CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208341Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208341 SUPPL # HFD #

Trade Name EPCLUSA

Generic Name sofosbuvir and velpatasvir fixed dose combination tablet

Applicant Name Gilead Sciences

Approval Date, If Known June 28, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☒ NO ☐

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

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

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5 years

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☒ NO ☐

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

NDA# 204671 Sovaldi (sofosbuvir)

NDA# 205834 Harvoni (sofosbuvir and ledipasvir)

NDA#

NDA 208341 contains velpatasvir, a new chemical entity, in combination with sofosbuvir, a previously approved active moiety. Under the Agency's new interpretation described in the Agency's Guidance for Industry, New Chemical Entity Exclusivity for Certain Fixed-Combination Drug Products, a drug substance is eligible for 5-year exclusivity, provided it meets the regulatory definition of new chemical entity, regardless of whether that drug substance is approved in a single-ingredient drug product or in a fixed-combination with another drug substance that contains no previously approved active moiety, or in a fixed-combination with another drug substance that contains a previously approved active moiety. This NDA is thus eligible for 5-year new chemical entity exclusivity pursuant to the new interpretation.

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:

==========

Name of person completing form: Linda C Onaga
Title: Senior Regulatory Project Manager
Date: June 27, 2016

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/

LINDA C ONAGA
06/27/2016

DEBRA B BIRNKRANT
06/27/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208341 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: EPCLUSA Established/Proper Name: sofosbuvir and velpatasvir Dosage Form: tablets		Applicant: Gilead Sciences, Inc Agent for Applicant (if applicable):
RPM: Linda C Onaga, MPH		Division: Division of Antiviral Products

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

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(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.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is June 28, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[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.

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

☒ Fast Track
☒ Rolling Review
☐ Orphan drug designation
☒ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

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

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

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: 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
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other HIV list serv
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

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) June 28, 2016
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)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ 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)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ 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	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	January 11, 2016 January 8, 2016
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None Dec 23, 2015 DMEPA: ☐ None June 8, 2016 March 03, 2016 DMPP/PLT (DRISK): ☐ None May 20, 2016 OPDP: ☐ None May 13, 2016 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	December 23, 2016 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC May 11, 2016 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☐ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	Granted May 15, 2015 Rescinded April 1, 2015 Intent to Rescind: February 4, 2015 Granted: April 22, 2014
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	N/A
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	May 14, 2014
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
• 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 May 26, 2015
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg June 5, 2014
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A February 11, 2016
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A April 19, 2016
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None June 28, 2016
Division Director Summary Review *(indicate date for each review)*	☐ None June 16, 2016
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None June 1, 2016
PMR/PMC Development Templates *(indicate total number)*	☐ None June 24, 2016

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	June 1, 2016 (Addendum) March 29, 2016
• 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)*	March 29, 2016 Page 160
❖ 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)*	☒ N/A
❖ 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 April 19, 2016
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested May 13, 2016
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None March 29, 2016 March 24, 2016
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None March 29, 2016
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None June 17, 2016 (Addendum) March 25, 2016
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review March 24, 2016
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None March 28, 2016
❖ 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	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None June 24, 2016 April 1, 2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(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)*	April 1, 2016 Page 140 Product Quality IQA
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☒ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

LINDA C ONAGA
06/28/2016

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: **208341**

Drug: **sofosbuvir/velpatisvir FDC**

Date: **June 17, 2016**

To: **Prachi Shah MBS, RAC, Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 208341 DAVP Proposed Labeling Changes**

Please find attached the Division's labeling edits for NDA 208341. A word copy of the label will be attached to this correspondence.

Please provide your response/revised labeling by June 21, 2016.

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 Onaga, MPH
Senior 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
06/17/2016

PeRC Meeting Minutes
May 11, 2016

PeRC Members Attending:
Lynne Yao
Meshaun Payne
Dianne Murphy
Gerri Baer
Peter Starke
Gil Burckart
Raquel Tapia
Greg Reaman
Dionna Green
Robert "Skip" Nelson
Kevin Krudys
Barbara Buch
Rosemary Addy
Shrikant Pagay
Adrienne Hornatko-Munoz
Wiley Chambers
Jackie Yancy
Thomas Smith
John Alexander
Karen Davis-Bruno

Non Responsive

11:30	NDA 208341	Sofosbuvir/Velpatasvir (Partial Waiver/Deferral/Plan) with Agreed iPSP	DAVP	Linda Onaga	Treatment of chronic hepatitis C infection in adults

Non Responsive

Non Responsive

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Non Responsive

Sofosbuvir/Velpatasvir (Partial Waiver/Deferral/Plan) with Agreed iPSP

- Proposed Indication: Treatment of chronic hepatitis C infection in adults
- This product triggers PREA as a new indication.
- The division noted that there is agreed iPSP and the division agrees with the plan as outlined in the agreed iPSP. The plan includes waiver for patients < 3 years of age (because of the potential for spontaneous resolution of HCV); and deferral for patients 3 to < 18 years of age. This product has high promise in the treatment of HCV in children because it appears to be effective in all major HCV genotypes and is a regimen that does not require interferon or ribavirin.
- The division stated the Written Request for this product is completed but has not been issued.
- *PeRC Recommendations*:
  - The PeRC agreed with the sponsors plan for a waiver in patients 0 - <3 years of age because studies are impossible or highly impractical and to the deferral in patients ages 3 to <18 years of age.

Non Responsive

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/s/

MESHAUN L PAYNE
06/08/2016

Onaga, Linda

From: Prachi Shah <Prachi.Shah@gilead.com>
Sent: Monday, June 06, 2016 4:53 PM
To: Onaga, Linda
Subject: RE: NDA 208341 PMR

Hi Linda,

I confirm receipt of these comments.
Thanks,
Prachi

From: Onaga, Linda [mailto:Linda.Onaga@fda.hhs.gov]
Sent: Monday, June 06, 2016 1:49 PM
To: Prachi Shah
Subject: NDA 208341 PMR
Importance: High

Good Afternoon Prachi,

We received Gilead's response with timelines for NDA 20834 PMR and PMCs. The review team is not in agreement with Gilead's proposed dates for the following:

Conduct a drug interaction study to evaluate the interaction between sofosbuvir/velpatasvir and atorvastin.

Schedule Milestones: Final Protocol Submission:	09/30/2016
Study/Trial Completion:	05/31/2017
Final Report Submission:	2/28/2018

Given that this study is a PMR, we are proposing the following timeline:

Schedule Milestones: Final Protocol Submission:	08/30/2016
Study/Trial Completion:	12/31/2016
Final Report Submission:	05/31/2017

In addition, we have updated the language for some of the PMRs. Please confirm your agreement with the updated language:

- Submit the final clinical study report and datasets for the ongoing trial GS-US-342-1202 (ASTRAL-5), titled "A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 weeks in Subjects with Chronic Hepatitis C Virus (HCV) and Human immunodeficiency Virus (HIV)-1 Coinfection," to provide (b) (4) -safety data in HIV-1/HCV co-infected subjects receiving sofosbuvir and velpatasvir concurrently with HIV antiretroviral therapy.

- Collect, analyze, and submit data from the HCV infected subjects (b) (4) with decompensated Child-Pugh Turcotte (CPT) C cirrhosis treated with sofosbuvir/velpatasvir regimen to obtain safety data in a broader decompensated cirrhosis population (genotype 1-6 HCV infection).

- Conduct a trial in hepatitis C virus genotype 3 infected subjects with cirrhosis treated with sofosbuvir and velpatasvir to determine if the addition of ribavirin improves the efficacy (i.e., sustained virologic response rate) and reduces the rate of virologic failure (b) (4)

Please provide your response by 3pm EST tomorrow, June 7, 2016.

Linda

Linda C. Onaga, MPH
Senior Regulatory Project Manager
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White Oak Complex, Bldg 22, Rm 6360
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/s/

LINDA C ONAGA
06/06/2016

From: Mosaddegh, Sohail
To: "Prachi Shah"; "Michele Anderson"
Cc: Onaga, Linda
Subject: SOF/VEL NDA 208341- labeling comments
Date: Wednesday, June 01, 2016 1:45:00 PM
Attachments: NDA 208341 Label-6-1-2016.docx

Hello:

Please see attached labeling and respond to your NDA by 06/10/2016.

Take care

Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6223
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SOHAIL MOSADDEGH
06/01/2016

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: **208341**

Drug: **sofosbuvir/velpatasvir tablet**

Date: **May 9, 2016**

To: **Prachi Shah, MBS, RAC, Manager Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 208341 PMR descriptions and timelines**

Please find attached the Division's PMR and PMC descriptions for NDA 208341. Please provide timelines for each PMR listed.

PMR:

1. Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of sofosbuvir/velpatasvir in pediatric subjects 12 through less than 18 years of age with chronic hepatitis C

Schedule Milestones:	Final Protocol Submission:	06/30/2016
	Study/Trial Completion:	03/31/2019
	Final Report Submission:	MM/DD/YYYY
	Other: _____	MM/DD/YYYY

2. Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of sofosbuvir/velpatasvir in pediatric subjects 3 through less than 12 years of age with chronic hepatitis C

Schedule Milestones:	Final Protocol Submission:	06/30/2016
	Study/Trial Completion:	10/31/2020
	Final Report Submission:	MM/DD/YYYY
	Other: _____	MM/DD/YYYY

3. Conduct a drug interaction study to evaluate the interaction between sofosbuvir/velpatasvir and atorvastatin.

Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY

	Final Report Submission:	MM/DD/YYYY
	Other: _____	MM/DD/YYYY

4. Submit the final clinical study report and datasets for the ongoing trial GS-US-342-1202 (ASTRAL-5) to provide additional safety data in HIV/HCV co-infected subjects receiving sofosbuvir and velpatasvir concurrently with HIV antiretroviral therapy. (b) (4)

Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
	Other: _____	MM/DD/YYYY

5. Conduct a trial to determine if the addition of ribavirin improves the efficacy (i.e., sustained virologic response rate) of sofosbuvir and velpatasvir for hepatitis C virus genotype 3 infected subjects with cirrhosis.

Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
	Other: _____	MM/DD/YYYY

6. Collect, analyze, and submit data from the HCV population with decompensated Child-Pugh C cirrhosis treated with sofosbuvir/velpatasvir regimen to obtain safety data in a broader decompensated cirrhosis population .

Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
	Other: _____	MM/DD/YYYY

Note: For PMR 6, please let us know if you have any ongoing or planned trials in Child-Pugh C subjects. If so, please provide the protocol or draft concept sheet so we can finalize the exact wording of the PMR. If you do not have any ongoing or planned trials, please provide a plan to collect safety data in this population.

PMC:

7. Collect, analyze, and submit data on subjects with cirrhosis including decompensated cirrhosis who achieve sustained virologic response following treatment with a sofosbuvir/velpatasvir-based regimen to evaluate durability of virologic response and to characterize clinical outcomes such as progression or regression of liver disease, liver-related mortality, occurrence of hepatocellular carcinoma, or liver failure requiring liver transplantation. Data collected should include 5 years of follow-up.

Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
	Other: _____	MM/DD/YYYY

8. Submit phenotypic assessment of NS5B_L314F, NS5B_L314I, and NS5B_L314P in the HCV genotype 3 replicon.

Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
	Other: _____	MM/DD/YYYY

Please submit your response by May 13, 2016.

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
05/09/2016

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: **208341**

Drug: **sofosbuvir /velpatasvir**

Date: **April 22, 2016**

To: **Prachi Shah, MBS, RAC Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 208341 labeling comments**

We are providing labeling comments for Table 3 in section 7.3 Established and Potentially Significant Drug Interactions. Please also find attached comments for your proposed carton labeling for EPCLUSA.

With regard to *Table 3 Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction*, and as discussed at the April 19, 2016 Late Cycle Meeting, we do not agree with your assessment. Patients should be advised that administration of EPCLUSA and PPIs is not recommended. We may revisit this statement when you provide additional data from ongoing trials with coadministration of EPCLUSA and PPIs.

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Please provide your responses by May 18, 2016.

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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LINDA C ONAGA
05/09/2016

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: **208341**

Drug: **sofosbuvir /velpatasvir**

Date: **April 22, 2016**

To: **Prachi Shah, MBS, RAC Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 208341**

We have the following comments for NDA 208341.

Regarding the labeling statements, "Dispense (b) (4) only in Original Container", our general recommendation is that these statement be reserved for cases where it relates to a specific risk. We acknowledge the response you have sent in when we inquired about this statement for NDA 208341 and other recently approved Gilead products.

For sofosbuvir and velpatasvir tablets, we see data in the NDA showing that tablets stored in an open-dish stress study at 40C/75% RH for 3 months had no change in assay, degradants, or morphic form. (b) (4). This doesn't suggest to us a specific risk if this product were dispensed in a pharmacy bottle. If other types of studies were done to address risk when dispensed in a pharmacy bottle, we would be interested to understand what those studies show.

(b) (4) We feel that these statements should be reserved for documented product-specific issues. We generally think of this being specific product quality issues, but if a product has specific clinical risks (not shared by all drugs in a class or indication) this could also be considered. Although FDA does not have specific guidance for these statements, we don't recommend including this statement in this label. We ask you to either confirm that it will be removed, or provide a justification that addresses the risks that are specific to the sofosbuvir and velpatasvir tablet.

Please provide your response by April 29, 2016.

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
04/22/2016

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: **208341**

Drug: **sofosbuvir/velpatisvir FDC**

Date: **April 6, 2016**

To: **Prachi Shah MBS, RAC, Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 208341 DAVP Proposed Labeling Changes**

Please find attached the Division's labeling edits for NDA 208341. A word copy of the label will be attached to this correspondence.

Please provide your response/revised labeling by April 15, 2016. If you are not able to submit a revised label by April 15th, please notify Linda Onaga.

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

Mammah Sia Borbor, MS, MBA
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAMMAH S BORBOR
04/08/2016

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: **208341**

Drug: **sofosbuvir /velpatasvir**

Date: **April 1, 2016**

To: **Prachi Shah, MBS, RAC Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 208341**

We have the following comments for NDA 208341.

At the late cycle meeting the Division would like to revisit the addition of RBV for certain HCV genotype 3 infected patients (in addition to those with decompensated cirrhosis). Our review efforts are focused on the supporting evidence from the SOF/VEL development program to determine if the addition of RBV could be beneficial, specifically for certain HCV genotype 3 infected patients such as compensated cirrhotics. We are open to your thoughts on whether there are additional or alternative HCV genotype 3 subpopulation(s) where the addition of RBV could further minimize relapse rates. Below is a summary of the types of data evaluated to support the contribution of RBV to SOF/VEL for 12 weeks in certain HCV genotype 3 infected patients.

In ASTRAL-3, we acknowledge the overall high SVR12 rate (95%) seen GT 3 patients receiving SOF/VEL for 12 weeks. Treatment with SOF/VEL for GT3 provides superior SVR12 rates compared to SOF/RBV for 24 weeks. Table 1 displays ASTRAL-3 subgroup analyses showing the impact of cirrhosis status and prior HCV treatment history on SVR12 rates. The results in ASTRAL-3 indicate SVR12 rates could be improved, for example for patients with GT3 infection and compensated cirrhosis. A numeric difference in SVR12 rates was observed between GT3 subjects with compensated cirrhosis (91%) and GT3 subjects without cirrhosis (97%). Furthermore, in ASTRAL-3, the relapse rate was 33% (3/9) for GT3 subjects with compensated cirrhosis and who had baseline NS5A resistance-associated polymorphisms (RAPs); both GT3 subjects with the Y93H NS5A polymorphism at baseline relapsed.

Table 1: ASTRAL-3 Subgroup Analysis of Impact of Cirrhosis and Prior HCV Treatment on SVR12 Rates

Cirrhosis & Prior HCV Treatment	SOF/VEL x 12 Weeks % (n)	SOF + RBV X 24 Weeks % (n)	Difference in SVR12 Rate (95% CI)
Cirrhotic, TE	89% (33/37)	58% (22/38)	31% (11%, 50%)
Non-cirrhotic, TE	91% (31/34)	71% (22/31)	20% (0.5%, 40%)
Cirrhotic, TN	93% (40/43)	73% (33/45)	20% (4%, 36%)
Non-cirrhotic, TN	98% (160/163)	90% (141/156)	8% (3%, 14%)

Additionally, in ASTRAL-3 we analyzed the baseline demographic and disease characteristics of those GT3 subjects who relapsed to help identify factors most likely to predict treatment failure. Baseline disease characteristics that serve as prognostic indicators of disease response are summarized in Table 2 below.

Table 2: Baseline Disease Characteristics of ASTRAL-3 Relapsers

Subject ID	Baseline HCV RNA ≥ 800,000 IU/mL	Treatment Experienced	Cirrhotic	IL28B non-CC Genotype	BL NS5A RAPs	NS5A RAPs at Relapse
00472-62512	X		X		Y93H	Y93H, A30V
00529-62069	X	X	X			Y93H
00529-62147	X		X	X	Y93H	Y93H
01065-62502		X		X		Y93H
01589-62011	X			X	Y93H	Y93H
02080-62118	X	X	X	X		Y93H
03314-62107	X	X				Y93H
04472-62202	X	X	X	X	A30K	Y93H, A30K
05730-62185	X		X	X		Y93H
05873-62186	X	X	X	X		Y93H

We also reviewed the results from relevant populations in ASTRAL-1 and ASTRAL-4 to put the ASTRAL-3 results in context and to estimate the potential benefit of adding RBV for certain GT3 subgroups with the lowest SVR12 rates. Of note, we view cirrhosis status as a continuum and therefore we believe that data from subjects with decompensated cirrhosis may help to inform potential treatment benefit in subjects with compensated cirrhosis when data in the latter

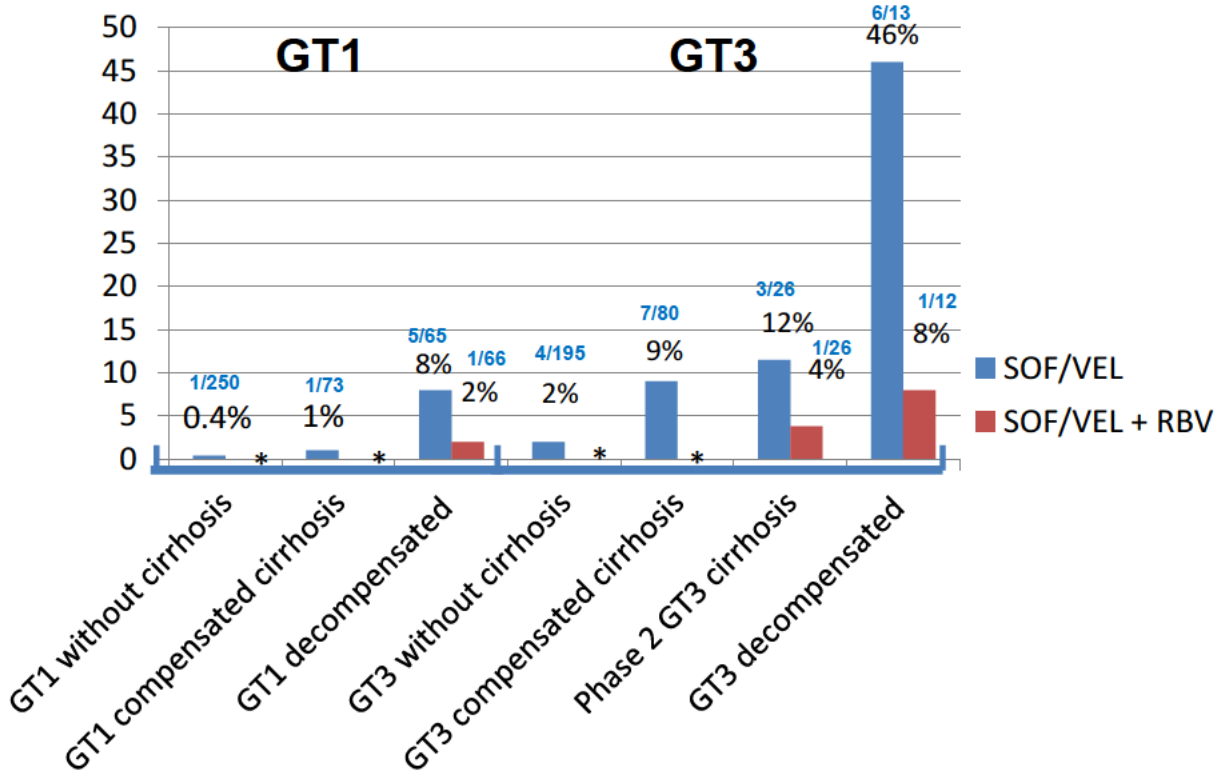
population are lacking. However, we also believe that the risk/benefit considerations for the addition of RBV are different for subjects with compensated cirrhosis versus decompensated cirrhosis.

In ASTRAL-4, among subjects with GT3 infection and decompensated cirrhosis, the addition of RBV to SOF/VEL for 12 weeks reduced the relapse rate to 8% (1/12) compared to 46% (6/13) for those who received SOF/VEL for 12 weeks without RBV (Table 3 and Fig. A). Insufficient data were available to determine the impact of HCV NS5A RAPs in GT3 subjects in ASTRAL-4. However, for GT1 subjects with baseline NS5A RAPs, the relapse rate was 0% (0/17) in the SOF/VEL + RBV 12 week arm compared to 17% (2/12) in the SOF/VEL 12 week no RBV arm (Table 3). When comparing results between GT1 and GT3 subjects in ASTRAL-4, we acknowledge the relapse rate for GT3 compensated cirrhotics in ASTRAL-3 was higher at 9% compared to 1% for GT1 compensated cirrhotics in ASTRAL-1 (Table 3 and Fig. A).

Table 3. Relapse Rate by Presence of Baseline RAPS (24, 28, 30, 31, 58, 92, and 93) and Cirrhosis with 12 Weeks SOF/VEL (unless noted otherwise)

	Overall	**No RAPs (15%)**	**Any RAPs**
ASTRAL 1			
GT1	1% (2/323)	0.4% (1/249)	1% (1/74)
Without cirrhosis	0.4% (1/250)	0.5% (1/188)	0% (0/62)
With cirrhosis	1% (1/73)	0% (0/61)	8% (1/12)
ASTRAL-4 GT1 decompensated Cirrhosis			
12 Weeks	8% (5/65)	6% (3/52)	17% (2/12)
SOF/VEL+RBV 12 Weeks	2% (1/66)	2% (1/49)	0% (0/17)
24 Weeks	4% (3/67)	2% (1/48)	11% (2/19)
ASTRAL-3			
GT3	4% (11/275)	3% (7/218)	7% (4/56)
Without cirrhosis	2% (4/195)	2% (3/147)	2% (1/47)
With cirrhosis	**9% (7/80)**	**6% (4/71)**	**33% (3/9)**
ASTRAL-4 GT3 decompensated cirrhosis			
12 Weeks	46% (6/13)	50% (5/10)	33% (1/3)
SOF/VEL+RBV 12 Weeks	8% (1/12)	8% (1/12)	0
24 Weeks	45% (5/11)	40% (4/10)	100% (1/1)

Figure A. Summary of Relapse Rates in GT1 and GT3 Subjects with and without Cirrhosis (* no SOF/VEL + RBV arm)



We also considered the results from the Phase 2 trial 109. We focused on trial Arms 7 and 8 because Arms 7 and 8 evaluated 12 week SOF + 100 mg VEL with and without RBV in GT3 treatment-experienced subjects with compensated cirrhosis as shown in Table 4. Only one of the subjects who relapsed had baseline NS5A resistance polymorphisms (A30K and L31M). We acknowledge the limited sample size for Arms 7 and 8 and the difference in SVR12 rates was not statistically significant because the 95% CI included zero.

However, the data from trial 109 along with data from ASTRAL-4 could be used to help show the contribution of RBV when used with SOF/VEL in a certain subgroup of HCV GT3 patients.

Table 4: Outcome for Trial 109 – Arms 7 and 8

	Without RBV	With RBV	Diff in SVR12 rate (without RBV– with RBV) [95% CI]
SVR12 rate [95% CI]	89% (23/26) [70%, 98%]	96% (25/26) [80%, 100%]	-8% [-28%, 10%]
Relapse	11.5% (3/26)	3.8% (1/26)	
BL RAPs	1 (A30K, L31M)	0	
Y93H at failure	2/3	1/1	

In summary, we acknowledge even though SVR rates are high overall for GT3 patients, relapse rates could be further reduced for certain subgroups such as GT3 treatment-experienced patients and GT3 patients with compensated cirrhosis. We are concerned about the consequences of virologic failure with development of Y93H in GT3 virologic failures and potential loss of subsequent treatment options. We also acknowledge that trial GS-US-342-2097 will provide an additional direct assessment of the role of RBV in GT3 patients; however, currently available information from the SOF/VEL development program could be used to assess the contribution of RBV.

We request you provide a written response to this document by April 12th. In your response please provide your thoughts on (1) the available data from the phase 2 trial 109 and ASTRAL-4 to support the use of RBV, (2) the use of RBV for certain GT3 patients (for example, GT3 patients with cirrhosis or another subgroup of GT3 patients) and (3) potential revisions to Section 2, Dosage and Administration such as a consideration to add RBV for a specific subgroup(s) of GT3 patients.

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_____

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
04/01/2016

From: Mosaddegh, Sohail
To: prachi.shah@gilead.com
Cc: Onaga, Linda
Subject: NDA 208341 (Gilead, sofosbuvir /velpatasvir) IR
Date: Friday, March 25, 2016 11:30:00 AM
Importance: High

Hello:

I am sending this information request on behalf of Linda Onaga who is currently on leave. Can you please provide an update on Gilead's retreatment trial in prior DAA failures (GS-US-342-1553) SOF/VEL/RBV x 24 weeks. The review team is primarily interested in the subjects who failed in the phase 2 SOF/VEL trials where lower VEL doses and/or shorter durations were used and what their SVR status is at this point. We kindly request a response no later than the COB Monday, March 28, 2016.

Thank you

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

SOHAIL MOSADDEGH
03/25/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208341

INFORMATION REQUEST

Gilead Sciences, Inc.
Attention: Prachi Shah, MBS, RAC
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Sir/Madam:

Please refer to your New Drug Application (NDA) dated and received October 28, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sofosbuvir and velpatasvir fixed dose combination tablet.

We are reviewing the Chemistry Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response in order to continue our evaluation of your NDA by April 6, 2016.

Based on the data provided in the NDA, we have the following recommendations for the acceptance criteria in the velpatasvir DS specification and the sofosbuvir & velpatasvir DP specification.

IMPURITY	Gilead Criteria DS	Gilead Criteria DP	FDA Recommendation DS	FDA Recommendation DP
[redacted]				(b) (4)

(b) (4)

If you have questions, call me at (240) 402-2691.

Sincerely,

Bamidele F. Aisida -A

Digitally signed by Bamidele F. Aisida -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001703308, cn=Bamidele F. Aisida -A
Date: 2016.03.23 15:16:32 -04'00'

Florence Aisida, Pharm.D, BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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: **208341**

Drug: **sofosbuvir /velpatasvir**

Date: **March 17, 2016**

To: **Prachi Shah, MBS, RAC, Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 208341**

We have the following comments for NDA 208341.

We have reviewed the preliminary safety data from ASTRAL-5 included in the Safety Update Report and have the following comments regarding coadministration of SOF/VEL with HIV antiretroviral drugs, specifically atazanavir (ATV) and tenofovir disoproxil fumarate (TDF).

1. Coadministration of SOF/VEL with TDF-containing regimens resulted in increased TFV exposures in all 6 ART regimens evaluated. Additional safety data from ASTRAL-5 are needed to assess the safety impact of higher TFV exposures over the full course of SOF/VEL treatment.

2. We note that 13/21 subjects receiving ATV/r had elevated bilirubin $\geq$ 2 x ULN. Based on Table 10 of your Safety Update Report, it appears that bilirubin begins to increase within 1-2 weeks of starting SOF/VEL, but there are insufficient results beyond Week 4 to determine whether the bilirubin values normalize over time.

    a. Please provide results though Week 12 (and beyond, if available) for all subjects with bilirubin $\geq$ 2 x ULN. Include both direct and indirect bilirubin in your report, along with ALT, AST, and alkaline phosphatase, as well as any clinical adverse events.

    b. Please provide your posited mechanism for why the bilirubin elevation occurs. We note that there is no significant drug-drug interaction between ATV/r and SOF/VEL based on the DDI study included with this application.

Please provide a target date for when a report could be submitted with complete 12 week safety data for all ASTRAL-5 participants. We appreciate a format similar to the reports submitted to NDA 205834 which summarized safety data from Study CO-US-337-0116 and GS-US-337-0115 (ION-4).

Please provide your response by March 31, 2016.

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
03/17/2016

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: **208341**

Drug: **sofosbuvir/velpatisvir FDC**

Date: **March 17, 2016**

To: **Prachi Shah MBS, RAC, Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 208341 DAVP Proposed Labeling Changes**

Please find attached the Division's labeling edits for NDA 208341. A word copy of the label will be attached to this correspondence.

Please provide your response/revised labeling by March 31, 2016.

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
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

43 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
03/17/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208341

MID-CYCLE COMMUNICATION

Gilead Sciences, Inc.
Attention: Prachi Shah, MBS, RAC
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Shah:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sofosbuvir/velpatasvir tablets, 400 mg/ 100 mg.

We also refer to the teleconference between representatives of your firm and the FDA on February 11, 2016. 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 me at (301) 796-0759 or the Division's main line at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Linda C. Onaga, MPH
Senior Regulatory Project Manager
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: February 11, 2016 3:00 PM – 4:00 PM

Application Number: NDA 208341
Product Name: sofosbuvir/velpatasvir
Proposed Indication: treatment of chronic hepatitis C infection
Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Debra Birnkrant, MD
Meeting Recorder: Linda C. Onaga, MPH

FDA ATTENDEES

1. Debra Birnkrant, MD, Director
2. Kimberly Struble, PharmD, Clinical Team Lead
3. Linda Lewis, MD, Clinical Reviewer
4. Prabha Viswanathan, MD, Clinical Reviewer
5. Sarah Connelly, MD, Clinical Reviewer
6. Stephen Miller, PhD, CMC Lead
7. Lisa Naeger, PhD, Virology Reviewer
8. Julian O'Rear, PhD, Virology Team Lead
9. Karen Qi, PhD, Biometrics Reviewer
10. Thamban Valappil, PhD, Acting Biometrics Team Lead
11. Jenny Zheng, PhD, Clinical Pharmacology Reviewer
12. Shirley Seo, PhD, Clinical Pharmacology Team Lead
13. Fang Li, PhD, Pharmacometrics Reviewer
14. Jeffry Florian, PhD, Pharmacometrics Team Lead
15. Karen Winestock, Chief, Project Management Staff
16. Linda C. Onaga, MPH Senior Regulatory Project Manager

GILEAD SCIENCES, INC ATTENDEES

1. John McHutchison, MD, Executive Vice President, Liver Diseases
2. Mani Subramanian MD, Senior Vice President, Liver Diseases
3. Diana Brainard, MD, Vice President, Liver Diseases
4. John McNally, PhD, Director, Liver Diseases
5. Brian Kearney, PharmD, Vice President, Clinical Pharmacology
6. Erik Mogalian, PhD, Sr. Clinical Pharmacologist
7. Michele Anderson, Director, Regulatory Affairs
8. Prachi Shah, Manager, 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

Clinical/Statistical/Virology

We do not have any significant issues with the clinical, statistical or virology data from ASTRAL 1, 2 and 4.

We would like to discuss dosing recommendations for HCV genotype 3 compensated cirrhotics, specifically recommending SOF/VEL/RBV for 12 weeks. Although SOF/VEL/RBV for 12 weeks was not evaluated in ASTRAL-3, we considered other evidence for this potential recommendation including:

- Overall ASTRAL-4 results
- Data from other regimens that suggest the addition of RBV improves SVR12 rates in HCV genotype 3 cirrhotics:
    - ELECTRON-2 trial results suggest the addition of RBV improved SVR12 rates from 25% with LDV/SOF for 12 weeks (n=4) to 100% for LDV/SOF/RBV for 12 weeks (n=6)
    - ALLY-3+ trial results show the SVR12 rates in those with compensated cirrhosis receiving DCV/SOF/RBV for 12 or 16 weeks were 83% and 89%, respectively. Of note, the SVR12 rate for DCV/SOF in ALLY-3 was 63% for HCV genotype 3 cirrhotic subjects. [source: 2015 AASLD Liver Meeting].

We acknowledge the overall high SVR12 rate seen in ASTRAL-3 (95%) and do note the numeric difference in SVR12 rate between subjects with compensated cirrhosis (91%) and subjects without cirrhosis (97%). The overall goal is to maximize SVR12 rates and minimize virologic failure rates. The results in ASTRAL-3 suggest there is room for improvement in SVR12 rates in the subgroup of HCV genotype 3 subjects with compensated cirrhosis. The addition of RBV could be beneficial based on the evidence cited above and could be further evaluated as a post marketing trial (b) (4)

Clinical Pharmacology

The following drug-drug interaction considerations are currently under review

- Coadministration with PPIs
- Review of ASTRAL-5 safety data to support use with ATV/RTV and other strong CYP3A/P-gp inhibitors
- Clinical recommendations for coadministration of SOF/VEL with tenofovir-based regimens
- Coadministration with rosuvastatin. Additionally should other statins that are transported by OATP/BCRP require specific dosage recommendations
- Coadministration with substrates of BCRP, P-gp or OATP with a narrow therapeutic index

Discussion:

The discussion was focused on the clinical/statistical/virology comments (b) (4) Gilead will conduct a trial (b) (4) to answer the Division's question regarding the optimal dosing recommendations for genotype 3 compensated cirrhotics. (b) (4)

Gilead will provide the Division with other data to support their rationale to wait for the above trial results (b) (4)

Gilead will also submit additional information regarding (b) (4)

3.0 INFORMATION REQUESTS

All pending information requests were sent to Gilead with response dates, prior to this meeting.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

The review team has not identified any major safety concerns at this time. We continue to discuss how best to present common adverse reactions in section 6, (b) (4)

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an advisory committee meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The proposed date for the late cycle meeting between the Division of Antiviral Products and Gilead Sciences is April 19, 2016 2:30 PM – 4:00 PM.

The Action Date for this NDA is June 28, 2016.

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/s/

LINDA C ONAGA
03/04/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 03/03/2016 05:11:48 PM
To: prachi.shah@gilead.com
CC: Linda.Onaga@fda.hhs.gov
BCC: Bamidele.aisida@fda.hhs.gov
Subject: NDA 208341 INFORMATION REQUEST

Dear Sir/Madam,

In reference to the Velpatasvir Quality Specification (GSPEC-272-00 (2.0):

• Please tighten the acceptance limit for assay, to (b) (4) %. This is supported by the batch analysis data provided
• Please tighten the acceptance limit for (b) (4) to be consistent with ICH Q3C option 1 limit of (b) (4) ppm. This is supported by the batch analysis data provided.

We request a written response in order to continue our evaluation of your NDA by March 10, 2016.

Please confirm receipt of this email.

Thanks,
Florence Aisida, Pharm.D,BCPS
RBPM, Office of Program and Regulatory Operations
Office of Pharmaceutical Quality/CDER/FDA.
(240) 402-2691 |Bamidele.aisida@fda.hhs.gov

confirm receipt

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE AGENDA/TOPICS FOR DISCUSSION

Meeting Date and Time: February 11, 2016 3:00 PM – 4:00 PM

Application Number: NDA 208341
Product Name: sofosbuvir/velpatasvir
Proposed Indication: treatment of chronic hepatitis C infection
Applicant Name: Gilead Sciences, Inc.

1.0 INTRODUCTION

We are providing these preliminary comments to you before we conduct the midcycle communication scheduled on February 11, 2016, 3:00 PM -4:00 PM.

2.0 Clinical/Statistical/Virology

Clinical/Statistical/Virology

We do not have any significant issues with the clinical, statistical or virology data from ASTRAL 1, 2 and 4.

We would like to discuss dosing recommendations for HCV genotype 3 compensated cirrhotics, specifically recommending SOF/VEL/RBV for 12 weeks. Although SOF/VEL/RBV for 12 weeks was not evaluated in ASTRAL-3, we considered other evidence for this potential recommendation including:

- Overall ASTRAL-4 results
- Data from other regimens that suggest the addition of RBV improves SVR12 rates in HCV genotype 3 cirrhotics:
    - ELECTRON-2 trial results in HCV genotype 3 treatment-naïve subjects with compensated cirrhosis suggest the addition of RBV improved SVR12 rates from 25% with LDV/SOF for 12 weeks (n=4) to 100% for LDV/SOF/RBV for 12 weeks (n=6) [source: ELECTRON-2 Second Interim Study Report, NDA 205834 SN 0059]

We acknowledge the overall high SVR12 rate seen in ASTRAL-3 (95%) and do note the numeric difference in SVR12 rate between subjects with compensated cirrhosis (91%) and subjects without cirrhosis (97%). The overall goal is to maximize SVR12 rates and minimize virologic failure rates. The results in ASTRAL-3 suggest there is room for improvement in SVR12 rates in the subgroup of HCV genotype 3 subjects with compensated cirrhosis. The addition of RBV could be beneficial based on the evidence cited above and could be further evaluated as a post marketing trial (b) (4)

(b) (4) We look forward to your thoughts during the midcycle telecon regarding this potential dosage recommendation.

3.0 Clinical Pharmacology

The following drug-drug interaction considerations are currently under review:

- Coadministration with PPIs
- Review of ASTRAL-5 safety data to support use with ATV/RTV and other strong CYP3A/P-gp inhibitors
- Clinical recommendations for coadministration of SOF/VEL with tenofovir-based regimens
- Clinical recommendations for statins other than rosuvastatin
- Coadministration with substrates of BCRP, P-gp or OATP with a narrow therapeutic index

4.0 Major Safety Concerns/Risk Management

The review team has not identified any major safety concerns at this time. We continue to discuss how best to present common adverse reactions in section 6, (b) (4)

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/s/

LINDA C ONAGA
02/04/2016

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: **208341**

Drug: **sofosbuvir /velpatasvir**

Date: **February 2, 2016**

To: **Prachi Shah, MBS, RAC Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 208341**

We have the following comments for NDA 208341.

Clinical Pharmacology:

We identified missing records in your population PK dataset for VEL. In GS-US-342-0109, there were 160 subjects who were treated with VEL 100 mg (SOF 400 mg + VEL 100 mg n=80; SOF 400 mg +VEL 100mg + RBV n=80), and 159 subjects who were treated with VEL 25 mg (SOF 400 mg + VEL 25 mg n=79; SOF 400 mg + VEL 25 mg + RBV n=80). However, in the population PK datasets, 158 subjects on VEL 100 mg were included while only 14 subjects on VEL 25 mg were included.

We request that you submit an updated population PK dataset that includes PK records from subjects treated with VEL 25 mg (SOF 400 mg + VEL 25 mg ; SOF 400 mg+ VEL 25 mg + RBV). In addition, we request you rerun your population PK model with the updated dataset, note any substantial changes in parameter estimates, and provide a separate dataset that includes estimated PK parameters (CL, AUC, C_{trough}). In the dataset, please include subject IDs to facilitate linking to the original unique subject IDs. Finally, using the exposure (AUC and C_{trough}) and outcome (SVR) data, conduct an exposure-response analysis for genotype 3 patients.

Please submit your updated dataset and analyses by February 10th.

Clinical:

1. The cause of death is unclear for four of the six subjects who died during ASTRAL-1, ASTRAL-2, and ASTRAL-3: subjects 1138-01386-63561, 1139-02111-65015, 1140-01154-62556, and 1140-3902-62126. We note that subjects 1138-01386-63561, 1139-02111-65015, and 1140-01154-62556 had no significant adverse events that would indicate poor health in the weeks preceding their deaths. Please provide your

interpretation of the deaths and submit any available follow-up information for all four cases. Please include the autopsy reports for subjects 1138-01386-63561 and 1140-3902-62126 in your response, and confirm that autopsies were not performed for the other two subjects.

2. In addition, we noted inconsistencies between the date of death and date of study completion for subjects 1139-03054-65012 and 1140-04262-62067. Please explain why the date of death precedes the date of study completion for these two subjects.
3. Subject 00731-63339 had QTc prolongation at treatment week 12, which subsequently improved. In order to facilitate our understanding of the contribution of SOF/VEL, please describe changes that were made to the subject's concomitant medications in response to this finding.

Pharmacology/Toxicology:

The Division agrees that (b) (4) poses little clinical risk based on the minimal degree of carryover. However, the Division would like to emphasize that the mutagenic potential of this impurity has not been adequately addressed. (b) (4) the rationale is based on insufficient information. The data used to support (b) (4) is taken from studies conducted in a limited number of bacterial tester strains and/or tested at extremely low doses (i.e., due to cytotoxicity). Given the suboptimal nature of these studies, it is not possible to conclude tha (b) (4) lack reactive potential. In the absence of additional information, we recommend that (b) (4) be classified as Class 3.

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
02/02/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208341

INFORMATION REQUEST

Gilead Sciences, Inc.
Attention: Jennifer Huber
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Huber:

Please refer to your New Drug Application (NDA) dated and received October 28, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sofosbuvir and velpatasvir fixed dose combination tablet.

We are reviewing the Chemistry Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response in order to continue our evaluation of your NDA by Feb 7, 2016. A partial response at that date with a timeline for the remaining questions is also acceptable.

1. In the Amendment of 1/6/16 tablet Batch SSVS is described in Table 12. This table indicates that 6 months of stability data are provided. However, the stability data in the original submission and the Amendment of 1/6/16 refer to Batch SSVT. Are these the same batches? Please clarify.

2. Please note that ICH guideline Q1E as applied to drug product stability requires annual stability batch in addition to stability data from the registration batches. Therefore, propose a post approval stability protocol for the (b) (4). If the (b) (4) looks stable after reasonable amount of annual stability batches (e.g., 2 -3 annual batches), you can propose to stop the annual stability batch test in the annual report. You are also reminded to submit the on-going stability data up to the (b) (4) month of proposed hold time for (b) (4) to the Agency.

3. The provided dissolution data for your proposed product do not support the proposed acceptance criterion of "NLT (b) (4)% (Q) of the labeled amount of SOF and VEL is dissolved in (b) (4) minutes" and therefore is inadequate. Based on the submitted data an

acceptance criterion of "NLT (b) (4)% (Q) of the labeled amount of velpatasvir and sofosbuvir in SOF/VEL tablets is dissolved in (b) (4) minutes" is recommended. Implement the above recommended dissolution acceptance criterion for your proposed product and provide the revised specifications table with the updated acceptance criterion for the dissolution test.

Alternatively, develop a dissolution method (and appropriate acceptance criterion) for your proposed drug product that is discriminating and bio-predictive towards the critical material attributes and process parameters identified for your drug product.

If you have questions, call me at (240) 402-2691.

Sincerely,

Bamidele F. Aisida -A

Digitally signed by Bamidele F. Aisida -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001703308, cn=Bamidele F. Aisida -A
Date: 2016.01.21 15:07:27 -05'00'

Florence Aisida, Pharm.D, BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

METHODS VERIFICATION
MATERIALS RECEIVED

NDA 208341 January 20, 2016

Gilead Sciences, Inc.
Attention: Jennifer Huber, M.S.
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City CA 94404

Dear Jennifer Huber, M.S.:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sofosbuvir / Velpatasvir Fixed-Dose Combination Tablets and to our December 18, 2015, letter requesting sample materials for methods verification testing.

We acknowledge receipt on January 19, 2016, 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 (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, 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/

LAURA POGUE
01/20/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 208341

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Jennifer Huber, M.S.
Senior Manager, Regulatory Affairs

Dear Ms. Huber:

Please refer to your New Drug Application (NDA) dated and received October 28, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sofosbuvir and Velpatasvir Tablets, 400 mg/100 mg.

We also refer to your correspondence, dated and received, October 30, 2015, requesting review of your proposed proprietary name, Epclusa. We have completed our review of the proposed proprietary name Epclusa, and have concluded it is conditionally acceptable.

If any of the proposed product characteristics as stated in your October 30, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

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

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

Sincerely,

{See appended electronic signature page}

Todd Bridges, 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
01/11/2016

TODD D BRIDGES
01/11/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208341

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Gilead Sciences, Inc.
Attention: Prachi Shah, MBS, RAC
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Shah:

Please refer to your New Drug Application (NDA) dated October 28, 2015, received October 28, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for sofosbuvir/velpatasvir tablet, 400 mg/100 mg.

We also refer to your amendments dated October 9, 2015, October 20, 2015, October 29, 2015, and November 5, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is June 28, 2016. 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.

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 March 31, 2016. In addition, the planned date for our internal mid-cycle review meeting is January 26, 2016. We are not currently planning to hold an advisory committee meeting to discuss this application.

We request that you submit the following information by January 11, 2016:

Clinical Pharmacology:

1. Please provide a PK property (ADME) table similar to the GENVOYA® US Package Insert Table 6.
2. We have the following comments relating to your proposal for concomitant use of proton pump inhibitors (PPIs) with sofosbuvir/velpatasvir (SOF/VEL):
    a. You have proposed to recommend administration of PPIs (b) (4) However, PPIs are generally recommended to be taken under fasted conditions. With consideration in mind, please provide an alternate proposal.
    b. If you propose to either coadminister PPIs with SOF/VEL under fasting conditions or stagger PPIs with SOF/VEL, please provide support to show that the coadministration of PPIs with SOF/VEL would not compromise efficacy in all proposed populations (due to lower exposures of either SOF, VEL, or both).
    c. Please provide justification for your proposal to (b) (4)
3. Please provide additional safety data, in particular long-term safety data to support the coadministration of strong P-gp inhibitors, e.g., atazanavir/ritonavir and cyclosporine, with SOF/VEL.
4. In your Phase 1 studies (GS-US-342-0104, GS-281-0101, and GS-US-28-0102), velpatasvir exhibited less than dose-proportional increase or near dose-proportional increase in exposure for doses between 25 mg and 450 mg, with or without sofosbuvir. While in 2 Phase 2 studies (GS-US-337-0122 and GS-US-342-0109), velpatasvir exhibited a greater than dose proportional increase in exposure for doses between 25 mg and 100 mg. Please provide a rationale for this difference in findings, including the potential for a formulation effect.

Pharmacology/Toxicology:

5. Table 1 in the justification of velpatasvir specification (section 3.2.S.4.5; page 8) lists maximum observed impurity levels (%) in toxicology studies. However, several values could not be confirmed by test article analytical reports/certificates of analysis from the referenced studies (i.e., TX-281-2003, TX-281-2007, and TX-281-2042). In order to facilitate Division review, the following issues need to be addressed:
    a. Impurities are sometimes identified by relative retention time. Please provide cross reference to corresponding Gilead ID#.

b. Some studies include multiple test article analytical reports/certificates of analysis. Please indicate the exact document used to establish maximum observed impurity levels.
c. Where a single value is reported for impurity pairs (e.g., (b) (4), COA for lot# 6451-009-38, reported on page 64 of Study no. TX-281-2042) please clarify contributions from each individual impurity and where this information is found.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

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

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:

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

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

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

Pediatric Research Equity Act (PREA)

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, MPH, Senior 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

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
12/23/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208341

INFORMATION REQUEST

Gilead Sciences, Inc.
Attention: Jennifer Huber
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Huber:

Please refer to your New Drug Application (NDA) dated and received July 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sofosbuvir and velpatasvir fixed dose combination tablet.

We are reviewing the Chemistry Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response in order to continue our evaluation of your NDA by Jan 6, 2016. A partial response at that date with a timeline for the remaining questions is also acceptable.

1. Please provide information on (b) (4) levels in (b) (4) Please also clarify whether (b) (4) can be detected by the residual solvent method? (Section 3.2.S.2.3)

2. We note that the (b) (4) Certificate of Analysis for (b) (4) Attachment 3) contains no actual analytical results, unlike the corresponding document for (b) (4) Please supply this information.

3. We did not see information on how particle size distributions or (b) (4) of excipients impact the manufacturing process. For example, the excipient microcrystalline cellulose can be obtained in a variety of grades. Please specify which grade of each excipient is used in the manufacturing process or justify that the quality of the product is not influenced by the grade of excipient that is used.

4. For UPLC method TM-254 please supply chromatograms of the system suitability solution obtained at (b) (4) nm and (b) (4) nm offset on the same trace, i.e., corresponding to

Figures 5 and 6 as well as 9 and 10. Please also supply similar traces corresponding to Figures 5a and 5b.

5. We note that UPLC Method TM-253 and the dissolution method (TM-252) have no System Suitability test for resolution of the active peaks at (b) (4) nm. Please add such a test or provide a justification for not doing so. In either event please provide resolution values obtained during the robustness testing.

6. Provide an estimate of the limit of detection for (b) (4) (3.2.P.3.3).

7. Please provide any available data that shows that the (b) (4) velpatasvir and sofosbuvir do not change when the tablets are manufactured or when the tablets are placed on stability.

8. We note that on stability the (b) (4) in the tablets is ≤(b) (4)% and that data are provided showing that tablets with (b) (4)% (b) (4) are stable. However, the proposed limit of ≤ (b) (4)% does not appear to be supported by any data. Please provide such data or reduce the (b) (4) to (b) (4)%.

9. We acknowledge that (b) (4) was included in the dissolution medium (b) (4) for velpatasvir. However, based on the provided data, the current proposed dissolution method and acceptance criterion lack discriminating ability against the indentified critical process parameters (CPPs). Provide justification for the inclusion of a relatively high concentration of (b) (4) which results in a dissolution method with low discriminating ability.

10. Provide actual hardness values for the lots listed in Figure 2 and Figure 3 of Justifications of Specifications (Section 3.2.P.5.6) and explain how these ranges in hardness values were used to define the related process parameters.

11. Lot 14SXG001UR showed (b) (4) at early time points compared to lot 14SXG002UR and lot 14SXG003UR (Justifications of Specifications, Section 1.7.3). You stated that this was the result of the (b) (4) Explain how (b) (4) impact the CQA of the drug product, e.g. (b) (4)

12. Provide available dissolution profiles from lots manufactured with the (b) (4) with particle size outside the range (i.e. D50 (b) (4) um), D90 (b) (4) um)) tested in phase 3 clinical lots (14SXG001UR, 14SXG002UR and 14SXG003UR).

13. Two drug product manufacturing sites were proposed. Explain the difference between these two sites and provide comparative dissolution profile data with similarity testing (e.g. f_2 testing) to demonstrate similarity of the drug products from the two sites.

14. The proposed hold time (b) (4) should be supported by the real time hold study data at the proposed hold condition and in the intended container. It should not be based on anticipated future stability data. Therefore, revise the proposed hold time for (b) (4) based on the real time hold study data and submit a revised hold time to this NDA to facilitate further review. If the on-going hold studies support the hold time beyond currently available data you can submit the data and proposal of extending the hold time in future annual reports.

If you have questions, call me at (240) 402-2691.

Sincerely,

Bamidele F. Aisida -A

Digitally signed by Bamidele F. Aisida -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001703308, cn=Bamidele F. Aisida -A
Date: 2015.12.16 15:48:41 -05'00'

Florence Aisida, Pharm.D, BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208341

NDA ACKNOWLEDGMENT

Gilead Sciences, Inc.
Attention: Jennifer Huber, M.S.
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Huber:

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/velpatasvir fixed dose combination tablet, 400 mg/100 mg

Date of Application: October 28, 2015

Date of Receipt: October 28, 2015

Our Reference Number: NDA 208341

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 December 27, 2015, in accordance with 21 CFR 314.101(a).

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

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

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

Sincerely,

{See appended electronic signature page}

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

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
11/09/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND118605

MEETING MINUTES

Gilead Sciences, Inc.
Attention: Jennifer Huber, MS
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Huber:

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-5816 fixed dose combination.

We also refer to the telecon between representatives of your firm and the FDA on May 26, 2015. The purpose of the meeting was to discuss the preparation and submission strategy for the NDA.

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

If you have any questions, call Nina Mani, Regulatory Project Manager at (240) 402-0333.

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
Sponsor Slide Set

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: May 26, 2015; 10:30 AM -12:00 PM (Eastern)
Meeting Location: Teleconference

Application Number: IND 118605
Product Name: Sofosbuvir/GS-5816 fixed-dose combination (FDC) tablets
Indication: Treatment of chronic hepatitis C infection
Sponsor/Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
Meeting Recorder: Nina Mani, PhD, MPH, Regulatory Project Manager, DAVP

FDA ATTENDEES

1. Debra Birnkrant, MD, Director, DAVP
2. Jeffrey Murray, MD, MPH, Deputy Director, DAVP
3. Poonam Mishra, MD, MPH, Deputy Director for Safety, DAVP
4. Sarah Connelly, MD, Clinical Reviewer, DAVP
5. Kimberly Struble, PharmD, Clinical Team Leader, DAVP
6. Shirley Seo, PhD, Clinical Pharmacology Team Lead, Office of Clinical Pharmacology (DCPIV)
7. Jenny Zheng, Clinical Pharmacology Reviewer, (DCPIV)
8. Lisa Naeger, PhD, Clinical Virology Reviewer, DAVP
9. Julian O'Rear, PhD, Clinical Virology Team Lead, DAVP
10. Stephen Miller, PhD, Office of Product Quality
11. Karen Qi, PhD, Biometrics Reviewer, Division of Biometrics IV
12. Jeffry Florian, PhD, Pharmacometrics Team Lead, OCP
13. Antoine El Hage, PhD, Office of Scientific Investigations, Office of Compliance
14. Jasminder Kumar, PharmD, RPh, Reviewer, Office of Surveillance and Epidemiology, Division of Risk Management (DRISK)
15. Russ Fleischer, PA, Medical Team Lead (Acting), DAVP
16. Karen Winestock, Chief, Project Management Staff, DAVP
17. Linda C. Onaga, MPH, Regulatory Project Manager, DAVP
18. Christian Yoder, BSN, MPH, Regulatory Project Manager, DAVP
19. Nina Mani, PhD, MPH, Regulatory Project Manager, DAVP

EASTERN RESEARCH GROUP ATTENDEES

1. Marc Goldstein, Independent Assessor

SPONSOR ATTENDEES

1. John McHutchison, MD, Executive Vice President, Liver Diseases
2. Mani Subramanian, MD, Vice President, Liver Diseases
3. Diana Brainard, MD, Vice President, Liver Diseases
4. John McNally, PhD, Director, Clinical Research
5. Michael Miller, PhD, Senior Director, Biology (Clinical Virology)
6. Hongmei Mo, MD, Director, Biology (Clinical Virology)
7. Neby Bekele, PhD, Senior Director, Biostatistics
8. Xiao Ding, PhD, Senior Manager, Biostatistics
9. Michele Anderson, Director, Regulatory Affairs
10. Jennifer Huber, MS, Senior Manager, Regulatory Affairs

1.0 BACKGROUND

A FDC tablet containing sofosbuvir (SOF), a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and GS-5816, a NS5A inhibitor (SOF/GS-5816) is proposed for pan-genotypic use for the treatment of chronic hepatitis C virus (HCV) infection. This combination was originally granted Fast Track designation on September 30, 2013 and was granted Breakthrough Therapy (BT) designation for genotypes 1, 3, 4, 5, and 6 treatment naïve patients on April 22, 2014. Due to the approval and availability of safe and effective therapies to treat genotype 1 HCV infection, the Agency rescinded Breakthrough Therapy Designation on April 1, 2015. The Agency and Gilead Sciences, Inc. agreed an unmet medical need for genotypes 3, 4, 5, and 6 HCV infections still exists. As a result, Gilead submitted a new request for Breakthrough Therapy for the treatment of genotype 3, 4, 5, and 6 HCV infection in treatment naïve patients. This request was granted on May 15, 2015.

Gilead submitted a pre-NDA meeting request on March 27, 2015 to discuss the content and strategy for their upcoming original NDA submission. FDA's preliminary comments were sent to the sponsor on May 19, 2015 in response to questions in their meeting package. Gilead reviewed the comments and indicated that they will respond in writing to all issues raised in the preliminary comments correspondence, but wanted to discuss the following items during the May 26, 2015 telecon:

- Timing of the proposed Type B meeting to discuss their top-line data from the ASTRAL1-4 trials
- Definition of resistance associated variants (RAVs) for the efficacy analysis

In addition, to the topics above, the FDA and Gilead will discuss and reach agreement on the content of a complete application, the need for a REMS, and the submission of late-cycle submissions.

2. DISCUSSION

Following introductions, the FDA review team agreed to the sponsor's Option 2 Slide 4: see attached slide set) for the Type B meeting in September, 2015 is the best option. Gilead will provide the following items in the Type B meeting package:

1. SVR4 data for all trials
2. SVR12 data for ASTRAL 1 and 2
3. Available SVR 12 data for all arms in ASTRAL 3 and 4
4. Available data on relapse from ASTRAL 1- 4.

The FDA clarified the efficacy analysis conducted by Gilead will include SVR12 by baseline HCV RNA (</≥ 800,000 IU/mL), as well as any other factors that might affect the analyses (Slide 5: see attached slide set).

The FDA agreed with Gilead's definition of RAVs (Slide 6: see attached slide set), but noted if new RAVs were identified during review, the new RAVs would be added to the list.

FDA requested Gilead provide topline efficacy data, including SVR12 rates by genotype and cirrhosis status from ASTRAL-1 and ASTRAL-2 trials sooner than the Type B meeting in September, 2015. Gilead agreed and noted they would try to provide the ASTRAL-1 and ASTRAL-2 clinical synopsis/summary earlier than August, 2015.

The FDA asked whether Gilead had considered submitting a rolling NDA to allow early submission of Module 3. Gilead will consider this recommendation and respond back to FDA with a decision.

Gilead will respond to FDA Preliminary Comments in writing by June 15, 2015.

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/G-5816 will be submitted on October 30, 2015.

  All applications are expected to include comprehensive and readily available lists of all clinical and manufacturing sites included or referenced in the application.

- Based on issues raised in the Preliminary Comments and sent earlier to the sponsor, the need for REMS is considered a review issue.

- Similarly, FDA could not commit to an expedited review because preliminary efficacy and safety data were not available and the review team is unclear if review issues exist at this time.

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

4.0 PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

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

5.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products

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

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

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 Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site

b. Number of subjects randomized at each site
c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

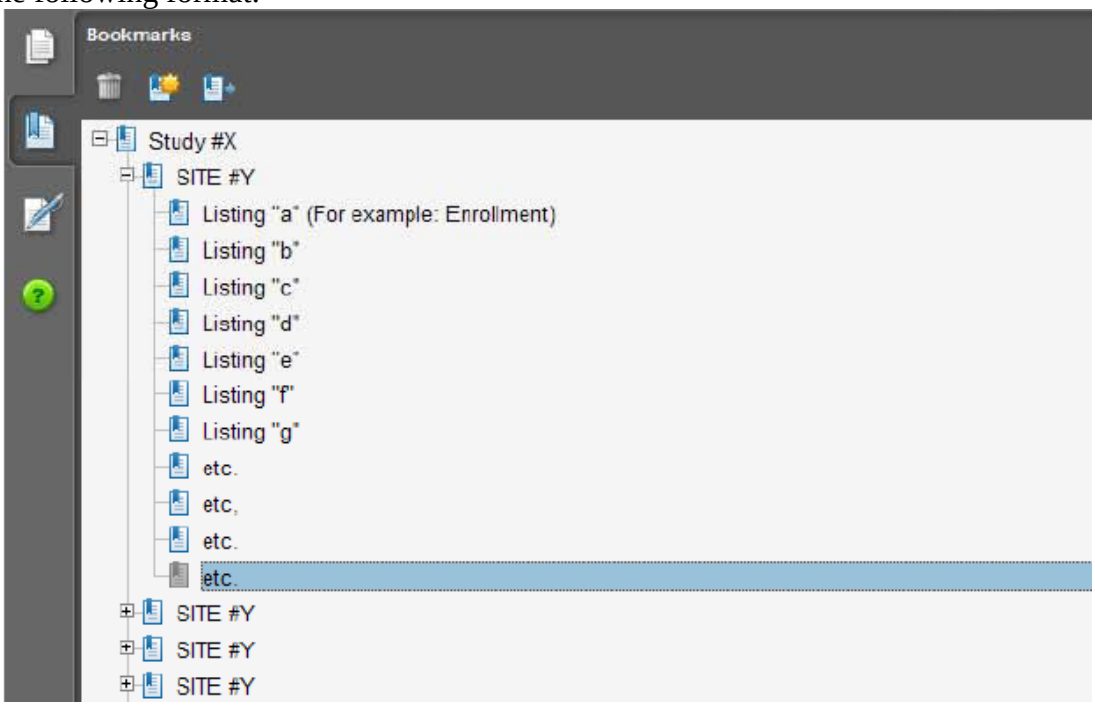
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.

i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

8.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

9.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Response to Preliminary Meeting comments	Gilead	June 15, 2015
Module 3 rolling submission	Gilead	
Clinical synopsis/summary from ASTRAL-1 and ASTRAL-2	Gilead	August, 2015, or earlier

10.0 ATTACHMENTS AND HANDOUTS

Please see attached.

6 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

DEBRA B BIRNKRANT
06/17/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118605

MEETING PRELIMINARY COMMENTS

Gilead Sciences, Inc.
Attention: Jennifer Huber, MS
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Huber:

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-5816 fixed dose combination.

We also refer to your correspondence, dated and received March 27, 2015 requesting a meeting to discuss the preparation and submission strategy for the NDA.

Our preliminary responses to your meeting questions are enclosed.

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

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (240) 402-0333.

Sincerely,

{See appended electronic signature page}

Nina Mani, PhD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comment

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: May 26, 2015; 10:30 AM -12:00 PM (Eastern)
Meeting Location: Teleconference

Application Number: IND 118605
Product Name: Sofosbuvir/GS-5816 Fixed-Dose Combination Tablets
Indication: Treatment of Chronic Hepatitis C Infection
Sponsor/Applicant Name: Gilead Sciences, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference meeting scheduled for May 26, 2015, 10:30 am – noon (Eastern) between Gilead Sciences, Inc. and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

A fixed dose combination tablet containing sofosbuvir (SOF), a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and GS-5816, a NS5A inhibitor (SOF/GS-5816) is proposed for pan-genotypic use in treatment of chronic hepatitis C virus (HCV) infection. This combination was originally granted Fast Track designation on September 30, 2013. It was granted Breakthrough Therapy (BT) designation for genotypes 1, 3, 4, 5, and 6 treatment naïve patients, which was rescinded on April 1, 2015. Following this, on May 15, 2015 the sponsor was granted BT designation for genotypes 3, 4, 5, and 6 treatment naïve patients.

The purpose of the meeting is to obtain feedback from the FDA regarding the acceptability of the proposed content and filing strategy, indication, and content of the NDA Safety Update for SOF/GS-5816 for the treatment of chronic HCV infection.

2.0 DISCUSSION

2.1 Submission Strategy

Question 1: Gilead will be seeking an indication for SOF/GS-5816 for the treatment of CHC genotype 1 to 6 infection in adults, including patients with decompensated cirrhosis. The proposed indication is based on the following Phase 3 studies:

- GS-US-342-1138 (ASTRAL-1): ASTRAL-1 has enrolled 740 subjects, of whom approximately 31% are treatment experienced and 19% have cirrhosis. The majority of subjects have genotype 1 HCV infection (53%), followed by genotype 4 (18%), genotype 2 (17%), genotype 6 (6%), and genotype 5 (5%).
- GS-US-342-1139 (ASTRAL-2): ASTRAL-2 has enrolled 266 genotype 2-infected subjects, of whom approximately 15% are treatment experienced and 14% have cirrhosis.
- GS-US-342-1140 (ASTRAL-3): ASTRAL-3 has enrolled 552 genotype 3-infected subjects, of whom approximately 26% are treatment experienced and 30% have cirrhosis.
- GS-US-342-1137 (ASTRAL-4): ASTRAL-4 has enrolled 267 subjects, of whom approximately 55% are treatment experienced. The majority of subjects have genotype 1 HCV infection (78%), followed by genotype 3 (15%), genotype 2 (4%), and genotypes 4 or 6 (3%).

As outlined in the draft proposed Table of Contents (Attachment 1), the safety and efficacy data from Phase 2 studies conducted with SOF+GS-5816 under IND 115670 will also support the proposed indication, including GS-US-342-0102 and GS-US-342-0109, as will non-IND study GS-US-337-0122 (ELECTRON-2 [Cohort 4]).
A tabular presentation of the Phase 2 and Phase 3 studies characterizing the safety and efficacy of SOF/GS-5816 to be included in the application in support of the proposed indication is provided in Table 1.

Does the Agency agree that the proposed indication for SOF/GS-5816 is supported by the clinical studies described in Table 1?

FDA Response to Question 1: We agree you have sufficient data to submit an NDA for the proposed indication; however, the exact indication will be a review issue as no Phase 3 efficacy and safety data were included in the pre-NDA meeting background package. In the absence of Phase 3 efficacy and safety data, the following major review issues have been identified.

Optimal SOF/GS-5816 Regimen in CPT B Population
ASTRAL-4 is the only trial that evaluates three different SOF/GS-5816-containing regimens (SOF/GS-5816 12 week, SOF/GS-5816 + RBV 12 week, SOF/GS-5816 24 week). Thus, data from this trial may support a different SOF/GS-5816-containing regimen for the CPT B population compared with the non-cirrhotic/compensated cirrhotic population, overall or in certain genotypes. For example, Phase 2 SOF+GS-5816 data in HCV genotype 3 subjects suggested the addition of RBV to a SOF/GS-5816 12 week regimen and/or a longer duration may optimize SVR rates, particularly in the cirrhotic

population. Based on the provided data from ASTRAL-4 15% of overall enrollment is genotype 3. We have concerns that the sample sizes may be too small if SVR and relapse data suggest either the SOF/GS-5816+ RBV 12 week or SOF/GS-5816 24 week duration is favored in this subgroup. If that is the case, an additional trial in the HCV genotype 3, CPT B subpopulation may be necessary to support an indication for SOF/GS-5816 use in this group.

Optimal SOF/GS-5816 Regimen in HCV Genotype 3 Population
It is also possible the ASTRAL-4 data may support a different SOF/GS-5816-containing regimen for certain genotype(s) based on the totality of the submitted Phase 3 data, particularly HCV genotype 3. For example, if ASTRAL-3 has lower than expected SVR, overall or in the cirrhotic subgroup, and ASTRAL-4 has improved SVR with either the SOF/GS-5816 + RBV 12 week or SOF/GS-5816 24 week regimens, we again have concern that the ASTRAL-4 sample sizes may be too small and that an additional trial in the HCV genotype 3 population, overall or in the cirrhotic subpopulation, may be necessary to support an indication for SOF/GS-5816 use in this group.

Safety of SOF/GS-5816 + RBV 12 Week and/or SOF/GS-5816 24 Week Regimen
As a separate issue, if a SOF/GS-5816 safety issue is identified, a larger safety database may be needed with the SOF/GS-5816 + RBV 12 week and/or SOF/GS-5816 24 week regimens to support an indication.

For these reasons, the NDA should include adequate efficacy and safety justification for the proposed SOF/GS-5816-containing regimen(s).

2.2 NDA Structure and Content

Question 2: The proposed draft Table of Contents for the SOF/GS-5816 NDA is provided in Attachment 1 and provides a list of nonclinical and clinical studies that will be included in Module 4 and Module 5, respectively. Gilead plans to resubmit, in the SOF/GS-5816 NDA, study reports previously provided in the SOF/GS-5816 IND or GS-5816 IND. Gilead will briefly summarize clinical studies of SOF within Module 2.7, and will cross-reference these studies to NDA 204671 (or other applications, if applicable). Tabular lists of nonclinical and clinical studies cross-referenced in this application will be provided under Module 1.4.4– Cross Reference to Other Applications. Consistent with previous NDA applications submitted to the DAVP, Gilead intends to provide information on primary pharmacodynamics, secondary pharmacodynamics (excluding virology data), safety pharmacology, virology (nonclinical and clinical) and nonclinical in vitro DMPK using human matrices as described in Table 2.

Table 2. Location of Discipline Specific Information in the SOF/GS-5816 NDA

Topic	Report	CTD Summary Location
Primary Pharmacodynamics	Module 5	• Briefly noted in Module 2.6.2 (Nonclinical Pharmacology Written Summary) • Specific details in Module 2.7.2,
Nonclinical Secondary Pharmacodynamics (excluding virology data)	Module 4.2.1.2	• Module 2.6.2 (Nonclinical Pharmacology Written Summary)
Safety Pharmacology	Module 4.2.1.3	• Module 2.6.2 (Nonclinical Pharmacology Written Summary) • Module 2.6.3 (Nonclinical Pharmacology Tabulated Summary)
Virology (nonclinical and clinical)	Module 5.3.5.4	• Module 2.7.2 (Summary of Clinical Pharmacology Studies)
Nonclinical In Vitro DMPK Using Human Matrices	Module 5.3.2, with cross-reference leaf in appropriate sections of Module 4	• Module 2.6.4 (Nonclinical Pharmacokinetics Written Summary) • Module 2.6.5 (Nonclinical Pharmacokinetics Tabulated Summary)
Cytotoxicity, mitochondrial toxicity, and cellular polymerases assessment	Module 5.3.5.4, with cross-reference leaf in appropriate sections of Module 4	• Module 2.6.2 (Summary of Pharmacology Written Summary)

a) Does the Agency agree with the report location and CTD summary location as presented in Table 2?

b) Does the Agency agree with the proposal to not resubmit previously submitted nonclinical and clinical SOF reports and to cross reference nonclinical and clinical studies with SOF to NDA 204671 (or other applications, if applicable)?

FDA Response to Question 2a: We agree.

FDA Response to Question 2b: We agree with this proposal.

Question 3: If the proposal to cross reference to NDA 204671 for the reports of SOF nonclinical studies containing data pertinent to the SOF/GS-5816 NDA (Question 2b) is acceptable, only reports of nonclinical studies of GS-5816, any additional nonclinical studies required to support the use of SOF/GS-5816, and nonclinical studies of SOF that

were completed after submission of NDA 205834 will be included in the initial SOF/GS-5816 NDA. These studies are listed in the proposed draft Table of Contents provided in Attachment 1 and include: a comprehensive set of primary and secondary pharmacodynamic studies; complete core battery of safety pharmacology studies; complete disposition, metabolism, pharmacokinetics and excretion (DMPK) evaluation; repeat dose oral toxicity studies in rodents and non-rodents; genotoxicity studies; assessment of fertility; early embryonic development; pre- and postnatal development; evaluation of antigenicity; skin and eye irritation; and qualification of impurities. Results from the study of the effects of GS-5816 on embryo-fetal development in mice (TX-281-2032) will also be included in this NDA, as recommended by the Agency at the End-of-Phase 2 meeting (Reference ID: 3536223). Summaries for all relevant SOF and GS-5816 nonclinical studies will be provided in Module 2.6.

Carcinogenicity studies with GS-5816 in transgenic mice and rats will be ongoing at the time of the NDA filing and will be submitted post-approval as noted in the End-of-Phase 2 meeting information package (25 April 2014; IND 118605 SN0013). Carcinogenicity studies with SOF in mice and rats are completed and will be incorporated via cross-reference in the SOF/GS-5816 NDA.

Does the Agency concur that the list of nonclinical studies included in proposed draft Table of Contents for the SOF/GS-5816 NDA included in Attachment 1 support the registration of SOF/GS-5816?

FDA Response to Question 3: Yes, we concur.

Question 4: Gilead proposes to include in Module 1 of the SOF/GS-5816 NDA documentation for investigator financial disclosure, source documents for treatment allocation codes, disclosure of financial agreement with vendors used to manage treatment allocation codes, and investigator contact information for the covered clinical studies as detailed in Table 3.

Gilead plans to include a ‘guide to reviewers’ in Module 1 (1.2). The guide to reviewers will provide a general overview of the information contained in the NDA, as well as the overall structure and format. The intention of this guide is to provide the reviewer with a tool for navigation through the application.

Table 3. List of Module 1 Documentation for Covered Clinical Studies[1,2]

Module 1 Section	Document Description
1.3.4	Financial certification and disclosure
1.11.3	Source documents for treatment allocation codes[3]
1.11.3	Disclosure of Financial Agreements with vendor(s) used to generate and manage treatment allocation codes[3]
1.11.3	AE Dictionary and Coding Process
1.11.3	Investigator contact information (to include name, address, phone number, fax, and email)

1. Includes covered studies as defined by 21 CFR § 54.2(e)
2. Covered studies include: GS-US-342-1138 (ASTRAL 1), GS-US-342-1139 (ASTRAL-2), GS-US-342-1140 (ASTRAL-3), GS-US-342-1137 (ASTRAL-4), GS-US-342-0102, GS-US-342-0109, and GS-US-337-0122 (ELECTRON-2).
3. Information regarding treatment allocation codes will only be provided for randomized studies

Does the Agency agree with the proposal for provision of the Module 1 documentation described above and in Table 3?

FDA Response to Question 4: Yes, the Division agrees with your proposed plan. Please include responses to the following items with the NDA submission:

- Total number of investigators identified (This total should include all Principal Investigators as well as Sub-Investigators for all covered trials)
- Number of investigators who are sponsor employees (including both full-time and part-time employees)
- Number of investigators with disclosable financial interests/arrangements (Form FDA 3455)
- If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):
    - Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:
    - Significant payments of other sorts:
    - Proprietary interest in the product tested held by investigator:
    - Significant equity interest held by investigator in sponsor of covered study:
- Number of investigators with certification of due diligence (Form FDA 3454, box 3)

Question 5: As with recent NDA submissions to the DAVP (e.g., NDAs 204671 and 205834), Gilead proposes to include in the SOF/GS-5816 NDA literature references cited in the Nonclinical and Clinical Overviews only (Modules 2.4 and 2.5, respectively). Reference to guidelines, prescribing information and other similar documents will not be

included in the application. All other documents referenced in the application will be available upon request.

Does the Agency agree with this proposal for provision of references?

FDA Response to Question 5: Yes, the Division agrees with your proposed plan.

Question 6: A thorough QT/QTc study has been conducted for SOF (Study P7977-0613), and will be incorporated in the SOF/GS-5816 NDA via cross-reference to SOF NDA 204671. A thorough QT/QTc study for GS-5816 (Study GS-US-281-1054) has been conducted per ICH E14 guidance. The ECG waveforms have been uploaded to the ECG warehouse and the clinical study report and the electronic datasets from this study have been submitted to IND 115670 (SN0058). No additional QT/QTc studies have been conducted. Consistent with agreements made with DAVP regarding other recent NDA submissions, Gilead plans to summarize the data from this study in Module 2.7.2 and provide the clinical study report from this study in Module 5.3.4.1, but does not plan to resubmit the electronic datasets in the original SOF/GS-5816 NDA or the ECG waveforms to the ECG warehouse.

Does the Agency agree with this proposal for provision of the thorough QT/QTc study in the NDA?

FDA Response to Question 6: Yes, the Division agrees with your proposed plan.

Question 7: The proposed draft Table of Contents for the SOF/GS-5816 NDA is provided in Attachment 1 and provides a list of Quality Content that will be included with Module 3. Gilead plans to utilize cross-application links to NDA 204671 for sofosbuvir drug substance details.

Does the Agency agree with the proposal?

FDA Response to Question 7: Yes, we agree, provided that the facilities involved with manufacturing or testing of sofosbuvir are included in 3.2.S.2 and listed on the 356h form. If applicable, justification that the sofosbuvir drug substance specification is appropriate for manufacture of the SOF/GS-5816 tablet could be included in 3.2.S.2.S.4 in addition to the cross-application link to NDA 204671.

Given that the SOF/GS-5816 FDC tablet is a confirmed BT application, we recommend that you include in the Type B briefing package proposed to be held in September, 2015, information on the manufacturing, testing and packaging facilities for the two active ingredients and the drug product. Please also indicate at that time, or earlier if possible, whether a rolling submission approach might be feasible for this NDA. An estimate of the date when Module 3, or the drug substance portions of Module 3, could be available as a possible rolling submission would be helpful.

2.3 Clinical/Statistical

Question 8: Gilead intends to present an integrated summary of safety (ISS) based on pooled data from three Phase 3 studies: GS-US-342-1138 (ASTRAL-1), GS-US-342-1139 (ASTRAL-2), and GS-US-342-1140 (ASTRAL-3). The data from these studies will be pooled by treatment regimen and duration:

- SOF/GS-5816 for 12 weeks
- Placebo
- SOF +RBV for 12 weeks
- SOF +RBV for 24 weeks

The SAP for the ISS specifies the planned subgroup analyses and is included as Attachment 2.

Gilead intends to present an ISE based on pooled data from three Phase 3 studies: GS-US-342-1138 (ASTRAL-1), GS-US-342-1139 (ASTRAL-2), and GS-US-342-1140 (ASTRAL-3). Only efficacy data from subjects treated with SOF/GS-5816 will be summarized in the ISE, and data will be grouped by HCV genotype (1, 2, 3, 4, 5, or 6) and overall. Forest plots of SVR12 will be utilized to assess consistency of response by subgroup. The SAP for the ISE specifies the planned subgroup analysis and is included as Attachment 3.

Does the Agency concur with the proposed pooling and analysis strategy for the ISS and ISE?

FDA Response to Question 8: In general, we agree with your proposed pooling and analysis strategy for the ISS and ISE. We have the following additional comments:

- Please ensure ISS subgroup analyses will also include related TEAEs, ≥Grade 3 TEAEs, discontinuations due to AEs.

Question 9: As with recent NDA submissions to the Division, Gilead proposes to include ISE text within the Summary of Clinical Efficacy (Module 2.7.3) and ISS text within the Summary of Clinical Safety (Module 2.7.4).

The 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 9: Yes, the Division agrees with your proposed plan. Please ensure the Summary of Clinical Safety will include direct narrative hyperlinks for all

deaths, SAEs, discontinuations due to AEs, pertinent AEs of interest (e.g., liver-related events).

Question 10: The Summary of Clinical Safety (Module 2.7.4) will include analysis of AEs that may be of particular interest due to their prior association with nucleoside/nucleotide inhibitors or other DAA-based regimens. These AEs of interest and the analyses to be performed are described in the ISS SAP, Section 6.1.3 (Attachment 2).

Does the Agency agree with the proposed AEs of Interest and associated integrated analysis?

FDA Response to Question 10: In general we agree with the selected proposed AEs of interest. We have the following additional comments:

- Subjects in ASTRAL-4 experiencing any of the identified proposed AEs of Interest should also be included in the overall analyses and summaries.
- Please provide the number of subjects enrolled in the Phase 2/3 SOF/GS-5816-containing trials receiving concomitant amiodarone.
- The NDA should include a summary of change from baseline in heart rate at all treatment time points for patients on a stable beta blocker, stable calcium channel blocker, or neither of these concomitant medications. It is important to ensure subjects in this analysis do not have a change in their beta blocker or calcium channel blocker regimen while on treatment. This summary should include the median, 90th percentile, and maximum change from baseline (provided there are sufficient subjects for these assessments) to better characterize subjects with outlying decreases in heart rate while on treatment.
- The NDA should also provide cumulative distribution plots of maximum on treatment change from baseline in heart rate for patients on a stable beta blocker, stable calcium channel blocker, or neither of these concomitant medications.
- Narrative information for any subjects on beta blockers or calcium channel blockers who may have experienced arrhythmias, cardiac adverse events, syncope, or dizziness within the first two weeks of initiating HCV treatment should be provided with the NDA submission.

Question 11: Narratives will be provided for subjects in the Phase 2 studies and in the Phase 3 integrated safety population with on-treatment liver-related laboratory abnormalities. An analysis of the incidence of these events in the Phase 2 studies and in the Phase 3 integrated safety population will be provided in m2.7.4, and the datasets and narratives will reside in m5.3.5.3.

On-treatment liver-related laboratory abnormalities for subjects in the Phase 2 studies and in the Phase 3 integrated safety population will be defined consistent with eDISH specifications as:
a) ALT or AST>3xULN and total bilirubin >2xULN,
or
b) ALT>5xULN,

or
c) Total bilirubin >2xULN.

As the GS-US-342-1137 (ASTRAL-4) study enrolled subjects with decompensated liver disease, the above specifications are not suitable for identification of subjects with liver injury. (b) (4) Gilead proposes to use a single criterion of an increase from baseline in direct bilirubin > 1 mg/dL for identification of cases requiring narratives in the GS-US-342-1137 (ASTRAL-4) study. An analysis of the incidence of these events in the GS-US-342-1137 (ASTRAL-4) study and narratives for these events will be provided in the CSR.

In addition, Gilead will ask the independent adjudication committee (IAC) convened for the SOLAR studies to review GS-US-342-1137 (ASTRAL-4) data. The IAC will adjudicate all cases with an increase from baseline of direct bilirubin >1mg/dL as well as fatal events and events of hepatic failure for possible DILI. The cases reviewed by the IAC and their assessment of the incidence of DILI will be provided in the CSR.

Does the Agency agree with this proposal regarding analysis of on-treatment liver injury for subjects:
1. In the Phase 2 study populations and the Phase 3 integrated safety population?
2. In the GS-US-342-1137 (ASTRAL-4) study?

FDA Response to Question 11: In general, the Division agrees with your proposed plan. We have the following additional comments:

- Please ensure the individual narratives include a single graphical display of the following parameters over time: HCV viral load, ALT, AST, total bilirubin, direct bilirubin, albumin, prothrombin time, platelet count, treatment start and stop, concomitant medication start and stop, and adverse event start and stop (for any concurrent AEs).
- (b) (4) In addition, the subject discontinuing HCV treatment in GS-US-342-0109 (5730-61176) due to elevated ALT and GGT along with any other phase 2 or 3 enrolled subjects meeting the updated adjudication criteria should be reviewed by the IAC and the assessment included with the NDA.

Question 12: Datasets for Phase 1, Phase 2, and Phase 3 studies will be provided in SAS transport files (*.xpt). SDTM datasets will follow CDISC SDTM version 1.2 (12 November 2008) and CDISC SDTM IG version 3.1.2 (12 November 2008). ADaM datasets will follow CDISC ADaM Implementation Guide Version 1.0 (December 17, 2009) and Analysis Data Model (ADaM) Version 2.1 (December 17, 2009). Gilead intends to submit DEFINE.XML to ensure the traceability back to the original data elements in SDTM and ADaM datasets (Electronic Common Technical Document

(eCTD) Study Data Specification (Updated 6/2011, version 1.6). Gilead also intends to split datasets larger than 1GB according to the CDER Common Data Standards Issues Document (Version 1.0/May 2011). Gilead will submit additional standardized datasets ("HCV Template datasets") (b) (4) that strive to be "One Statistical Procedure Away" from the statistical results to reduce programming required by the statistical reviewers.

The initial SOF/GS-5816 NDA will contain ADaM datasets built from the SDTM datasets. All of the Tables, Figures, and Listings (TFLs) will be developed from the ADaM and SDTM datasets. Gilead will also include the non-executable programs (written under a Linux Operating System) that were used to create the ADaM datasets from the SDTM datasets and to generate TFLs.

For Phase 2 and 3 studies, the EPOCH variable will be in the SDTM domains listed by the Agency (b) (4)) (ie, adverse events, laboratory, concomitant medications, exposure, and vital signs). Additionally, baseline flags will be available for laboratory, vital signs, and ECG data; however, this flag is not relevant for PK concentration data and therefore will not be available in the PK concentration data.

Regarding population pharmacokinetic and pharmacodynamics analyses, the following datasets and codes/scripts will be provided for Reviewers to recreate modeling and simulations for the population pharmacokinetic and pharmacodynamics analyses:

- All datasets used for model development and validation will be submitted as SAS transport files (*.xpt). A description of each data item will be provided in a define.pdf file. Any datapoints and/or subjects that have been excluded from the analysis will be flagged and maintained in the datasets.
- Model codes or control streams and output listings will be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files will be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

Does the Agency have any comments regarding Gilead's proposal for structure and format of datasets for the NDA?

FDA Response to Question 12: Overall we agree with your proposal and have the following comments:

- Refer to the Study Data Technical Conformance Guide (March 2015): http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

- Provide sample datasets before final NDA submission
    - SDTM and ADaM and corresponding DEFINE.XML

Question 13: As described in Sections 4.3.5 and 4.4.1, Gilead proposes to submit SDTM, ADaM, HCV Template (standardized datasets that strive to be "One Statistical Procedure Away"), eDISH, ADVR (population sequencing), and NGS (deep sequencing) datasets to the Agency.

Table 4. Datasets Proposed to be Included in SOF/GS-5816 NDA

Study Phase	Standard SDTM/ ADaM Datasets	HCV Template Datasets	eDISH Datasets/ Narratives	ADVR Datasets	NGS Datasets
Phase 3	Yes	Yes	Yes	Yes	Yes
Phase 2	Yes	No	Yes	Yes	Yes
Phase 1	Yes	No	No	No	No

Does the Agency agree with the proposed scope for datasets to be submitted to the SOF/GS-5816 NDA?

FDA Response to Question 13: Yes, the Division agrees with your proposed plan.

2.4 Virology

Question 14: Gilead will summarize virology data and provide clinical virology listings in the CSRs for the individual Phase 2 (GS-US-342-0102, GS-US-342-0109, and GS-US-337-0122 [ELECTRON-2]) and Phase 3 (GS-US-342-1138 [ASTRAL-1], GS-US-342-1139 [ASTRAL-2], GS-US-342-1140 [ASTRAL-3], and GS-US-342-1137 [ASTRAL-4]) studies.

In addition, an integrated virology study report (VSR) for the Phase 2 studies (GS-US-342-0102, GS-US-342-0109, and GS-US-337-0122 [ELECTRON-2]), and an integrated VSR for the Phase 3 studies (GS-US-342-1138 [ASTRAL-1], GS-US-342-1139 [ASTRAL-2], GS-US-342-1140 [ASTRAL-3], and GS-US-342-1137 [ASTRAL-4]) will be provided in the SOF/GS-5816 NDA. A complete resistance dataset including consensus sequencing data (generated from deep sequencing using a 15% sensitivity cutoff) for the SOF/GS-5816 Phase 2 and 3 studies (ADVR) will be provided in the SOF/GS-5816 NDA. The resistance dataset (ADVR) of the same genotype from different studies will be integrated so that the pooled ADVR dataset per genotype will be provided. Virology and resistance datasets (ADVR) included in the NDA will be consistent with FDA's February 2013 draft *Guidance for Submitting HCV Resistance Data*.

Next generation sequencing (NGS) (deep sequencing) data will be provided for all subjects at baseline and at posttreatment timepoints for subjects with virologic failure in the SOF/GS- 5816 studies.

Does the Agency agree with the proposal for provision of virology data?

FDA Response to Question 14: Yes, we agree.

2.5 Labeling

Question 15: Section 505-1 of the Federal Food, Drug, and Cosmetic Act authorizes the FDA to require applicants submitting NDAs to submit and implement a Risk Evaluation and Mitigation Strategy (REMS) if necessary to ensure that the benefits of a drug outweigh the risks of the drug. An applicant may voluntarily submit a proposed REMS without having been required to do so or may be required to submit one if the Agency believes a REMS would be necessary to ensure that the benefits of the drug outweigh its risks. Based on the nonclinical and clinical information that has been previously submitted to IND 115670 (GS-5816) and IND 118605 (SOF/GS-5816), and pending the availability of the Phase 3 data, no risks have been identified that would require a REMS to ensure that the benefits of SOF/GS-5816 outweigh its risks; therefore, Gilead does not intend to include a REMS in the NDA for SOF/GS-5816.

Does the Agency agree that the currently available safety information for SOF/GS-5816 does not warrant inclusion of a REMS?

FDA Response to Question 15: At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.

2.6 CMC

Question 16: Gilead is committed to making SOF/GS-5816 tablets available in the developing world through the Gilead Access Program. The trade dress intended for the US market, along with the alternate trade dress that Gilead is developing for the Access program, is described in Table 5.

Table 5. SOF/GS-5816 Tablets – US and Alternate Trade Dress

Tablet Shape and	US Trade Dress	Alternate Trade Dress
Diamond-shaped tablet, 20.6 (L) X 10.4 (W) X 6.6 (T)	Debossing: GSI/7916 Color: Pink, (b) (4)	Debossing: GSI/7916 Color: Red, (b) (4)

Gilead plans to include in the NDA submission the required quality information in Module 3 for this alternate trade dress, including the required stability data to support the use of the tablet in climatic zones where the drug will be distributed as part of the Gilead Access Program. In Module 1 of the NDA, Gilead will include the container label and carton presentation for the Access presentation.

Does the Agency agree with this proposal?

FDA Response to Question 16: We agree, under the assumption that the quality information provided in the initial NDA submission to support the alternative trade dress will include stability data at 30°C/75%RH and comparative dissolution profiles.

2.7 Regulatory Review

Question 17: Per the CDER MAPP 6025.7 "*Good Review Practice: Review of Marketing Applications for Breakthrough Therapy-Designated Drugs and Biologics That Are Receiving an Expedited Review*," if a marketing application for a Breakthrough Therapy designated product is designated as a priority review, CDER review staff and managers will consider whether the marketing application qualifies for an expedited review; and a decision to conduct an expedited review should be made before the FDA internal premeeting before the presubmission meeting.

Given the Breakthrough Therapy designation for SOF/GS-5816 for the treatment of genotype 3, 4, 5, and 6 treatment-naïve patients with chronic hepatitis C infection, does the Agency support an expedited review of the SOF/GS-5816 marketing application?

FDA Response to Question 17: Due to the lack of Phase 3 efficacy and safety data submitted with your pre-NDA meeting briefing package, and due to important review issues outlined in our response to Question 1, we are unable to make a determination with regard to an expedited review at this time.

Question 18: Per 21 CFR 314.50(d)(5)(vi)(b), Gilead proposes to submit an NDA Safety Update Report 90 days (priority or expedited review) or 120 days (standard review) following the submission of the NDA in October 2015 for the clinical studies listed in Table 6.

Updated safety information from studies included in the original SOF/GS-5816 NDA will be provided as described below. Additionally, for SOF/GS-5816 studies that will be ongoing while the SOF/GS-5816 NDA is under review, Gilead intends to provide safety information to present a complete safety profile of SOF/GS-5816. Gilead does not intend to provide safety data from ongoing or completed studies of (b) (4) in the NDA Safety Update Report.

The NDA Safety Update Report will include an analysis of deaths, serious adverse events (SAEs), discontinuations due to adverse events, pregnancies, and selected adverse events and laboratories abnormalities of interest through the data cut-off dates as described in Table 6 for Gilead-sponsored studies in which subjects will be on treatment during the data cut-off. For any Phase 1 studies ongoing at the time of the NDA (and not included in the initial application), CIOMS II line listings, narratives, and CRFs will be provided for deaths, SAEs, and pregnancies. For non-Gilead-sponsored studies, CIOMS II line listings will be provided for deaths, SAEs, and pregnancies.

Table 6. List of Information for Inclusion in SOF/GS-5816 NDA Safety Update

Study Number	Study Title	Data Cut-Off
GS-US-342-1202 (ASTRAL-5)	A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 weeks in in Subjects with Chronic Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV)-1 Co-infection	October 2015
GS-US-342-1446[a]	An Open Label Study of Sofosbuvir/GS-5816 Fixed-Dose Combination in Subjects with Chronic HCV Infection	October 2015
GS-US-342-1553	An Open Label Study to Evaluate The Efficacy And Safety Of Sofosbuvir/GS-5816 Fixed Dose Combination With Ribavirin For 24 Weeks In Chronic HCV Infected Subjects Who Participated In A Prior Gilead Sponsored HCV Treatment Study	October 2015
		(b) (4)

a This clinical study is designed to provide treatment with SOF/GS-5816 for 12 week to subjects who received placebo in the GS-US-342-1138 (ASTRAL-1) study.

Does the Agency agree with the proposal for the timing and content of the NDA Safety Update Report?

FDA Response to Question 18: Yes, the Division agrees with your proposed plan. To facilitate review:

- Include information for the ASTRAL-1, -2, -3, -4 treatment population in a separate subsection distinct from updates for all other populations.
- Submit only new information for this population in the update with an integrated assessment of these events with those occurring in ASTRAL-1, -2, -3, -4 submitted previously in the sNDA.
- Submit information on deaths, SAEs, and specific safety adverse events of special interest. Also include a summary of any data available in these subpopulations from observational cohorts.
- Propose and include the rationale for any labeling changes based upon assessment of the Safety Update Report information. Alternatively, include the rationale if no labeling changes are proposed.

Please provide a timeline for expected EOT, SVR4, SVR12 data for the Table 6 trials not available for inclusion in the original NDA.

Question 19: As noted in Section 1 above, prior to the NDA filing, Gilead intends to request an additional Type B meeting with the Agency to share and discuss topline data from the Phase 3 studies ASTRAL-1, ASTRAL-2, ASTRAL-3, and ASTRAL-4; and to verify that they are supportive of the proposed indication. The proposed meeting will be requested to occur in October, and a briefing package containing an executive summary of the topline safety and efficacy data would be submitted in September (ie, 1 month before the meeting date).

Does the Agency agree with this proposal?

FDA Response to Question 19: We advise having an earlier additional Type B meeting (e.g., in September) to allow sufficient time to review the topline ASTRAL-1, ASTRAL-2, ASTRAL-3 and ASTRAL-4 data and identify key review issues that should be addressed in the planned NDA submission.

The briefing package, as well as the planned NDA submission, should include adequate efficacy and safety justification for the proposed dosing regimen(s) in the CPT B population and/or in certain genotypes (e.g., genotype 3) based upon the ASTRAL-4 data as described in our response to Question 1**,** addressing each of the identified major review issues. Additional NDA review issues may be identified following review of the submitted Phase 3 data.

In addition, the briefing package, as well as the planned NDA should also include the following SVR12 analyses for all the pivotal Phase 3 trials:

- Response by baseline NS5A polymorphisms
- Response by baseline HCV RNA
- Response by multiple baseline factors (cirrhosis, NS5A polymorphisms, high viral load)

Additional Division Comments

1. Please comment on planned labeling considerations for (b) (4) (b) (4). The NDA should contain adequate justification for any outcome data proposed in labeling.

2. Optional pharmacovigilance plan:
   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.

3. Refer to CDER Clinical Review Template:

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP 6010.3R) http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM236903.pdf

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 1, 2015 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance

below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

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

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

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

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

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.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the **site level dataset is voluntary** and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is

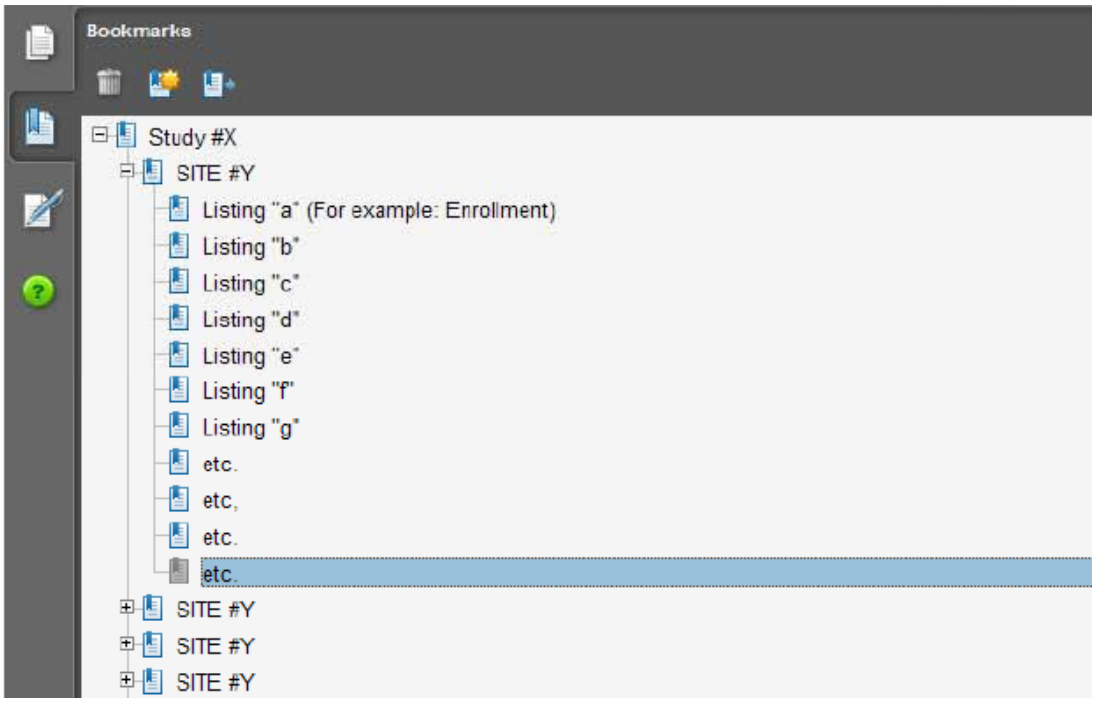
maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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/s/

NINA MANI
05/19/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118605

GRANT –
BREAKTHROUGH THERAPY DESIGNATION

Gilead Sciences, Inc.
Attention: Jennifer Huber, M.S.
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Huber:

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-5816 fixed dose combination tablet.

We also refer to your April 8, 2015, request for Breakthrough Therapy designation indicating your intent to continue the breakthrough therapy designation drug development program for sofosbuvir/GS-5816 fixed dose combination for the treatment of chronic hepatitis C (CHC) in genotypes 3, 4, 5, and 6 treatment-naïve patients[1]. We are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of the sofosbuvir/GS-5816 fixed dose combination for the treatment of chronic hepatitis C in genotypes 3, 4, 5, and 6 treatment-naïve patients to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the draft *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.*[2]

When breakthrough therapy designation is granted, sponsors are asked to submit a Type B meeting request for a multidisciplinary comprehensive discussion of the drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. We note your Pre-New Drug Application meeting scheduled for May 26, 2015. We will also use this meeting as the initial breakthrough therapy meeting. Please refer to

[1] Our April 1, 2015, letter rescinded the breakthrough designation for the treatment of CHC genotype 1 treatment naïve patients.
[2] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics,* Attachment 1, for potential topics for discussion at this initial breakthrough therapy meeting[3]. If you have already submitted your meeting package, please contact the Regulatory Project Manager noted below to determine if any additional information is required in order to allow for a full discussion of the overall drug development plan.

If the breakthrough therapy designation for sofosbuvir/GS-5816 fixed dose combination for the treatment of chronic hepatitis C in genotypes 3, 4, 5, and 6 treatment-naïve patients is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Linda C. Onaga, MPH, Senior 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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[3] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

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/s/

DEBRA B BIRNKRANT
05/15/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118605

RESCIND –
BREAKTHROUGH THERAPY DESIGNATION

Gilead Sciences, Inc.
Attention: Nicole Inocencio
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Inocencio:

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-5816 fixed dose combination tablet.

We also refer to our April 22, 2014, letter granting Breakthrough Therapy designation to sofosbuvir/GS-5816 fixed dose combination tablet for the treatment of chronic hepatitis C (CHC) in genotypes 1, 3, 4, 5, and 6 treatment naïve patients and our February 4, 2015 Intent to Rescind Breakthrough Therapy designation letter. We are rescinding this Breakthrough Therapy designation and any associated Rolling Review agreements for the treatment of CHC genotype 1 treatment naïve patients because the criteria for designation are no longer being met for the following reasons:

- Treatment with recently approved regimens, Harvoni and Viekira Pak, demonstrate SVR12 rates in patients with chronic hepatitis C genotype 1 infection ranging from 94-100% depending on prior treatment history and genotype 1 subtype (1a or 1b). The data you have provided to support sofosbuvir/GS-5816 fixed dose combination tablet no longer demonstrates substantial improvement in SVR12 rates compared to these currently available therapies for CHC genotype 1 infection.

- Overall the safety profiles of Harvoni and Viekira Pak are favorable. Discontinuation rates due to adverse events are $\leq 1\%$ even when ribavirin is included in one of the regimens. While your sofosbuvir/GS-5816 fixed dose combination tablet product may show an incremental benefit in terms of frequency or type of adverse events or laboratory abnormalities, a substantial improvement in the safety profile over available therapies is no longer demonstrated.

Please submit a cover letter indicating your intent to continue the breakthrough therapy designation drug development program for sofosbuvir/GS-5816 fixed dose combination tablet for the treatment of CHC in genotypes 3, 4, 5, and 6 treatment naïve patients. A new breakthrough therapy designation granted letter will be issued for this portion of the designation

previously granted on April 22, 2014. No additional information or supporting documents are required.

For further information regarding Breakthrough Therapy designation, refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf)

If you have any questions, contact Linda C. Onaga, Senior 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
04/01/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118605

INTENT TO RESCIND –
BREAKTHROUGH THERAPY DESIGNATION

Gilead Sciences, Inc.
Attention: Nicole Inocencio
Associate Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Inocencio:

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-5816 fixed dose combination tablet.

We also refer to our April 22, 2014, letter granting Breakthrough Therapy designation to sofosbuvir/GS-5816 fixed dose combination for the treatment of chronic hepatitis C in genotypes 1, 3, 4, 5, and 6 treatment-naïve patients. We are notifying you of our intent to rescind this Breakthrough Therapy designation for the treatment of chronic hepatitis C in genotype 1 treatment-naïve patients because the criteria for designation are no longer being met for the following reasons:

- Treatment with recently approved regimens, Harvoni and Viekira Pak, demonstrate SVR12 rates in patients with chronic hepatitis C genotype 1 infection ranging from 94-100% depending on prior treatment history and genotype 1 subtype (1a or 1b). The data you have provided to support sofosbuvir/GS-5816 fixed dose combination tablet no longer demonstrates substantial improvement in SVR12 rates compared to these currently available therapies for CHC genotype 1 infection.

- The safety profiles of Harvoni and Viekira Pak are favorable. Discontinuation rates due to adverse events are $\leq 1\%$ even when ribavirin is included in one of the regimens. While your sofosbuvir/GS-5816 fixed dose combination tablet product may show an incremental benefit in terms of frequency or type of adverse events or laboratory abnormalities, a substantial improvement in overall safety profile over available therapies is no longer demonstrated.

You have 60 days to provide additional data and justification to support continuing Breakthrough Therapy designation for sofosbuvir/GS-5816 fixed dose combination tablet for treatment of

chronic hepatitis C in genotype 1 treatment-naïve patients. You may also request a meeting with the FDA during this 60 day time frame to discuss Breakthrough Therapy designation for this drug. Please contact the Regulatory Health Project Manager to discuss how you plan to respond to our intent to rescind this designation.

Breakthrough therapy designation for sofosbuvir/GS-5816 fixed dose combination tablets will remain for the treatment of chronic hepatitis C infection in naïve patients with genotypes 3, 4, 5, and 6.

For further information regarding Breakthrough Therapy designation, refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf)

If you have any questions, contact 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
02/04/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118605

MEETING MINUTES

Gilead Sciences, Inc.
Attention: Sharon Casey, M.S.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Casey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sofosbuvir (SOF)/GS-5816 fixed-dose combination tablets, 400mg/100 mg.

We also refer to the meeting between representatives of your firm and the FDA on June 5, 2014. The purpose of the meeting was to discuss the Phase 3 development program and the proposed registration plan to support a pangenotypic indication for SOF/GS-5816 fixed-dose combination tablet.

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, Senior 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

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, 2014 9:30 AM – 11:00 AM
Meeting Location:	10903 New Hampshire Ave Bldg 22, Room 1415 Silver Spring, MD 20993
Application Number:	IND 118605
Product Name:	Sofosbuvir/GS-5816 fixed dose combination tablet
Proposed Indication:	[TRADENAME] is indicated for the treatment of chronic HCV in adults
Sponsor/Applicant Name:	Gilead Sciences, Inc.
Meeting Chair:	Debra Birnkrant, MD
Meeting Recorder:	Linda C. Onaga, MPH

FDA ATTENDEES

1. Edward Cox, MD, MPH, Director, Office of Antimicrobial Products (OAP)
2. David Roeder, MS, Associate Director, Regulatory Affairs, OAP
3. Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
4. Jeffrey Murray, MD, MPH, Deputy Director, DAVP
5. Poonam Mishra, M.D., Clinical Reviewer, DAVP
6. Sarah Connelly, M.D., Clinical Reviewer, DAVP
7. Kimberly Struble, Pharm.D., Clinical Team Leader, DAVP
8. Stanley Au, Pharm.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology IV (DCPIV)
9. Shirley Seo, PhD, Clinical Pharmacology Team Lead (DCPIV)
10. Lisa Naeger, PhD, Clinical Virology Reviewer, DAVP
11. Eric Donaldson, PhD, Clinical Virology Reviewer, DAVP
12. Julian O'Rear, PhD, Clinical Virology Team Lead, DAVP
13. Pritam Verma, PhD, Pharmacology Toxicology Reviewer, DAVP
14. Chris Ellis, PhD, Acting Pharmacology Toxicology Team Lead, DAVP
15. Jeffry Florian, Ph.D., Pharmacometrics Reviewer, OCP
16. Karen Qi, Ph.D., Biometrics Reviewer, Division of Biometrics IV (DBIV)
17. Greg Soon, Ph.D., Biometrics Team Leader, DBIV
18. William Tauber, Acting Deputy Director of Safety, DAVP

19. Monica Calderon, PharmD, BCPS, Reviewer, DMEPA
20. Karen Winestock, Chief, Project Management Staff, DAVP
21. Linda C. Onaga, M.P.H., Regulatory Project Manager, DAVP

SPONSOR ATTENDEES

1. John McHutchison, MD Executive Vice President, Clinical Research
2. Mani Subramanian, MD, PhD Vice President, Clinical Research
3. Diana Brainard, MD Senior Director, Clinical Research
4. John McNally, PhD Director, Clinical Research
5. Roy Bannister, PhD, DABT Senior Director, Drug Safety Evaluation (Toxicology)
6. Anita Mathias, PhD Director, Clinical Pharmacology
7. Jenny Svarovskaia, PhD Senior Research Scientist II, Clinical Virology
8. Neby Bekele, PhD Senior Director, Biostatistics
9. Paul Tomkins, PhD Senior Director, Regulatory Affairs
10. Sharon Casey, MS Associate Director, Regulatory Affairs

1.0 BACKGROUND

Gilead Sciences, Inc. (Gilead) is developing a fixed-dose combination (FDC) tablet containing Sovaldi (sofosbuvir, SOF) and GS-5816, an investigational product for the treatment of chronic hepatitis C infection in adults. Sovaldi is a nucleotide NS5B polymerase inhibitor currently approved in the U.S. for the treatment of genotype 1, 2, 3, and 4 chronic hepatitis C infection with different regimens and durations. GS-5816 is a NS5A inhibitor with antiviral activity across six genotypes.

Gilead planned three Phase 3 trials to support the initial new drug application (NDA) for the SOF/GS-5816 FDC. The trials, GS-US-342-1140, GS-US-342-1138, and GS-US-342-1137 are multicenter, randomized, placebo controlled or open-label studies to investigate the efficacy and safety of SOF/GS-5816 FDC in treatment-naïve and treatment-experienced, genotype 1-6, HCV-infected subjects. GS-US-342-1140 is an open-label study comparing SOF/GS-5816 for 12 Weeks to SOF/RBV for 24 Weeks in subjects with chronic genotype 3 HCV infection. GS-US-342-1137 is an open-label study evaluating SOF/GS-5816 with and without RBV for 12 weeks and SOF/GS-5816 for 24 weeks in subjects with chronic genotype 1-6 HCV Infection and Child-Pugh class B cirrhosis. GS-US-342-1138 is a double-blind, placebo-controlled study evaluating the FDC for 12 weeks in subjects with chronic genotype 1, 2, 4, 5, and 6 infection.

On April 22, 2014, the Division of Antiviral Products granted Breakthrough Therapy Designation for SOF/GS-5816 FDC for the treatment of chronic hepatitis C in genotypes 1, 3, 4, 5, and 6 treatment-naïve patients.

Gilead requested a type B End-of-Phase 2 meeting with the Division of Antiviral Products to discuss the SOF/GS-5816 Phase 3 development program and proposed registration plan to support a pangenotypic indication for the FDC.

The objectives of this meeting are:

1. To seek agreement with the Agency on the proposed Phase 3 clinical studies that will support the proposed indication for SOF/GS-5816 for the treatment of chronic HCV infection in adults.
2. To seek agreement with the Agency on the planned toxicology program that will support registration of the FDC
3. To seek agreement with the Agency on the planned clinical pharmacology program that will support registration of the FDC

2. DISCUSSION

This meeting focused on the Division's responses to Questions 1 and 3.

2.1. Question 1: Phase 3 Development Plans

Does the Agency agree that the Phase 3 development plan is adequate to support the proposed indication for SOF/GS-5816?

Specifically, Gilead seeks the Agency's comments on the following:

a) The protocol designs for the Phase 3 studies.
b) The protocol-specified statistical analyses for the Phase 3 studies.
c) The enrollment targets for subjects with HCV genotypes 4, 5, and 6.

FDA Response to Question 1:

1. Please provide further details on your overall drug development strategy for SOF/GS-5816. (b) (4)

2. We have the following recommendations for the proposed Phase 3 development program.

   Study GS-US-342-1138:

   - We recommend you conduct two separate trials; one for genotypes 1, 4, 5, and 6 subjects, and a second trial in genotype 2 subjects.
   - For genotype 1, we recommend you conduct a non-inferiority trial comparing SOF/LDV to SOF/GS-5816. We acknowledge that SOF/LDV FDC is still under review; however, comparative effectiveness trials are important and informative and you are in the unique position to conduct this comparative trial. Within this trial you could enroll genotype 4, 5, and 6 subjects and all subjects can receive SOF/5816 regimen. The proposed enrollment targets for genotype 4, 5, and 6 appear appropriate.

   - For genotype 2, we recommend you conduct a non-inferiority trial comparing SOF/GS-5816 to SOF/RBV. SOF/RBV is the current standard of care

treatment for genotype 2 HCV patients and a comparative trial evaluating the two therapies should be conducted.

- In both trials we recommend you enroll 50% treatment-experienced subjects and at least 30% cirrhotic subjects to achieve adequate number of subjects in these "harder-to-treat" subpopulations

Study GS-US-342-1140:

- Based on the available efficacy data in genotype 3 subjects, we recommend you evaluate a longer treatment duration (>12 weeks) to optimize SVR rates in this "harder-to-treat" patient population such as subjects with cirrhosis.

- We recommend you modify the recruitment criteria and include 50% of treatment-experienced subjects and at least 30% cirrhotic subjects

3. Based on the above comments, please revise your protocol designs, including statistical considerations accordingly.

4. Please provide, if available, the SVR12 data in genotype 1 PI-failure subjects evaluated in trial GS-US-342-0109.

Discussion:

Drug Development Strategy GS5816/SOF and LDV/SOF:

Gilead discussed their rationale for the Phase 3 protocol designs. Their goal was to create a simple regimen to treat hepatitis C infection globally, regardless of genotype. Gilead noted that in many countries tests to determine HCV genotype/subtype are not conducted. (b) (4) Both products could be on the market simultaneously. If approved, LDV/SOF will be a viable treatment option for patients with genotype 1, HCV infection in the US, while GS-5816/SOF FDC is considered the pangenotypic product, treating patients with genotype 1-6, chronic HCV infection (b) (4) Gilead stated for genotype 1 HCV-infected patients, there is no advantage switching from the LDV FDC to the GS-5816 FDC.

Study GS-US-342-1138:

Gilead reviewed the Division's response regarding Study GS-US-342-1138. Feasibility was cited as the biggest reason subjects with genotype 2 were included in this trial. Gilead noted that, even with aggressive recruitment and intensive strategies, treatment experienced, genotype 2 patients with cirrhosis are becoming more difficult to find, especially with the recent approval of SOVALDI (sofosbuvir) in December 2013. (b) (4) it was still difficult to find patients. With this knowledge, there was a lack of confidence that a randomized clinical trial

of 240 patients with genotype 2, chronic HCV could be conducted in a timely manner. Therefore, Gilead proposed to enroll 120 genotype 2, HCV subjects into the 1138 trial.

Gilead proposed to conduct a separate open-label trial comparing GS-5816/SOF and SOF/RBV in genotype 2 patients. This separate study will most likely not be included in the NDA package.

The Division found this approach reasonable and understood the recruitment challenges related to treatment experienced, genotype 2 subjects. A comparative study would be beneficial to clinicians so they can compare relapse rates. The Division recommended that genotype 2 patients randomized to the placebo arm of Study1138 study can roll-over into the open label study and receive a SOF-containing regimen (GS-5816/SOF or SOF/RBV).

Gilead will incorporate this recommendation into the design of the second study.

Study GS-US 342-1140

After review of the Phase 2 data, Gilead proposed a 12 week treatment regimen of GS-5816/SOF FDC without ribavirin. The data showed 126/132 genotype 3 treatment naive and 48/52 (92%) genotype 3 treatment experienced subjects achieved SVR.

The Division acknowledged the low relapse rate, but recommended Gilead evaluates longer treatment duration to minimize the relapse rate. Enriching the study with genotype 3 treatment experienced patients and patients with cirrhosis could answer the question about duration, but the Division would like to review Gilead's proposal.

Gilead will revise the protocol and submit to the Division for review.

Study GS-US-342-1137

Gilead is committed to enrolling genotype 2/3 subjects, however, these populations are becoming more difficult to find. The enrollment percentages of treatment experienced and cirrhotic subjects are not "caps", but more target percentages. They will not cap enrollment of these populations.

Gilead has 25 sites that will enroll 2 out of the 3 studies and 10 sites will do the other. Approximately 2/3 of the sites are ex-US. Study 1137 will have sites only in the U.S. There will be no restrictions on the number of cirrhotic subjects enrolled and Gilead plans to provide incentives to sites to enroll treatment-experienced and cirrhotic subjects.

2.2. Question 3: Nonclinical Program

Does the Agency agree that the completed and planned nonclinical toxicology studies conducted with SOF and GS-5816 are adequate to support the registration of SOF/GS-5816?

FDA Response to Question 3:

1. In general, the Agency agrees that the completed and planned nonclinical toxicology program for SOF and GS-5816 are adequate. However, GS-5816 exposure in the rabbit embryo-fetal development study was not sufficient (*i.e*. exposure in rabbits was less than that in humans at the dose level selected for Phase 3 trials). Therefore, we recommend that you conduct an additional embryo-fetal developmental study (evaluating higher GS-5816 exposures) to support approval. For example, you could consider conducting a study in rabbits using an IV formulation or you may choose to select a different species altogether.

Discussion:

Gilead acknowledged the poor GS-5816 exposure achieved in the pivotal rabbit oral embryo-fetal development study. Given the poor solubility of GS-5816 and issues related to the appropriateness of using organic intravenous formulations in embryo-fetal development studies, Gilead proposed to conduct an oral embryo-fetal development study with GS-5816 in mice (instead of conducting the study in rabbits with an intravenous formulation). Gilead stated that they anticipate achieving high GS-5816 exposure in mice compared to human exposures expected at the dose level selected for their Phase 3 trials. .

The Division acknowledged the issues with the solubility of GS-5816 and restated a preference of achieving animal drug exposure greater than that expected in humans. The Division also stated a willingness to consider Gilead's proposal to conduct the study in mice and asked Gilead to provide additional data to the Division. Gilead agreed to provide additional data and justification to the Division to support conducting the study in mice. The Division agreed to review Gilead's proposed alternative study plan and provide additional feedback.

2.3 Additional Discussion

Gilead will provide written responses to the Division's additional comments, including the clinical pharmacology comments. Gilead plans to evaluate HCV-HIV co-infected adults during the Phase 3 development program.

3.0 PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End

of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

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

4.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and 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 clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical 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: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

5.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

6.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

7.0 ACTION ITEMS

Action Item/Description	Owner
Written response to FDA preliminary comments	Gilead
Submit new protocol to evaluate the GS-5816/SOF FDC in genotype 2 patients	Gilead
Submit protocol amendment for GS-US-342-1137 which address relapse rate	Gilead
Modify recruitment criteria to include 50% treatment experienced and 3% cirrhotic subjects	Gilead
Submit an embryo fetal development study in mice.	Gilead
Submit supportive data for the embryo fetal devilment study in mice	Gilead

8.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

DEBRA B BIRNKRANT
07/02/2014

CDER Medical Policy Council Brief
Breakthrough Therapy Designation
Division of Antiviral Products
May 16, 2014

Summary Box

1. IND 118,605
2. Gilead Sciences, Inc
3. GS-5816/sofosbuvir Fixed-Dose Combination Tablets
4. Indication: Treatment of Chronic Hepatitis C
5. GS-5816/sofosbuvir is intended to treat a serious or life-threatening disease or condition.
6. The preliminary clinical evidence indicates that the drug combination of GS-5816/sofosbuvir may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints (safety and efficacy).

1. Brief description of the drug

GS-5816 is a direct acting antiviral (DAA) being developed for the treatment of chronic hepatitis C virus (HCV) infection. GS-5816 is an HCV NS5A replication complex inhibitor (also referred to as an "NS5A inhibitor"). Currently, no NS5A replication complex inhibitors are approved. GS-5816 has antiviral activity against genotype 1 through 6 for which this Breakthrough Therapy Designation request applies. This Breakthrough request is specific to the combination regimen of GS-5816 and sofosbuvir (SOF, Sovaldi™, marketed by Gilead) a uridine nucleotide analog inhibitor of HCV NS5B RNA-dependent RNA polymerase. SOF has nanomolar antiviral activity against HCV genotypes 1 through 6. SOF is approved for treatment of chronic hepatitis C infection as a component of a combination antiviral treatment regimen (with pegylated interferon and ribavirin, or with ribavirin). SOF efficacy was established in subjects with HCV genotype-1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection.

Gilead is applying for Breakthrough Therapy Designation for GS-5816/SOF fixed dose combination based on phase 2 data from trial GS-US-342-0102 (further detailed in section 6) for treatment of genotype (b) (4) (b) (4) HCV infection in subjects who are treatment-naive. DAVP agrees that the GS-5816/SOF fixed dose combination meets the standards for Breakthrough Therapy Designation for treatment-naïve subjects with genotypes 1, 3, 4, 5 and 6. (b) (4) (b) (4)

(b) (4) however, SVR12 data is the primary endpoint and is required for the Division to make assessments.

2. Brief description of the disease and intended population

Approximately 2.7 million people in the United States and 170 million worldwide have chronic HCV infection, which can lead to cirrhosis and hepatocellular carcinoma[1]. Chronic hepatitis C is currently the most common reason for liver transplantation in the United States. A recent CDC analysis of death certificate data found that HCV-attributable deaths increased significantly between 1999 and 2007. CDC estimates that there were 15,106 deaths caused by HCV in 2007. HCV now surpasses HIV as a cause of death in the United States. Cirrhosis is the 12th leading cause of death in the US, but 4th among those ages 45 to 54 years old.[2] The Division considers chronic HCV infection a serious and life-threatening condition.

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

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

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

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

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

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

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

4. Brief description of available therapies (if any)

The following table provides a brief summary of available therapies specifically for treatment of genotype 1, 2, and 3 HCV. Please note that all regimens contain pegylated interferon and ribavirin (PegIFN/RBV), except for SOF/RBV indicated for HCV genotype 1 infected subjects ineligible for a PegIFN/RBV containing regimen, and for HCV genotypes 2 and 3. Of note, no current approved therapies are available for genotypes 5 and 6.

Treatment Regimen	Duration	Approved Indication	SVR rates
Sofosbuvir/PegIFN/RBV	12 weeks	GT1	GT1 Overall: 89%* 1a: 92% 1b: 82%
Sofosbuvir/RBV	12 weeks	GT2	Tx-naïve: 93-97% Tx-experienced: 82- 90%
Sofosbuvir/RBV	24 weeks	GT1 ineligible for PR	GT1 Overall: 66% - 76%
Sofosbuvir/RBV	24 weeks	GT3	Tx-naïve: 93% Tx-experienced: 77%
Simeprevir/PegIFN/RBV	24-48 weeks	GT1	Tx-naïve: 80% Tx-experienced†:53%-79%
Telaprevir/PegIFN/RBV	24-48 weeks (Response Guided Therapy)	GT1	Tx-naïve: 74-79% Tx-experienced†:32%-86%
Boceprevir/PegIFN/RBV	28-48 weeks (Response Guided Therapy)	GT1	Tx-naïve: 63% Tx-experienced†: 38%-59%

GT=genotype

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

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

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

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

Sponsor	DAA Combination	BT Designation	Date
(b) (4)			
Gilead	SOF/ledipasvir FDC	GT 1 HCV	July 22, 2013
Gilead	SOF (with RBV)	GT 1, 2, and 3 HCV	October 10, 2013
(b) (4)			

GT= genotype

(b) (4)

FDC= fixed dose combination

6. Description of preliminary clinical evidence

Data from (b) (4) phase 2 trial (b) (4) GS-US-342-0102 (b) (4) are provided to support the request for Breakthrough Designation. In brief, GS-US-342-0102 is an ongoing open-label trial evaluating the safety and efficacy of GS-5816/SOF with and without RBV for 8 or 12 weeks in treatment-naïve, non-cirrhotic subjects with genotype 1-6 HCV infection. The trial design is presented in the table below. Of note, data on the 8 week regimens were not available; however, sufficient information from the 12 week regimen was available for consideration.

Table 1. GS-US-342-0102: Study Design

Treatment Group	N	HCV Genotype	Study Drugs Administered	Treatment Duration (weeks)
1	27	1	SOF 400mg + GS-5816 25mg	12
2	28	1	SOF 400mg + GS-5816 100mg	12
3	27	3	SOF 400mg + GS-5816 25mg	12
4	28	3	SOF 400mg + GS-5816 100mg	12
5	23	2,4,5, 6	SOF 400mg + GS-5816 25mg	12
6	22	2,4,6	SOF 400mg + GS-5816 100mg	12
7	30	1	SOF 400mg + GS-5816 25mg	8
8	30	1	SOF 400mg + GS-5816 25mg +RBV	8
9	29	1	SOF 400mg + GS-5816 100mg	8
10	31	1	SOF 400mg + GS-5816 100mg +RBV	8
11	26	2	SOF 400mg + GS-5816 25mg	8
12	25	2	SOF 400mg + GS-5816 25mg +RBV	8
13	26	2	SOF 400mg + GS-5816 100mg	8
14	26	2	SOF 400mg + GS-5816 100mg +RBV	8

Overall, the efficacy results from this trial showed that the combination of GS5816/SOF in treatment-naïve subjects with HCV genotype 1, 4, 5 and 6 were high (86-100% SVR12). Only 1 true virologic failure was observed in a genotype 1 subject. The SVR results achieved in treatment-naïve subjects were similar for both GS5816 dose groups (25 mg and 100 mg). Although the SVR12 rate was < 90% for the 100 mg dose group in genotype 4 subjects, no subjects reported a virologic failure. The SVR12 rate was affected by one subject lost to follow-up. Despite the limited number of subjects with genotype 5 and 6, we consider the amount of data acceptable given this genotype is rare in the US, no current therapies are approved and the preliminary SVR12 rates (100%) are encouraging. The following table provides the efficacy results from the treatment Genotype 1, 4, 5 and 6 groups.

Table 2 GS-US-342-0103: Preliminary SVR12 Results for SOF/GS5816 for 12 Weeks

	Genotype 1[a]		Genotype 4		Genotype 5	Genotype 6	
	SOF 400mg+ GS-5816 25 mg N=27	SOF 400mg+ GS-5816 100 mg N=28	SOF 400mg+ GS-5816 25 mg N=7	SOF 400mg+ GS-5816 100 mg N=7	SOF 400mg+ GS-5816 25 mg N=1	SOF 400mg+ GS-5816 25 mg N=4	SOF 400mg+ GS-5816 100 mg N=5
SVR12	96% (26/27)	100% (28/28)	100% (7/7)	86% (6/7)	100% (1/1)	100% (4/4)	100% (5/5)
Virologic failure	4% (1/27)	0	0	0	0	0	0
Other	0	0	0	1 (1/7)[b]	0	0	0

[a]80% and 20% had genotype 1a and 1b HCV infection, respectively

[b]subject 6007 is lost to follow-up

(b) (4)

In treatment-naïve genotype 3 subjects, the SVR rate for GS-5816/SOF for 12 weeks is similar to SOF + RBV for 24 weeks in genotype 3 subjects. The GS-5816/SOF regimen is 12 weeks shorter and therefore represents an improvement over existing therapy.

Table 3 GS-US-342-0103: Preliminary SVR12 Results for SOF/GS5816 for 12 Weeks

(b) (4)

	Genotype3	
	SOF 400mg+ GS-5816 25 mg N=27	SOF 400mg+ GS-5816 100 mg N=27
SVR12	93% (25/27)	93% (25/27)
Virologic failure	7% (2/27)	7% (2/27)
Other	0	0

(b) (4)

(b) (4)

(b) (4)

. Gilead's request for Breakthrough Designation for these populations is premature and can be considered at a later date once the SVR12 data are available.

Overall, the GS-5816/SOF combination appears well tolerated. One death due to suicide occurred in one subject with underlying severe psychiatric disease and not considered related to study drug. The most common AEs were fatigue and headache. GS-5816/SOF regimen has improved safety and tolerability compared to the approved regimens containing PegIFN/RBV.

7. Division's recommendation and rationale

In conclusion, the Breakthrough Designation for GS-5816/SOF, an all oral, interferon and ribavirin-free treatment regimen for genotype 1, 3, 4, 5, and 6 treatment-naïve subjects is supported by the following:

1. GS-5816 has a novel mechanism of action that represents a previously untargeted pathway. Currently, there are no other approved NS5A replication complex inhibitors
2. The overall SVR rate of 86-100% was achieved in genotype 1,3, 4, 5, and 6 with only one true virologic failure reported
3. The all-oral combination provides a simple one pill once-daily treatment regimen
4. The safety profile of GS-5816/SOF is promising and avoids the toxicities of IFN and RBV such as significant cytopenias, flu-like syndromes, mood disorders, depression, anemia and the potential for teratogenicity (avoidance of pregnancy for both males and females during treatment and for 6 months post-administration)

Based on the data available, DAVP believes GS-5816/SOF regimen meets the definition of Breakthrough Therapy for the treatment of chronic hepatitis C in genotype 1, 3, 4, 5, and 6 treatment-naïve patients as outlined in Section 903 of the Food and Drug Administration Safety and Innovation Act, and recommends GS-5816/SOF be given the specified Breakthrough Therapy Designation.

(b) (4)

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

The Division plans to work with the Sponsor to fully review and provide guidance for their planned development program GS-5816/SOF. An end of phase 2 meeting with Gilead is planned for June 2014.

9. References

1. Denniston MM, Jiles RB, Drobeniuc J, Klevens RM, Ward JW, McQuillan GM, et al. Chronic Hepatitis C Virus Infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. Ann Intern Med 2014;160:293-300.
2. Deaths. Preliminary Data for 2007. National Vital Statistics Report 2009: 58.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118605

GRANT –
BREAKTHROUGH THERAPY DESIGNATION

Gilead Sciences, Inc.
Attention: Sharon M. Casey, M.S.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Casey:

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-5816 fixed dose combination tablet.

We also refer to your March 24, 2014, request for Breakthrough Therapy designation. We have reviewed your request and have determined that sofosbuvir/GS-5816 fixed dose combination for the treatment of chronic hepatitis C in genotypes 1, 3, 4, 5, and 6 treatment-naïve patients meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of sofosbuvir/GS-5816 fixed dose combination for the treatment of chronic hepatitis C in genotypes 1, 3, 4, 5, and 6 treatment-naïve patients to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the draft *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.*[1]

When breakthrough therapy designation is granted, sponsors are asked to submit a Type B meeting request for a multidisciplinary comprehensive discussion of the drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy.

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

We note your End-of-Phase 2 meeting scheduled for June 5, 2014. We will also use this meeting as the initial breakthrough therapy meeting. Attachment 1 lists potential topics for discussion at this initial breakthrough therapy meeting. If you have already submitted your meeting package, please contact the Regulatory Project Manager noted below to determine if any additional information is required in order to allow for a full discussion of the overall drug development plan.

If the breakthrough therapy designation for sofosbuvir/GS-5816 fixed dose combination for the treatment of chronic hepatitis C in genotypes 1, 3, 4, 5, and 6 treatment-naïve patients is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Linda C. Onaga, MPH, Senior 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

Attachments:

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

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

General/Regulatory:

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

Clinical Activity and Data Analysis:

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

- Pre-approval
- Post-approval

➢ Plans to mitigate/minimize risk, proposed Risk Evaluation and Mitigation Strategy (REMS)

- Specific Populations
  - ➢ Dose, study design, efficacy endpoints, size and composition of population, additional safety trials, for populations such as:
    - Geriatrics
    - Pediatrics
    - Hepatically/Renally Impaired
  - ➢ Proposed pediatric development plan with outlines/synopses of additional studies.

Clinical Pharmacology and Pharmacokinetics:

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

Nonclinical Pharmacology, Pharmacokinetics, and Toxicology

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

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

- Evidence of mechanism of action
- Safety pharmacology, where appropriate

- Disease specific animal models

Chemistry, Manufacturing, and Controls:

- Drug product:
  - Dosage form
  - Formulation description
  - Administration instructions, delivery systems (e.g. vials, pre-filled syringes, etc.) proposed draft packaging, and disposal instructions
  - Critical quality attributes
  - Control and stability strategies
  - Proposed shelf life and required stability studies

- Drug substance:
  - Characterization
  - Critical quality attributes
  - Control and stability strategies
  - Proposed shelf life or retest period and required stability studies

- Proposed commercial processes:
  - Manufacturing process, in process controls, scale-up plans
  - Comparison of proposed commercial manufacturing processes to clinical manufacturing processes
  - Physico-chemical comparability of lots used in clinical studies and commercial lots or a plan to establish analytical comparability
  - Current manufacturing site(s) and proposed commercial site(s), if different, registration numbers, readiness, and manufacturing timelines
  - Current release and stability testing site(s) and proposed commercial testing site(s), if different
  - Anticipated market demand at launch

- Proposed validation approaches:
  - Drug substance and drug product manufacturing process
  - Microbial control and sterility assurance
  - Viral clearance
  - Analytical methods

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/s/

DEBRA B BIRNKRANT
04/22/2014

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208341

LATE-CYCLE MEETING MINUTES

Gilead Sciences, Inc.
Attention: Prachi Shah, MBS, RAC
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Shah:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sofosbuvir/velpatasvir tablets, 400 mg/ 100 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on April 19, 2016.

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, Senior Regulatory Project Manager at (301) 796-0759 or (301)796-1500.

Sincerely,

{See appended electronic signature page}

Kimberly Struble, Pharm D
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: April 19, 2016
Meeting Location: Teleconference

Application Number: NDA 208341
Product Name: sofosbuvir/velpatasvir
Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Kim Struble, PharmD
Meeting Recorder: Linda C Onaga, MPH

FDA ATTENDEES

1. John Farley, MD, Deputy Director, Office of Antimicrobial Products (OAP)
2. Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
3. Jeffrey Murray, MD, MPH, Deputy Director, DAVP
4. Kim Struble, Pharm D, Cross-Discipline Team Lead, DAVP
5. Prabha Viswanathan, MD, Clinical Reviewer, DAVP
6. Sarah Connelly, MD, Clinical Reviewer, DAVP
7. Jenny Zheng, PhD, Clinical Pharmacology Reviewer, OCP, DCPIV
8. Shirley Seo, Clinical Pharmacology Team Lead, OCP, DCPIV
9. Fang Li, PhD, Pharmacometrics Reviewer, OCP
10. Stacey Min, Pharm D, Associate Director for Labeling, DAVP
11. John Dubinion, PhD, Pharmacology Toxicology Reviewer, DAVP
12. Jules O'Rear, PhD, Virology Team Lead, DAVP
13. Lisa Naeger, PhD, Virology Reviewer, DAVP
14. Eric Donaldson, PhD, Virology Reviewer, DAVP
15. Karen Qi, PhD, Statistician, OB, DBIV
16. Thamban Valappil, PhD, Acting Biometrics Team Lead, OB, DBIV
17. Karen Winestock, Chief, Project Management Staff, DAVP
18. Linda Onaga, MPH, Senior Regulatory Project Manager
19. Jamie Wilkins-Parker, PharmD, DRISK Team Lead, OSE

EASTERN RESEARCH GROUP ATTENDEES

1. Peggah Khorrami, Independent Assessor

APPLICANT ATTENDEES

1. John McHutchison, MD, Executive Vice President, Liver Diseases
2. Mani Subramanian MD, Senior Vice President, Liver Diseases
3. Diana Brainard, MD, Vice President, Liver Diseases

4. John McNally, PhD, Director, Liver Diseases
5. Brian Kearney, PharmD, Vice President, Clinical Pharmacology
6. Erik Mogalian, PhD, Sr. Clinical Pharmacologist
7. Richard Polniaszek, Sr. Director, Process Development
8. Hongmei Mo, MD, Director, Clinical Virology
9. Michele Anderson, Director, Regulatory Affairs
10. Farzaneh Nakhjiri, Manager, Regulatory Affairs CMC
11. Prachi Shah, Manager, Regulatory Affairs

1.0 BACKGROUND

NDA 208341 was submitted on October 28, 2015 for sofosbuvir/velpatasvir.

Proposed indication: treatment of chronic hepatitis C virus infection in adults

PDUFA goal date: June 28, 2016

FDA issued a Background Package in preparation for this meeting on April 8, 2016.

2.0 DISCUSSION

1. Introductory Comments

   The purpose of this Late-Cycle Meeting for NDA 208341, sofosbuvir/velpatasvir (SOF/VEL) tablet is to share information and discuss any substantive review issues that we have identified to date and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director and the cross-discipline team lead and therefore, this 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.

2. Discussion of Review Issues
   - Addition of ribavirin (RBV) for certain HCV genotype 3 infected patients
     - Discuss the available data from the Phase 2 trial (109) and ASTRAL-4 to support the use of RBV
     - Discuss the use of RBV for certain HCV genotype 3 infected patients
     - Discuss potential revisions to Section 2, Dosage and Administration
   - Clinical recommendations for use of SOF/VEL in combination with proton-pump inhibitors and atorvastatin

   Discussion:

   - Addition of RBV

The Division clarified the addition of RBV for certain genotype 3-infected patients. The intent of the comment was to add a footnote to the Dosing and Administration section of labeling

recommending the use of SOF/VEL plus RBV in genotype 3 compensated cirrhotic patients. Section 12.4 of the proposed label shows the 33% relapse rate in the genotype 3 compensated cirrhotic subgroup with baseline NS5A polymorphisms. Currently, there is no optimal dosing recommendation for a patient who has a baseline NS5A polymorphism in this subgroup, and a physician may not know the best regimen option for treating this patient.

(b) (4)

Gilead intends to conduct a (b) (4) clinical study (b) (4) which will address the questions related to the contribution of RBV to the SOF/VEL regimen in the HCV genotype 3 compensated cirrhotic population.

The Division informed Gilead that this (b) (4) study will be a post-marketing requirement for this NDA.

- Clinical Recommendations for use of SOF/VEL in combination with proton-pump inhibitors and atorvastatin:

The Division commented on the clinical recommendation for the use of SOF/VEL in combination with proton-pump inhibitors (PPI) and atorvastatin. There is concern on the practicality of dosing in the real world when a patient needs to consider dose of omeprazole to take, time of day to take two different drugs, and prandial condition of each drug administration. In considering the worst case scenario, there were significant decreases in exposure for both sofosbuvir and velpatasvir that could impact efficacy. In ASTRAL 3, velpatasvir AUC exposures were 30% lower in relapsers compared to non-relapsers. Thus, even this degree of decrease in velpatasvir AUC may be problematic.

Gilead recognized the Division's concerns, (b) (4)

The Division did not agree with the analysis and emphasized that a relationship seen in Study (b) (4) cannot be directly applied to patients. There are PK differences between the healthy volunteer study and HCV infected patients. For instance, PK dose proportionality is different between healthy volunteers and patients.

(b) (4)
. The Division indicated that there are not sufficient data to recommend coadministration of PPI and SOF/VEL at this time. However, the Division may revisit this issue when the new data become available.

3. Information Requests
   - The Evaluation of manufacturing facilities is currently on-going.
   - We are revaluating your April 6 response to the March 23 Information Request

Discussion:

None.

4. Postmarketing Requirements/Postmarketing Commitments
   - Pediatric PREA requirements
   - Submission of:
     - ASTRAL-5 results to assess the safety of treatment with SOF/VEL in subjects with HIV/HCV coinfection who are receiving antiretroviral therapy
     - Trial GS-US-342-2097 to assess the role of RBV in HCV genotype 3 infected subjects with cirrhosis
     - Trial data in the HCV population with decompensated CPT C cirrhosis to obtain SOF/VEL safety data in a broader decompensated cirrhosis population
     - The 5 year follow-up data from the ongoing long-term registry trial (GS-US-337-1431)
     - Results from the drug-drug interaction trial with atorvastatin
   - Phenotypic assessment of NS5B_L314F, NS5B_L314I, and NS5B_L314P in the HCV GT3a replicon

Discussion:

Gilead agreed with the PMR/PMCs presented. .

5. Major Labeling Issues
   - Full Prescribing Information
     - (b) (4) indicated genotypes in the Indications and Usage, Dosage and Administration, and Adverse Reactions sections
     - (b) (4) the addition of rash and depression to Adverse Reaction section
     - Adverse Reactions, (b) (4)
     - How Supplied/Storage and Handling, Dispense only in original container statement

Discussion:

- Indicated Genotypes in Indications and Usage, Dosage and Administration, and Adverse Reactions sections

The Division will retain the proposed labeling changes in Indications and Use, Dosage and Administration, and Adverse Reactions section of labeling which indicated the specific genotypes studied in the SOF/VEL development program. Retaining genotypes 1-6 it important because the development program was specific to genotypes 1-6.

(b) (4)

The Division acknowledged Gilead's approach, however stated that the development program for this product studied HCV infected patients with genotypes 1-6, and the label should reflect that information.
Gilead agreed.

- Addition of rash and depression to Adverse Reaction section:

(b) (4)

The Division reminded Gilead that sofosbuvir is a part of this regimen and rash and depression events were seen in the SOF/VEL drug development program. The Division will provide a detailed rationale for the inclusion of these adverse reactions in the next round of labeling.

- Adverse Reactions, (b) (4)

The Division will respond back to Gilead with additional comments to their proposed revisions in the next labeling round. (b) (4) Additionally the review team noted elevations in indirect bilirubin in subjects receiving SOF/VEL plu an atazanavir/ritonavir based ARV regimen. The Division will propose wording for the laboratory abnormality subsection to note the observed increases in indirect bilirubin and dose adjustment or treatment interruption was not needed. (b) (4)

  - How Supplied/Storage and Handling, Dispense only in original container statement

The Division provided a detailed rationale as to why we would like to remove "Dispense (b) (4) only in original container" statement for this product. . The review team generally considers "dispense (b) (4) in original container" language as related to a specific product quality issues. The Division reviewed data in the NDA submission that showed tablets stored in an open-dish stress study at 40C/75% RH for 3 months had no change in assay, degradants, or morphic form. (b) (4) The information did not suggest a specific risk if this product were dispensed in a pharmacy bottle. The Division requested additional information if other types of studies were done to address risk when dispensed in a pharmacy bottle.

FDA does not have specific guidance for "dispense (b) (4) in original container" statements; however, believe theses statement should be limited to instances where product quality risk associated with the product exists or if a product has specific clinical risk (not shared by all drugs in a class or indication) then the "dispense (b) (4) n original container" language could be considered .

Gilead will respond to the Division's inquiry/request.

6. Review Plans
   - Complete application review by Cross-Discipline Team Leader, Division Director, and Signatory Authority
   - Await completion of CMC and Clinical Inspections, including addressing issues that may arise
   - Finalize labeling
   - Review and finalize PMR/PMCs
   - Review and Finalize pediatric deferral and waivers

Discussion:

The Division reminded Gilead that inspections are ongoing. Gilead noted a CMC inspection at the end of May. Given this date, the Division does not anticipate taking an early or expedited action for this product. The Division needs to wait for the final inspection report and will likely be completed close to the PDUFA goal date.

7. Wrap-up and Action Items

   - The Division will provide Gilead with their response to proposed labeling and PMR/PMC language

Conclusion:

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

KIMBERLY A STRUBLE
05/25/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208341

LATE CYCLE MEETING
BACKGROUND PACKAGE

Gilead Sciences, Inc.
Attention: Prachi Shah, MBS, RAC
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Shah:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sofosbuvir/velpatasvir tablet, 400 mg/ 100 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for April 19, 2016. 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 Antiviral Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	April 19, 2016 2:30 PM – 4:00 PM
Meeting Location:	10903 New Hamsphire Ave White Oak Campus Bldg 22 Room 1415 Silver Spring MD 20993
Application Number:	NDA 208341
Product Name:	sofosbuvir/velpatasvir (SOF/VEL)
Proposed Indication:	treatment of chronic hepatitis C
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 (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and cross-discipline team leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

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:

- Please refer to the April 1, 2016 information request regarding the addition of ribavirin (RBV) for certain HCV genotype 3 infected patients. We are awaiting your written response to the April 1, 2016 document and will discuss the respective positions during the Late Cycle Meeting.
- Drug-drug interaction recommendations for proton pump inhibitors and atorvastatin

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (Linda Onaga/Kimberly Struble)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Review Issues – 45 minutes

   Each issue will be introduced by the FDA and followed by a discussion.

   - Addition of RBV for certain HCV genotype 3 infected patients
     - Discuss the available data from the Phase 2 trial (109) and ASTRAL-4 to support the use of RBV
     - Discuss the use of RBV for certain HCV genotype 3 infected patients
     - Discuss potential revisions to Section 2, Dosage and Administration
   - Clinical recommendations for use of SOF/VEL in combination with proton-pump inhibitors and atorvastatin

3. Information Requests

   - The evaluation of all manufacturing facilities is currently on-going. Additionally, we are evaluating your April 6 response to the March 23 Information Request.

4. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

   - Pediatric PREA requirements
   - Submission of:
     - ASTRAL-5 results to assess the safety of treatment with SOF/VEL in subjects with HIV/HCV coinfection who are receiving antiretroviral therapy
     - Trial GS-US-342-2097 to assess the role of RBV in HCV genotype 3 infected subjects with cirrhosis

    - Trial data in the HCV population with decompensated CPT C cirrhosis to obtain SOF/VEL safety data in a broader decompensated cirrhosis population
    - The 5 year follow-up data from the ongoing long-term registry trial (GS-US-337-1431)
    - Results from the drug-drug interaction trial with atorvastatin
- Phenotypic assessment of NS5B_L314F, NS5B_L314I, and NS5B_L314P in the HCV GT3a replicon

5. Major labeling issues – 20 minutes

    - In addition to the discussion under 2 above, the Division will send a proposed list of outstanding labeling issues following the next round of labeling comments in advance of the Late Cycle Meeting. We acknowledge members of your team will be at EASL next week. If you are not able to submit a revised label by April 15th, please notify Linda Onaga and identify any additional labeling issues you would like to discuss on April 19, 2016.

6. Review Plans – 5 minutes

    - The review team is working on the following review activities
        - Complete application review by the signatory authority, division director, and cross-discipline team leader
        - Await completion of CMC and clinical inspections and address any issues that may arise
        - Finalize labeling
        - Finalize PMR/PMCs: content, dates, additional review and concurrence by SRT
        - Finalize pediatric deferral, waivers and plan for review by PeRC

7. Wrap-up and Action Items – 5 minutes (Linda Onaga)

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/s/

JEFFREY S MURRAY
04/08/2016