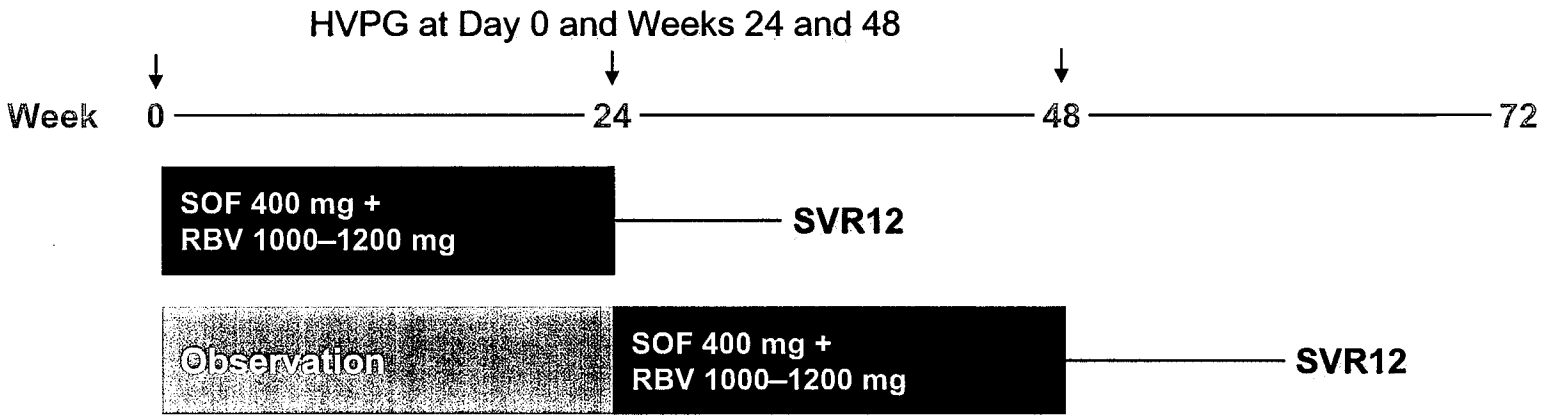


Post transplant,	Post-Transplant Viral Response Rate n/N (%)
Week 1	21/25 (84)
Week 2	20/25 (80)
Week 4	16/22 (73)
Week 8	10/15 (67)
Week 12	8/13 (62)
Week 24	1/1 (100)

Transplants: Individual Patients

(b) (4)

Decompensated Liver Disease Study: GS-US-334-0125

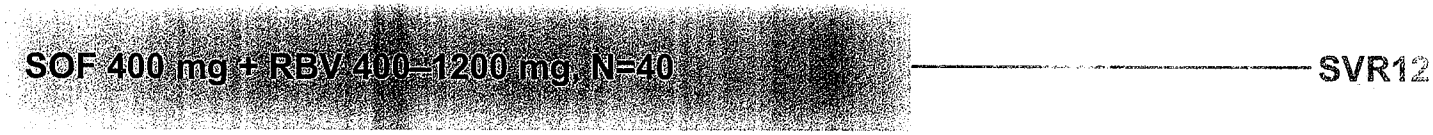


- Objective: SVR in patients with decompensated disease
  - Effects of 24 wk of dosing on hepatic portal pressure and hepatic function
- Study criteria
  - CPT 5–10 (60% CPT 7–10) with evidence of varices on endoscopy
  - HVPG >6 mmHg
- Status
  - Enrollment began October 2012 at 9 centers globally
  - 14/50 subjects enrolled to date

Decomp Liver Disease Study: GS-US-334-0125

(b) (4)

Post-Liver Transplant Study: GS-US-334-0126



- Objective: SVR in patients with recurrent HCV post-LT
- Study criteria
  - Liver transplant ≥6 months and ≤150 months
  - CPT ≤7 and MELD ≤17
- Status:
  - 10 sites in North America, Europe, New Zealand
  - 36/40 enrolled to date
  - 28 subjects with HCV RNA values available past W1

Post-Liver Transplant Study: GS-US-334-0126

(b) (4)

Visit

Predicted Exposure in HCV-Infected Subjects with Renal Impairment

Geometric Mean PK Parameters		GS-331007		Sofosbuvir	
Predicted Steady-State Exposure		**AUC_{tau} (hr*ng/mL)**	**C_{max} (ng/mL)**	AUC_{tau} (hr*ng/mL)	C_{max} (ng/mL)
SOF 400 mg QD	Normal RF (n=6)	**8130**	**727**	838	997
	Mild RI (n=6)	**12,700**	**965**	1330	1310
	Moderate RI (n=6)	**15,300**	**929**	1730	1540
	Severe RI (n=6)	**44,300**	**1930**	2270	1780
	ESRD Before Dialysis (n=3{007}, 5{SOF})	**105,000**	**3910**	1080	1460
	ESRD After Dialysis (n=3{007}, 5{SOF})	**171,000**	**6160**	1340	1230
Phase 3 Exposure (POPPK Estimates)		**6860**	**540**	814	864
Supratheapeutic QTc (1200 mgvsingle dose, n=60)		**26,900**	**2010**	2270	2010
NOAEL Exposure Ranges	Rat 4, 26 wk	**55,000-66,500**		N/A	
	Dog 4, 39 wk	**39,700-104,000**		5200-11,200	

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

/s/

DEBRA B BIRNKRANT
03/22/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106739

MEETING MINUTES

Gilead Sciences, Inc.
Attention: Shalini Gidwani, M.Sc., RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Gidwani:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sofosbuvir (GS-7977) 400 mg tablets.

We also refer to the teleconference between representatives of your firm and the FDA on October 17, 2012. The purpose of the meeting was to discuss the strategy related to format and content of your anticipated New Drug Application.

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

If you have any questions, call me at (301) 796-0759.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type C
Meeting Category:	Guidance
Meeting Date and Time:	October 17, 2012, 3:00 pm – 4:30 pm EST
Application Number:	106739
Product Name:	sofosbuvir, GS-7977
Indication:	treatment of chronic HCV infection
Sponsor/Applicant Name:	Gilead Sciences, Inc.
Meeting Chair:	Jeffery Murray, MD, MPH
Meeting Recorder:	Linda C. Onaga, MPH

FDA ATTENDEES

1. Jeffrey Murray, M.D., M.P.H., Deputy Director, DAVP
2. Sarah Connelly, M.D., Clinical Reviewer, DAVP
3. Kimberly Struble, Pharm.D., Clinical Team Leader, DAVP
4. Christopher Ellis, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
5. Lisa Naeger, Ph.D., Clinical Virology Reviewer, DAVP
6. Jules O'Rear, Ph.D., Clinical Virology Team Leader, DAVP
7. Ruben Ayala, Pharm.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
8. Jeffry Florian, Ph.D., Pharmacometrics Reviewer, OCP
9. Shirley Seo, Ph.D., Acting Clinical Pharmacology Team Leader, OCP
10. Karen Qi, Ph.D., Biometrics Reviewer, Division of Biometrics IV (DBIV)
11. Fraser Smith, Ph.D., Acting Biometrics Team Leader, DBIV
12. Karen Winestock, Chief, Project Management Staff, DAVP
13. Linda C. Onaga, M.P.H., Regulatory Project Manager, DAVP

SPONSOR ATTENDEES

1. John McHutchison, M.D., Senior Vice President, Liver Disease Therapeutics
2. Mani Subramanian, M.D., Vice President, Clinical Research Liver Disease Therapeutics
3. William T. Symonds, Pharm.D., Vice President, Clinical Research Liver Disease Therapeutics
4. Diana Brainard, M.D., Senior Director, Clinical Research Liver Disease Therapeutics

5. Neby Bekele, Ph.D. Senior Director, Biostatistics
6. Brian Kearney, Pharm.D., Project Lead/Senior Director, Clinical Research, Clinical Pharmacology
7. Hongmei Mo, M.D., Director, Clinical Virology
8. Paul Tomkins, Ph.D., Senior Director, Regulatory Affairs
9. Shalini Gidwani, M.Sc., RAC, Associate Director, Regulatory Affairs
10. Anita Mathias, Ph.D., Director, Clinical Pharmacology
11. Michael Miller, Ph.D., Senior Director, Clinical Virology
12. Sujatha Narayan, M.S., Senior Director, CMC Regulatory Affairs
13. Reza Oliyai, Ph.D., Vice President, Formulation and Process Development
14. Chin H. Tay, Ph.D., DABT, Associate Director, Drug Safety Evaluation
15. Michele Anderson, Associate Director, Regulatory Affairs

1.0 BACKGROUND

Gilead Sciences, Inc. (Gilead) is developing sofosbuvir, a direct-acting antiviral agent for the treatment of chronic hepatitis C (CHC) infection. Two End-of-Phase two meetings were held between Gilead and the Division of Antiviral Products in which, agreements were reached on the design of three pivotal trials in genotypes 2 and 3 and a pivotal trial in genotypes 1, 4, 5, and 6. These trials could support a broader indication and comprehensive product labeling for all major hepatitis C virus genotypes upon initial review and FDA approval.

Gilead requested a pre-NDA meeting with DAVP to discuss the strategy related to the format and content of the New Drug Application (NDA) for sofosbuvir. Gilead informed the Division that top-line data would not be available in time for this meeting. Based on this information, the Division determined that this is a type C meeting.

The primary purposes of this meeting are:

1. To seek agreement with the Agency on the strategy for the submission of a NDA for sofosbuvir in March/April 2013.

2. To seek agreement with the Agency on key aspects related to the content and format of the application.

The objectives of this meeting are:

1. To seek agreement with the Agency that the planned data package to be included in the NDA is supportive of the proposed indication.

2. To seek comments and agreement from the Agency on the content, scope, and format of the sofosbuvir NDA and NDA Safety Update.

3. To seek agreement from the agency on the planned statistical analyses for the Phase 3 clinical studies, and the content, format and proposed pooling strategy for the Integrated Summaries of Efficacy and Safety.

4. To obtain feedback from the Agency on the proposed pediatric development plan for sofosbuvir

The Division of Antiviral Products (DAVP) provided Gilead with preliminary comments on October 15, 2012.

2. DISCUSSION

Gilead proposed that the meeting focus on reviewing the Agency's preliminary comments to Questions 2, 11, and 14 and FDA additional comments 3.3. To convey the discussion points from this meeting, the original Gilead questions are in bold, followed by preliminary FDA comments in italics and discussion points in regular text.

Gilead provided an update of the development program for sofosbuvir and timeline for new drug application (NDA) registration. FUSION SVR12 data will be available by mid-February 2013. If there are no unforeseen circumstances, Gilead intends to submit the NDA for sofosbuvir to the Agency the first half of April 2013.

The Division inquired about Gilead's plans to request a pre-NDA meeting. Sofosbuvir is a new molecular entity and will be subject to "The Program" under PDUFA V. Gilead does not plan to request a pre-NDA meeting, because a pre-NDA does not fit into their current expedited timeline. The Division stressed the importance of having a complete NDA package in the original submission. All major components of the application are expected to be included in the original application. Although not mandatory, the pre-NDA meeting is an important meeting to discuss and agree on the completeness of the original application, identify any additional analyses necessary and potential filing issues.

2.1. Clinical/Statistical Questions

Question 2:

Does the Agency agree that the data available in treatment-naïve genotype 2 and 3 HIV/HCV co-infected subjects at the time of the NDA filing supports the proposed indication?

FDA Response to Question 2:

At this time, SVR4 data are not sufficient to support an indication in HIV/HCV treatment-naïve genotype 2 and 3 subjects; however, we do expect these data to be submitted with the initial NDA. SVR12 data are needed to support an indication. Fewer than 300 HIV/HCV subjects may be acceptable for a future indication in the setting of favorable safety and efficacy data, and we encourage further discussion with the Division to reach agreement on the details of such a proposal.

Discussion:

Gilead stated they no longer plan for an HIV/HCV treatment-naïve genotype 2 and 3 indication with the original NDA submission; however, the submission would include SVR4 data for 31 HIV/HCV treatment-naïve genotype 2 and 3 subjects enrolled through the end of September 2012. Gilead had difficulty getting the expected enrollment for the genotype 2/3 co-infected population as agreed upon at the End-of-Phase 2 meeting held in June 2012. Logistical issues related to biopsies were the biggest contributor to the delay, because HIV physicians were not use to requesting this type of test.

Gilead expects to submit a supplemental NDA to support the HIV/HCV co-infection indication following the approval of the original NDA.

Question 11:

As with recent NDA submissions to the Division, Gilead proposes to include a summary of efficacy (as described in Question 10) and ISS text within the Summary of Clinical Efficacy (Module 2.7.3) and Summary of Clinical Safety (Module 2.7.4), respectively. eCTD cross-reference leaves to Modules 2.7.3 and 2.7.4 will be provided in Module 5.3.5.3 together with supporting statistical outputs and electronic datasets. The length of Modules 2.7.3 and 2.7.4, including the integrated data analyses described in the ISE and ISS SAPs, will be consistent with those described in the FDA's April 2009 *Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document.*

Does the Agency agree with this proposal?

FDA Response to Question 11:

Yes, the Division agrees with your proposed plan. In addition to the proposed pooling and analysis ISS SAP strategy, we expect the ISS text/Summary of Clinical Safety to include information on deaths, SAEs, discontinuations due to AEs, and pertinent other significant adverse events (e.g., liver-related events, pancytopenia) from all completed SOF-containing trials. We also request the Summary of Clinical Safety include direct hyperlinks to narratives for these events.

Discussion:

Gilead proposed to provide this additional information for all completed phase 2 and 3 trials. The Division agreed and expects the Safety Update Report to include any other notable significant events in other trials. Gilead will include information on deaths, SAEs, discontinuations due to AEs, and pertinent other significant adverse events (e.g., liver-related events, pancytopenia) for all future trials.

2.2. Virology

Question 14:

Given that > 96% of relapses in the Phase 2 studies occurred no later than the post-treatment Week 4 time point without evidence for resistance, does the Agency agree with the proposal to provide SVR12 resistance analysis data from Phase 2 studies and SVR4 resistance analysis data from Phase 3 studies within the initial NDA filing, supplemented with Phase 3 SVR12 sequencing data in the NDA Safety Update?

FDA Response to Question 14:

Phase 3 SVR12 resistance data cannot be submitted with the NDA Safety Update. In accordance with "The Program" under PDUFA V, this information is expected to be submitted with the original application and is not subject to agreement for late submission.

Discussion:

Gilead originally requested to submit the phase 3 resistance data during the NDA Safety Update because of their internal short timelines and there could be potential logistical challenges to get these data in the original application. However, Gilead acknowledged the Division's request and agreed to provide the phase 3 SVR12 resistance data with the original NDA submission.

Given that their vendor for phenotypic data, (b) (4) reports EC_{50} and EC_{95} values, Gilead inquired whether submitting EC_{95} phenotypic data is acceptable as opposed to the EC_{90} data recommended by the Division. Using EC_{95} values is acceptable to the Agency.

The Division stated that they will send updated draft guidance on HCV resistance data and a document giving guidance on submitting next generation sequencing data. The Division is seeking input regarding deep sequencing analysis and requests that Gilead submit a meeting request to obtain feedback and guidance on how they plan to submit this data to the Division.

2.3. Additional FDA Comment

3.3 Will datasets be submitted with the NIH 11-I-0258 clinical study report? If so, will the datasets be in a compatible format to allow integrative safety review?

Discussion:

Gilead stated their intent is to submit a clinical study report based on SVR12 data without accompanying datasets. This approach was acceptable to the Division.

2.4 Additional Discussions

The Division acknowledged that SVR12 data from all phase 3 trials would be available in February 2013 and asked, in the absence of a pre-NDA meeting, does Gilead intend to submit to the Agency top-line safety data? Gilead stated they plan to continue with their standard practice of publically disclosing and submitting safety data with top-line efficacy data to the Agency. Gilead will also provide an Executive Summary of the phase 3 efficacy and safety program by the end of February 2013.

The Division requested submission of sample datasets using the phase 2 data as this information would assist the review teams understanding of the planned data organization. Gilead will provide sample datasets to the Agency and plan to have additional internal discussions on what information needs to be submitted including data in eDISH format for liver related safety evaluations. The Division preferred to have the individual trial datasets submitted, as this will be helpful for the statistical reviewer; the clinical reviewer will use these sample datasets to help identify the appropriate review analysis programs.

3.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Draft Guidance for Industry on HCV Resistance Data and next generation sequencing document	FDA	Sent to sponsor on October 17, 2012 after the teleconference
Written Executive Summary and individual trial phase 2 datasets for Agency	Gilead	February 2013

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

/s/

LINDA C ONAGA
10/31/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106739

MEETING MINUTES

Gilead Sciences, Inc
Attention: Michele Anderson
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Anderson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GS-7977.

We also refer to the meeting between representatives of your firm and the FDA on June 5, 2012. The purpose of the meeting was to obtain Agency concurrence on the design of an additional pivotal, phase 3 clinical trial that will support an indication for the use of GS-7977 in combination with peg interferon and ribavirin for the treatment of treatment-naïve adults infected with genotypes 1, 4, 5, or 6, chronic hepatitis C virus (HCV) infection. In addition, we discussed your proposal to advance the development of GS-7977 plus GS-5885 as a single tablet regimen for the treatment of genotype 1 treatment-naïve and -experienced, interferon-eligible and -ineligible/intolerant HCV patients.

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

If you have any questions, call me at (301) 796-0759.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	June 5, 2012 1:00 PM -2:30 PM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 2205 Silver Spring, Maryland 20903
Application Number:	106739
Product Name:	GS-7977
Indication:	GS-7977 in combination with ribavirin for the treatment of genotype 2 and 3 chronic hepatitis C (CHC) in adults or in combination with ribavirin plus peg interferon alfa for the treatment of genotype 1, 4, 5, and 6 CHC in treatment naïve adults with compensated liver disease including cirrhosis
Sponsor/Applicant Name:	Gilead Sciences
Meeting Chair:	Debra Birnkrant, M.D.
Meeting Recorder:	Linda C. Onaga, M.P.H.

FDA ATTENDEES

1. Robert Temple, M.D., Deputy Director for Clinical Science, Office of the Center Director
2. Debra Birnkrant, M.D., Director, Division of Antiviral Products (DAVP)
3. Jeffrey Murray, M.D., M.P.H., Deputy Director, DAVP
4. Kendall Marcus, M.D., Deputy Safety Director, DAVP
5. Sarah Connelly, M.D., Clinical Reviewer, DAVP
6. Wendy Carter, M.D., Clinical Reviewer, DAVP
7. Kimberly Struble, Pharm.D., Clinical Team Leader, DAVP
8. Linda Lewis, M.D., Clinical Team Leader, DAVP
9. Mary Singer, M.D., Clinical Team Leader, DAVP
10. Christopher Ellis, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
11. Lisa Naeger, Ph.D., Clinical Virology Reviewer, DAVP
12. Patrick Harrington, Ph.D., Clinical Virology Reviewer, DAVP
13. Jules O'Rear, Ph.D., Clinical Virology Team Leader, DAVP

14. Ruben Ayala, Pharm.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
15. Leslie Chinn, Ph.D., Clinical Pharmacology Reviewer, OCP
16. Jeffry Florian, Ph.D., Pharmacometrics Reviewer, OCP
17. Shirley Seo, Ph.D., Acting Clinical Pharmacology Team Leader, OCP
18. Karen Qi, Ph.D., Biometrics Reviewer, Division of Biometrics IV (DBIV)
19. Susan Zhou, Ph.D., Biometrics Reviewer, DBIV
20. Fraser Smith, Ph.D., Acting Biometrics Team Leader, DBIV
21. Yanming Yin, Ph.D., Biometrics Reviewer, DBIV
22. Greg Soon, Ph.D., Biometrics Team Leader, DBIV
23. Clotilde Billard, Pharmacy Student Intern, DAVP
24. Marianne Astic, Pharmacy Student Intern, DAVP
25. Victoria Tyson, Chief, Project Management Staff, DAVP
26. Linda C. Onaga, M.P.H., Regulatory Project Manager, DAVP

SPONSOR ATTENDEES

1. John McHutchison, M.D., Senior Vice President, Liver Disease Therapeutics
2. Mani Subramanian, M.D., Vice President, Clinical Research Liver Disease Therapeutics
3. William T. Symonds, Pharm.D., Vice President, Clinical Research Liver Disease Therapeutics
4. Diana Brainard, M.D., Senior Director, Clinical Research Liver Disease Therapeutics
5. Neby Bekele, Ph.D. Senior Director, Biostatistics
6. Brian Kearney, Pharm.D., Project Lead/Senior Director, Clinical Research, Clinical Pharmacology
7. Hongmei Mo, M.D., Director, Clinical Virology
8. Paul Tomkins, Ph.D., Senior Director, Regulatory Affairs
9. Mae J. Lai, Director, Regulatory Affairs
10. Michele Anderson, Associate Director, Regulatory Affairs

1.0 BACKGROUND

Gilead Sciences, Inc. is continuing development of GS-7977 from the previous owner, Pharmasset, Inc. for the treatment of genotype 2 and 3 chronic hepatitis C (CHC) infection. After the review of recent clinical trial data in hepatitis C genotype 1 subjects, Gilead proposed broadening the indication previously discussed at the End-of-Phase 2 meeting between the Division of Antiviral Products (DAVP) and Pharmasset, Inc held on August 18, 2011.

Gilead submitted an additional pivotal, phase 3, multicenter, single arm open-label trial to evaluate the safety and efficacy of GS-7977 in combination with peg interferon alfa 2a (PEG) and ribavirin (RBV) for 12 weeks in treatment-naïve subjects with CHC genotype 1, 4, 5, and 6. This trial would provide additional support for the broader indication and comprehensive product labeling for all major hepatitis C virus genotypes upon initial review and FDA approval.

In addition, Gilead informed the Division of their intent to pursue GS-7977 and GS-5885 (IND 108214) as a fixed dose combination (FDC) product with and without RBV for the treatment of CHC infection. Gilead submitted a protocol synopsis of the phase 2/3 protocol evaluating the FDC in treatment-naïve genotype 1 subjects.

Gilead requested a second End-of-Phase 2 meeting with DAVP to discuss the additional pivotal phase 3 protocol, the revised indication, and proposed FDC phase 2/3 protocol. The meeting objectives are:

1. To seek concurrence from the Agency that the proposed additional Phase 3 study evaluating GS-7977 + PEG/RBV for 12 weeks is adequate to support an indication for GS-7977 in combination with PEG/RBV for the treatment of genotype 1, 4, 5, and 6 CHC in treatment-naïve adults

2. To seek advice from the Agency on the acceptability of small numbers of genotype 4, 5, and 6 HCV-infected subjects in the proposed GS-7977 + PEG/RBV Phase 3 study to support including these genotypes in the label indication

3. To seek advice from the Agency that an NDA for GS-7977 would be eligible for priority review designation as defined by the Prescription Drug User Fee Act

4. To discuss Gilead's intention to advance GS-7977+ GS-5885 as a FDC tablet with and without RBV into Phase 3 development for the treatment of HCV genotype 1 treatment naïve infection supported by the large individual safety databases for GS-7977 and GS-5885 and emerging data on GS-7977 in combination with an HCV specific NS5A inhibitor

DAVP provided Gilead with preliminary comments on June 1, 2012.

2.0 DISCUSSION

Gilead proposed that the meeting focus on reviewing the Agency's preliminary comments to Questions 1 and 4 and FDA additional comments 4 and 5. To convey the discussion points from this meeting, the original Gilead questions are in bold, followed by preliminary FDA comments in italics and discussion points in regular text.

2.1 Protocol GS-US-334-0110, Phase 3 study evaluating GS-7977 + PEG/RBV for 12 weeks

QUESTION 1

Does the Agency agree that the proposed additional Phase 3 study, GS-US-334-0110, evaluating GS-7977 + PEG/RBV for 12 weeks is adequate to support the broader indication for GS-7977 that includes use in combination with PEG + RBV for the treatment of genotype 1, 4, 5 and 6 treatment-naïve CHC in adult patients?

FDA Response:

The proposed additional phase 3 trial design may be adequate to support the broader indication for GS-7977 + PEG/RBV for the treatment of genotype 1 treatment-naïve CHC in adult patients. Please refer to Question 2 for response to the genotype 4, 5, 6 populations.

At this time, we have not reached full agreement on the trial design, historical SVR rate of 60% and the assumptions for the sample size calculations. We plan to provide follow-up comments after the meeting. Ultimately, the adequacy of the GS-US-334-0110 efficacy and safety data to support an indication in HCV GT1 treatment-naive patients using an historical control is a review issue.

One element of GS-US-334-0110 that requires additional discussion is the proposed treatment duration with GS-7977 + PEG/RBV. This trial will enroll up to 20% subjects with cirrhosis, a population in which GS-7977 + PEG/RBV has not been evaluated because phase 2 data are lacking. Historically, subjects with cirrhosis treated with PEG/RBV-containing regimens achieve lower SVR compared with subjects without cirrhosis. We recognize the similar ATOMIC SVR4 rates between the GS-7977 + PEG/RBV 12 and 24 week arms in patients without cirrhosis; however, we believe an additional evaluation is needed to define the optimal GS-7977 + PEG/RBV duration in subjects with cirrhosis. One proposal is a separate GS-US-334-0110 cohort in which HCV GT1 subjects with cirrhosis are randomized to one of two treatment durations. Such a trial design would provide comparative data to guide GS-7977 + PEG/RBV duration in cirrhotics.

As part of the EOP2 discussion, please address if you have used the HCV RNA data from P2938-0515 and other genotype 1 studies in your drug development program to simulate the optimal treatment duration in cirrhotics.

Discussion:

The goal of Gilead's HCV development program is to show improvement over existing therapies in the treatment options for hepatitis C patients. Gilead reviewed data in HCV genotype 1 subjects from ATOMIC and observed similar on- and end-of-treatment responses for both the 12- and 24-week regimens of GS-7977 + PEG/RBV and concluded the shorter duration regimen could be a viable option. Gilead acknowledged the lack of data in genotype 1 cirrhotic patients in their phase 2 clinical trials; however, data in subjects with bridging fibrosis showed similar on- and end-of-treatment responses compared to subjects with portal, minimal, or no fibrosis from the 12-week GS-7977 + PEG/RBV regimen in ATOMIC. This observation is in contrast to previous observations in subjects with bridging fibrosis administered a protease inhibitor (PI) + PEG/RBV or PEG/RBV alone, who typically had lower response rates than subjects with portal, minimal, or no fibrosis.

(b) (4)

(b) (4) In the preliminary comments, the Division proposed a separate cohort for cirrhosis patients and inquired as to why Gilead did not accept or agree to this approach. According to Gilead, an additional cohort treated up to 24 weeks is not advancing the field. The Division responded that there are some advantages with such a 24-week regimen compared to the approved regimens including once daily dosing, potentially less adverse events and favorable drug-drug interaction profile. The Division presented the option of dividing the subjects with cirrhosis between 12- and 24-week treatment duration cohorts, within the same trial. Gilead proposed a future separate trial in subjects with cirrhosis, if needed based on the 12 week duration SVR12 results; however, restated there is no evidence that 24-week treatment would do any better than 12-week treatment in subjects with cirrhosis.

Gilead confirmed GS-US-334-0110 will enroll 20% cirrhotics. This assurance is based on the fact that, in previous trials, Gilead has stopped the enrollment of this patient population because the target was reached early in the enrollment process. Therefore, based on this previous experience, the expectation is there will not be a lack of patients with cirrhosis for future trials. The Division asked, if there are a number of cirrhotics who would like to participate in this phase 3 trial, why not increase the percentage allowed into the trial (e.g. up to 40% cirrhotics).

The Division mentioned if subjects with cirrhosis treated for 12 weeks have low SVR rates in GS-US-334-0110, the community will be disappointed with the lack of a treatment option or lack of data to inform treatment duration in this population, particularly because HCV genotype 1 patients with cirrhosis have lower SVR rates with currently approved PI-based treatment. The Division suggested that Gilead conduct an interim analysis with cirrhosis subjects to identify if these subjects have a slower on-treatment response (e.g. at week 4) or disproportionately experience relapse following treatment. If a big difference were seen in the RVR rates between cirrhotic and non-cirrhotic subjects the study design could be altered to include on-treatment futility rules if necessary. Gilead stated that many subjects in the ATOMIC trial had undetectable HCV RNA by Week 2, and there was not sufficient information for predicting the relapse seen in subjects. It may be difficult to stop or amend the trial, particularly if there is fast enrollment of

subjects with cirrhosis. Gilead considered reviewing viral kinetics data from previous trials to see if a subject should continue treatment for a longer duration or restart after relapse on the proposed regimen.

Following the meeting exchange with the Agency regarding GS-US-334-0110 trial design options, Gilead determined they would like the Agency to review the phase 3 protocol as proposed in the meeting package. Gilead provided a detailed explanation of the protocol's statistical calculations and assumptions for sample size, including the argument for the tradeoff for better safety. The Division stated that there are several perspectives to consider for these point estimate calculations and that the confidence intervals should be narrow. The Division plans to hold additional internal discussions and provide feedback to the proposed statistical calculations.

Gilead is prepared to begin enrollment of protocol GS-US-334-0110 on June 18, 2012. The timeline for an NDA submission in genotype 1, 2 and 3 is dependant on rate of enrollment in protocol GS-US-334-0110. Of note, the genotype 2/3 phase 3 trials are ongoing. The Division explained the NDA must be complete at the time of submission (refer to Section 7.0 Post Meeting Note). Gilead will have additional internal discussions about the initial NDA filing strategy for genotype 1, 2 and 3. Additionally Gilead will submit a proposal in writing for the treatment of genotype 4, 5 and 6.

The Division inquired about early viral kinetic data in their hepatic impairment trial. Gilead has not reviewed these data but plans to submit a protocol for GS-US-334-0125 (GS-7977 + RBV in HCV-infected subjects with decompensated cirrhosis) soon.

2.2 GS-7977 + GS-5885 Fixed Dose Development Program

QUESTION 4

(b) (4)

FDA Response:

(b) (4)

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2.3 FDA Additional Comments

General Comment 4:

Please comment on your future GS-7977 development plans for the following populations:

a. *GT1 prior treatment-experienced patients*
b. *GT1 pegylated interferon ineligible/intolerant/unwilling patients*
c. *Prior null responder patients*
d. *Prior DAA (e.g. PI)-failure patients*

Discussion:

Gilead intends to identify the best regimen in genotype 1 treatment-naïve patients, then will proceed with trials in the more difficult to treat patients. They acknowledged there is more work to be done; however, they are waiting for the QUANTUM study data to inform these future trials. If the FDC product shows promise, it may be the regimen used in these more difficult populations. Gilead will provide additional comments in writing.

General Comment 5:

Please comment on plans for obtaining an indication in HIV/HCV co-infected patients. To support a full indication for the treatment of HIV/HCV co-infected patients or to include a description of efficacy in the co-infected population, data demonstrating efficacy and safety in at least 300 co-infected patients who received the proposed dose(s) for the proposed duration of therapy are recommended based on our draft guidance. We will review the full protocol upon submission; however, based on trial summary, we recommend a longer treatment duration in GS2/3 prior treatment-experienced subjects. Please also comment on plans to study GS-7977 + PEG/RBV in HIV/HCV GT1 co-infected patients.

Discussion:

Gilead finished their drug-drug interaction (DDI) study with GS-7977, Atripla®, darunavir, raltegravir, and rilpivirine in healthy subjects, and there were neither interactions requiring dose adjustments nor safety concerns observed with co-administration. Gilead also stated their plans to submit a late-breaker abstract to the upcoming 2012 AIDS meeting in Washington, D.C on the viral dynamics from the DDI study between GS-7977 and antiretrovirals in HIV/HCV co-infected subjects. Gilead has opened up this trial to now add PEG/RBV and expect to have data on 30 HIV/HCV co-infected subjects at the time of NDA submission.

The plan for co-infected studies is to start with the genotype 2/3 population, because data are available to support dosing GS-7977 + RBV for 12 weeks, and then expand to genotype 1. There are also plans to start a European based co-infected study, with 200 subjects. Gilead notes this trial design may differ to include all genotypes. Presently, there is no plan to study GS-7977 + PEG/RBV in the HIV/HCV treatment-naïve genotype 1 population.

Gilead intends to have HIV/HCV co-infected data and even possibly a final study report as part of the initial GS-7977 NDA submission.

Gilead stated that there were no drug-drug interactions observed with cyclosporine and tacrolimus.

(b) (4)

FDA inquired about the VALANCE study, mentioned in the meeting package. The VALANCE study is a European study with approximately 400 HCV genotype 2/3 subjects randomized 4 to 1 to GS-7977 + RBV or placebo for 12 weeks in treatment-naïve, -experienced, interferon ineligible or unwilling. Gilead anticipates starting in September 2012. Since this is a safety study, Gilead does not expect these data will be included in the NDA submission. Their goal is not to rush through the trial, but to get participation from eight to nine European countries.

3.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

4.0 ISSUES REQUIRING ADDITIONAL DISCUSSIONS

DAVP will review protocol GS-US-334-0110 "A Phase 3, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of GS-7977 with Peginterferon Alfa 2a and Ribavirin for 12 Weeks in Treatment-Naïve Subjects with Chronic Genotype 1, 4, 5 or 6 HCV Infection", as submitted in the meeting background package and provide Gilead with feedback.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Additional internal discussion and feedback on Protocol GS-US-334-0110	FDA	As soon as possible
Provide Written responses to questions proposed in preliminary comments by the Division	Gilead	As soon as possible

6.0 ATTACHMENTS AND HANDOUT

No attachments or handouts for the meeting minutes.

7.0 POST MEETING NOTE*

The investigational product that is the subject of this meeting is for a new molecular entity or an original biologic and the date of submission is on or after October 1, 2012, the application will be subject to "The Program" under PDUFA V, if signed into law. Therefore, at the Pre-NDA meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. The major components of the application (e.g., the complete study report of a Phase 3 clinical trial or the full study report of required long-term safety data) are expected to be submitted with the original application and are not subject to agreement for late submission. Discussions and agreements on the content of a complete application will be summarized at the conclusion of the pre-NDA meeting and reflected in FDA's pre-NDA meeting minutes. Information on PDUFA V and "The Program" is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

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/s/

LINDA C ONAGA
06/26/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106,739

MEETING MINUTES

Pharmasset, Inc.
Attention: Ashley Lister, Ph.D.
Director, CMC Regulatory Strategy and Manufacturing Support
303A College Road East
Princeton, NJ 08540

Dear Dr. Lister:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PSI-7977 Tablets.

We also refer to the Type B End-of-Phase 2 (EOP2) Chemistry, Manufacturing, and Controls (CMC) meeting between representatives of your firm and the FDA on October 11, 2011. The purpose of the meeting was to discuss the Phase 3 CMC development program to support the proposed indication.

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

If you have any questions, contact Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:
Meeting Minutes
Meeting Slides from Pharmasset, Inc.

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	CMC End-of-Phase 2
Meeting Date and Time:	October 11, 2011, 10:00 AM – 11:00 AM EST
Meeting Location:	10903 New Hampshire Avuenue White Oak Building 22, Conference Room 1421 Silver Spring, Maryland 20903
Application Number:	IND 106,739
Product Name:	PSI-7977 Tablets
Indication:	Treatment of chronic hepatitis C infection
Sponsor/Applicant Name:	Pharmasset, Inc.
Meeting Chair:	Rapti D. Madurawe, Ph.D.
Meeting Recorder:	Jeannie David, M.S.

FDA ATTENDEES

1. Mark Seggel, Ph.D., Review Chemist, ONDQA
2. Stephen Miller, Ph.D., CMC Lead, Office of New Drug Quality Assessment (ONDQA)
3. Angelica Dorantes, Ph.D., Biopharmaceutics Review Team Lead, ONDQA
4. Sarah Connelly, M.D., Medical Officer, Division of Antiviral Products (DAVP)
5. Rapti D. Madurawe, Ph.D., Branch Chief, ONDQA
6. Jeannie David, M.S., Regulatory Health Project Manager, ONDQA

SPONSOR ATTENDEES

1. Stephen Biroc, Director Project Management, PSI-7977 Project Leader, Pharmasset, Inc.
2. Darryl Cleary, Ph.D., Vice President, Manufacturing, Pharmasset, Inc.
3. Melanie Compropst, Pharm.D., Director, Clinical Pharmacology, Pharmasset, Inc.
4. Laura Kupsch, M.S., Director, Regulatory/Quality, Pharmasset, Inc.
5. Ashley Lister, Ph.D., Director, CMC Regulatory, Pharmasset, Inc.
6. Hass Patel, Ph.D., Director, Product Development, Pharmasset, Inc.
7. Mike Rogers, Ph.D., Chief Development Officer, Pharmasset, Inc.
8. Bruce Ross, Ph.D., Director, Process Research, Pharmasset, Inc.
9. Michael Sofia, Ph.D., Vice President, Chemistry, Pharmasset, Inc.
10. Joseph Sonk, Ph.D., Vice President, Regulatory, Pharmasset, Inc.
11. Joseph Woolley, Ph.D., Senior Director, DMPK/Toxicology, Pharmasset, Inc.

1.0 BACKGROUND

Pharmasset, Inc. requested a Type B End-of-Phase 2 (EOP2) Chemistry, Manufacturing, and Controls (CMC) meeting, dated August 25, 2011, to discuss the Phase 3 CMC development program to support the proposed indication. Pharmasset provided a CMC EOP2 briefing package received on September 13, 2011.

The Office of New Drug Quality Assessment provided Pharmasset with preliminary responses to the questions in the CMC EOP2 briefing package on October 7, 2011. Pharmasset provided slides as responses to the preliminary comments on October 10, 2011 (see attachment). The original Pharmasset questions, preliminary FDA responses (in italics), and official minutes are provided below.

2.0 DISCUSSION

Pharmasset agreed with the preliminary comments provided by the Office of New Drug Quality Assessment. Pharmasset proposed that the meeting focus on question 1, question 2, additional FDA comment 2, question 8, question 13, and the remaining FDA comments, in that order (see attachment, slide 1).

The major points of discussion were:

- Update on bioequivalence trial (question 1)
- Proposed starting materials (question 2)
- Control of (b) (4) (additional FDA comment 2)
- Drug substance and drug product proposed specifications (questions 8 and 13)
- (b) (4) additional FDA comment 7)

Pharmasset stated that with the clarifications provided, they accept all Agency comments. Please note Action Items (Section 5.0) below.

2.1 CMC END-OF-PHASE 2 MEETING

Chemistry, Manufacturing and Controls/BioPharm

Question 1: The current plan is to conduct the first Phase 3 study with (b) (4) tablets and to subsequently introduce the 400mg tablet into the Phase 3 program. Does the Agency have additional advice for this approach that was not addressed at the August 18th meeting?

FDA Response:

At this time we have no additional advice regarding introduction of the 400-mg tablet into the Phase 3 program.

Meeting Discussion:

Pharmasset gave an update on their bioequivalence (BE) trial (P7977-1318). From preliminary statistical analysis of data as of the last week of September 2011, using a 95% confidence interval, the (b) (4) and 400 mg tablets show bioequivalence, and Pharmasset will likely only pursue the 400 mg tablet.

The Agency acknowledged this. (b) (4) (b) (4)

Drug Substance

(b) (4)

FDA Response:

At this time we do not agree with the proposal to designate (b) (4) as a GMP starting material. Please propose alternative starting materials (b) (4) In support of a proposed starting material, please provide representative batch analyses of the material. In addition, please provide data demonstrating that impurities (b) (4) are adequately removed during drug substance (b) (4) Impurities (b) (4) (b) (4) should be adequately controlled (b) (4) Acceptance criteria for assay, specified impurities, organic volatile impurities, etc. should be proposed; reporting results only is not acceptable. The synthesis of (b) (4) can be reported in the NDA or in Drug Master Files.

Meeting Discussion:

Pharmasset agreed to continue their evaluation of (b) (4) as potential starting materials. Pharmasset asked if the Agency would be open to considering (b) (4) as the starting material if they were to submit a qualification plan to the IND (see attachment, slides 2-5).

The Agency stated that they would consider [(b) (4)] but requested that Pharmasset demonstrate process ability to purge impurities, and to provide this data from all proposed alternative starting materials, including [(b) (4)] and [(b) (4)] [(b) (4)] The FDA advised Pharmasset to conduct fate and purge studies in order to determine what impurities are carried from each proposed starting material forward, how well the process would purge and control these impurities, as well as to track the fate of impurities that are converted into other impurities by the synthesis. FDA also requested that Pharmasset look at proposed starting material from different manufacturers, if they are considering multiple vendors.

Pharamasset agreed with the Agency and will follow up with the requested data as amendments to the IND. FDA advised Pharmasset to include their progress on these studies in the pre-NDA discussions.

Question 3: We intend to designate [(b) (4)] [(b) (4)] as a GMP starting material for the synthesis of PSI-7977 drug substance. Does the Agency agree with this approach?

FDA Response:

The designation of [(b) (4)] *as a GMP starting material appears reasonable. Please provide batch analyses for representative batches of* [(b) (4)] *Please provide data demonstrating that impurities in* [(b) (4)] *can be adequately removed during the manufacturing process. The proposed specification for* [(b) (4)] [(b) (4)] *should include proposed acceptance criteria for specified impurities, etc. Reporting results only is not acceptable.*

[(b) (4)]

Meeting Discussion:

No discussion was requested.

Question 4: We intend to designate [(b) (4)] as a GMP starting material for the synthesis of PSI-7977 drug substance. Does the Agency agree with this approach?

FDA Response:

The designation of [(b) (4)] *as a GMP starting material is acceptable. Please provide batch analyses for representative batches of* [(b) (4)] [(b) (4)] *Please provide data demonstrating that impurities in* [(b) (4)] [(b) (4)] *can be adequately removed during the manufacturing process. The proposed specification for* [(b) (4)] *should include*

proposed acceptance criteria for specified impurities, each unspecified impurity, etc. Reporting results only is not acceptable.

Meeting Discussion:

No discussion was requested.

Question 5: Pharmasset intends to include a secondary drug substance manufacturer in the original NDA submission. The same manufacturing process will be qualified at each site and both end products will be the same. Does the Agency agree with this approach?

FDA Response:

The proposal to include a secondary drug substance manufacturer in the original NDA submission is acceptable, provided adequate data are provided, including sufficient batch analyses to confirm equivalence of chemical and relevant physical properties between drug substance lots made by the two manufacturers.

We recommend that the NDA include 6-month stability data under long-term and accelerated conditions on 3 batches of drug substance from the secondary manufacturer. Please follow ICH Q1A recommendations for the stability data on drug substance from the primary manufacturer.

We also strongly recommend that drug product stability data on batches manufactured from the alternative drug substance supplier be provided, as noted in ICH Q1A.

Meeting Discussion:

No discussion was requested.

Question 6: Based on the ICH Guidance for impurities in drug substances (ICH Q3A) and a maximum daily dose of 400 mg, all impurities will be reported ≥ (b) (4) identified ≥ (b) (4) and qualified ≥ (b) (4) Does the Agency agree with this approach?

FDA Response:

This approach appears adequate based on a maximum daily dose of 400 mg, pending completion of the evaluation of potential genotoxic impurities.

Meeting Discussion:

No discussion was requested.

Question 7: We anticipate submitting 12 month stability data at 25°C/60%RH and 6 month data at 40°C/75%RH in the initial NDA submission. Does the Agency agree that this approach supports a retest period of (b) (4) months?

FDA Response:

The proposal to submit 12-month long-term and 6-month accelerated stability data from the primary stability batches to support the proposed retest period is acceptable. However, the assigned retest period will be based on review of all data submitted in the original NDA.

Meeting Discussion:

No discussion was requested.

Question 8: Does the Agency agree with our proposed specification and acceptance criteria for PSI-7977 drug substance?

FDA Response:

The proposed drug substance specification appears adequate to support Phase 3 clinical studies. However, please propose acceptance criterion for (b) (4) content, melting range, etc. The proposed limit of (b) (4) Total Residual Solvents is not justified; please propose an alternative limit. Please add a test and acceptance criterion for particle size distribution or provide a justification for not including this test in the drug substance specification. Finally, please note that the acceptability of the acceptance criterion for each of the proposed tests will be evaluated based on all information submitted to the original NDA.

Meeting Discussion:

Pharmasset stated that they are still in the process of collecting data and intend to set an updated specification prior to release of registration batches. Pharmasset will convert "Report" into numerical acceptance criteria.

Regarding the proposed limit for Total Residual Solvents, Pharmasset acknowledged that this was included in error, and will remove this (b) (4) limit. Pharmasset clarified that the Total Residual Solvents is currently set to the ICH limit, and will review the actual levels as they get closer to the NDA.

Regarding particle size distribution, Pharmasset clarified that they are currently testing for particle size distribution (reported in the batch analysis), but do not have an acceptance criterion at present. The effect of particle size on drug product performance is still under evaluation. Once it has been determined that it is a critical attribute, Pharmasset will set an appropriate acceptance criterion.

FDA requested that Pharmasset also evaluate the effect of particle size [redacted] (b) (4)

Drug Product

Question 9: Dissolution methods have been developed for [redacted] (b) (4) 400 mg tablet formulations. Does the Agency agree that the dissolution method development report and proposed specifications are appropriate?

FDA Response:

We are unable to provide an answer at this time. The selected dissolutions testing conditions appear to be appropriate. However, the dissolution data demonstrating the discriminating power of the selected dissolution method [redacted] (b) (4) *were not provided. Please provide these data.*

With respect to the dissolution acceptance criterion, we recommend that you collect complete dissolution profile data from the bio-batches and stability batches for your product. These data would be used for the setting of the dissolution acceptance criterion of your product (i.e., specification-sampling time point and specification value). For the setting of the acceptance criterion, the following points should be considered:

- *The dissolution profile should encompass the timeframe over which at least* [redacted] (b) (4) *of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.*
- *The specification-time point should be set when Q =* [redacted] (b) (4) *of dissolution occurs.*

Note that the acceptability of the dissolution acceptance criterion is a review issue during the NDA.

Meeting Discussion:

No discussion was requested.

Question 10: In order to maintain a sufficient supply of PSI-7977 drug product, Pharmasset intends to include a secondary/additional drug product manufacturer in addition to Metrics. The same manufacturing process will be qualified at each site and both end products will be the same. Does the Agency agree with this approach?

FDA Response:

The addition of a second drug product manufacturing facility is acceptable. In support of the additional site, please submit to the original NDA release data from 3 batches of drug product as well as 6-months long-term and accelerated

stability for these batches. Please follow ICH Q1A recommendations for the stability data on drug product from the primary manufacturer (b) (4)

Meeting Discussion:

No discussion was requested.

Question 11: Based on the ICH Guidance for degradation products in drug products (ICH Q3B R2) and a maximum daily dose of 400 mg, all impurities will be reported ≥ (b) (4) and identified and qualified ≥ (b) (4) Does the Agency agree with this approach?

FDA Response:

This approach appears adequate. Please note that acceptance criteria for drug product impurities will be evaluated based on all available information in an NDA.

Meeting Discussion:

No discussion was requested.

Question 12: Stability data for the drug product has shown that PSI-7977 (b) (4) tablets perform well with no significant changes observed at 25°C/60%RH and 40°C/75%RH. We expect that the 400 mg tablet formulation will also perform well in the accelerated studies. Does the Agency agree to 6 months' accelerated stability at the time of initial NDA submission for a shelf-life of 24-months?

FDA Response:

A minimum of 12-months primary stability data at 25°C/60%RH and 6-months at 40°C/75%RH on 400-mg tablets from the primary manufacturer (b) (4) *would be expected to support a 24-month shelf life. However, the assigned expiration dating period will be based on review of all data submitted in the original NDA. We generally follow the approaches recommended in ICH Q1E.*

Meeting Discussion:

No discussion was requested.

Question 13: Does the Agency agree with our proposed specification and acceptance criteria for PSI-7977 Tablets, (b) (4) 400 mg?

FDA Response:

The proposed drug product specification appears adequate to support the proposed Phase 3 clinical studies.

However, the suitability of the acceptance criterion will be evaluated based on all data submitted to the original NDA. In addition, please add a second, complementary identification test. Please provide a justification for use of the EP test for microbial quality rather than the USP test.

Meeting Discussion:

Regarding addition of a second, complementary identification test, Pharmasset notified the Agency that they are in the process of establishing FTIR and ID test.

Regarding use of the EP test for microbial quality, Pharmasset acknowledged that this was included in error, and that they do use the USP tests <61> and <62> for microbial quality.

ADDITIONAL FDA PRELIMINARY COMMENTS

1. *Do you anticipate submitting any elements of QbD in the application?*

   Meeting Discussion:

   No discussion was requested.

2. *Please provide additional data characterizing the potential* (b) (4) *of* (b) (4) *PSI-7977. Please provide evidence that a second,* (b) (4) *(mentioned on p. 30 of the background package) does not form during drug product manufacture or storage.*

   Meeting Discussion:

   Pharmasset will be submitting characterization reports for the potential (b) (4) (b) (4) of PSI-7977 in an upcoming IND amendment. Pharmasset is currently looking into the control of the second (b) (4). They report that the (b) (4) (b) (4) (b) (4) so Pharmasset has been working to control the (b) (4)

   Pharmasset clarified to the Agency that there is no evidence that (b) (4) is produced during the (b) (4). In fact, Pharmasset has found that if (b) (4) is present, (b) (4) Pharmasset also reported that although (b) (4) but it is still (b) (4).

FDA requested that Pharmasset continue to collect data on the [(b) (4)] drug substance batches to show that the process produces only [(b) (4)] Pharmasset confirmed that this is monitored as part of the drug substance specification. FDA also requested that Pharmasset provide data on [(b) (4)] the drug substance and drug product over stability to determine an appropriate control strategy. Pharmasset agreed, and stated that they use [(b) (4)]

3. *Please submit the protocol for primary drug substance stability study, incorporating the comments made above regarding the testing of drug substance manufactured at two sites, when it becomes available.*

Meeting Discussion:

No discussion was requested.

4. *Please submit the protocol for primary drug product stability study, incorporating the comments made above regarding the testing of product manufactured at two sites and from two sources of drug substance, when it becomes available.*

Meeting Discussion:

No discussion was requested.

5. *Please indicate your plans to seek approval of the* [(b) (4)]

Meeting Discussion:

No discussion was requested.

6. *At the time of the pre-NDA meeting, please provide a report on your evaluation of potential genotoxic impurities.*

Meeting Discussion:

No discussion was requested.

7. *Please determine the* [(b) (4)] *of the drug product as it relates to microbial quality.*

Meeting Discussion:

Pharmasset agreed to determine the [(b) (4)] of the drug product, and requested clarification on the intent of the request since they are running full microbiological testing. The Agency responded that if sufficient data show that [(b) (4)] is low, [(b) (4)]

3.0 DATA STANDARDS FOR STUDIES

In addition, we would like to remind you that CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced documents that provide specifications for sponsors regarding implementation and submission of study data in a standardized format. These documents will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. These documents may be found at the following webpage: http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

5.0 ACTION ITEMS

1. Pharmasset to demonstrate process ability to purge impurities, and to provide this data from all proposed alternative starting materials, including (b) (4) (b) (4)

2. Pharmasset to conduct fate and purge studies in order to determine what impurities are carried from each proposed starting material forward, how well the process would purge and control these impurities, as well as to (b) (4) (b) (4)

3. Pharmasset to look at proposed starting material from different manufacturers, if they are considering multiple vendors.

4. Pharmasset to continue to collect data on the (b) (4) drug substance batches, per the current specification, to show that the process produces (b) (4) (b) (4)

5. Pharmasset to provide data on the (b) (4) drug product, at release and over stability, to determine an appropriate control strategy.

6. Pharmasset to evaluate the effect of (b) (4) on drug product performance, as well as on (b) (4)

6.0 ATTACHMENTS AND HANDOUTS

Slides provided by Pharmasset, Inc. for the meeting discussion are attached.

CONCURRENCE

[See appended electronic signature page]

Jeannie David, M.S.
Regulatory Project Manager
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

[See appended electronic signature page]

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

Pharmasset proposes the following order for addressing responses

- Question #1
- Question #2
- Additional comment #2
- Question #8
- Question #13
- Remaining FDA comments/all other business
  - Pharmasset accepts and appreciates the feedback provided by the agency for all other questions

(b) (4)

Starting Material Qualification Plan

(b) (4)

(b) (4)

Starting Material Qualification Plan

(b) (4)

(b) (4)

(b) (4)

Starting Material Qualification Plan

(b) (4)

(b) (4)

Starting Material Qualification Plan

(b) (4)

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/s/

JEANNIE C DAVID
10/18/2011

RAPTI D MADURAWE
10/19/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106,739

MEETING MINUTES

Pharmasset, Inc.
Attention: Joseph Sonk, Ph.D.
Vice President, Regulatory Affairs
303A College Road East
Princeton, NJ 08540

Dear Dr. Sonk:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PSI-7977.

We also refer to the End-of-Phase 2 meeting between representatives of your firm and the FDA on August 18, 2011. The purpose of the meeting was to obtain Agency concurrence for the Phase 3 clinical development program to support the proposed indication.

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

If you have any questions, call me at (301) 796-0759.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End-of-Phase 2
Meeting Date and Time:	August 18, 2011 9:00 AM – 10:30 AM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	106,739
Product Name:	PSI-7977
Indication:	Treatment of chronic hepatitis c infection
Sponsor/Applicant Name:	Pharmasset, Inc
Meeting Chair:	Debra Birnkrant, MD
Meeting Recorder:	Linda C. Onaga, MPH

FDA ATTENDEES

1. Robert Temple, M.D., Deputy Director for Clinical Science, Office of the Center Director
2. Edward Cox, M.D., Director, Office of Antimicrobial Products (OAP)
3. Debra Birnkrant, M.D., Director, Division of Antiviral Products (DAVP)
4. Jeffrey Murray, M.D., M.P.H., Deputy Director, DAVP
5. Sarah Connelly, M.D., Clinical Reviewer, DAVP
6. Kimberly Struble, Pharm.D., Clinical Team Leader, DAVP
7. Mary Singer, M.D., Clinical Team Leader, DAVP
8. Adam Sherwat, M.D., Clinical Reviewer, DAVP
9. Poonam Mishra, M.D., Clinical Reviewer, DAVP
10. Christopher Ellis, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
11. Takashi Komatsu, Ph.D., Clinical Virology Reviewer, DAVP
12. Patrick Harrington, Ph.D., Clinical Virology Reviewer, DAVP
13. Julian O'Rear, Ph.D., Clinical Virology Team Leader, DAVP
14. Ruben Ayala, Pharm.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
15. Jeffry Florian, Ph.D, Pharmacometrics Reviewer, OCP
16. Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader, OCP
17. Michael Pacanowski, Pharm.D., Genomics Team Leader, OCP
18. Karen Qi, Ph.D., Biometrics Reviewer, Division of Biometrics IV (DBIV)

19. Greg Soon, Ph.D., Biometrics Team Leader, DBIV
20. Mark Seggel, Ph.D., CMC Reviewer, Office of New Drug Quality Assessment (ONDQA)
21. Karen Winestock, Chief, Project Management Staff, DAVP
22. Linda C. Onaga, M.P.H., Regulatory Project Manager, DAVP

SPONSOR ATTENDEES

1. Michael Rogers, Ph.D. Chief Development Officer
2. William T. Symonds, PharmD. Senior Vice President, Clinical Pharmacology/Translational Medicine
3. Robert Hindes, MD Vice President, Medical Affairs, Infectious Diseases specialty and Medical Lead
4. Effie Albanis, MD Director, Medical Affairs, Hepatology Specialty
5. Melanie Cornpropst, PharmD. Director, Clinical Pharmacology
6. Yuao Zhu, Ph.D. Director, Virology
7. Joseph Woolley, Ph.D. Senior Director, DMPK/Toxicology
8. Lei Fang, MS Lead Statistician Consultant to Pharmasset
9. Laura Kupsch, MS Director, Regulatory/Quality
10. Ashley Lister, Ph.D. Director, CMC Regulatory
11. Joseph S. Sonk, Ph.D. Vice President, Regulatory, Regulatory Lead

1.0 BACKGROUND

Pharmasset, Inc. is developing PSI-7977 for the treatment of chronic hepatitis C virus (HCV) infection. PSI-7977 has been investigated in Phase 1 clinical trials including a relative bioavailability study with PSI-7851, a single-dose, mass balance study, a thorough QT study, and a methadone interaction study. In addition, there are 2 ongoing Phase 1 trials with PSI-7977 including renal and hepatic impairment studies. Their Phase 2 program is exploring the use of PSI-7977 in the treatment of subjects with HCV genotypes (GT) 1- 6. For their initial Phase 3 pivotal trials and subsequent NDA submission, Pharmasset would like to pursue an indication for PSI-7977 in combination with peginterferon alfa and ribavirin (PR) or ribavirin (RBV) alone for the treatment of HCV GT 2 or 3 in (b) (4) adults with compensated liver disease and PSI-7977 in combination with RBV for the treatment of HCV GT 2 or 3 patients in whom interferon (IFN) is contraindicated or not tolerated.

Pharmasset requested an End-of-Phase 2 meeting with the Division of Antiviral Products to discuss the Phase 3 clinical development program to support their proposed indication. The meeting objectives were:

1. To reach agreement that the proposed indication is sufficient for the first NDA submission for PSI-7977:
    a. Indicated for the treatment of chronic HCV infection in patients infected with HCV GT 2 or 3. PSI-7977 should be used with PR or with RBV in (b) (4) (b) (4) patients infected with HCV GT 2 or 3

    b. PSI-7977 should be used with RBV in IFN-contraindicated/intolerant patients infected with HCV GT 2 or 3

2. Discuss the proposed Phase 3 clinical protocols

3. Obtain Agency feedback on any other aspects of the proposed PSI-7977 development program.

The Division of Antiviral Products provided Pharmasset with preliminary responses on August 12, 2011. Pharmasset provided responses to the preliminary comments on August 16, 2011 (see attachment).

2. DISCUSSION

Pharmasset agreed with the preliminary comments provided by the Division of Antiviral Products. Pharmasset proposed that the meeting focus on reviewing the preliminary comments and provide additional insight where needed. To convey the discussion points from this meeting, the original Pharmasset questions are in bold, followed by preliminary FDA comments in italics and discussion points in regular text. Original Pharmasset questions that were not discussed at this meeting are not included in these meeting minutes; however, the attachment contains the complete questions, preliminary FDA comments and Pharmasset responses.

The major points of discussion Pharmasset focused on were:

- Agreement to the conduct of two pivotal trials to seek an indication in the GT 2/3 population. The first trial (P7977-1231) will be conducted in treatment-naïve GT 2 and 3 subjects, and Pharmasset plans to fully power Arm C (PSI-7977/RBV x 12 weeks). The second trial (P7977-1533) will be conducted in IFN intolerant/contraindicated subjects, with the final trial design being contingent upon results of the ongoing ELECTRON trial (P7977-0523).

- To determine the clinical benefit of RBV in a direct acting antiviral (DAA) regimen, Pharmasset proposes to incorporate a 12-week PSI-7977 monotherapy arm in the IFN intolerant/contraindicated trial (P7977-1533) and will increase the number of subjects to provide a statistical comparison between PSI-7977/RBV and PSI-7977 monotherapy and the placebo control arm.

- Additional studies in patient populations considered to have a high unmet medical need.

2.1. CMC End-of-Phase 2 Meeting

Question 1: The current plan is to conduct the first Phase 3 study (b) (4) and the second study will employ a to-be-marketed 400mg tablet. Does the Agency agree that the full clinical program will support the initial launch of the 400mg tablet? If not, please explain which additional supportive data would be required to do so.

FDA Response:

CMC:

We recommend a separate EOP2 CMC meeting to discuss the drug substance and drug product development plans. Please include the dissolution method development report in the meeting background package. See Clinical Pharmacology comments on the proposed human relative bioavailability study that will support use of the 400 mg tablet.

Clinical Pharmacology:

We agree with your proposal to evaluate the new 400 mg tablets in Phase 3 trials. Before doing so, we recommend waiting for results from your ongoing bioequivalence (BE) trial (P7977-1318) to ensure that (b) (4) and 400 mg tablets are bioequivalent. In this BE trial, you should use a 90% confidence interval with a typical BE range of 80 to 125%. The BE trial becomes pivotal if the 400 mg tablets are not used in all Phase 3 trials.

Discussion:

Pharmasset will submit an End of Phase 2 CMC meeting request by August 25, 2011. They also stated they would amend the BE study to use an 80-125% limit for the 90% CI. The first

trial will likely use the [redacted] (b) (4) tablet and the second trial the 400 mg tablet; the BE study will be used to link the two formulations.

2.2. Phase 3 Clinical Development Program

Question 3: Is the proposed clinical development plan sufficient to form the basis of an NDA to obtain this indication? If not, please explain why.

FDA Response:

In general, the clinical development plan is sufficient to form the basis of an NDA to obtain this indication. You must enroll an adequate number of US subjects and ensure a safety database of approximately 1000 to 1500 subjects exposed to the proposed dose and duration of treatment as outlined in the Draft Guidance for Industry Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment. ***While there is no specific number of subjects from the US that must be included, there should be adequate representation to ensure safety in a broader US population of HCV genotype 2 and 3 infected subjects, including minority populations and women. It is important you include adequate numbers of women and Black/African American and Hispanic subjects to better characterize important clinical, pharmacokinetic and pharmacodynamic information on the use of PSI-7977. Please comment on your recruitment and retention plans for these minority populations.***

Discussion:

Pharmasset did not anticipate any issues with acquiring an adequate number of subjects to ensure a robust safety database. Pharmasset believed they may have more than what is recommended by the FDA. Pharmasset assured the FDA of their ability to recruit and maintain an adequate number of minority populations and women in the trials and discussed targeting appropriate clinical sites. Approximately 35% female, 16% Hispanic/Latino, and 12% African American subjects have been enrolled in the Phase 2 program.

FDA Additional Comment:

Please comment on your development plans for the following populations: HIV/HCV co-infected, transplant, bleeding disorders, substance abuse. We encourage development in these populations prior to NDA submission.

Discussion:

Pharmasset stated they plan to conduct a drug-drug interaction (DDI) study with common HIV regimens, including tenofovir and emtricitabine. Pharmasset will submit the protocol for the DDI study in the fourth quarter of 2011. Once the results of the DDI study are analyzed and a dose of PSI-7977 is selected, Pharmasset will begin an HIV-HCV co-infected study targeted for the second half of 2012.

Pharmasset also stated they plan to conduct a pre-liver transplant study and a DDI study between PSI-7977 and cyclosporine and tacrolimus in the upcoming calendar year. After the completion of the pre-liver transplant study, Pharmasset will evaluate PSI-7977 in post-transplant subjects.

Pharmasset will enroll subjects with bleeding disorders and hemoglobinopathies in the Phase 3 clinical trial, P7977-1533.

Pharmasset conducted a methadone DDI study and currently is allowing enrollment of subjects with concurrent methadone use in all of their clinical trials. Pharmasset stated that drug screens are not required as part of the inclusion criteria for the open clinical trials.

FDA Additional Comment:

The summary data submitted to date suggest that PSI-7977 is likely to have a public health benefit in pediatric patients. If a substantial treatment benefit is confirmed, you will be required to study PSI-7977 in pediatric patients with chronic HCV. We encourage you to begin discussing your pediatric development plan with DAVP. These initial discussions should include plans for age-specific formulation development and your assessment of whether juvenile animal toxicity studies are warranted.

Discussion:

Pharmasset stated they will discuss their pediatric plan with the FDA (b) (4) (b) (4) (b) (4) Pharmasset plans to submit a plan for pediatric clinical development during the first half of 2012.

The FDA agreed to this approach and will review the plan once submitted to the Agency

Question 4: Does the Agency agree with the design of the three proposed Phase 3 trials presented in the background document? Any Agency advice will be incorporated into the versions submitted for final Agency review.

a. **Specifically, does the Agency agree with the placebo control arm in the IFN-free study in IFN-intolerant/contraindicated patients?**

b. **Is it sufficient for Pharmasset to show that a 12-week regimen of PSI-7977+SOC is non-inferior to the 24-week regimen of SOC to gain approval or is a demonstration of superiority required?**

FDA Response:

In general, the available PSI-7977 safety and efficacy data support Phase 3 development in the HCV genotype 2 and 3 population. However, providing specific feedback on the design of the two proposed Phase 3 trials is challenging in the setting of emerging data. We agree

with the choice of the PEG/RBV x 24 week control arm in P7977-1231 and the placebo control arm in P7977-1533. Please provide your rationale for selecting RBV weight-based dosing instead of the (b) (4) ***A non-inferiority design in P7977-1231 is acceptable given the important clinical benefit of decreasing PEG/RBV exposure, and we request further justification for the selected 10% non-inferiority margin. Is it now your intent to compare Arm C (PSI-7977/RBV x 12 weeks) to Arm B (control) in a similar fashion? We will be able to provide additional comments once we review the final protocol(s).***

Discussion:

Pharmasset's decision for weight-based RBV dosing was influenced by the fact they were pursuing shorter treatment duration. Pharmasset stated that data from prior studies used to support progression to Phase 3 were generated using weight-based dosing and believe it is best for data analysis to keep the RBV dose consistent across studies and genotypes. Pharmasset stated that a post-hoc analysis from prior trials would be conducted to evaluate the amount of RBV that was actually used because some subjects received fixed doses and other used weight-based doses.

Pharmasset further discussed the possibility of conducting a single clinical trial in the HCV GT 2/3 treatment-naïve population (P7977-1231), instead of two identically designed trials as originally proposed (see attachment Summary Question 9, FDA Response). This Phase 3 trial would have three adequately-powered arms: Arm A – 12 weeks with PSI-7977 plus PEG/RBV, Arm B – 24 weeks of PEG/RBV alone, and Arm C – 12 weeks with PSI-7977 plus RBV. FDA supports this general trial design; however, FDA would like to see Pharmasset's justification for the proposed 10% NI margin in detail. As part of the non-inferiority margin justification, Pharmasset should factor in weight-based RBV. FDA also stated justification of the NI margin should include the contribution of PSI-7977. Therefore, the treatment difference in PEG/RBV over 12 weeks and over 24 weeks should be assessed based on literature reviews to determine the NI margin between Arms A and B. Comparison of Arms B and C can be used for approval as well. Due to the limited efficacy of RBV alone, the NI margin for Arms B and C can be larger than the one for Arms A and B. Pharmasset inquired about the possibility of conducting one Phase 3 trial in HCV GT 2 and 3 and adequately powering Arm A (12 weeks with PSI-7977 plus PEG/RBV) to establish superiority over Arm B (24 weeks of PEG/RBV alone). Pharmasset may want to pursue a strict superiority trial. However, if the trial fails to show superiority, they can not use the data to support a NI claim. Also, superiority is more difficult to achieve compared with NI given the same conditions.

FDA inquired about the relevance of Arm A, 12 weeks of PSI-7977 plus PEG/RBV. Pharmasset responded that Arm A is included for security.

FDA asked if Pharmasset considered an arm with PSI-7977 for 12 weeks plus less than 12 weeks of PEG/RBV. Pharmasset stated they have considered this approach and referred to the ELECTRON trial, which used PSI-7977 plus PEG/RBV for 12 weeks and now includes

an arm with PSI-7977 for 12 weeks plus PEG/RBV for 8 weeks. Pharmasset plans to include additional arms using a variety of patient populations in the ongoing ELECTRON trial, including GT 1 null responders. The amendment will be sent to the FDA for review. FDA also requested that the GT 2/3 data from the PROTON trial (P7977-0422) be submitted for review.

The FDA recommended that Pharmasset include in their ELECTRON study GT 1a null responders with NS5B F415Y amino acid substitution. Vertex Pharmaceuticals has presented data at the HCV Resistance Conference held in June 2011 that there was a statistically significant association between amino acid substitution F415Y and treatment failure of a RBV containing regimen. It was also recommended that Pharmasset submit the resistance data from all of their studies in a common format so that these could be combined. There may be multiple pathways to resistance with none of these occurring frequently and pooled data may be necessary to identify the pathways. The FDA will provide Pharmasset a copy of the Vertex presentation that was presented at the HCV Resistance Conference.

FDA Response:

We remind you that as more SVR data become available, your development program may change. For example, if P7977-1231 demonstrates PSI-7977/RBV x 12 weeks is superior to PEG/RBV control, the proposed P7977-1533 trial design in an interferon ineligible/intolerant population may not be necessary. If the PSI-7977 x 12-week monotherapy arm in P7977-0523 demonstrates robust SVR, a larger Phase 2 or 3 trial could incorporate a PSI-7977 monotherapy arm to determine if RBV is needed to achieve SVR. These examples illustrate the complexity of providing specific feedback in the setting of limited, though compelling, Phase 2 data.

Discussion:

Pharmasset discussed adding a third arm to P7977-1533 in HCV GT 2/3 infected subjects who are intolerant or have contraindications to interferon. The originally proposed Phase 3 trial has two arms, Arm A (12 weeks with PSI-7977 plus RBV) and Arm B (12 weeks with placebo). The additional arm would evaluate the efficacy of PSI-7977 monotherapy for 12 weeks. The addition of the third arm would be dependant on the efficacy data results from the Phase 2 ELECTRON clinical trial, and Pharmasset stated ELECTRON SVR data from the PSI-7977 monotherapy arm would be available within the next few weeks. In P7977-1533, Pharmasset proposes a non-inferiority comparison between PSI-7977 monotherapy and PSI-7977/RBV dual therapy arms and stated the expected clinical benefit from RBV would be 15%.

FDA stated more justification for a non-inferiority margin is needed and noted challenges for this trial design including the fact there is no M1 and that clinical judgment would factor into statistical design. FDA recommended the trial size should be large enough for meaningful comparisons and to assess development of resistance. In addition, there should be a data monitoring committee overseeing the trial.

FDA Additional Clinical Comment:

The protocol synopsis (for P7977-1533) *states enrollment begins November 2011; however, the GANTT chart indicates 3rd quarter 2012. Please clarify this discrepancy.*

Discussion:

Pharmasset provided clarification to the FDA's comments and stated that the protocol for P7977-1231 will begin enrollment in November 2011 and P7977-1533 will begin in the first quarter 2012. They note this time period corrects an error in the submitted August 16, 2011 responses to FDA preliminary comments where "3rd quarter 2012" was stated. Pharmasset will send the FDA an updated GANTT chart.

FDA Additional Clinical Comment:

The exclusion criteria appear to contradict several proposed interferon intolerance/ineligible criteria. For example, interferon intolerance is defined as "subjects who have been previously treated (at least one dose) with interferon (either PEG or short acting interferon) and RBV"; however, the exclusion criteria state subjects must be naïve to all HCV antiviral treatment(s). In addition, exclusion criteria 4, 7 and 9 appear to eliminate potentially eligible subjects.

Discussion:

Pharmasset updated the FDA with their plans to change the exclusion criteria as outlined in the FDA preliminary comment. Pharmasset plans to broaden the population and include subjects exposed to interferon with or without other DAAs except for NS5B polymerase inhibitors.

FDA agreed with this approach.

FDA Additional Clinical Comment:

Patients with decompensated liver disease (CP B or C) are an important population for whom PegIFN is contraindicated. We encourage you to include patients with decompensated liver disease in the trial, following completion of the ongoing hepatic impairment study.

Discussion:

Pharmasset stated their intention to include CP class B and C patients as appropriate as data become available from the ongoing hepatic impairment study. They study is almost done dosing the CP class B cohort and will soon start with the class C cohort. In addition to safety and PK data, they are collecting viral dynamic data, since this study is being completed in HCV patients. So far, Pharmasset stated the data look good with respect to safety. They plan to offer these patients IFN-free treatment in a roll-over study. Pharmasset plans to evaluate

PSI-7977 in pre and post-liver transplant settings. In addition, Pharmasset has collaborated with Bristol Myers Squib to treat a post-liver transplant patient with PSI-7977 + BMS 790052 as compassionate use.

FDA Clinical Pharmacology Comment:

Please consider collecting intensive PK sampling at steady state from a subset of subjects in each Phase 3 trial. These PK data could be integrated in a population PK model to better understand the pharmacokinetics of PSI-7977.

Discussion:

Pharmasset did not agree to the FDA suggestion to collect intensive PK data in their Phase 3 trials. Pharmasset stated they have collected intensive samples throughout the clinical development program of PSI-7977. Pharmasset stated their intentions of continuing to collect sparse blood samples throughout the Phase 3 trials and combine this with previously collected data to better understand the pharmacokinetics of PSI-6206 and covariates that may explain pharmacokinetic variability.

The FDA agreed with this approach since they have already collected extensive PK data, including intensive sampling in a number of previous studies.

FDA Clinical Pharmacology Comment:

Please prohibit the intake of sensitive substrates of OATP1B1 and OATP1B3 (e.g. rosuvastatin and pravastatin) during the trials, until data from in vitro studies are available.

Discussion:

Pharmasset provided preliminary data regarding PSI-7977 and transporters OATP1B1 and OATP1B3 in an amendment to the meeting backgrounder. The in vitro study results showed that PSI-7977 and PSI-6206 have a low potential for clinically relevant inhibition of OATP1B1 and OATP1B3. Therefore, coadministration of sensitive substrates of OATP1B3/1B3 will be permitted in the trial. FDA agreed with this interpretation.

FDA Clinical Virology Comments:

Please note that we regard clinical association with failure as resistance associated regardless of cell culture phenotype. Therefore, even if your phenotypic studies do not show a significant reduction in susceptibility to PSI-7977, the amino acid substitutions will be considered resistance associated if they are observed in multiple subjects who failed treatment to PSI-7977. We recommend testing such substitutions for cross resistance to other HCV NS5B inhibitors that are late in development.

Discussion:

FDA requests the columns be aligned from all the trials so that the resistance pathways can be seen across the clinical development program. Pharmasset agreed to provide data to the FDA in this format.

FDA Clinical Virology Comments:

For the (b) (4) ***version that you are planning to use to quantify HCV RNA, please clarify why you are not using the approved version of the assay.***

Discussion:

Pharmasset confirmed their intentions to use the approved version of the (b) (4) (b) (4) as requested by the FDA.

Summary Question 9: Does the Agency agree that the supportive information from the ongoing trials in the background document, and the proposed plan to keep the Agency informed as new data accrue, adequately support the initiation and conduct of the proposed Phase 3 studies? If not, please explain why.

FDA Response:

Please refer to our previous responses. In general, the available PSI-7977 safety and efficacy data support Phase 3 development in the HCV genotype 2 and 3 population, and your plan to keep the Agency informed is acceptable. It may not be necessary to conduct two identical Phase 3 trials in the HCV genotype 2 and 3 treatment naïve population. An adequate safety database is needed to support an NDA submission; however, we are open to alternative Phase 3 trial designs to address issues such as treatment duration, PSI-7977 monotherapy, etc.

Discussion:

Pharmasset inquired about the FDA's thoughts on an additional study that would investigate PSI-7977 monotherapy in GT 1 subjects who are intolerant or for whom interferon is contraindicated. Pharmasset will have data from a limited number of subjects from ELECTRON to support this trial design, and Pharmasset would like to pursue this protocol if the results are robust. The FDA indicated this proposed trial design sounds like an appropriate step; however the design is based on limited data and it is premature to provide further comments at this time.

FDA asked for more details about the PSI-7977 safety profile. Pharmasset stated that there were no safety signals observed to date. Pharmasset looked at rash, hepatic toxicities and laboratory abnormalities and they have not seen anything to date. Adverse events associated with interferon use were decreased in IFN-sparing arms. Pharmasset will submit a future detailed safety summary of PSI-7977.

3.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

- Pharmasset will submit an End of Phase 2 CMC meeting request by August 25, 2011.
- Pharmasset will amend P7977-1318 to use an 80-125% limit for the 90% CI.
- FDA will provide Pharmasset a copy or link to the Vertex data presented at the HCV Resistance Conference. The link to the presentation is http://regist2.virology-education.com/2011/6HEPC/docs/08_Bartels.pdf
- Pharmasset will provide:
    a. An updated GANTT chart
    b. Data from the PROTON trial HCV GT 2/3 arm
    c. Data from the ELECTRON trial, including all ongoing and planned treatment arms along with safety, efficacy and resistance data when available.
- Pharmasset will provide a thorough justification for the non-inferiority margin for protocols P7977-1231 and P7977-1533.

6.0 ATTACHMENTS AND HANDOUTS

Pharmasset's response to the Division's preliminary comments.

Pharmasset's Response - Questions and Preliminary Responses

We thank the Division for the extremely useful responses to the issues in the background document. We believe that there are substantial areas of agreement and the encouragement and examples provided are especially appreciated. We agree with your comment in the letter that milestone meetings such as this can be valuable even if the pre-meeting comments are considered sufficient to answer the questions. Therefore we propose that the meeting take the form of reviewing the letter so that we can benefit from hearing your perspective and incorporating it wherever possible. The Pharmasset responses are provided in ***bold italics*** after the FDA Response.

While the proposed meeting objective is clear agreement on each of the items in the letter (including protocol submission for final Agency review) our major points for the meeting can be summarized as the following:

- We agree to the conduct of two pivotal trials to seek an indication in the Genotype 2/3 population. The first study will be conducted in treatment naïve genotype 2 and 3 subjects, and we plan to fully power Arm C. The second study will be conducted in interferon intolerant/contraindicated subjects, with the final study design being contingent upon results of the Electron study (P7977-0523).

- To determine the clinical benefit of ribavirin in a DAAV regimen, we propose to incorporate a 12-week PSI-7977 monotherapy arm in the IFN intolerant/contraindicated trial (P7977-1533). We will increase the number of subjects to provide a statistical comparison between PSI-7977/RBV and PSI-7977 monotherapy and the control arm.

- We would like to discuss additional studies in patient populations considered to have a high unmet medical need.

QUESTIONS AND PRELIMINARY RESPONSES

CHEMISTRY, MANUFACTURING AND CONTROLS/BIOPHARM

1. The current plan is to conduct the first Phase 3 study (b) (4) the second study will employ a to-be-marketed 400mg tablet. Does the Agency agree that the full clinical program will support the initial launch of the 400mg tablet? If not, please explain which additional supportive data would be required to do so.

FDA Response:

CMC:
We recommend a separate EOP2 CMC meeting to discuss the drug substance and drug product development plans. Please include the dissolution method development report in the meeting background package. See Clinical Pharmacology comments on the proposed human relative bioavailability study that will support use of the 400 mg tablet.

Pharmasset Response:
We will submit an EOP2 CMC meeting request by August 25, 2011.

Clinical Pharmacology:

We agree with your proposal to evaluate the new 400 mg tablets in Phase 3 trials. Before doing so, we recommend waiting for results from your ongoing bioequivalence (BE) trial (P7977-1318) to ensure (b) (4) and 400 mg tablets are bioequivalent. In this BE trial, you should use a 90% confidence interval with a typical BE range of 80 to 125%. The BE trial becomes pivotal if the 400 mg tablets are not used in all Phase 3 trials.

Pharmasset Response:
We agree to wait for these results and we will amend this study to use a 90% confidence interval with a BE range of (b) (4)

NONCLINICAL

2. Does the Agency agree that the proposed submission timetable for the reproductive toxicology and teratology studies is adequate to support the initiation of the proposed Phase 3 clinical program? If not, please explain why. Please note the proposed Phase 3 study design is influenced by the (b) (4) **Warning, especially with regard to prevention of pregnancy.**

FDA Response:

Your proposed submission timetable is acceptable. Please let the Agency know of your plans to conduct a post-natal development study (i.e. segment 3) including the approximate timeframe of study report submission.

Pharmasset Response:
We appreciate this response and plan to initiate the study in 1Q 2012 and submit the report in 1Q 2013.

CLINICAL

3. Is the proposed clinical development plan sufficient to form the basis of an NDA to obtain this indication? If not, please explain why.

FDA Response:

In general, the clinical development plan is sufficient to form the basis of an NDA to obtain this indication. You must enroll an adequate number of US subjects and ensure a safety database of approximately 1000 to 1500 subjects exposed to the proposed dose and duration of treatment as outlined in the Draft Guidance for Industry Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment. *While there is no specific number of subjects from the US that must be included, there should be adequate representation to ensure safety in a broader US population of HCV genotype 2 and 3 infected subjects, including minority populations and women. It is important you include adequate numbers of women and Black/African American and Hispanic subjects to better characterize important clinical, pharmacokinetic and pharmacodynamic information on the use of PSI-7977. Please comment on your recruitment and retention plans for these minority populations.*

Pharmasset Response:
Based upon the advice in your letter, we intend to conduct two well-controlled pivotal trials in genotype 2/3 subjects, one in treatment naive subjects and the other in interferon intolerant/contraindicated subjects. We intend to enroll the recommended number of subjects required for an adequate safety database. Our intent is to include adequate numbers of minority populations and women. In addition we will have in place a retention program for all subjects. To date, across our Phase 2 program, a preliminary review shows that we have enrolled approximately 35% female subjects, 16 % Hispanic/Latino subjects, and 12% African American/ Black subjects.

Please comment on your development plans for the following populations: HIV/HCV co- infected, transplant, bleeding disorders, substance abuse. We encourage development in these populations prior to NDA submission.

Pharmasset Response:
We have plans to study the special populations you have identified and provide the following:

- *HIV/HCV co-infected: Planning a DDI study with common HIV regimens which will be submitted 4Q 2011. We also plan to conduct a clinical study in this population once the results of the DDI study are analyzed and we pick a dose.*
- *Transplant: We plan to initiate a pre-liver transplant study in the next calendar year as well as conducting a DDI study with PSI-7977 and cyclosporine and tacrolimus.*
- *Bleeding disorders: We will enroll patients with hemoglobinopathies and bleeding disorders in the P7977-1533 study.*

- *Substance abuse: We have completed a methadone DDI study and currently allow patients with concurrent methadone use to be enrolled into our clinical studies. Note that we do not require urine drug screens as an inclusion criterion.*

The summary data submitted to date suggest that PSI-7977 is likely to have a public health benefit in pediatric patients. If a substantial treatment benefit is confirmed, you will be required to study PSI-7977 in pediatric patients with chronic HCV. We encourage you to begin discussing your pediatric development plan with DAVP. These initial discussions should include plans for age-specific formulation development and your assessment of whether juvenile animal toxicity studies are warranted.

Pharmasset Response:
Pediatric plan: We plan to submit a plan for pediatric clinical development during the first half of 2012 which will include a plan for development of a pediatric formulation and preclinical assessment.

4. Does the Agency agree with the design of the three proposed Phase 3 trials presented in the background document? Any Agency advice will be incorporated into the versions submitted for final Agency review.

a. Specifically, does the Agency agree with the placebo control arm in the IFN-free study in IFN-intolerant/contraindicated patients?

b. Is it sufficient for Pharmasset to show that a 12-week regimen of PSI-7977+SOC is non-inferior to the 24-week regimen of SOC to gain approval or is a demonstration of superiority required?

FDA Response:

Clinical:

In general, the available PSI-7977 safety and efficacy data support Phase 3 development in the HCV genotype 2 and 3 population. However, providing specific feedback on the design of the two proposed Phase 3 trials is challenging in the setting of emerging data. We agree with the choice of the PEG/RBV x 24 week control arm in P7977-1231 and the placebo control arm in P7977-1533. Please provide your rationale for selecting RBV weight-based dosing instead of the (b) (4) *A noninferiority design in P7977- 1231 is acceptable given the important clinical benefit of decreasing PEG/RBV exposure, and we request further justification for the selected 10% noninferiority margin. Is it now your intent to compare Arm C (PSI-7977/RBV x 12 weeks) to Arm B (control) in a similar fashion? We will be able to provide additional comments once we review the final protocol(s).*

Pharmasset Response:
We initially chose weight-based ribavirin dosing as we were pursuing a shorter treatment duration. The data from prior studies used to support progression to Phase 3 were generated using weight-based dosing and we believe it is best for data analysis to keep RBV dose consistent across studies and genotypes.

We will adequately power the study to compare Arm A (PSI-7977+PEG/RBV x 12 week) and Arm C (PSI-7977+RBV x 12 week) to Arm B (PEG+RBV x 24 week). The selection of the non-inferiority margin is based upon a combination of statistical reasoning and clinical judgment. We think that the 10% NI margin is justified based on the potential clinical benefit of PSI-7977 in relation to current standard of care.

We remind you that as more SVR data become available, your development program may change. For example, if P7977-1231 demonstrates PSI-7977/RBV x 12 weeks is superior to PEG/RBV control, the proposed P7977-1533 trial design in an interferon ineligible/intolerant population may not be necessary. If the PSI-7977 x 12-week monotherapy arm in P7977-0523 demonstrates robust SVR, a larger Phase 2 or 3 trial could incorporate a PSI-7977 monotherapy arm to determine if RBV is needed to achieve SVR. These examples illustrate the complexity of providing specific feedback in the setting of limited, though compelling, Phase 2 data.

Pharmasset Response:

Depending on emerging data, we propose to change the design of P7977-1533 to assess the efficacy of PSI-7977+RBV versus PSI-7977 monotherapy in the intolerant contraindicated population to determine the clinical benefit of ribavirin. Both arms will also be compared to placebo control.

Additional Clinical Comments:

- *Based on our review of the SVR12 and SVR24 data from other DAA + pegIFNα/RBV programs and the available Phase 2 data from the PSI-7977 development program, FDA is agreeable to SVR12 as the primary endpoint for the PSI-7977 registrational trials. Available SVR24 data should be submitted at the time of the NDA; however, complete SVR24 data would be expected to be submitted after all subjects complete the trials as a PMR, as would the long-term trial data. If you agree to this approach, prior to submission of the finalized protocol(s) using the SVR12 primary endpoint, we request you provide analyses of follow-up viral load data from all PSI-7977 clinical trials conducted to date to demonstrate the concordance of SVR12 and SVR24 results, and identify any subjects who have experienced virologic relapse after Follow-up Week 12.*

Pharmasset Response:
We agree.

- *Please comment on the regulatory intent of the Patient Reported Outcomes.*

Pharmasset Response:
There is no regulatory intent to utilize PROs.

P7977-1231 comments

- *We agree with the Arm C Stopping rules for Individual Arms (Section 11.6) based on the limited P7977-0532 PSI-7977/RBV SVR12 data; however, these stopping rules may need to be modified following additional SVR data from the P7977-0532 PSI-7977/RBV cohort.*

- *Ensure pregnancy testing is performed every 4 weeks until at least 6 months following last study medication dose*

Pharmasset Response:
We agree to both comments.

P7977-1533 comments

- *The protocol synopsis states enrollment begins November 2011; however, the GANTT chart indicates 3rd quarter 2012. Please clarify this discrepancy.*

Pharmasset Response:
We can clarify that November 2011 pertains to study P7977-1231 and 3rd quarter 2012 pertains to study P7977-1533.

- *The exclusion criteria appear to contradict several proposed interferon intolerance/ineligible criteria. For example, interferon intolerance is defined as "subjects who have been previously treated (at least one dose) with interferon (either PEG or short acting interferon) and RBV"; however, the exclusion criteria state subjects must be naïve to all HCV antiviral treatment(s). In addition, exclusion criteria 4, 7 and 9 appear to eliminate potentially eligible subjects.*

Pharmasset response:
We have changed the "previously treated" criterion to include patients naïve to NS5B polymerase inhibitors and we will adjust the exclusion criteria for consistency. We understand that the intent is to include a broader

population. Therefore, we will open the population to include patients exposed to interferon with or without other DAAs except for NS5B polymerase inhibitors.

- *Patients with decompensated liver disease (CP B or C) are an important population for whom PegIFN is contraindicated. We encourage you to include patients with decompensated liver disease in the trial, following completion of the ongoing hepatic impairment study.*

Pharmasset response:
Our strategy is to evaluate CP B or C patients in clinical studies as supported by data from the hepatic impairment study. (b) (4)

(b) (4)

Clinical Pharmacology:

- *Specify if trial drugs will be ingested in the fed or fasted state or without regard to food.*

Pharmasset Response:
We will specify without regard to food.

- *Consider analyzing blood samples for determining concentrations of ribavirin and pegylated interferon during the trial. Ribavirin and pegylated interferon concentrations may be integrated in the exposure-response analysis to better understand the role of ribavirin and pegylated interferon in antiviral activity and toxicity.*

Pharmasset Response:
We will collect and store the appropriate samples and may analyze them dependent upon the outcome of the studies.

- *Please consider collecting intensive PK sampling at steady state from a subset of subjects in each Phase 3 trial. These PK data could be integrated in a population PK model to better understand the pharmacokinetics of PSI-7977.*

Pharmasset Response:
Pharmasset collects trough and random samples for PSI-6206 analysis for all subjects treated with PSI-7977 in clinical studies. Moreover, intensive steady-state concentrations in all or a subset of HCV-infected subjects are obtained in each of the following studies, including P7977-0221 (n = 49), P7977-0422 (subset), P7977-0523 (n = 70), P7977-0724 (subset), P2938-0212 (n = 24), P2938-0721(minimum of n = 40), AI444040 BMS IND (n = 28 + subset) and TMC435HPC2002 (subset). These data, along with Phase 3Psi-6206 plasma concentration data, will be incorporated in a population pharmacokinetic model to better understand the pharmacokinetics of PSI-6206 and covariates that may explain pharmacokinetic variability.

Given the complexities and limited numbers of clinical sites capable of collecting intensive PK samples, coupled with the plethora of intensive and sparse sampling in other studies outlined above, Pharmasset is not planning to perform steady-state pharmacokinetic evaluations in the Phase 3 studies.

- *Please clarify why oral hormonal contraceptives or other systemic hormonal contraceptives cannot be used as one of the two effective methods of contraception by female participants. A drug-drug interaction between PSI-7977 and oral hormonal contraceptives is unlikely because PSI-7977 did not substantially induce or inhibit CYP450 isoenzymes in vitro.*

Pharmasset Response:
We agree to allow hormonal oral contraceptives as noted.

- *Please prohibit the intake of sensitive substrates of OATP1B1 and OATP1B3 (e.g. rosuvastatin and pravastatin) during the trials, until data from in vitro studies are available.*

Pharmasset Response:
PSI-7977 and its major metabolite PSI-6206 have been examined in in vitro models for OATP1B1 and OATP1B3 transporter interactions. The aim of the study was to examine the interaction of PSI-7977 and PSI-6206 with OATP1B1 and OATP1B3 in the uptake transporter inhibition assay at a dose range of 0.4 to 300 μM. Neither compound inhibited OATP1B1 at concentrations up to 300 μM (Table 1). PSI-7977 exhibited a concentration-dependent inhibition of the probe substrate for OATP1B3. The IC50 value was estimated around 200 μM (Table 1). The functional integrity of the transporters was verified with respective reference inhibitors. A final report is targeted for submission 4Q2011.

Table 1: Reaction Parameters from Vesicular Transport Inhibition Assay (OATP1B1 and OATP1B3)

	OATP1B1		OATP1B3	
Compound	IC_{50} (μM)	Inhibition at highest concentration* (%)	IC_{50} (μM)	Inhibition at highest concentration* (%)
PSI-7977	ND	23	~ 200	60
PSI-6206	ND	20	ND	46

ND: not determined in the dose-range investigated
*** Values are average % of control at the highest concentration investigated (300 μM)**

Maximal plasma concentrations of PSI-7977 obtained are 100-fold less than the estimated IC50 for inhibition of OATP1B3, indicating a low potential for clinically significant inhibition. Therefore, co administration of OATP1B1- and OATP1B3- sensitive substrates such as rosuvastatin and pravastatin will be permitted.

- *Please prohibit the intake of strong inhibitors of p-glycoprotein during the trials.*

Pharmasset Response:
We agree to prohibit strong inhibitors of p-glycoprotein during the trials, pending results of the planned cyclosporine DDI trial.

- *Protocol P7977-1231 (page 46) mentions urine collection for analysis of PSI-6206, but urine collection is not mentioned anywhere else in the protocol. Please clarify if you intend to collect urine samples for analysis of PSI-6206.*

Pharmasset Response:
The protocol will be amended to delete the reference to urine samples for analysis of PSI-6206.

Clinical Virology:

- *For P7977-1231, certain subpopulations not included or underrepresented in Phase 2 studies (e.g., patients with cirrhosis) may experience a slower viral load decline and therefore may benefit from a longer treatment duration. We recommend you incorporate plans to extend the total treatment duration for late responders in Arms A or C beyond 12 weeks (e.g., Peg-IFNα/RBV for an additional 12 weeks) if initial data indicate that a significant number of subjects fail to achieve RVR and experience virologic relapse after stopping treatment at Week 12.*

Pharmasset Response:
We will continue to monitor the clinical trials and act accordingly. We will have the re-treatment protocol open concurrently so that subjects with virologic failure will have un-interrupted treatment.

- *For Arm C in P7977-1231, please include an option for subjects who experience virologic failure to receive Peg-IFNα/RBV SOC (either alone or in combination with PSI-7977).*

Pharmasset Response:
We intend to provide this option in the re-treatment protocol, which we expect to submit prior to the initiation of Phase 3. Virologic failures in both active treatment and control arms will be eligible for inclusion in the retreatment study.

- *For P7977-1231, please clarify the discrepancy on when you will confirm the virologic failures, i.e. 1 week (pg. 38) vs 2 week (pg. 45). Please note that we prefer 1 week.*

Pharmasset Response:
One week is correct.

- *Please clarify what the matching placebo is for P7977-1533. Do you mean PSI-7977 placebo/RBV or PSI-7977 placebo/RBV placebo?*

Pharmasset Response:
The match will be PSI-7977 placebo/ RBV placebo.

5. Does the agency agree that genotype 2 and 3 can be combined for the statistical comparison between experimental and control arms?

FDA Response:

It may be acceptable to combine genotypes 2 and 3 for the statistical comparison between experimental and control arms; however, this approach will be a review issue.

6. Does the agency agree that enrollment of 75% genotype 3 and 25% genotype 2 is acceptable given that genotype 3 is more difficult to treat with the current SOC?

FDA Response:

Yes, it is acceptable to enroll 75% genotype 3 and 25% genotype 2.

7. Does the Agency agree that the viral kinetics modeling presented supports the selection of PSI-7977 400 mg QD for study in the Phase 3 clinical program? If not, please explain why.

FDA Response:

We agree with the selection of PSI-7977 400 mg QD for study in the Phase 3 clinical program. PSI-7977 had similar potency against genotypes 1a, 1b, 2 and 3.

CLINICAL VIROLOGY

8. Does the agency agree with the plan for monitoring resistant variants as outlined in the Virology Action Plan (VAP)? If not, please explain which additional data would be required to support the proposed initial indication.

FDA Response:

- *Please include subjects who experience rebound (>1 log10 IU/mL increase in HCV RNA from nadir, while on treatment) in the "virologic failure" definition in your VAP*

Pharmasset Response:
We agree.

- *Please note that we regard clinical association with failure as resistance associated regardless of cell culture phenotype. Therefore, even if your phenotypic studies do not show a significant reduction in susceptibility to PSI-7977, the amino acid substitutions will be considered resistance associated if they are observed in multiple subjects who failed treatment to PSI-7977. We recommend testing such substitutions for cross resistance to other HCV NS5B inhibitors that are late in development.*

Pharmasset Response:
We understand that there could be instances in which the in vitro phenotyping assay would not detect a reduced drug susceptibility potentially associated with clinical resistance. However, virologic failure identified by HCV RNA kinetics alone does not necessarily imply clinical resistance, which may be related to other factors, i.e., insufficient drug levels. In addition, the natural viral polymorphism frequently observed among HCV isolates, which may exist in multiple patients, could also complicate data interpretation. Therefore, we propose to follow the recommendation by the DRAG expert panel when defining clinical resistance, to include all relevant factors when assessing whether an observed amino acid substitution is resistance associated. These factors would include assay method, biological or clinical cut-offs, virus replication capacity, sequence analysis, phenotyping results, drug pharmacokinetics, inherent potency, previous treatment history, and clinical response data.

Pharmasset agrees to test such observed amino acid substitutions against various HCV NS5B inhibitors that are late in development.

- *Please include susceptibility to ribavirin in your resistance and cross-resistance studies.*

Pharmasset Response:
We agree.

- *All post-baseline samples for resistance analysis with the exception of those from relapsers should be on-therapy isolates (unless viral load is not adequate).*

Pharmasset Response:
We agree.

Other Virology Recommendations:

- *For the* (b) (4) *version that you are planning to use to quantify HCV RNA, please clarify why you are not using the approved version of the assay.*

Pharmasset Response:
We agree to use the approved version of the assay, the (b) (4) *for use with the* (b) (4)

- *We recommend using the assay lower limit of quantification (LLOQ) as the viral load cutoff during follow-up for determination of SVR. If you prefer to define SVR based on an undetectable viral load, we recommend re-testing any follow-up samples with viral loads that are detected but <LLOQ. Also, for determination of end-of-treatment responses and virologic relapse, we recommend re-testing any end-of-treatment samples with viral loads that are detected but <LLOQ.*

Pharmasset Response:

We have changed the LLOQ <25 which will be the primary endpoint for the Phase 3 studies.

- *Please note that we have become aware of contract laboratory-specific differences in the rates at which on treatment and follow-up HCV RNA results are reported as detectable/<LLOQ versus undetectable. It is the sponsor's responsibility to carefully review reported viral load results and contract laboratories' internal assay validation documentation to ensure the HCV viral load assay is performing as expected. When you submit finalized clinical trial protocols and clinical study reports, please include the following information regarding the quantitative HCV RNA assay used:*
    - *Name of assay*
    - *Performance characteristics of the assay reported by assay manufacturer or in FDA-approved documentation, as appropriate*
    - *Central laboratory conducting the analyses, and internal assay performance validation documentation (e.g., assay specificity, linear range, limit of detection)*

Pharmasset Response:
We agree and will submit this information with the protocol(s).

Summary Question

9. Does the Agency agree that the supportive information from the ongoing trials in the background document, and the proposed plan to keep the Agency informed as new data accrue, adequately support the initiation and conduct of the proposed Phase 3 studies? If not, please explain why.

FDA Response:

Please refer to our previous responses. In general, the available PSI-7977 safety and efficacy data support Phase 3 development in the HCV genotype 2 and 3 population, and your plan to keep the Agency informed is acceptable. It may not be necessary to conduct two identical Phase 3 trials in the HCV genotype 2 and 3 treatment naïve population. An adequate safety database is needed to support an NDA submission; however, we are open to alternative Phase 3 trial designs to address issues such as treatment duration, PSI-7977 monotherapy, etc.

Pharmasset Response:
We agree that it is not necessary to conduct two identical Phase 3 trials in the HCV genotype 2 and 3 treatment naïve population. We propose discussing additional study designs which would include PSI-7977 monotherapy arms.

GENERAL FDA COMMENTS FOR DRUG DEVELOPMENT:

Clinical Pharmacology:

We concur with your plans to further evaluate potential drug interactions with PSI-7977 and drugs typically used by HCV-infected subjects. Based on the in vitro metabolic profile of PSI-7977 and its metabolites, we suggest conducting the following clinical trials:

- *A clinical trial between PSI-7977 and an immunosuppressant agent, preferably cyclosporine. Cyclosporine inhibits p-glycoprotein, as well as BCRP and OATP1B1/3, and may increase systemic exposures of PSI-7977 and its metabolites.*

Pharmasset Response:
We agree and we plan to include cyclosporin and tacrolimus in an upcoming DDI study design.

- *If results of the in vitro studies of OATP1B1 and 1B3 indicate potential inhibition of either transporter, a clinical trial between PSI-7977 and a statin, preferably atorvastatin or rosuvastatin.*

Pharmasset Response:

The results of the in vitro studies of OATP1B1 and 1B3 show that PSI-7977 and PSI-6206 are not inhibitors of these transporters.

- *A clinical trial between PSI-7977 and tenofovir and emtricitabine, because of their route of elimination. However, a clinical trial with efavirenz and atazanavir may not be necessary because PSI-7977 has minimal potential to induce or inhibit CYP450 enzymes.*

Pharmasset Response:
We intend to conduct a clinical DDI study with a number of the currently used HIV regimens as described previously, which will include tenofovir and emtricitabine.

Genomics:

- *We recommend that you collect DNA for exploratory efficacy, safety, or pharmacokinetic analyses (e.g., CES1).*

Pharmasset Response:
We agree.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

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

/s/

LINDA C ONAGA
09/16/2011

JEFFREY S MURRAY
09/16/2011

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204671

LATE-CYCLE MEETING MINUTES

Gilead Sciences, Inc.
Attention: Shalini Gidwani, MSc, RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 99404

Dear Ms. Gidwani:

Please refer to your New Drug Application (NDA) dated April 8, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for sofosbuvir tablets, 400 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 10, 2013.

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

If you have any questions, call Linda C. Onaga, MPH Regulatory Project Manager at (301) 796-0759 or the Division mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Sarah Connelly, MD
Cross Discipline Team Lead
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: October 10, 2013 3:00 PM – 4:30 PM
Meeting Location: 10903 New Hampshire Ave
Bldg 22, RM 1421
Silver Spring, MD 20903

Application Number: NDA 204671
Product Name: sofosbuvir
Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Sarah Connelly, MD
Meeting Recorder: Linda C. Onaga, MPH

FDA ATTENDEES (*via telephone)

1. Edward Cox, MD, MPH, Director, Office of Antimicrobial Products
2. Debra Birnkrant, MD, Director, DAVP
3. Jeffrey Murray, MD, MPH, Deputy Director, DAVP
4. Sarah Connelly, MD, Cross Discipline Team Lead, DAVP
5. Poonam Mishra, MD, Clinical Reviewer, DAVP
6. Julian O'Rear, PhD, Virology Team Lead, DAVP
7. Lisa Naeger, PhD, Virology Reviewer, DAVP
8. Eric Donaldson, PhD, Virology Reviewer, DAVP
9. Shirley Seo, PhD, Clinical Pharmacology Team Leader, DCP4
10. Jenny Zheng, PhD, Clinical Pharmacology Reviewer
11. Jeffry Florian, PhD, Pharmacometrics Reviewer
12. Kellie Reynolds, PharmD, Deputy Director, OTS/DCP4*
13. Chris Ellis, PhD, Acting Pharmacology and Toxicology Team Lead, DAVP
14. Sarah Pope Miksinski, PhD, Acting Director, Division II, ONDQA
15. Rapti Madurawe, PhD, Branch Chief, ONDQA
16. George Lunn, PhD, CMC Reviewer, ONDQA
17. Krishnakali Ghosh, PhD, Reviewer, OC/OMPQ/DGMPA
18. Mahesh Ramanaham, PharmD, Team Lead, OC/OMPQ/DGMPA
19. Tara Gooen, Branch Chief, OC/OMPQ/DGMPA
20. Alison Aldridge, Team Lead, OC/OMPQ/DIDQ
21. Karen Qi, PhD, Biometrics Reviewer
22. Wen Zeng, PhD, Secondary Reviewer, OTS/OB/DBIV
23. Dionne Price, PhD, Acting Director, OTS/OB/DBIV*
24. Linda Onaga, MPH, Regulatory Project Manager, DAVP
25. Kendra Worthy, PharmD, Team Lead, DRISK
26. Morgan Walker, PharmD, DMEPA/OSE

27. Kimberly Struble, PharmD, Clinical Team Lead, DAVP*
28. Linda Lewis, MD, Clinical Team Lead, DAVP*
29. Mary Singer, MD, Clinical Team Lead, DAVP*
30. Fuqiang Liu, PhD, CMC Reviewer, ONDQA*
31. Minerva Hughes, PhD, CMC BioPharm Reviewer, ONDQA*
32. Kemi Asante, Reviewer, OPDP
33. Mihaela P. Jason, PharmD, BCPS, Safety Evaluator, OSE

EASTERN RESEARCH GROUP ATTENDEES

1. Patrick Zhou, Independent Assessor

APPLICANT ATTENDEES (*via telephone)

1. John McHutchinson, MD, Senior Vice President, Liver Disease Therapeutics
2. William T. Symonds, PharmD, Vice President, Clinical Research Liver Disease Therapeutics
3. Mani Subramanian, MD, Vice President, Clinical Research Liver Disease Therapeutics
4. Diana Brainard, MD, Senior Director, Clinical Research Liver Disease Therapeutics
5. Neby Bekele, PhD, Senior Director, Biostatistics
6. Brian Kearney, PharmD, Senior Director, Clinical Research, Clinical Pharmacology
7. Reza Oliyai, PhD, Vice President, Formulation and Process Development
8. Chin Tay, PhD, DABT, Associate Director, Drug Safety Evaluation
9. Hongmei Mo, PhD, Director, Clinical Virology
10. Taiyin Yang, PhD, Senior Vice Preside, Pharmaceutical Development and Manufacturing
11. Shalini Gidwani, MSc, RAC, Associate Director, Regulatory Affairs
12. Paul Tomkins Senior Director, Regulatory Affairs
13. Norbert Bishofberger, PhD, Executive Vice President, Research and Development, Chief Scientific Officer*
14. Joe Steele, Vice President, Commercial Strategy*

1.0 BACKGROUND

The purpose of this late-cycle meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, the Advisory Committee meeting plans, and the objectives for the remainder of the review. The application has not yet been fully reviewed by the Signatory Authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application.

NDA 204671 (sofosbuvir, 400 mg tablets) was submitted on April 8, 2013 by Gilead Sciences, Inc. for the treatment of genotype 1 to 6 chronic hepatitis C virus infection in adults. The Agency is reviewing this application under the PDUFA V's "The Program" and a priority review was granted (8 month review clock). The action date for this application is December 8, 2013.

No previous action has been taken on this NDA.

2.0 DISCUSSION

- **Introductory Comments (Welcome, Introduction, Ground rules, Objectives of the meeting)**

  After introductory comments, Gilead was informed that IND 106739 for sofosbuvir was granted breakthrough therapy designation.

- **Discussion of Substantive Review Issues**

  Chemistry Manufacturing and Controls

  - The review of the CMC component of this application is complete and there are no outstanding issues. However, there were significant GMP issues identified during various FDA inspections and they need to be addressed by the applicant.

  Office of Compliance

  - The Office of Compliance is still evaluating the status of facilities submitted in the NDA. Inspections at Foster City concluded on (b) (4) and several 483's were issued at the conclusion of the inspection.
  - The Agency informed Gilead that this NDA cannot be approved with the API site, (b) (4) (b) (4) in the application based on the issues discussed during the August 20, 2013 teleconference. Gilead understood the Agency's concerns and will remove (b) (4) from the application. After the August 20, 2013 teleconference with the Agency about (b) (4) Gilead increased API production at the two remaining sites in September and October. Gilead is working with (b) (4) with their GMP issues in preparation for a future FDA inspection.
  - Gilead informed the Agency that the majority of the sofosbuvir API was produced at (b) (4) and foresee challenges meeting patient demands beyond the launch period. The Applicant's plans are to launch the product in the US (b) (4) .

  Clinical

  - The Agency acknowledged receipt of the VALENCE and PHOTON-1 study reports and datasets to support sofosbuvir plus ribavirin for 24 week duration (received October 10, 2013). The Agency is reviewing these data in an expedited timeframe and requested that Gilead provide a quick response to any additional clarifications or questions that may be raised by the Agency.
  - Gilead confirmed the additional VALENCE clinical investigator information will be provided to the Agency by October 11, 2013.

- **Information Requests**

  - Gilead will review the information request sent regarding the modeling analyses used to support use of SOF+PEG+RBV for 12 weeks in GT 1 subjects who had previously failed PEG and RBV therapy, and the request regarding clinical trial GS-US-334-0109. The company will provide a response to the Agency early next week (October 14, 2013).

A. Discussion of Upcoming Advisory Committee Meeting

- The Agency received Gilead's draft Advisory Committee meeting slide deck and requested clarification on the misclassification of subjects. Gilead stated further analysis showed these subjects had GT2/GT1 intergenotypic recombinant HCV. The core sequences were GT2 and correctly identified as GT2 by the LiPA assay, but the NS5B for these viruses was identified as GT1 by sequencing analysis. For the Advisory Committee meeting, the Agency requested the slides reflect the intent to treat (ITT) analyses and the LiPA assay results, because these results would be used in clinical practice.
- Gilead should not present information at the Advisory Committee meeting about PHOTON-1 (HIV/HCV co-infection trial). Members of the Advisory Committee were not screened to discuss the co-infected trial.
- The Agency will follow up with Gilead on who will introduce the data about SOF+PEG+RBV treatment for GT 1 treatment-experienced patients.
- Gilead should be prepared to address any questions or comments on cardiac findings presented at the Advisory Committee meeting.
- The Agency will provide Gilead a draft copy of the slide presentation prior to the Advisory committee meeting. Gilead will present the VALENCE data at the meeting.
- The Agency requested sequences and breakpoints for the intergenotypic recombinant viruses and publications describing HCV intergenotypic recombinant.

B. Postmarketing Requirements/Postmarketing Commitments

Pediatric Postmarketing Requirement

- The pediatric study requirement for age group less than three years of age will be waived.
- Pediatric study requirements for children ages three to less than 18 years will be deferred because the adult studies are complete and the pediatric study has not been completed
- The Agency is developing the PREA PMR language for this application. The pediatric PMR will include a trial in pediatric subjects 3 through 17 years of age with chronic hepatitis C and at least 5 years follow-up data will be needed.

Severe renal impairment/End Stage Renal Disease

- Provide the final study report and datasets for protocol GS-US-334-0154, currently entitled, "A Phase 2b, Open-Label Study of 200 mg or 400 mg Sofosbuvir+RBV for 24

Weeks in Genotype 1 or 3 HCV-Infected Subjects with Renal Insufficiency", in order to provide dosing recommendations for chronic hepatitis C patients with severely impaired renal function and ESRD.
- For this ongoing trial, Gilead should provide the datasets and final study report in order to determine dosing recommendations for patients with severe renal impairment.

Carcinogenicity data

- Carcinogenicity studies will be a PMR if the treatment regimen of sofosbuvir plus ribavirin for 24 weeks is approved.

General indication

- Internal Agency discussions are ongoing regarding use of the proposed broader indication (for sofosbuvir use) "in combination with other agents" versus how the sofosbuvir regimens were studied.

Pre-transplant indication (Poonam)

- The Agency is reviewing the data from the ongoing trial P7977-2025, which is evaluating a subgroup of pre-transplant population. Gilead will need data from the trial in patients with decompensated cirrhosis to support a broader indication for the pre-transplant population. The protocol-defined treatment duration was amended from 24 to 48 weeks in the ongoing pre-transplant trial. The current label proposed treatment duration of (b) (4) (b) (4) which is different from how the duration was studied in the trial. The Agency is still reviewing these data and Gilead's proposed labeling. Gilead will submit updated treatment duration information from this trial, and will propose labeling language to the Agency to address the treatment duration.

C. Review Plans

- The Agency will continue its review of the NDA including the new data from VALENCE and PHOTON-1.
- The Agency will continue discussions on labeling for sofosbuvir with Gilead.
- The proposed trade name is under review by the Agency.

D. Wrap-up and Action Items

Action Items

a. Gilead will submit a formal correspondence withdrawing (b) (4) from the application.
b. Gilead will submit a commitment letter stating that no sofosbuvir API manufactured at (b) (4) will be used to manufacture commercial batches.
c. Gilead will provide the sofosbuvir launch plans without sofosbuvir API from (b) (4)
d. Gilead will respond to the 483s issued at Foster City within the 14 day timeframe.

e. The Agency will provide Gilead with draft Advisory Committee slides before the meeting.
f. Gilead will submit updated duration data from the pre-transplant trial, P7977-2025. Gilead will provide sequences and breakpoints for the intergenotypic recombinant viruses and publications describing HCV intergenotypic recombinant to the Agency.
g. The Agency will provide Gilead with the status of the tradename by the designated due date.
h. Gilead will provide the Agency with the presentations presented at AASLD.

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/s/

SARAH M CONNELLY
11/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204671

LATE CYCLE MEETING
BACKGROUND PACKAGE

Gilead Science, Inc.
Attention: Shalini Gidwani, MSc, RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Gidwani:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sofosbuvir 400mg tablets.

We also refer to the Late-Cycle Meeting (LCM) scheduled for October 10, 2013. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Linda C. Onaga, MPH, Regulatory Project Manager, at (301) 796-0759 or the Division mainline at (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

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: October 10, 2013 3:00 PM – 4:40 PM
Meeting Location: 10903 New Hampshire Ave
Bldg 22 RM 1415
Silver Spring MD, 20903

Application Number: NDA 204671
Product Name: sofosbuvir
Proposed Indication: Treatment of chronic hepatitis C in adults (genotype 1 to 6)
Sponsor/Applicant Name: Gilead Sciences, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

Chemistry, Manufacturing and Controls (CMC):

a. CMC/Inspectional Issues

Inspections and compliance evaluations for manufacturing sites submitted in the new drug application (NDA) package for sofosbuvir are ongoing, including Foster City. The Agency requests that Gilead provide an update of their plans for the (b) (4) facility.

ADVISORY COMMITTEE MEETING

Date of AC meeting: October 25, 2013

Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: On or before October 3, 2013

Potential questions and discussion topics for AC Meeting are as follows:

1. Considering potential risks and benefits do the available data support approval of sofosbuvir in combination with ribavirin for treatment of chronic hepatitis C in adult patients with genotype 2 and 3 infection?
    - Please comment on the strength of evidence for use of sofosbuvir and ribavirin for 16 weeks duration in subgroups of genotype 2 patients who may benefit from an extended duration of therapy.

2. Considering potential risks and benefits do the available data support approval of sofosbuvir in combination with pegylated interferon and ribavirin for treatment of chronic hepatitis C in treatment-naïve adult patients with genotype 1 and 4 infection?

3. Please comment on the strength of evidence for use of sofosbuvir in combination with pegylated interferon and ribavirin for treatment of chronic hepatitis C in patients with genotype 1 infection who are nonresponders to a prior course of pegylated interferon and ribavirin. Please comment if additional data are needed in this population.

4. Please comment on the strength of evidence for use of sofosbuvir in combination with ribavirin in HCC patients meeting Milan criteria awaiting liver transplantation. Are the available data sufficient for dosing recommendation? If not, what additional studies are recommended?

5. Please comment on postmarketing studies/trials that are needed to further define the optimal use of sofosbuvir.

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:
http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm

LCM AGENDA

1. Introductory Comments – 5 minutes (Linda Onaga, MPH/Sarah Connelly, MD)
    a. Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues – 15 minutes

   Each issue will be introduced by FDA and followed by a discussion.
    a. Chemistry, Manufacturing and Controls; Office of Compliance
3. Information Requests – 10 minutes

   Clinical/Statistics
    a. Clinical Study Reports and datasets for the following trials
        - GS-US-334-0133 (VALENCE)
        - GS-US-334-0123 (PHOTON-1)
    b. Comprehensive assessment of collective evidence to support 24 week sofosbuvir and ribavirin treatment regimen as an alternative therapeutic option for genotype 1 subjects who are ineligible to receive an interferon-based therapy.
    c. VALENCE clinical investigator information, site specific
    d. Modeling analyses done by the Applicant to support the use of SOF+PEG+RBV for 12 weeks in genotype 1 subjects who had previously failed pegylated interferon and ribavirin therapy.
    e. Submission of SVR results for genotype 1 subjects from the ongoing trial GS-US-334-0109, entitled, "An Open-Label Study of GS-7977 + Ribavirin with or without Peginterferon Alfa-2a in Subjects with Chronic HCV Infection who Participated in Prior Gilead HCV Studies"
4. Discussion of Upcoming Advisory Committee Meeting – 30 minutes
    a. Coordination of presentations, including statistical analyses, VALENCE data, use in HCV genotype 1 prior pegylated interferon/ribavirin nonresponders.
    b. Review of potential AC questions
5. Postmarketing Requirements/Postmarketing Commitments – 5 minutes
    a. Pediatric Postmarketing Requirement

       The pediatric study requirement for age group less than 3 years of age will be waived.

       The pediatric study requirement for ages 3 to less than 18 years for this application will be deferred because adult studies are completed and the pediatric study has not been completed.
    b. Severe renal impairment/End Stage Renal Disease

Provide the final study report and datasets for protocol GS-US-334-0154, currently entitled, "A Phase 2b, Open-Label Study of 200 mg or 400 mg Sofosbuvir+RBV for 24 Weeks in Genotype 1 or 3 HCV-Infected Subjects with Renal Insufficiency", in order to provide dosing recommendations for chronic hepatitis C patients with severely impaired renal function and ESRD.

6. Major labeling issues – 10 minutes
   a. General indication

      Discussions are ongoing regarding use of the proposed broader indication (for sofosbuvir use) "in combination with other agents".

   b. Pre-transplant indication

      The Division recommends that the indication should be (b) (4) defined for use in patients with hepatocellular carcinoma awaiting liver transplantation. In addition, the indicated duration of therapy should be for maximum of 24 weeks, as was initially studied in P7977-2025, until additional data with longer duration has been submitted and reviewed by the Division.

      Additionally, available data from both population and deep sequencing of subjects who had on-treatment failure (n=5) and subjects who relapsed (n=20) in P7977-2025 will be included in the label, because it provided supportive information for the FDA resistance findings in the SOF Phase 3 trials. For example, the L159F substitution emerged on treatment in two subjects who were infected with GT1a HCV (one breakthrough and one relapse) and one subject infected with GT2b HCV (breakthrough). In addition, an S282R and L320F substitution were detected by deep sequencing in the on-treatment sample from a subject infected with GT1a HCV who did not respond to SOF.

      DAVP believes that the review of data from ongoing GS-US-334-0125 in decompensated HCV subjects will be needed for a broader indication in all pretransplant HCV subjects.

   c. Misclassified subjects

      The Division performed their analyses using the Intent-to-Treat approach. Discussions are ongoing regarding the analyses to include in the label.

7. Review Plans – 10 minutes
   a. Await inspection report
   b. Review VALENCE and PHOTON-1 data
   c. Await feedback from the Advisory Committee Meeting
   d. Continue with labeling review and discussions

e. Await the status of the trade name review

8. Wrap-up and Action Items – 5 minutes

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/s/

DEBRA B BIRNKRANT
10/03/2013