CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209195Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>BLA #</th>
<th>NDA Supplement #</th>
<th>BLA Supplement #</th>
<th>If NDA, Efficacy Supplement Type: (an action package is not required for SE8 or SE9 supplements)</th>
</tr>
</thead>
<tbody>
<tr>
<td>209195</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- **Proprietary Name:** VOSEVI
- **Established/Proper Name:** sofosbuvir/velpatasvir/voxilaprevir
- **Dosage Form:** tablets
- **Applicant:** Gilead Sciences, Inc
- **Agent for Applicant:** Jill Haggerty
- **RPM:** Andrew Gentles, PharmD, BCPS AQ-ID
- **Division:** Antiviral Products

### NDA Application Type:
- [ ] 505(b)(1)
- [ ] 505(b)(2)

### BLA Application Type:
- [ ] 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)*

**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 **August 8, 2017**

- **Previous actions** *(specify type and date for each action taken)*
  - [ ] None

### Application Characteristics

- [ ] Received

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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):  □ Fast Track  □ Rolling Review  □ Orphan drug designation  □ Breakthrough Therapy designation

☐ Accelerated approval (21 CFR 314.510)  ☐ Restricted distribution (21 CFR 314.520)  ☑ Approval based on animal studies
☐ Submitted in response to a PMR  ☐ Submitted in response to a PMC  ☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E  □ Accelerated approval (21 CFR 601.41)  □ Restricted distribution (21 CFR 601.42)  □ Approval based on animal studies
REMS:  □ MedGuide  □ Communication Plan  □ ETASU  □ MedGuide w/o REMS  □ REMS not required

Comments:

- BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)
  - Yes  □ No

- Public communications (approvals only)
  - Office of Executive Programs (OEP) liaison has been notified of action  □ Yes  □ No LaShawn Sykes
  - Indicate what types (if any) of information were issued

- Exclusivity
  - Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?
    - Yes  □ No
  - If so, specify the type

- 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) | 7/18/17 |

## 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
    - [X] Included - 12.8.16
- **Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling** (*write submission/communication date at upper right of first page of each piece*)
  - Most recent draft labeling (*if it is division-proposed labeling, it should be in track-changes format*)
    - □ Included
  - Original applicant-proposed labeling
    - [X] Included - 12.8.16
- **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
    - [X] Included - 7/7/17, 7/6/17,
- **Proprietary Name**
  - Acceptability/non-acceptability letter(s) (*indicate date(s))
    - 3/1/17
  - Review(s) (*indicate date(s))
    - 3/1/17

## Administrative / Regulatory Documents

- **RPM Filing Review**/*Memo of Filing Meeting** (*indicate date of each review*)
  - 1/31/17
- **All NDA 505(b)(2) Actions**: Date each action cleared by 505(b)(2) Clearance Committee
  - [X] Not a (b)(2)
- **NDAs/NDA supplements only**: Exclusivity Summary (*signed by Division Director*)
  - [□] Completed *(Do not include)*
- **Application Integrity Policy (AIP) Status and Related Documents**
  - [http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm](http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm)
  - Applicant is on the AIP
    - □ Yes   [X] No

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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)*

- Pediatrics *(approvals only)*
  - Date reviewed by PeRC 4/19/17
  - If PeRC review not necessary, explain: _____

- Breakthrough Therapy Designation
  - N/A
  - Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 2/19/16
  - CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)* 3/25/16
  - 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)*

- 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 OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*

- 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) 7/11/17

- Minutes of Meetings
  - If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*
  - Pre-ND/BLA meeting *(indicate date of mtg)*
  - EOP2 meeting *(indicate date of mtg)*
  - Mid-cycle Communication *(indicate date of mtg)*
  - Late-cycle Meeting *(indicate date of mtg)*
  - Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*
  - Advisory Committee Meeting(s)
    - Date(s) of Meeting(s)

### Decisional and Summary Memos

- Office Director Decisional Memo *(indicate date for each review)*
  - None 7/18/17

- Joint Cross-Discipline Team Leader (CDTL) and Division Director Summary Review *(indicate date for each review)*
  - None 7/13/17

- PMR/PMC Development Templates *(indicate total number)* -2
  - None 7/3/17

#### Clinical
Clinical Reviews

- Clinical Team Leader Review(s) *(indicate date for each review)*
- Clinical review(s) *(indicate date for each review)*
- Social scientist review(s) *(if OTC drug, indicate date for each review)*
- Financial Disclosure review(s) or location/date if addressed in another review OR
  - If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*
- Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*
- Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*
- 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)*
- OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*

Clinical Microbiology ☐ None

- Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*
- Clinical Microbiology Review(s) *(indicate date for each review)*

Biostatistics ☐ None

- Statistical Division Director Review(s) *(indicate date for each review)*
- Statistical Team Leader Review(s) *(indicate date for each review)*
- Statistical Review(s) *(indicate date for each review)*

Clinical Pharmacology ☐ None

- Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*
- Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*
- Clinical Pharmacology review(s) *(indicate date for each review)*
- OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*

5 For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).
### Nonclinical

<table>
<thead>
<tr>
<th>Review Type</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADP/T Review(s) <em>(indicate date for each review)</em></td>
<td>No separate review 5/15/17</td>
</tr>
<tr>
<td>Supervisory Review(s) <em>(indicate date for each review)</em></td>
<td>No separate review</td>
</tr>
<tr>
<td>Pharm/tox review(s), including referenced IND reviews <em>(indicate date for each review)</em></td>
<td>None 5/5/17</td>
</tr>
<tr>
<td>Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <em>(indicate date for each review)</em></td>
<td>None</td>
</tr>
<tr>
<td>Statistical review(s) of carcinogenicity studies <em>(indicate date for each review)</em></td>
<td>No carc</td>
</tr>
<tr>
<td>ECAC/CAC report/memo of meeting</td>
<td>None</td>
</tr>
<tr>
<td>OSI Nonclinical Inspection Review Summary <em>(include copies of OSI letters)</em></td>
<td>None requested</td>
</tr>
</tbody>
</table>

### Product Quality

<table>
<thead>
<tr>
<th>Review Type</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertiary review <em>(indicate date for each review)</em></td>
<td>None</td>
</tr>
<tr>
<td>Secondary review *(e.g., Branch Chief) <em>(indicate date for each review)</em></td>
<td>None</td>
</tr>
<tr>
<td>Integrated Quality Assessment *(contains the Executive Summary and the primary reviews from each product quality review discipline) <em>(indicate date for each review)</em></td>
<td>None 7/14/17, 6/4/17</td>
</tr>
<tr>
<td>Reviews by other disciplines/divisions/Centers requested by product quality review team <em>(indicate date of each review)</em></td>
<td>None</td>
</tr>
<tr>
<td>Environmental Assessment *(check one) <em>(original and supplemental applications)</em></td>
<td>None</td>
</tr>
<tr>
<td>Categorical Exclusion *(indicate review date) <em>(all original applications and all efficacy supplements that could increase the patient population)</em></td>
<td>6/4/17</td>
</tr>
<tr>
<td>Review &amp; FONSI <em>(indicate date of review)</em></td>
<td>None</td>
</tr>
<tr>
<td>Review &amp; Environmental Impact Statement <em>(indicate date of each review)</em></td>
<td>None</td>
</tr>
<tr>
<td>Facilities Review/Inspection</td>
<td></td>
</tr>
<tr>
<td>Facilities inspections *(indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) <em>(only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change))</em></td>
<td>Acceptable, 7/14/1 in IQA #2</td>
</tr>
</tbody>
</table>

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6 Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Reference ID: 4125985
### Day of Approval Activities

<table>
<thead>
<tr>
<th>Activity</th>
<th>Status</th>
</tr>
</thead>
</table>
| For all 505(b)(2) applications:  
  - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) | ![No changes](image)  
  ![New patent/exclusivity](image)  
  ![Notify CDER OND IO](image)  
  ![N/A](image) |
| Finalize 505(b)(2) assessment | ![Done](image) |
| For Breakthrough Therapy (BT) Designated drugs:  
  - Notify the CDER BT Program Manager | ![Done](image)  
  ![Send email to CDER OND IO](image) |
| For products that need to be added to the flush list (generally opioids):  
  - Notify the Division of Online Communications, Office of Communications | ![Done](image)  
  ![N/A](image) |
| Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email | ![Done](image) |
| If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter | ![Done](image)  
  Notify Theresa Eisenman |
| 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](image) |
| Ensure Pediatric Record is accurate | ![Done](image) |
| Send approval email within one business day to CDER-APPROVALS | ![Done on 7/18/17](image) |
| Take Action Package (if in paper) down to Document Room for scanning within two business days | ![Done on 7/18/17](image)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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ANDREW A GENTLES
07/18/2017
EXCLUSIVITY SUMMARY

NDA # 209195 SUPPL # HFD #

Trade Name VOSEVI

Generic Name sofosbuvir/velpatasvir/voxilaprevir

Applicant Name Gilead Sciences, Inc

Approval Date, If Known August 8, 2017

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).
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# 208341 Epclusa (sofosbuvir/velpatasvir)
NDA# 205834 Harvoni (sofosbuvir/ledipasvir)
NDA# 204671 Sovaldi (sofosbuvir)

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.

NDA 209195 contains voxilaprevir, a new chemical entity, in combination with sofosbuvir and velpatasvir, 2 previously approved active moieties. Under the Agency’s new interpretation described in the Agency’s Guidance for Industry, *New Chemical Entity Exclusivity Determinations 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, in a fixed-combination with another drug substance that contains no other previously approved active moiety, or in a fixed-combination with another drug substance that contains a previously approved active moiety. NDA 209195 is therefore eligible for 5-year new chemical entity exclusivity pursuant to the new interpretation.

**PART III THREEx- 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  YES □  NO □
                        !
                        !
                        ! Explain:

Investigation #2  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: Andrew Gentles
Title: Regulatory Project Manager
Date: June 21, 2017

Name of Division Director signing form: Debra Birnkrant
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/

ANDREW A GENTLES
07/05/2017

DEBRA B BIRNKRANT
07/05/2017
MEMORANDUM OF TELECONFERENCE

Teleconference Date: June 27, 2017
Application Number: 209195
Product Name: VOSEVI (sofosbuvir/velpatasvir/voxilaprevir)
Sponsor/Applicant Name: Gilead Sciences, Inc

Subject: Teleconference between FDA and Gilead Sciences, Inc regarding labeling comments sent on June 23, 2017

FDA Participants
Debra Birnkrant, MD, Division Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, MD, MPH, Deputy Director, DAVP
Andrew Gentles, PharmD, BCPS AQ-ID, Regulatory Project Manager, DAVP
Kim Struble, PharmD, Clinical Team Lead, DAVP
Kirk Chan-Tack, MD Clinical Reviewer, Medical Officer, DAVP
Karen Qi, PhD, Office of Biometrics, Division of Biometrics IV (DBIV)

Sponsor/Applicant Participants
Diana Brainard, MD, Vice President, Liver Diseases
Luisa Stamm, MD, PhD, Director, Liver Diseases
Michele Anderson, Senior Director, Regulatory Affairs
Jill Haggerty, Associate Director, Regulatory Affairs

1.0 BACKGROUND: On June 23, 2017, labeling comments were sent to Gilead Sciences, Inc, the sponsor for NDA 209195. In this communication, the FDA provided their response in Section 14 (Table 10), on the rationale of why one of the SOF/VEL subject in the POLARIS-4 trial must be classified as “Other” instead of “Relapse” as proposed by the Sponsor. Based on this rationale and the revised Table 10, the sponsor requested an informal teleconference to gain clarity on the first comment regarding Section 14 (Table 10) and classification of one of the subjects as “Other”.

2.0 DISCUSSION: After introductory remarks, the Division indicated that Gilead’s concern regarding classification of the SOF/VEL subject as “Relapse” vs “Other” was discussed internally. The Division indicated there was overall consensus on the definition of “Other” which is used to describe subjects who have discontinued due to adverse events; were lost to follow-up or withdrew from the study. The HCV GT1b patient in POLARIS-4 who discontinued SOF/VEL on Day 56 due to Grade 2 headache would fall under the “Other” category.

Gilead indicated that their definition of the term “relapse” is anyone who was HCV RNA negative at the time of treatment discontinuation, irrespective of the treatment duration who then became HCV RNA positive in the post treatment follow-up period. Gilead acknowledged receipt of the Division’s comment regarding the need for additional clarity of their statistical analysis plan (SAP) and the interpretation of end of treatment (EOT). Gilead responded that in the past, those with relapse were placed into 2 different groups (completers vs. non-completers) consistent
with the approach that a relapse is anyone treated for any duration as long as the subject was negative. Gilead felt it would be most appropriate to treat this subject as relapser and provided additional rationale that this definition has been utilized across various SOF-containing development programs as seen in the Sovaldi, Harvoni and Epclusa labels.

The Division acknowledged their comments but indicated that the definition of relapser did not affect the labeling of previous SOF-containing development programs. However, in the SOF/VEL/VOX program, the Division indicated that this definition actually highlights whether or not the contribution of the VOX component is evident in treatment of the various HCV genotypes in the POLARIS-4 trial.

Gilead stated that they did not believe that interpretation of the data should play a role in the characterization of this patient and emphasized their intention of remaining consistent in how the definition of relapsers has been used in the other SOF-containing programs.

The Division stated that the HCV field has advanced substantially resulting in fewer treatment failures in clinical studies and it becomes challenging to identify differences in these trials; therefore, classification of treatment failure may need to become more stringent.

Gilead acknowledged the FDA’s feedback and position on the classification of the SOF/VEL subject as “Relapse” vs “Other”. As an alternative to the Division’s recommendation, Gilead proposed [REDACTED].

3.0 ACTION ITEMS:

- Gilead proposed [REDACTED].
- Gilead will submit meeting minutes of this teleconference to the NDA 209195.
- The Division indicated they would conduct further internal discussions on Gilead’s proposal.
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/s/

ANDREW A GENTLES
07/11/2017
PeRC Meeting Minutes
June 14, 2017

PeRC Members Attending:
John Alexander
Gettie Audain
Donna Snyder
Lily Mulugeta
Victor Baum
Rosemary Addy
Wiley Chambers
Gerri Baer
Adrienne Hornatko-Munoz
Barbara Buch
Greg Reaman
Jinging Ye
Susan McCune
Meshaun Payne
Rachel Tapia
Robert “Skip” Nelson
Gilbert Burkhart
Dionna Greene
Shrikant Pagay
Hari Cheryl Sachs
Maura O’Leary
<table>
<thead>
<tr>
<th>Time</th>
<th>NDA 209195</th>
<th>Sofosbuvir/Velpatasvir/Voxilaprevir Written Request</th>
<th>DAVP</th>
<th>Andrew Gentles</th>
<th>Treatment of Chronic Hepatitis C infection</th>
</tr>
</thead>
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</tbody>
</table>
Sofosbuvir/Velpatasvir/Voxilaprevir

• For the treatment of adolescents 12 to less than 18 years of age with chronic genotype 1 through 6 HCV infection and have failed a prior direct-acting antiviral (DAA) regimen.
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/s/

MESHAUN L PAYNE
07/07/2017
DATE: July 5, 2017

TO: Jill Haggerty
   Associate Director, Regulatory Affairs
   Phone: 650-522-1308
   Fax: 650-522-5489
   Email: jill.haggerty@gilead.com

SPONSOR: Gilead Sciences, Inc.

SUBJECT: Update proposed container label for NDA 209195

We have the following comments regarding updates to the proposed container label for NDA 209195 and request an updated container label be submitted to the Agency this Friday, July 7, 2017 no later than 12pm EST.

1. Revise the established name on the container label, “(sofosbuvir, velpatasvir, voxilaprevir),” to read “(sofosbuvir, velpatasvir, and voxilaprevir)” to be consistent with the Agency’s recommended presentation of established names for multi-ingredient antivirals.

2. Add the lot number and expiration date on the immediate container label per 21 CFR 201.10(i)(1) and 21 CFR 201.17, respectively. Ensure that the lot number is clearly differentiated from the expiration date to reduce the risk of medication errors resulting from administration of expired medication.

3. Replace “Tradename” with the proprietary name, Vosevi, found conditionally acceptable per Agency letter dated March 1, 2017.

Please verify the receipt of this email and contact me at 240-402-5708 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Andrew Gentles, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration
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/s/

ANDREW A GENTLES
07/05/2017
DATE: June 30, 2017

TO: Jill Haggerty
Associate Director, Regulatory Affairs
Phone: 650-522-1308
Fax: 650-522-5489
Email: jill.haggerty@gilead.com

SPONSOR: Gilead Sciences, Inc.

SUBJECT: Reply to labeling response submitted on June 27, 2017

We have the following comments regarding your labeling response submitted on June 27, 2017 and request a response by July 6, 2017.

For the definitions of “Relapse” and “Other”, to ensure clarity and to improve consistency with other HCV DAA labeling, the following wording (revisions in bold font) should be used:

Section 14.1
Relapse is defined as HCV RNA greater than or equal to LLOQ after end-of-treatment response among subjects who completed treatment.

Section 14.2 (footnote in Tables 9 and 10)
The denominator for relapse is the number of subjects with HCV RNA <LLOQ at the end-of-treatment assessment.

Section 14.2 (footnote in Tables 9 and 10)
We believe “Other” is most clearly described using the wording: Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

We appreciate your discussion during the June 27, 2017 teleconference and the footnote proposal in your June 27, 2017 submission. We do not agree (changes in bold font) and should also incorporate the above footnote revisions:

Table 10 should display the information below (changes in bold font) and should also incorporate the above footnote revisions:
Table 1  POLARIS-4 Trial: Virologic Outcomes by HCV Genotype in VOSEVI-Treated Subjects* and SOF/VEL-Treated Subjects* Without Cirrhosis or With Compensated Cirrhosis (12 Weeks After Treatment)

<table>
<thead>
<tr>
<th>*Subjects with prior exposure to a SOF-containing regimen</th>
<th>VOSEVI 12 Weeks (N=139)</th>
<th>SOF/VEL 12 Weeks (N=125)</th>
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<tbody>
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<td>97% (135/139)</td>
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<tr>
<td>SVR12</td>
<td>97% (135/139)</td>
<td>88% (110/125)</td>
</tr>
<tr>
<td>Not achieving SVR12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On-treatment virologic failure</td>
<td>0% (0/139)</td>
<td>1% (1/125)</td>
</tr>
<tr>
<td>Relapse&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1% (1/139)</td>
<td>10% (13/124)</td>
</tr>
<tr>
<td>Other&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2% (3/139)</td>
<td>1% (1/125)</td>
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<tr>
<td>Genotype 1</td>
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<td></td>
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<tr>
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<tr>
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<td></td>
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<tr>
<td>On-treatment virologic failure</td>
<td>0% (0/54)</td>
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<tr>
<td>Relapse&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2% (1/54)</td>
<td>13% (5/40)</td>
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<tr>
<td>Other&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>3% (1/40)</td>
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<tr>
<td>Genotype 1a</td>
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<tr>
<td>SVR12</td>
<td>97% (35/36)</td>
<td>82% (23/28)</td>
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<tr>
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<td></td>
</tr>
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<tr>
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<td>Genotype 1b</td>
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<tr>
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<td>94% (17/18)</td>
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<td>0% (0/12)</td>
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<td>6% (1/18)</td>
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<td>Genotype 2</td>
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<td>0% (0/31)</td>
<td>0% (0/33)</td>
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<tr>
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<td>96% (52/54)</td>
<td>85% (44/52)</td>
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<td>15% (8/52)</td>
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<tr>
<td>Other&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4% (2/54)</td>
<td>0% (0/52)</td>
</tr>
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</table>

<sup>a</sup> The denominator for relapse is the number of subjects with HCV RNA < LLOQ at the end-of-treatment assessment.

<sup>b</sup> Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

Please verify the receipt of this email and contact me at 240-402-5708 or 301-796-1500 if you have any questions regarding the contents of this transmission.

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

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

ANDREW A GENTLES
06/30/2017
Hello Nicole,

I’ve noted Jill’s out of office. Reference is made to the TCON with Gilead on June 27, 2017. Please provide us with the following:

1). Reference used in the SAP
2). Submission of minutes from the TCON

Please let me know if you have any questions.

Thanks,

AG

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Center for Drug Evaluation and Research
OND/OAP/Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240-402-5708
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/s/

ANDREW A GENTLES
06/29/2017
As a follow-up, the PDF version of the comments does not seem to show [REDACTED] if you are also seeing this apparent software related glitch, please know that under Patient Information:

We accept your proposed deletion, [REDACTED]

Thanks,
AG

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Center for Drug Evaluation and Research
OND/OAP/Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240-402-5708

Please see attached. Additional communication might be forthcoming and I will let you know by 6.30.17. In the meantime, we are looking for a response to this document by 6.27.17.

Thanks,
AG

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Center for Drug Evaluation and Research
OND/OAP/Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240-402-5708
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/s/

ANDREW A GENTLES
06/23/2017
DATE:       June 23, 2017

TO:         Jill Haggerty
            Associate Director, Regulatory Affairs
            Phone: 650-522-1308
            Fax: 650-522-5489
            Email: jill.haggerty@gilead.com

SPONSOR:   Gilead Sciences, Inc.

SUBJECT:   Reply to labeling response submitted on June 21, 2017

We have the following comments regarding your labeling response submitted on June 21, 2017.

Section 14
Background
In response to FDA’s comments “Relapse must be revised to 13% (5/40)” and “Other must be revised to 8% (1/12)” as outlined in the Division’s Late-Cycle Backgrounder:

Gilead proposes to present the virologic outcome data by category in a manner that is consistent with definitions used for all SOF-containing regimens in the pre-specified statistical analysis plan for the study; i.e., subjects who have HCV RNA < LLOQ at their last on-treatment visit and have a subsequent HCV RNA > LLOQ are categorized as relapers irrespective of the duration of treatment.

FDA Reply
Our interpretation of end-of-treatment (EOT) is the pre-specified or assigned treatment duration.

Our review identified the following definition of relapse in POLARIS-4 statistical analysis plan (SAP):
“HCV RNA >= LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at EOT, confirmed with 2 consecutive values or last available posttreatment measurement.”

We note that your SAP did not have “irrespective of the duration of treatment” in the definition of relapse.

Additionally, to be classified as a relapse, the subject must have completed the assigned treatment and had undetectable HCV viral load (VL) at the end of such treatment. If a subject prematurely discontinues while on assigned treatment then there is no chance of him/her being categorized as a relapse. Unless they prematurely discontinued due to having an increasing VL, then they are placed into the “Other” category for failing to achieve SVR12.
Based on the above rationale, we conclude that the following SOF/VEL subject must be classified as “Other” instead of “Relapse”:

- SOF/VEL: Subject 00407-27557 (HCV GT1b) discontinued on Day 56 due to Grade 2 headache; HCV RNA was < 15 IU/mL at the Week 4 visit, the last visit prior to study drug discontinuation.

The revised Table 10 is provided below (changes in bold font):

**Table 1**  POLARIS-4 Trial: Virologic Outcomes by HCV Genotype in VOSEVI-Treated Subjects* and SOF/VEL-Treated Subjects* Without Cirrhosis or With Compensated Cirrhosis (12 Weeks After Treatment)

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<tr>
<td>Other&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4% (2/54)</td>
<td>0% (0/52)</td>
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</tbody>
</table>

<sup>a</sup> The denominator for relapse is the number of subjects with HCV RNA < LLOQ at [ ]

<sup>b</sup> Other includes subjects [ ]
Patient Information
1) Following additional discussions, OPDP recommends retaining the original language that was proposed for the indication and not this revised language by the Sponsor. From a promotional perspective, we want to ensure that it is clear what prior treatments/therapies corresponded with which genotypes and ensure that this is communicated in a manner consistent with the Indications and Usage section of the PI.

2) We accept your proposed deletion, ““.

Please verify the receipt of this email and contact me at 240-402-5708 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Andrew Gentles, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration
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/s/

ANDREW A GENTLES
06/23/2017
DATE: June 15, 2017

TO: Jill Haggerty
   Associate Director, Regulatory Affairs
   Phone: 650-522-1308
   Fax: 650-522-5489
   Email: jill.haggerty@gilead.com

SPONSOR: Gilead Sciences, Inc.

SUBJECT: Reply to Labeling Response and Response to Information Request

Please refer to your labeling response submitted on June 2, 2017 and your information request submitted on June 9, 2017.

During our May 30, 2017 Late Cycle meeting, we acknowledged you requested removal of the Division’s proposed text in the INDICATIONS AND USAGE section regarding “no additional benefit of SOF/VEL/VOX has been established over sofosbuvir/velpatasvir for the treatment of HCV genotypes 1b, 2, 4, 5 and 6 in adults previously treated with sofosbuvir without an NS5A inhibitor.”

We noted your concerns and provided additional feedback that these issues had undergone detailed discussions with Senior Management, including the OND Director and Center Director, Dr. Janet Woodcock, who concurred with the review team’s conclusion including labeling recommendations for the Indications and Usage section. Our intent was not to include a negative statement in Section 1; however, the sub-bullet was intended to provide context as to why a broad indication was given for NS5A inhibitor experienced patients (HCV genotypes 1-6) while the indication for NS5A inhibitor naïve patients was limited to HCV genotypes 1a and 3 only. Additionally the sub-bullet was added to provide clarification to providers that based on the results from POLARIS-4, NS5A inhibitor treatment-naïve subjects receiving SOF/VEL are likely to have similar SVR12 rates to those receiving SOF/VEL/VOX.

After additional internal discussions, we concluded that this information remains important to describe in the Indications and Usage section. Below we have provided the following options for the Indications and Usage section of the label. Please update the label accordingly based on the recommendations provided in this document along with the changes provided in the attached label.

Reference ID: 4112435
Option 1
INDICATIONS AND USAGE
VOSEVI is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have [see Dosage and Administration (2) and Clinical Studies (14)]:

• genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor.
• genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.
  o Additional benefit of VOSEVI was not shown over sofosbuvir/velpatasvir for the treatment of HCV genotypes 1b, 2, 4, 5 and 6 in adults previously treated with sofosbuvir-without an NS5A inhibitor [see Dosage and Administration (2.2) and Clinical Studies (14)].

Option 2
INDICATIONS AND USAGE
VOSEVI is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have [see Dosage and Administration (2) and Clinical Studies (14)]:

• genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor.
• genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor. Additional benefit of VOSEVI was not shown over sofosbuvir/velpatasvir for the treatment of HCV genotypes 1b, 2, 4, 5 and 6 in adults previously treated with sofosbuvir-without an NS5A inhibitor [see Dosage and Administration (2.2) and Clinical Studies (14)].

Option 3
INDICATIONS AND USAGE
VOSEVI is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have [see Dosage and Administration (2) and Clinical Studies (14)]:

• genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor.
• genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.
  o The benefit of adding voxilaprevir to sofosbuvir/velpatasvir for the treatment of HCV genotypes 1b, 2, 4, 5 and 6 in adults previously treated with sofosbuvir-without an NS5A inhibitor was not shown when compared to sofosbuvir/velpatasvir [see Dosage and Administration (2.2) and Clinical Studies (14)].

Option 4
INDICATIONS AND USAGE
VOSEVI is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have [see Dosage and Administration (2) and Clinical Studies (14)]:

• genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor.
• genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor. The benefit of adding voxilaprevir to sofosbuvir/velpatasvir for the treatment of HCV genotypes 1b, 2, 4, 5 and 6 in adults previously treated with sofosbuvir-without an NS5A inhibitor was not shown when compared to sofosbuvir/velpatasvir [see Dosage and Administration (2.2) and Clinical Studies (14)].

Our additional labeling comments are provided in track changes to the label. Some additional discussion is summarized below:

In Section 12.4, 
(b) (4) were removed to further streamline this section, and the information on EC50 ranges and the subtypes evaluated was described in text.

In Section 14, Table [9] must be revised to show comparative data (i.e. genotypes 1a, 1b, 2, and 3) in subjects with prior exposure to a SOF-containing regimen. The genotype 4 data can be described in text and some draft wording is provided for your consideration.

Please provide the updated label by June 21, 2017.

Please verify the receipt of this email and contact me at 240-402-5708 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

ANDREW A GENTLES
06/15/2017
DATE: June 14, 2017

TO: Jill Haggerty
   Associate Director, Regulatory Affairs
   Phone: 650-522-1308
   Fax: 650-522-5489
   Email: jill.haggerty@gilead.com

SPONSOR: Gilead Sciences, Inc.

SUBJECT: Information Request – Virology PMR

We have the following information request regarding your proposed study to determine the phenotype of NS5A H54R against velpatasvir in the GT4d replicon and report fold shifts in the EC_{50} value.

Please provide a timetable with the following additional information for conducting this trial:

- Final Protocol Submission
- Trial Completion
- Final Report Submission

Please provide the requested information by **June 16, 2017 by 12pm**.

Please verify the receipt of this email and contact me at 240-402-5708 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

Reference ID: 4111593
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/s/

ANDREW A GENTLES
06/14/2017
DATE: June 7, 2017

TO: Jill Haggerty  
Associate Director, Regulatory Affairs 
Phone: 650-522-1308 
Fax: 650-522-5489 
Email: jill.haggerty@gilead.com 

SPONSOR: Gilead Sciences, Inc. 

SUBJECT: Information Request 

We have the following information request regarding your labeling response submitted on June 2, 2017. 

The labeling provided by the Division on May 19, 2017 describes the following virologic outcomes for genotype 3 subjects in POLARIS-4: 

<table>
<thead>
<tr>
<th>Subjects with prior exposure to a SOF-containing regimen</th>
<th>VOSEVI 12 Weeks</th>
<th>SOF/VEL 12 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 3 SVR12 Not achieving SVR12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On-treatment virologic failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The SVR12 and “Other” outcomes for genotype 3 subjects in the SOF/VEL/VOX group in POLARIS-4 reflect the review team’s findings (i.e. Subject 02024-27777, Subject 02024-27810, and Subject 05969-27808 did not have a posttreatment Week 12 assessment and are considered as “Other”). The above information is also consistent with your prior labeling and information from your December 8, 2016 submission. 

Your June 2, 2017 labeling has the following revision (in bold font) for genotype 3 subjects in the SOF/VEL/VOX group in POLARIS-4: 

<table>
<thead>
<tr>
<th>Subjects with prior exposure to a SOF-containing regimen</th>
<th>VOSEVI 12 Weeks</th>
<th>SOF/VEL 12 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 3 SVR12 Not achieving SVR12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On-treatment virologic failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 4108751
Please clarify your rationale for the above revision to the SVR12 (52/54, 96%) and “Other” (2/54, 4%) information for genotype 3 subjects in the SOF/VEL/VOX group in POLARIS-4.

Please provide the requested information by **June 9, 2017**.

Please verify the receipt of this email and contact me at Andrew Gentles, PharmD at 240-402-5708 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, MPH  
Senior Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration
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/s/

LINDA C ONAGA
06/07/2017
PeRC Meeting Minutes
April 19, 2017

PeRC Members Attending:
John Alexander
Jacqueline Yancy
Gettie Audain
Lily Mulugeta
Hari Cheryl Sachs
Kevin Krudys
Wiley Chambers
Gil Burkhart
Gerri Baer
Julia Pinto
Greg Reaman
Jinging Ye
Susan McCune
Megha Kaushal
Barbara Buch
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00</td>
<td>NDA 209195 Vosevi (Sofosbuvir/Velpatasvir/Voxilaprevir) (Partial Waiver/Deferral) with Agreed iPSP DAVP Andrew Gentles Treatment of Chronic Hepatitis C infection</td>
</tr>
<tr>
<td>9:15</td>
<td>NON-RESPONSIVE</td>
</tr>
<tr>
<td>9:35</td>
<td></td>
</tr>
<tr>
<td>9:55</td>
<td></td>
</tr>
<tr>
<td>10:15</td>
<td></td>
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<tr>
<td>10:25</td>
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<td>10:35</td>
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<td>10:45</td>
<td></td>
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<tr>
<td>11:00</td>
<td></td>
</tr>
<tr>
<td>11:10</td>
<td></td>
</tr>
<tr>
<td>11:20</td>
<td></td>
</tr>
</tbody>
</table>
Sofosbuvir/Velpatasvir/Voxilaprevir (Partial Waiver/Deferral) with Agreed iPSP

- Proposed indication: Treatment of chronic Hepatitis C infection
- The PREA trigger is new active ingredient, dosing regimen, dosage form, route of administration, and indication with a PDUFA date of August 8, 2017.
- The division clarified that the deferral for 12 years and older because there will be a high level of treatment response. The division stated that the sponsor estimates enrolling children into the deferred study. The deferral study report due date is April 2021.
- **PeRC Recommendations:**
  - The PeRC concurs with the division to grant a partial waiver from birth to less than <12 years of age because the product is directed to treatment failures and the existing direct-acting antivirals are expected to have extremely low rates of treatment failure for this age group.
  - The PeRC concurs with the division to grant a deferral in pediatric studies for ages 12 to 17 years of age as per the Agreed iPSP.
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/s/

-------------------------------
GETTIE AU DAIN
05/17/2017
DATE: May 8, 2017

TO: Jill Haggerty
   Associate Director, Regulatory Affairs
   Phone: 650-522-1308
   Fax: 650-522-5489
   Email: jill.haggerty@gilead.com

SPONSOR: Gilead Sciences, Inc.

SUBJECT: NDA 209195 PMR Description and timeline

Please find below the Division’s PMR description for NDA 209195.

PMR:
Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of VOSEVI in pediatric subjects 12 through less than 18 years of age with chronic HCV GT 1-6 infection and who are DAA-experienced.

We received, reviewed, and agree with your proposed milestones:

PMR Schedule Milestones:
- Final Protocol Submission: March 2018
- Study/Trial Completion: January 2021
- Final Report Submission: July 2021

Please verify the receipt of this email and contact me at 240-402-5708 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration
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/s/

ANDREW A GENTLES  
05/08/2017
DATE:    April 28, 2017

TO:    Jill Haggerty  
       Associate Director, Regulatory Affairs  
       Phone: 650-522-1308  
       Fax: 650-522-5489  
       Email: jill.haggerty@gilead.com

SPONSOR:    Gilead Sciences, Inc.

SUBJECT:    Information Request

We have the following information request regarding Subject 00632-27709 (genotype 2 HCV-infected subject who experienced virologic breakthrough during SOF/VEL treatment in POLARIS-4).

Your April 28, 2017 submission states this subject did not have low plasma concentrations of GS-331007 or VEL at Week 8. However, your submitted dataset contains no PK concentrations for subjects administered SOF/VEL in POLARIS-4.

Please provide PK concentrations for this subject and please provide the requested information by May 1, 2017.

Please verify the receipt of this email and contact me at 240-402-5708 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Andrew Gentles, PharmD, BCPS AQ-ID    
Regulatory Project Manager    
Division of Antiviral Products    
Center for Drug Evaluation and Research    
Food and Drug Administration
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/s/

ANDREW A GENTLES
04/28/2017
From: Gentles, Andrew  
To: Jill Haggerty  
Cc: Gentles, Andrew  
Subject: NDA209195 - Labeling edits for FSection 12.4 Microbiology  
Date: Thursday, April 27, 2017 7:19:44 AM  
Attachments: VOSEVI 12.4 edits.docx  
Importance: High

Good Morning Jill,

Attached you will find the Division’s labeling edits for Section 12.4. Please provide a response to this before 5.4.17. In the meantime, please confirm receipt of this email.

Thanks

AG

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Center for Drug Evaluation and Research
OND/OAP/Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240-402-5708

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/s/

ANDREW A GENTLES
04/27/2017
DATE: April 25, 2017

TO: Jill Haggerty  
Associate Director, Regulatory Affairs  
Phone: 650-522-1308  
Fax: 650-522-5489  
Email: jill.haggerty@gilead.com

SPONSOR: Gilead Sciences, Inc.

SUBJECT: Information Request

Please provide a timetable with the following additional information for conducting this trial:
- Final Protocol Submission
- Trial Completion
- Final Report Submission

Please provide the requested information by May 1, 2017.

Please verify the receipt of this email and contact me at 240-402-5708 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Andrew Gentles, PharmD, BCPS AQ-ID  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration
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/s/

ANDREW A GENTLES
04/25/2017
METHOD VERIFICATION
MATERIALS RECEIVED

NDA 209195

April 24, 2017

Jill Haggerty
Associate Director, Regulatory Affairs
jill.haggerty@gilead.com
Gilead Sciences Inc.
333 Lakeside Drive
Foster City CA 94404

Dear Jill Haggerty:

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/voxilaprevir tablets (400mg/100mg/100mg) and to our March 29, 2017, letter requesting sample materials for method verification testing.

We acknowledge receipt on April 20, 2017, 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) or email (Laura.Pogue@fda.hhs.gov).

Sincerely,
Laura C. Pogue
Laura C. Pogue, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

U.S. Food and Drug Administration
645 S. Newstead Ave
St. Louis MO 63110
www.fda.gov

Phone 314.539.2135
FAX 314.539.2113
REQUEST FOR METHOD VERIFICATION MATERIALS

NDA 209195

March 29, 2017

Jill Haggerty
Associate Director, Regulatory Affairs
jill.haggerty@gilead.com
Gilead Sciences Inc.
333 Lakeside Drive
Foster City CA 94404

Dear Jill Haggerty:

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/voxilaprevir tablets (400mg/100mg/100mg).

We will be performing method verification studies on sofosbuvir/velpatasvir/voxilaprevir tablets (400mg/100mg/100mg) as described in NDA 209195.

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

Method, current version
1) (b)(4) 192: Identification, Assay, and Impurities of Sofosbuvir Drug Substance by UPLC
2) 246: Identification, Assay, and Impurity Content of Velpatasvir Drug Substance by UPLC
3) (b)(4) 255: Determination of GS-646828 Content in Velpatasvir Drug Substance by UPLC
4) (b)(4) 286: Identification, Assay, and Impurity Content of Voxilaprevir Drug Substance by UPLC
5) (b)(4) 292: Content in Voxilaprevir Drug Substance by HPLC
6) (b)(4) 288: Identification and Content Uniformity of SOF/VEL/VOX Tablets
7) 289: Strength and Degradation Product Content of SOF/VEL/VOX Tablets by UPLC

U.S. Food and Drug Administration
645 S. Newstead Ave
St. Louis MO 63110
www.fda.gov
Chemicals, Samples and Reference Standards

1) Sofosbuvir (GS-7977) reference standard (2 x 500mg)
2) Sofosbuvir Drug Substance (2 x 500mg)
3) Sofosbuvir system suitability (SS) identity standard (500 mg)
4) Provide all impurities individually as listed in Table 1 of (b)(4) 192 (200 mg)
5) Velpatasvir (VEL, GS-5816) reference standard (2 x 500mg)
6) Velpatasvir Drug Substance (2 x 500mg)
7) Velpatasvir (VEL, GS-5816) SS identity standard (500 mg)
8) Provide all impurities individually as listed in Table 1 of (b)(4) 246, specifically those included in the SS Identity Standard (200 mg)
9) GS-646828 reference standard (300 mg)
10) Voxilaprevir (VOX, GS-9857) Reference Standard (2 x 500mg)
11) Voxilaprevir Drug Substance (2 x 500mg)
12) Voxilaprevir (VOX, GS-9857) SS Mixture (500 mg)
13) Provide all impurities individually as listed in Table 1 of (b)(4) 286 (200 mg)
14) SOF/VEL/VOX Drug Product (2 x 100 tablets)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials as well as impurities if available.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110
Please notify me upon receipt of this email. You may contact me by telephone (314-539-2155) or email (Laura.Pogue@fda.hhs.gov).

Sincerely,
Laura C.
Pogue -S
Laura C. Pogue, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Hello Ms. Haggerty,

Andrew Gentles is on leave this afternoon and I am covering his assignments. Attached is the FDA’s April 21, 2017, labeling proposal (word) and a response to Gilead Sciences’ March 24, 2017 and March 30, 2017 submissions (pdf). Please confirm receipt of this email message. In addition, if you have questions or need assistance, please contact Andrew at 240-402-5708.

Best,

Karen Winestock
Chief, Project Management Staff
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products
301-796-0834 or 301-796-1500
Karen.Winestock@fda.HHS.gov
DATE: April 21, 2017

TO: Jill Haggerty
Associate Director, Regulatory Affairs
Phone: 650-522-1308
Fax: 650-522-5489
Email: jill.haggerty@gilead.com

SPONSOR: Gilead Sciences, Inc.

SUBJECT: Response to March 24, 2017 and March 30, 2017 submissions

Please refer to your March 24, 2017 submission that included recommendations for the use of statins with SOF/VEL/VOX as well as a summary of data to support the benefit of VOX in DAA-experienced population and the March 30, 2017 submission that provided a response to the agency’s labeling comments. Our main comments are outlined below and a label with our proposed revisions is attached. Please provide your revised label by April 28, 2017, noon EST.

**Indications and Usage and Dosage and Administration**

We agree the data support VOSEVI 12 weeks in patients who are NS5A inhibitor treatment-experienced without cirrhosis or with compensated cirrhosis.

We reviewed in detail the additional data and rationale provided in the March 24 and 30, 2017 submissions to support the benefit of VOX in patients who are NS5A inhibitor treatment-naïve. We have considered your position that the difference in SVR12 rates between the SOF/VEL/VOX and SOF/VEL groups is due to the cumulative negative host factors associated with lower response rates rather than viral factors. We do not agree that the POLARIS-4 data demonstrate that all DAA-experienced patients will benefit from SOF/VEL/VOX over SOF/VEL. We also do not agree that the increased likelihood of failure to SOF/VEL in this population is based on cumulative negative host factors versus HCV genotype. Our rationale for the indication and patient population description based on POLARIS 4 is summarized below:

The document did not clearly specify how the five negative host factors (cirrhosis, non-CC IL28B, male, baseline HCV RNA ≥ 800,000 IU/mL, BMI ≥30 kg/m²) were identified. These negative host factors were historically associated poorer response with interferon based regimens. For approved non-interferon containing DAA regimens, gender, BMI and IL28B do not appear to be predictive for negative virologic outcomes. Cirrhosis status has been predictive for negative virologic outcomes and is included in labeling for currently approved DAAs. To
date, Harvoni is the only DAA label that defines a population for whom treatment is guided by a baseline HCV viral load cut-off.

Even with the uncertainty about your selection of host factors and our differing perspective on the clinical significance of each of these factors, the distribution of the number of these negative host factors was overall balanced between the two groups, as would be expected in your randomized trial.

Your analysis suggested that the contribution of VOX was not evident in subjects with 1 or 2 negative host factors and therefore SOF/VEL was sufficient for these subjects. However, this subset included some cirrhotic subjects, including subjects with HCV GT3 infection and cirrhosis who are generally considered the most difficult to treat with DAA regimen (Table 1).

Table 1: SVR12 rates by HCV genotype and cirrhotic status among subjects with 1 or 2 negative host factors in POLARIS-4

<table>
<thead>
<tr>
<th></th>
<th>SOF/VEL/VOX 12 Weeks</th>
<th>SOF/VEL 12 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1a Cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>100% (10/10)</td>
<td>92.9% (13/14)</td>
</tr>
<tr>
<td>Yes</td>
<td>100% (1/1)</td>
<td>n/a</td>
</tr>
<tr>
<td>GT1b Cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>87.5% (7/8)</td>
<td>90.0% (9/10)</td>
</tr>
<tr>
<td>Yes</td>
<td>100% (1/1)</td>
<td>n/a</td>
</tr>
<tr>
<td>GT2 Cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>100% (8/8)</td>
<td>100% (7/7)</td>
</tr>
<tr>
<td>Yes</td>
<td>100% (1/1)</td>
<td>n/a</td>
</tr>
<tr>
<td>GT3 Cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>100% (8/8)</td>
<td>100% (9/9)</td>
</tr>
<tr>
<td>Yes</td>
<td>66.7% (2/3)</td>
<td>n/a</td>
</tr>
<tr>
<td>GT4 Cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>100% (2/2)</td>
<td>n/a</td>
</tr>
<tr>
<td>Yes</td>
<td>100% (1/1)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Furthermore, your analysis indicated the contribution of VOX was more evident among subjects with 3-5 negative host factors. When evaluating these subjects, the differences between treatment groups are primarily driven by GT1a and GT3 subjects (Table 2).

Table 2: SVR12 rates by HCV genotype and cirrhotic status among subjects with 3, 4 or 5 negative host factors in POLARIS-4

<table>
<thead>
<tr>
<th></th>
<th>SOF/VEL/VOX 12 Weeks</th>
<th>SOF/VEL 12 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1a Cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>100% (27/27)</td>
<td>92.9% (13/14)</td>
</tr>
<tr>
<td>Yes</td>
<td>93.8% (15/16)</td>
<td>81.3% (13/16)</td>
</tr>
</tbody>
</table>
For GT2, our analyses concluded that no relapse was observed with either SOF/VEL/VOX or SOF/VEL and both treatments had similar SVR12 rates. We conveyed these findings to you in our Mid-Cycle communication and meeting, and these findings are reflected in our proposed label.

During March 21, 2017 Mid-Cycle Meeting, we noted your discussion about Subject 00632-27709 (58-year-old NC black male, HCV GT2) who had on-treatment virologic failure in POLARIS-4. This subject represents the difference in SVR12 rates (100% versus 97%) among GT2 subjects in POLARIS-4. Our evaluation of Subject 00632-27709 identified the following:

- Baseline HCV RNA level of 230,000 IU/mL, with GT2a/2d/2j; NS5A T24S and L31M substitutions at Baseline
- No HCV RNA detected at Weeks 2 and 4
- Viral breakthrough at Week 8 with HCV RNA level of 80,500 IU/mL.
  - Emergent Y93H and low-level F28C (4%), L31V (5%), P58Q (1%), and Y93N (1%) in NS5A
  - Emergent S282T and M289I in NS5B
- Review of the records of study drug dispensed and returned showed 100% adherence during the first 4 weeks.
- 28 tablets dispensed at Week 4 (04/28/2016)
- Week 8 visit on 05/26/2016 showed a viral load of 80,500 copies/mL indicating viral breakthrough
- 9 of 28 pills returned on 06/14/2016 were not used, consistent with non-adherence (68% adherence). He was discontinued from SOF/VEL due to a lack of efficacy

The above findings, including that viral breakthrough in Subject 00632-27709 was likely due to non-adherence, factor into our conclusion that the contribution of VOX is not evident for GT2.

For GT2, we acknowledge your summary of SOF/VEL results in DAA-naïve subjects from ASTRAL-1, ASTRAL-2 and POLARIS-2 studies, as well as the abstract by Curry et al. (Utilization of sofosbuvir/velpatasvir in genotype 2-6 HCV: Real-world experience from the TRIO Network, EASL 2017) with observational data. We also considered the data in your top-line summary of the ongoing non-IND study GS-US-342-3921 (Phase 3 randomized, open-label...
study assessing SOF/VEL+RBV for 12 or 24 weeks in DAA-experienced subjects with HCV GT 1 or 2) showing 7/10 subjects (70%) with GT2 achieved SVR12. However, we cannot fully assess these data without reviewing in detail all the baseline characteristics for these subjects.

We note the overall SVR12 97% (32/33) in GT2 in POLARIS-4. Based on the totality of the data, including your additional GT2 data, we conclude that the data does not provide sufficient evidence for VOX’s contribution in the POLARIS-4 study population.

Our rationale for defining the POLARIS-4 patient population in the proposed labeling is based on the findings that the majority of subjects had failed a sofosbuvir (SOF)-containing regimen and that the treatment difference tended to be numerically large among the subjects with previous exposure to SOF (Table 3). The contribution of VOX was not evident in those receiving non SOF-containing regimens, including GT1a.

**Table 3: POLARIS-4: SVR12 rates by genotype and regimen (SOF-containing vs. non-SOF containing)**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>SOF/VEL/VOX 12 weeks</th>
<th>SOF/VEL 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOF-containing regimen</td>
<td>97.2% (35/36)</td>
<td>82.1% (23/28)</td>
</tr>
<tr>
<td>Non SOF-containing regimen</td>
<td>100% (18/18)</td>
<td>100% (16/16)</td>
</tr>
<tr>
<td>GT1b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOF-containing regimen</td>
<td>94.4% (17/18)</td>
<td>91.7% (11/12)</td>
</tr>
<tr>
<td>Non SOF-containing regimen</td>
<td>100% (6/6)</td>
<td>100% (10/10)</td>
</tr>
<tr>
<td>GT2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOF-containing regimen</td>
<td>100% (31/31) n/a</td>
<td>97.0% (32/33) n/a</td>
</tr>
<tr>
<td>Non SOF-containing regimen</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>GT3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOF-containing regimen</td>
<td>94.4% (51/54) n/a</td>
<td>84.6% (44/52) n/a</td>
</tr>
<tr>
<td>Non SOF-containing regimen</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>GT4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOF-containing regimen</td>
<td>100% (18/18)</td>
<td>n/a</td>
</tr>
<tr>
<td>Non SOF-containing regimen</td>
<td>100% (1/1)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

In summary, the review team concludes the contribution of VOX is demonstrated in for HCV genotypes 1a or 3 who are NS5B polymerase inhibitor treatment-experienced adults who are NS5A inhibitor treatment-naïve. To further explain why an indication is granted for all HCV genotypes in NS5A inhibitor treatment-experienced patients; whereas, only HCV genotypes 1a and 3 are indicated for NS5A inhibitor treatment-naïve patients, we included the following statement in section 1 and provided a similar explanation in section 14 to accompany the trial results.

- No additional benefit of VOSEVI has been established over sofosbuvir/velpatasvir for the treatment of HCV genotypes 1b, 2, 4, 5, or 6 in nucleotide analog NS5B polymerase inhibitor treatment-experienced adults who are NS5A inhibitor treatment-naïve[see Dosage and Administration (2.2) and Clinical Studies (14)].

The results from POLARIS 4 can be used to update the Epclusa labeling as appropriate.
Established and Potentially Significant Drug Interactions

1. **Statins**
   Based on your response dated March 24, 2017, you indicated that you do not intend to conduct further statin DDI studies, and your proposed labeling for unstudied statins is: [Section with sensitive information redacted]

   SOF/VEL/VOX demonstrated a greater DDI effect on both pravastatin and rosuvastatin (AUC and C\text{max} ratios ranging from 7 to 19), as compared with SOF/VEL, likely due to the inhibition of BCRP caused by VOX. For some of the unstudied statins, recent research has suggested a potential role of OATP as well as BCRP and P-gp in their transport. Transporter inhibitors with overlapping inhibition pathways with SOF/VEL/VOX (e.g., cyclosporine) have demonstrated significant interactions with most of the statins (AUC and C\text{max} ratios ranging from 4 to 12).

   Therefore, due to the observed higher degree of interaction with rosuvastatin from SOF/VEL/VOX (as compared to cyclosporine) demonstrating the unpredictability of a potentially significant DDI with most of the unstudied statins, our recommendation for labeling is: for unstudied statins, including atorvastatin, fluvastatin, lovastatin, pitavastatin, simvastatin, coadministration is not recommended.

2. **Rifampin**
   Rifampin decreases the exposures of SOF, VEL, and VOX following multiple doses and significantly increases the exposure of VOX following a single dose, thus coadministration should be contraindicated.

Please verify the receipt of this email and contact me at 240-402-5708 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration
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/s/

KAREN D WINESTOCK
04/21/2017
DATE: April 6, 2017

TO: Jill Haggerty
   Associate Director, Regulatory Affairs
   Phone: 650-522-1308
   Fax: 650-522-5489
   Email: jill.haggerty@gilead.com

SPONSOR: Gilead Sciences, Inc.

SUBJECT: Information Request

We have the following information request regarding the POLARIS-1 subject (ID# 02140-24070, 60-year-old cirrhotic black male with HCV GT1a).

We note your descriptions that this subject had previously relapsed following LDV/SOF for 12 weeks. He had baseline HCV RNA level of 1,870,000 IU/mL, no HCV RNA detected at Weeks 2, 4, and 8, and HCV RNA level of 1180 IU/mL at Week 12. Plasma concentrations of GS-331007 (the predominant SOF metabolite), VEL, and/or VOX were lower at Weeks 8 and 12 than had been observed at Weeks 1, 2, and 4. We note your conclusion that these findings were consistent with non-adherence.

Please provide additional information (e.g. returned pill counts, etc.) to support your non-adherence claim.

Please provide the requested information by April 13, 2017.

Please verify the receipt of this email and contact me at 240-402-5708 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Andrew Gentles, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration
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/s/

ANDREW A GENTLES
04/06/2017
DATE: March 28, 2017

TO: Jill Haggerty
   Associate Director, Regulatory Affairs
   Phone: 650-522-1308
   Fax: 650-522-5489
   Email: jill.haggerty@gilead.com

SPONSOR: Gilead Sciences, Inc.

SUBJECT: Information Request

Please refer to your March 24, 2017 submission with the information amendment for sofosbuvir/velpatasvir/voxilaprevir fixed-dose combination (FDC) tablet (400/100/100 mg) for the treatment of adult patients with chronic hepatitis C virus (HCV) infection. This amendment contains the additional information that was discussed at the Mid-Cycle meeting on March 21, 2017. We acknowledge you consider this information to be supportive of a pangenotypic label for SOF/VEL/VOX in DAA-experienced subjects who have not received an NS5A inhibitor. We plan to have additional internal discussions with Senior Management on April 4, 2017 about the data showing the contribution of VOX in DAA experienced patients who have never received an NS5A inhibitor.

To help facilitate our review discussion, please submit your proposal for Section 14 of the label in efforts to describe the information included in the March 24, 2017 submission and to show the contribution of VOX for this population.

Please provide the requested information by April 3, 2017, noon EST. If this information can be submitted earlier, e.g. March 31, 2017, that would be helpful to the review team to prepare for our April 4, 2017 internal meeting.

Please verify the receipt of this email and contact me at 240-402-5708 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Andrew Gentles, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration
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/s/

ANDREW A GENTLES
03/28/2017
DATE: March 22, 2017

TO: Jill Haggerty
   Associate Director, Regulatory Affairs
   Phone: 650-522-1308
   Fax: 650-522-5489
   Email: jill.haggerty@gilead.com

SPONSOR: Gilead Sciences, Inc.

SUBJECT: Clinical Pharmacology Information Request

Please refer to your December 8, 2016 submission for sofosbuvir/velpatasvir/voxilaprevir fixed-dose combination (FDC) tablet (400/100/100 mg) for the treatment of adult patients with chronic hepatitis C virus (HCV) infection. We have the following clinical pharmacology information request.

During the review of the individual PK studies, we noticed that all the validation reports and the bioanalytical reports from (for VOX analysis) have illegible representative chromatograms.

We would like you to send updated chromatograms no later than April 10, 2017.

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration
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/s/

ANDREW A GENTLES
03/22/2017
NDA 209195

MID-CYCLE COMMUNICATION

Gilead Sciences, Inc.
Attention: Jill Haggerty
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Haggerty:

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

We also refer to the teleconference between representatives of your firm and the FDA on March 21, 2017. 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 (240) 402-5708 or the mainline (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication
Meeting Date and Time: March 21, 2017 1:30 PM – 2:30 PM
Application Number: NDA 209195
Product Name: sofosbuvir/velpatasvir/voxilaprevir
Indication: treatment of chronic hepatitis c virus infection
Applicant Name: Gilead Sciences, Inc
Meeting Chair: Debra Birnkrant, MD
Meeting Recorder: Andrew Gentles, PharmD, BCPS AQ-ID

FDA ATTENDEES
John Farley, MD, MPH, Deputy Director, Office of Antimicrobial Products (OAP)
Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, MD, MPH, Deputy Director, DAVP
Poonam Mishra, MD, Deputy Director for Safety, DAVP
Stephen Miller, PhD, Chemistry, Manufacturing and Controls Lead, Office of Pharmaceutical Quality (OPQ)
Kimberly Struble, PharmD, Clinical Team Lead, DAVP
Wendy Carter, MD, Clinical Team Lead, DAVP
Kirk Chan-Tack, MD, Clinical Reviewer, DAVP
Virginia Sheikh, MD, MHS, Clinical Reviewer, DAVP
Karen Winestock, Chief Project Management Staff, DAVP
Andrew Gentles, PharmD, BCPS AQ-ID, Regulatory Project Manager, DAVP
Hanan Ghantous, PhD, Pharmacology/Toxicology
Mark Powley, PhD, Pharmacology/Toxicology Reviewer, DAVP
Julian O’Rear, PhD, Lead Clinical Virology, DAVP
Lisa Naeger, PhD, Clinical Virology Reviewer, DAVP
Eric Donaldson, PhD, Clinical Virology Reviewer, DAVP
Kellie Reynolds, PharmD, Deputy Director, Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology IV (DCP IV), Office of Translational Science (OTS)
Qin Sun, PhD, Clinical Pharmacology Reviewer, (DCP IV)
Jeffry Florian, PhD, Team Leader, (OCP), (OTS), Division of Pharmacometrics
Thamban Valappil, PhD, Biometric Team Lead, OTS, Office of Biometrics, Division of Biometrics IV (DBIV)
Karen Qi, PhD, Biometric Reviewer, DBIV
Mingfeng Zhang, MD, PhD, Epidemiologist, Division of Epidemiology II, Office of Surveillance and Epidemiology
Valerie Wilson, PharmD, Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Elizabeth Everhart, MSN, ACNP, Senior Drug Risk Analyst

APPLICANT ATTENDEES
John McHutchison, MD, Executive Vice President, Liver Diseases
Mani Subramanian, MD, Senior Vice President, Liver Diseases
Diana Brainard, MD, Vice President, Liver Diseases
Brian Kearney, PharmD, Vice President, Clinical Pharmacology

Reference ID: 4086257
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. 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

No significant issues have been identified to date as remaining review issues relate to labeling.

Indications and Usage and Dosage and Administration:

- We do not have any significant issues with the clinical, statistical, or virology data from POLARIS-1 and we agree the data support VOSEVI 12 weeks for all genotypes in NS5A inhibitor failures without cirrhosis or with compensated cirrhosis.
- As stated throughout the development of VOX, the ability to show the contribution of VOX is challenging particularly for different subgroups. Based on the POLARIS-4 trial results the contribution of VOX is not evident for GT1b, 2, 4, 5 and 6. For GT1b, SOF/VEL/VOX and SOF/VEL had almost identical SVR12 rates. For GT2, no relapse was observed with either SOF/VEL/VOX or SOF/VEL and both treatments had similar SVR12 rates. NS5A naïve subjects receiving SOF/VEL are likely to have similar SVR12 rates to those receiving SOF/VEL/VOX; therefore, additional direct evidence is needed to demonstrate VOX’s contribution to efficacy. During the mid-cycle communication we would like to discuss with you an indication for GT 1a and 3 for NS5A inhibitor naïve subjects. The label would also reflect treatment experience from the enrolled patient population.

Meeting Discussion

The discussion was focused on the Indications and Usage and Dosage and Administration comments as the Division restated the comments above which were provided to Gilead ahead of the Mid-Cycle Meeting. The Division highlighted the challenge in identifying the contribution
of VOX, particularly for different subgroups and the POLARIS-4 results where the contribution of VOX was not evident for GT1b, 2, 4, 5 and 6. Gilead acknowledged the Division's comments and concerns and indicated that there are approximately 5,000 DAA-experienced patients who are NS5A inhibitor naïve in the US and who could potentially benefit from using SOF/VEL/VOX as a retreatment option.

Gilead referenced the POLARIS trials and outlined their position that the difference in SVR12 rates between the SOF/VEL/VOX and SOF/VEL groups is not due to viral factors but attributed to the cumulative negative host factors associated with lower response rates. In addition to observational studies, Gilead indicated there was an ongoing trial in Japan that provides additional evidence that SOF/VEL, even with the addition of RBV, may not be optimal for the subset of patients failing highly effective DAA therapy, even in the absence of prior NS5A inhibitor exposure.

Gilead will provide the Division with the observational studies as well as data from the ongoing study to support their rationale for the contribution of VOX.

Clinical pharmacology DDI labeling issues:

- We note that you have provided labeling recommendations for rosuvastatin and pravastatin based on clinical DDI study results. However, there are no labeling recommendations for other statins including atorvastatin, pitavastatin, simvastatin, and lovastatin, which may be co-administered and may have the potential for DDI. Please provide appropriate labeling suggestions for those statins.

Meeting Discussion

The Division requested an update on the clinical pharmacology DDI labeling issues. Gilead indicated that they would provide the Division with a response to these Mid-Cycle comments and the information request.

Adverse Reactions:

Our changes to Section 6 include a different display of clinical trial data. Instead of pooling POLARIS 1 and 4 and only presenting the placebo group from POLARIS-1, we recommend displaying trial results separately so that both placebo and SOF/VEL arms are described. Adverse reactions from both of these comparator groups comprise the best available data to display the safety information and to help inform the safety profile of VOSEVI. According to the Guidance for Industry on Adverse Reaction Section of Labeling, the data in the listing of common ADVERSE REACTIONS should be derived from the best available data. In general, if placebo controlled data are sufficiently large to be informative, this information should be used in development of the adverse reaction table. However, DAVP considers active comparison to SOF/VEL also important to display the contribution of VOX to the adverse reaction profile therefore we recommend you add both the placebo controlled data from POLARIS-1 as well as
the SOF/VEL comparison from POLARIS-4 in displaying the common adverse reaction rates. Specific recommendations will be forthcoming after our review of the label is completed.

Meeting Discussion

Gilead acknowledged DAVP’s proposal and will provide comments after the revised proposal has been received.

3.0 INFORMATION REQUESTS
There are no information requests at this time.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT
There are no major safety concerns identified at this time and there is currently no need for a REMS.

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, Inc is May 30, 2017 2:30-4:00 PM.

The action date for this NDA is August 8, 2017
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/s/

ANDREW A GENTLES
04/19/2017
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. 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.

1. Significant Review Issues
   
   • No major safety issues identified at this time
   
   • Remaining review issues relate to labeling
     
     • Indications and Usage and Dosage and Administration
       
       o We do not have any significant issues with the clinical, statistical, or virology data from POLARIS-1 and we agree the data support VOSEVI 12 weeks for all genotypes in NS5A inhibitor failures without cirrhosis or with compensated cirrhosis.
       
       o As stated throughout the development of VOX, the ability to show the contribution of VOX is challenging particularly for different subgroups. Based on the POLARIS-4 trial results the contribution of VOX is not evident for GT1b, 2, 4, 5 and 6. For GT1b, SOF/VEL/VOX and SOF/VEL had almost identical SVR12 rates. For GT2, no relapse was observed with either SOF/VEL/VOX or SOF/VEL and both treatments had similar SVR12 rates.
naïve subjects receiving SOF/VEL are likely to have similar SVR12 rates to those receiving SOF/VEL/VOX; therefore, additional direct evidence is needed to demonstrate VOX’s contribution to efficacy. During the mid-cycle communication we would like to discuss with you an indication for GT 1a and 3 for NS5A inhibitor naïve subjects. The label would also reflect treatment experience from the enrolled patient population.

- Clinical pharmacology DDI labeling issues:

  We note that you have provided labeling recommendations for rosuvastatin and pravastatin based on clinical DDI study results. However, there are no labeling recommendations for other statins including atorvastatin, pitavastatin, simvastatin, and lovastatin, which may be co-administered and may have the potential for DDI. Please provide appropriate labeling suggestions for those statins.

- Adverse Reactions:
  - Our changes to Section 6 include a different display of clinical trial data. Instead of pooling POLARIS 1 and 4 and only presenting the placebo group from POLARIS-1, we recommend displaying trial results separately so that both placebo and SOF/VEL arms are described. Adverse reactions from both of these comparator groups comprise the best available data to display the safety information and to help inform the safety profile of VOSEVI. According to the Guidance for Industry on Adverse Reaction Section of Labeling, the data in the listing of common ADVERSE REACTIONS should be derived from the best available data. In general, if placebo-controlled data are sufficiently large to be informative, this information should be used in development of the adverse reaction table. However, DAVP considers active comparison to SOF/VEL also important to display the contribution of VOX to the adverse reaction profile therefore we recommend you add both the placebo controlled data from POLARIS-1 as well as the SOF/VEL comparison from POLARIS-4 in displaying the common adverse reaction rates. Specific recommendations will be forthcoming after our review of the label is completed.
  - Similar to SOF/VEL, your adverse reactions should be described using related, all grades, observed in greater than or equal to 5% of subjects. The remaining forthcoming labeling comments include
changes for consistency with SOF, LDV/SOF and SOF/VEL labels, including recommendations for a “Less Common Adverse Reaction” section to include rash and depression (both events in current SOF/VEL label) and display of Laboratory Abnormalities. Of note, according to the Guidance for Industry on Adverse Reaction Section of Labeling, the ADVERSE REACTION section should present less common adverse reactions when there is some basis to believe there is a causal relationship between the drug and the event.

2. Risk Management Update

- No plans for REMS at this time

3. Proposed Date for Other Projected Milestones

Preliminary Labeling due by May 8, 2017

PMR PMC labeling due by May 8, 2017

Action Date: August 8, 2017
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/s/

ANDREW A GENTLES
03/15/2017
DATE: March 13, 2017

TO: Jill Haggerty  
Associate Director, Regulatory Affairs  
Phone: 650-522-1308  
Fax: 650-522-5489  
Email: jill.haggerty@gilead.com

SPONSOR: Gilead Sciences, Inc.

SUBJECT: Clinical Pharmacology Information Request

Please refer to your December 8, 2016 submission for sofosbuvir/velpatasvir/voxilaprevir fixed-dose combination (FDC) tablet (400/100/100 mg) for the treatment of adult patients with chronic hepatitis C virus (HCV) infection. We have the following clinical pharmacology information request.

1. Please provide your plans to conduct clinical DDI studies between SOF/VEL/VOX and other statins, including atorvastatin, pitavastatin, simvastatin, and lovastatin due to the potential for significant DDI.

2. We note that VOX demonstrated IC\textsubscript{50} at > 10 µM for BCRP inhibition \textit{in vitro}, while in the rosuvastatin \textit{in vivo} DDI study, SOF/VEL/VOX increased rosuvastatin AUC by 639%, mainly due to inhibition of BCRP, since SOF/VEL/VOX only increased pravastatin (OATP substrate) AUC by 116%. In addition, in the DDI study with SOF/VEL, rosuvastatin AUC was only increased by 169%, although VEL had IC\textsubscript{50} at 0.23 µM for BCRP inhibition \textit{in vitro}. (Thus, the additional effect on rosuvastatin exposure is most likely attributed to VOX inhibition of BCRP).
   a. Please provide your rationale for the observed discrepancy between \textit{in vitro} and \textit{in vivo} study results.
   b. Please provide percentage of recovery or any data from the transporter inhibition assays to support there is no non-specific binding.

3. The VOX AUC was decreased by 63% after co-administration with SOF/VEL under fasted conditions, likely via inhibition of the intestinal uptake transporter OATP2B1, based on your proposal. However, this rationale is still not clear; please provide more details and/or data to support the proposal.

4. In study GS-US-338-1130 cohort 1, VOX was dosed at 200 mg using conventional formulation with 10 or 50 mg strength in Treatment B and C. Please provide details for how the 200 mg of VOX was dosed for each subject in treatment B and C (e.g., how
many tablets for 10 and 50 mg, respectively).

Please verify the receipt of this email and contact me at 240-402-5708 or 301-796-1500 if you have any questions regarding the contents of this transmission. We would like a response to this information request no later than March 20, 2017.

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration
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/s/

ANDREW A GENTLES
03/14/2017
DATE: March 9, 2017

TO: Jill Haggerty  
Associate Director, Regulatory Affairs  
Phone: 650-522-1308  
Fax: 650-522-5489  
Email: jill.haggerty@gilead.com

SPONSOR: Gilead Sciences, Inc.

SUBJECT: Information Request

Please refer to your March 3, 2017 submission with the safety update report for sofosbuvir/velpatasvir/voxilaprevir fixed-dose combination (FDC) tablet (400/100/100 mg) for the treatment of adult patients with chronic hepatitis C virus (HCV) infection. We have the following information request:

If an autopsy was performed for Subject 5586-27542 (GS-US-367-1170), please submit the autopsy results.

Please provide the requested information by March 17, 2017.

Please verify the receipt of this email and contact me at 240-402-5708 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Andrew Gentles, PharmD, BCPS AQ-ID  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration
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/s/

ANDREW A GENTLES
03/09/2017
INFORMATION REQUEST

Gilead Sciences, Inc.
Attention: Jill Haggerty
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Haggerty:

Please refer to your New Drug Application (NDA) dated December 7, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- GS-7977/GS-5816/GS-9857, sofosbuvir/velpatasvir/voxilaprevir, SOF/VEL/VOX, Tablet

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a written response by Thursday, March 16, 2017, in order to continue our evaluation of your NDA. A partial response at that time, with clarification of the timeline for the remaining questions, would also be satisfactory.

1. To justify the proposed in vitro dissolution method please provide the following:
   - Solubility data for the drug substances covering the physiological pH range;
   - Detailed description of the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. Include the data supporting the selection of the type and amount

2. For the in vitro dissolution data used to demonstrate the method’s discriminating ability (Module 3.2.P.5.6), please provide the numerical data (i.e., mean % dissolved at individual time points, RSD, range and number of tested units), in addition to the graphic data for each batch manufactured with variations.
If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
NDA 209195

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

ATTENTION: Jill Haggerty
Associate Director, Regulatory Affairs

Dear Ms. Haggerty:

Please refer to your New Drug Application (NDA) dated and received December 8, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sofosbuvir/Velpatisavir/Voxilaprevir Tablets, 400 mg/100 mg/100 mg.

We also refer to your correspondences dated and received December 19, 2016, and February 9, 2017, requesting review of your proposed proprietary name, Vosevi.

We have completed our review of the proposed proprietary name, Vosevi and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your December 19, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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:

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 Andrew Gentles, Regulatory Project Manager in the Office of New Drugs, at 240-402-5708.

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
03/01/2017

DANIELLE M HARRIS on behalf of TODD D BRIDGES
03/01/2017
Gilead Sciences, Inc.
Attention: Jill Haggerty
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Haggerty:

Please refer to your New Drug Application (NDA) dated December 8, 2016, received December 8, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for sofosbuvir, velpatasvir, and voxilaprevir tablet, 400mg/100mg/100mg.

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 August 8, 2017. 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.](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 May 8, 2017. In addition, the planned date for our internal mid-cycle review meeting is March 3, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

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

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 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.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

- A horizontal line must separate the TOC from the Full Prescribing Information (FPI).

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by February 13, 2017.

**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:  

Reference ID: 4051617
Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI (as applicable), and you believe the labeling is close to the final version.

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

**REQUIRED PEDIATRIC ASSESSMENTS**

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

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

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

If you have any questions, call Andrew Gentles, PharmD, BCPS AQ-ID, Regulatory Project Manager, at (240) 402-5708.

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
02/06/2017
INFORMATION REQUEST

Gilead Sciences, Inc.
Attention: Jill Haggerty
Associate Director, Regulatory Affairs
333 Lakeside Drive
Palo Alto, CA 94304

Dear Ms. Haggerty:

Please refer to your New Drug Application (NDA) dated December 7, 2016, submitted under section 505(b) 1 of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- GS-7977/GS-5816/GS-9857, sofosbuvir/velpatasvir/voxilaprevir, SOF/VEL/VOX, 400mg/100mg/100mg Tablet

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a written response by Feb 9, 2017, in order to continue our evaluation of your NDA.

1. Please clarify the thickness of the commercial tablet and provide some representative samples.
   - The samples may be sent to the attention of:
     FDA – White Oak
     Luz E. Rivera, Psy.D.
     LCDR, US Public Health Service
     Quality Assessment Lead (Acting), Div. I, Branch I
     Bldg 75, Room 4649
     10903 New Hampshire Avenue
     Silver Spring, MD 20993

If you have any questions, please call Luz Rivera at (301) 796-4013 and Thao Vu at (240) 402-2690 or email luz.e.rivera@fda.hhs.gov and thao.vu@fda.hhs.gov.
Sincerely,

{See appended electronic signature page}

On Behalf of
LCSR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Date: January 17, 2017

To: Jill Haggerty
Associate Director, Regulatory Affairs
Phone: 650-522-1308
Fax: 650-522-5489
Email: jill.haggerty@gilead.com

Sponsor: Gilead Sciences, Inc.

Subject: Information Request

Please refer to your December 8, 2016 submission for sofosbuvir/velpatasvir/voxilaprevir fixed-dose combination (FDC) tablet (400/100/100 mg) for the treatment of adult patients with chronic hepatitis C virus (HCV) infection. We have the following information request:

1) Please submit the autopsy results for Subject 00380-27734 (GS-US-367-1170).

2) For Subject 04472-26730 (GS-US-367-1172) who experienced a serious adverse event (SAE) of cerebral hemorrhage on study Day 28, the outcome was described as ongoing at the time of data finalization and the last submitted follow-up (dated 11/10/16) stated there was no new significant information. Please provide any additional follow-up and outcome on this SAE.

Please provide the requested information by January 31, 2017.

Please verify the receipt of this email and contact me at 240-402-5708 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration
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/s/

ANDREW A GENTLES
01/17/2017
Dear Ms. Haggerty:

Please refer to your New Drug Application (NDA) dated and received December 8, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sofosbuvir/Velpatisavir/Voxilaprevir Tablets, 400 mg/100 mg/100 mg.

We acknowledge receipt of your correspondence dated and received December 19, 2016, requesting a review of your proposed proprietary name, Vosevi.

The target date is March 19, 2017.

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 Andrew Gentles, Regulatory Project Manager, in the Office of New Drugs at (240) 402-5708.

Sincerely,

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

Reference ID: 4036666
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/s/

AZEEM D CHAUDHRY
01/04/2017
NDA 209195

NDA ACKNOWLEDGMENT

Gilead Sciences, Inc.
Attention: Jill Haggerty
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Haggerty:

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/voxilaprevir fixed dose combination 400mg/100mg/100mg tablet

Date of Application: December 8, 2016

Date of Receipt: December 8, 2016

Our Reference Number: NDA 209195

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 February 6, 2017, 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:
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 Andrew Gentles, PharmD, BCPS AQ-ID, Regulatory Project Manager, at (240) 402-5708.

Sincerely,

{See appended electronic signature page}

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
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/s/

ANDREW A GENTLES
12/19/2016
DATE: December 12, 2016

TO: Jill Haggerty  
Associate Director, Regulatory Affairs  
Phone: 650-522-1308  
Fax: 650-522-5489  
Email: jill.haggerty@gilead.com

SPONSOR: Gilead Sciences, Inc.

SUBJECT: Information Request

Please refer to your December 8, 2016 submission for sofosbuvir/velpatasvir/voxilaprevir fixed-dose combination (FDC) tablet (400/100/100 mg) for the treatment of adult patients with chronic hepatitis C virus (HCV) infection. We also refer to the October 26, 2016 pre-NDA meeting. We have the following information request:

Please provide additional justification that details the contribution of VOX for each genotype and various subgroups, as this will be a key review issue and would also impact the specific language for labeling.

Please provide the requested information by December 23, 2016.

Please verify the receipt of this email and contact me at 240-402-5708 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Andrew Gentles, PharmD, BCPS AQ-ID  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration
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/s/

ANDREW A GENTLES
12/12/2016
Hello Jill,
The Biometrics Reviewer who will be receiving this information is Dr. Therri Usher. Below is her address.

Therri Usher, Ph.D
Biometric Reviewer
Division of Biometrics IV
10903 New Hampshire Ave
Bldg. 21 Room 3646
Silver Spring MD 20993

Thanks,
AG

Hi Andrew,

For the upcoming SOF/VEL/VOX NDA 209195, Gilead intends to submit source documentation for treatment allocation codes for the Phase 3 POLARIS studies as described in the Type B meeting information package (SN0042, IND 125751) dated 21 April 2016 and as we have done for previous HCV NDAs. As such, we will send a FedEx package containing the randomization codes from our IWRS vendor in tamper proof envelopes directly to the biometrics reviewer, Dr. Karen Qi immediately after submission of the original NDA 209195. A copy of the SOF/VEL/VOX NDA cover letter will be included in the package.

Could you please confirm that I have correct biometrics reviewer and address for NDA 209195?

Karen Qi, PhD
Biometrics Reviewer
Division of Biometrics IV
10903 New Hampshire Ave
Bldg. 21 Room 3651
Silver Spring MD 20903

Thanks,
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/s/

ANDREW A GENTLES
11/18/2016
IND 125751

Gilead Sciences, Inc.
Attention: Jill Haggerty
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Haggerty:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX).

We also refer to the telecon between representatives of your firm and the FDA on June 2, 2016. The purpose of the meeting was to discuss Gilead’s plan for submission of SOF/VEL/VOX NDA in December 2016.

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 me at (240) 402-5708.

Sincerely,

{See appended electronic signature page}

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: June 2, 2016 at 9:00 AM – 10:00 AM
Meeting Location: TCON

Application Number: 125751
Product Name: SOF/VEL/VOX
Indication: Treatment of Chronic Hepatitis C Virus (HCV)
Sponsor/Applicant Name: Gilead Sciences, Inc

Meeting Chair: Wendy Carter, DO
Meeting Recorder: Andrew Gentles, PharmD, BCPS AQ-ID

FDA ATTENDEES
Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, MD, MPH, Deputy Director, DAVP
Kimberly Struble, PharmD, Clinical Team Lead, DAVP
Wendy Carter, DO, Clinical Reviewer, DAVP
Karen Winestock, Chief Project Management Staff, DAVP
Andrew Gentles, PharmD, BCPS AQ-ID, Regulatory Project Manager, DAVP
Mark Powley, PhD, Pharmacology/Toxicology Reviewer, DAVP
David McMillan, PhD, Pharmacology/Toxicology Reviewer, DAVP
Julian O’Rear, PhD, Lead Clinical Virology, DAVP
Lisa Naeger, PhD, Clinical Virology Reviewer, DAVP
Eric Donaldson, PhD, Clinical Virology Reviewer, DAVP
Jenny Zheng, PhD, Clinical Pharmacology Reviewer
Karen Qi, PhD, Biometric Reviewer

EASTERN RESEARCH GROUP ATTENDEES
Peggah Khorrami, Independent Assessor
Christopher Sese, Independent Assessor

SPONSOR ATTENDEES
Mani Subramanian MD, Senior Vice President, Liver Diseases
Diana Brainard, MD, Vice President, Liver Diseases
Richard Polniaszek, PhD, Senior Director, Process Development
1.0 BACKGROUND

A fixed dose combination tablet containing sofosbuvir (SOF), a NS5B polymerase inhibitor, velpatasvir (VEL), a NS5A inhibitor, and voxilaprevir (VOX), a NS3/4A protease inhibitor is being proposed for the treatment of genotype 1-6 chronic hepatitis C virus (HCV) infection in adults. At the EOP2 Type B meeting held on September 30, 2015, Gilead Sciences, Incorporated discussed their Phase 3 development strategy with DAVP and plans for an NDA submission in patients with chronic hepatitis C virus infection. SOF/VEL/VOX was granted Fast Track designation on June 12, 2015 and Breakthrough Therapy (BT) designation for the treatment of chronic HCV genotype 1 infection in patients who have previously failed an NS5A inhibitor containing DAA regimen on February 19, 2016. Gilead then submitted a Type B Pre-NDA meeting request on March 23, 2016 to obtain feedback from the FDA on key aspects related to the NDA submission strategy, proposed indication, content and format of the application as well as content of the NDA safety update. A Type B Pre-NDA meeting was granted by the FDA for June 2, 2016 but converted to a teleconference at the request of the sponsor on May 24, 2016. FDA sent preliminary comments to the sponsor on May 31, 2016 and sponsor requested the agenda of telecon focus on Questions 9, 11, and 16.

2. DISCUSSION

Clinical/Statistical Questions

**Question 9:** Does the Agency agree with the proposal for inclusion of the ISE and ISS text and supporting statistical outputs and electronic datasets in the eCTD modules as described in Section 4.3.2?

**FDA Response to Question 9:** No, according to FDA’s April 2009 Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document, Module 5 is the appropriate location for the ISE and ISS. The rare exception to include the ISE and ISS in Module 2 is reserved for applications that are small and consist of a single study or a number of small studies. You are proposing four phase 3 trials with supportive safety from an additional four phase 2 trials. The ISE and ISS are not intended as summaries but rather detailed integrated analyses of all relevant data (including tables and appendices) from the clinical study reports that belong in Module 5. Therefore, to be consistent with the guidance, the text for the ISE and ISS should be placed in Module 5, section 5.3.5.3 and appropriate summaries should be placed in Modules 2.7.3 and 2.7.4. Additionally, combining the text of the ISE and ISS into a single document with the supporting statistical outputs allows for easier navigation with hyperlinks. We are agreeable to allowing the same text to be used from the ISE and ISS as the Summary of Clinical Efficacy and Summary of Clinical Safety, respectively, if the text will be under the 400 page limit acceptable for Module 2.
**Discussion:** FDA described the navigational challenges when the ISS and ISE are located in Module 2 and not combined as single document allowing for easier navigation with hyperlinks. FDA recommended the sponsor place text for both ISE and ISS in Module 5 as per the guidance outlined in the FDA’s April 2009 “Guidance for Industry: Integrated Summaries of Effectiveness and Safety.” The Sponsor thanked the FDA for clarifying this question and indicated they would discuss this internally and submit a written response to either agree or propose an alternative.

**Question 11:** Does the Agency agree with this proposal regarding analysis of on-treatment liver injury for subjects in the Phase 2 study populations and the Phase 3 integrated safety population?

**FDA Response to Question 11:** Yes, we agree with the proposal. Your ISS analysis plan proposes to include only phase 3 trials in the ISS datasets. Please clarify that there will be an integrated analysis dataset(s) submitted with both the phase 2 and phase 3 trials combined to conduct independent analyses for the liver-related laboratory and adverse event analyses. Please clarify that you will have an Independent Adjudication Committee (IAC) evaluate all pre-specified liver-related laboratory abnormalities, treatment-emergent deaths, liver transplants, hepatic failure events and hepatic events leading to discontinuation of study drug in the integrated phase 3 and phase 2 safety populations, consistent with what has been done with prior submissions.

**Discussion:** Due to recently updated labels on liver safety concerning approved FDA HCV drugs, the FDA reiterated the need to have independent analyses for all liver-related laboratory and adverse events. Given the addition of a protease inhibitor in this fixed dose combination, the FDA also felt it was important for the Sponsor to have an independent adjudication committee (IAC) evaluate all liver-related laboratory abnormalities, treatment-emergent deaths, liver transplants, hepatic failure events and hepatic events. The Sponsor affirmed understanding and indicated they would convene an IAC so that the scope of the review would be consistent with what has been done with prior submissions.

**Question 16:** Does the Agency agree with the proposed presentation of efficacy data based on subject genotype determined by baseline sequencing?

**FDA Response to Question 16:** Please clarify the limitations of the Abbott assay you are referring to (i.e., determination of subtype?), which prevent the results being used for the presentation of efficacy.

**Discussion:** The Sponsor indicated that the Abbott assay was selected by an IRB as it is the only assay currently FDA approved for determination of HCV genotypes and subtypes. This is in comparison to the line probe assay (LiPA) 2.0 which is frequently used to determine HCV genotypes and subtypes. The main limitation with the Abbott assay is the inability to distinguish some genotypes and subtypes, such as genotype 2, 4 and 6 and subtypes 1a and 1b, which would impact approximately 15% of the study samples. The Agency stated that the preference is for efficacy to be presented by the screening genotype assay results rather than post-hoc genotype analysis results. The Sponsor agreed to submit preliminary screening and analysis genotype/subtype data for our review.
DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed. The Sponsor was reminded that all applications should be complete at the time of submission and for applications reviewed under PDUFA V’s “The Program”, only minor NDA components can be submitted within 30 days of receipt of the NDA. The Sponsor confirmed understanding of this and indicated that no minor components are intended to be submitted within the 30 days after the original NDA submission date.

Post Meeting Comment: Based upon the table of contents included in the meeting briefing package, it appears the application will be complete at time of submission.

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

- A preliminary discussion on the need for a REMS was held and the Division concluded sufficient information was currently not available 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. A final determination for the need for a REMS will occur during the review of your application.

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

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

**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 *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- 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
- 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 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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* ([http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf)).

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

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. Beginning May 5, 2017, the following submission types: NDA, ANDA, BLA and Master Files must be submitted in eCTD format. Commercial IND submissions must be submitted in eCTD format beginning May 5, 2018. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ctd.

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.”

<table>
<thead>
<tr>
<th>Site Name</th>
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<th>Federal Establishment Indicator (FEI) or Registration Number (CFN)</th>
<th>Drug Master File Number (if applicable)</th>
<th>Manufacturing Step(s) or Type of Testing [Establishment function]</th>
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<td>2.</td>
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Corresponding names and titles of onsite contact:

<table>
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<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Onsite Contact (Person, Title)</th>
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<td>2.</td>
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</table>
**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

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.”

<table>
<thead>
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<th>DSI Pre-NDA Request Item&lt;sup&gt;1&lt;/sup&gt;</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
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</thead>
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<td>I</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
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<tr>
<td>I</td>
<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
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</tr>
<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study (Line listings, by site)</td>
<td>.pdf</td>
</tr>
<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

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

```
[ m5 ]
  └─ datasets
     └─ bimo
        └─ site-level
```

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

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

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

ISSUES REQUIRING FURTHER DISCUSSION
Results from Phase 3 trials will determine potential review issues or identify additional analysis/information need at the time of submission.

ACTION ITEMS

<table>
<thead>
<tr>
<th>Action Item/Description</th>
<th>Owner</th>
<th>Due Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide written response to Question #9 and #16</td>
<td>Sponsor</td>
<td>Prior to submitting the NDA</td>
</tr>
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</table>

ATTACHMENTS AND HANDOUTS
Preliminary comments attached.
MEETING PRELIMINARY COMMENTS

Gilead Sciences, Inc.
Attention: Jill Haggerty
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Haggerty:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX).

We also refer to your March 23, 2016, correspondence, received March 23, 2016, requesting a pre-NDA meeting to discuss the plan for submission of SOF/VEL/VOX fixed dose combination tablet and to agree on key components of the NDA submission.

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.

Our preliminary responses to your meeting questions are enclosed.

If you have any questions, call me at (240) 402-5708.

Sincerely,

[See appended electronic signature page]

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Reference ID: 3951114
ENCLOSURE:
  Preliminary Meeting Comments
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: June 2, 2016, 9:00 - 10:30 am
Meeting Location: TCON

Application Number: IND 125751
Product Name: Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX)
Indication: Treatment of Chronic Hepatitis C infection
Sponsor/Applicant Name: Gilead Sciences, Inc.

FDA ATTENDEES (tentative)
Edward M. Cox, MD, MPH, Director, Office of Antimicrobial Products (OAP)
John Farley, MD, Deputy Director, OAP
Katherine Schumann, MS, Acting Associate Director Regulatory Affairs, OAP
Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, MD, MPH, Deputy Director, DAVP
Kimberly Struble, PharmD, Clinical Team Lead, DAVP
Wendy Carter, MD, Clinical Reviewer, DAVP
Karen Winestock, Chief Project Management Staff, DAVP
Andrew Gentles, PharmD, BCPS AQ-ID, Regulatory Project Manager, DAVP
Stephen Miller, PhD, Chemistry, Manufacturing and Controls Lead, Office of Pharmaceutical Quality (OPQ)
Florence Aisida, Regulatory Business Project Manager, OPQ
Mark Powley, PhD, Pharmacology/Toxicology Reviewer, DAVP
Hanan Ghantous, PhD, DABT, Pharmacology/Toxicology Team Lead, DAVP
Lisa Naeger, PhD, Clinical Virology Reviewer, DAVP
Eric Donaldson, PhD, Clinical Virology Reviewer, DAVP
Julian O’Rear, PhD, Lead Clinical Virology, DAVP
Jenny Zheng, PhD, Clinical Pharmacology Reviewer, Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology IV (DCP IV)
Shirley Seo, PhD, Clinical Pharmacology Team Lead
Karen Qi, PhD, Biometric Reviewer
Thamban Valapill, PhD, Biometric Team Lead, OTS, Office of Biometrics, Division of Biometrics IV (DBIV)
Poonam Mishra, MD, Deputy Director for Safety, DAVP

Reference ID: 3951114
Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the upcoming teleconference scheduled for June 2, 2016, 9:00 – 10:30 am between Gilead Sciences, Inc and the Division of Antiviral Products (DAVP). We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

A fixed dose combination tablet containing sofosbuvir (SOF), a NS5B polymerase inhibitor, velpatasvir (VEL), a NS5A inhibitor and voxilaprevir (VOX), a NS3/4A protease inhibitor is being proposed for the treatment of genotype 1-6 chronic hepatitis C virus (HCV) infection in adults. At the EOP2 Type B meeting held on September 30, 2015, Gilead Sciences, Incorporated discussed their Phase 3 development strategy with DAVP and plans for an NDA submission in patients with chronic hepatitis C virus infection. SOF/VEL/VOX was granted Fast Track designation on June 12, 2015 and Breakthrough Therapy (BT) designation for the treatment of chronic HCV genotype 1 infection in patients who have previously failed an NS5A inhibitor containing DAA regimen on February 19, 2016. Gilead has now submitted a Type B Pre-NDA meeting request on March 23, 2016 to obtain feedback from the FDA on key aspects related to the NDA submission strategy, proposed indication, content and format of the application as well as content of the NDA Safety update.
2.0 DISCUSSION

2.1 Submission Strategy Question

Question 1: Does the Agency agree that the proposed indication for SOF/VEL/VOX is supported by the clinical studies described in Table 1, provided the totality of the data support demonstration of the contribution of VOX to the regimen as outlined in previous discussions with the Agency?

FDA Response to Question 1: You proposed a broad indication for SOF/VEL/VOX for the treatment of genotype 1-6 chronic HCV infection in adults. However, determination of the specific indication for SOF/VEL/VOX for each HCV genotype is a review issue. As discussed at the EOP2 meeting, the contribution of VOX to the regimen of SOF/VEL must be supported by the data submitted. At this time we are unable to determine that the totality of the data supports the contribution of VOX to the regimen in all genotypes and proposed populations.

2.2 NDA Structure and Content Questions

Question 2:

a) Does the Agency agree with the proposal not to resubmit previously submitted nonclinical and clinical SOF, VEL, and SOF/VEL reports and to cross reference nonclinical and clinical studies to NDA 204671 and NDA 208341 (or other applications, as applicable)?

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

FDA Response to Question 2: Yes, we agree to both a and b.

Question 3: Does the Agency concur that the nonclinical studies listed in the draft proposed Table of Contents for the SOF/VEL/VOX NDA included in Attachment 1 support the registration of SOF/VEL/VOX?

FDA Response to Question 3: The listed non-clinical safety studies listed are of the types needed to support an NDA submission. Note that additional data may be needed to follow-up on any concerns identified in ongoing/planned non-clinical studies or clinical trials.

Question 4: Does the Agency agree with the proposal to use cross-application links to provide information on SOF and VEL drug substance?

FDA Response to Question 4: We agree in general with this approach, with the following specific recommendations. All facilities involved with the manufacture and testing of the SOF and VEL drug substances should be listed in the S.2 sections of Modules 2 and 3. Additionally, those facilities should be included in the 356h form. The application should also describe general
properties of the SOF and VEL drug substances that are relevant to the quality of the SOF, VEL, and VOX drug product.

**Question 5**: Does the Agency agree with the proposal for provision of the documentation in Modules 1 and 5 described above and in Table 3?

**FDA Response to Question 5**: Yes, we agree.

**Question 6**: Does the Agency agree with this proposal for provision of references?

**FDA Response to Question 6**: Yes, we agree.

**Question 7**: Does the Agency agree with this proposal for provision of the thorough QT/QTc study with VOX in the NDA?

**FDA Response to Question 7**: Yes, we agree.

2.3 Clinical/Statistical Questions

**Question 8**: Does the Agency concur with the proposed analysis strategy for the ISE and ISS?

**FDA Response to Question 8**: Yes, the proposed analysis strategy is acceptable.

**Question 9**: Does the Agency agree with the proposal for inclusion of the ISE and ISS text and supporting statistical outputs and electronic datasets in the eCTD modules as described in Section 4.3.2?

**FDA Response to Question 9**: No, according to FDA’s April 2009 Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document, Module 5 is the appropriate location for the ISE and ISS. The rare exception to include the ISE and ISS in Module 2 is reserved for applications that are small and consist of a single study or a number of small studies. You are proposing four phase 3 trials with supportive safety from an additional four phase 2 trials. The ISE and ISS are not intended as summaries but rather detailed integrated analyses of all relevant data (including tables and appendices) from the clinical study reports that belong in Module 5. Therefore, to be consistent with the guidance, the text for the ISE and ISS should be placed in Module 5, section 5.3.5.3 and appropriate summaries should be placed in Modules 2.7.3 and 2.7.4. Additionally, combining the text of the ISE and ISS into a single document with the supporting statistical outputs allows for easier navigation with hyperlinks. We are agreeable to allowing the same text to be used from the ISE and ISS as the Summary of Clinical Efficacy and Summary of Clinical Safety, respectively, if the text will be under the 400 page limit acceptable for Module 2.

**Question 10**: Does the Agency agree with this proposal regarding AEs of interest?

**FDA Response to Question 10**: Yes, we agree.
**Question 11:** Does the Agency agree with this proposal regarding analysis of on-treatment liver injury for subjects in the Phase 2 study populations and the Phase 3 integrated safety population?

**FDA Response to Question 11:** Yes, we agree with the proposal. Your ISS analysis plan proposes to include only phase 3 trials in the ISS datasets. Please clarify that there will be an integrated analysis dataset(s) submitted with both the phase 2 and phase 3 trials combined to conduct independent analyses for the liver-related laboratory and adverse event analyses. Please clarify that you will have an Independent Adjudication Committee (IAC) evaluate all pre-specified liver-related laboratory abnormalities, treatment-emergent deaths, liver transplants, hepatic failure events and hepatic events leading to discontinuation of study drug in the integrated phase 3 and phase 2 safety populations, consistent with what has been done with prior submissions.

**Question 12:** Does the Agency have any comments regarding Gilead’s proposal for structure and format of datasets for the NDA?

**FDA Response to Question 12:** The proposal for structure and format of datasets for the NDA is acceptable.

**Question 13:** Does the Agency agree with the proposed scope for datasets to be submitted to the SOF/VEL/VOX NDA?

**FDA Response to Question 13:** Yes, however, we request that all the Phase 3 studies are submitted with the new vertical template format from the pilot guidance, as well as datasets consistent with the 2013 Guidance. The NGS submissions and other datasets noted in the table are acceptable.

2.4 Virology

**Question 14:** Does the Agency agree with the proposal for provision of virology data?

**FDA Response to Question 14:** Yes.

**Question 15:** Does the Agency agree with the proposed definition for NS5A RAPs and the proposed reference strains to be used for analyzing the effect of baseline NS5A variants on treatment outcome?

**FDA Response to Question 15:** The Division defines polymorphisms as the predominant amino acid in a treatment-naïve individual’s virus population that differs from the reference amino acid. Please include NS5A amino acid positions 24, 58 and 92 in the list. For GT4, please only report variants as RAPs that differ from the GT4 reference at amino acid 31.
**Question 16:** Does the Agency agree with the proposed presentation of efficacy data based on subject genotype determined by baseline sequencing?

**FDA Response to Question 16:** Please clarify the limitations of the Abbott assay you are referring to (i.e., determination of subtype?), which prevent the results being used for the presentation of efficacy.

**Question 17:**

a) Does the Agency agree with the proposal for provision of virology ADVR and NGS data in the SOF/VEL/VOX NDA?

b) Does the Agency agree with the content and format of the sample ADVR dataset reflecting the new template format from the pilot guidance provided by the Agency?

**FDA Response to Question 17 (a and b):** We request that all the Phase 3 studies are submitted with the new template format from the pilot guidance, as well as datasets consistent with the 2013 Guidance. We will be reviewing this NDA using the new format, but may need to reference the old format. We are including with this correspondence the updated version of the pilot guidance for your reference. In addition, we have included at the end of this correspondence general comments and responses to your questions/assumptions in Table 5. Please note that the new template format from the pilot guidance allows for the NGS frequency table to be incorporated into the resistance dataset, and the new format will be used to review the NGS data. However, NGS frequency tables in the old format should also be provided for reference.

### 2.5 Labeling Questions
**Question 19:** Does the Agency agree that the currently available safety information for SOF/VEL/VOX does not warrant inclusion of a REMS?

**FDA Response to Question 19:** At this time, the Office of Antimicrobial Products and the Office of Surveillance and Epidemiology do not have sufficient 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 Regulatory Review Questions

**Question 20:** Given the Breakthrough Therapy designation for SOF/VEL/VOX, does the Agency support an expedited review of the SOF/VEL/VOX marketing application?

**FDA Response to Question 20:** Due to the lack of Phase 3 efficacy and safety data submitted with present 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 21:** Does the Agency agree with the proposal for the timing and content of the NDA Safety Update Report?

**FDA Response to Question 21:** We agree with the timing of the SUR. We refer you to the response to question 18 however, otherwise the proposed content is acceptable.

**Question 22:** Does the Agency agree with this proposal for the timing and scope of a Type B meeting in advance of the NDA filing?

**FDA Response to Question 22:** Typically preNDA meetings contain both procedural questions and topline safety and efficacy results from the Phase 3 program to support an NDA submission. As mentioned with your previous NDA submissions, we find preNDA meetings without safety and efficacy data challenging. One goal of a preNDA meeting is to identify potential review issues and discuss additional analyses needed in the NDA based on preliminary data. In the absence of data, key interactions on additional data requests or requests for analyses are limited. Requesting a second meeting weeks prior to the actual NDA submission is not ideal and does not allow for sufficient time to address potential issues prior to an NDA submission. We have suggested in the past you alter timelines accordingly. For other preNDA meetings SVR12 data are part of the briefing package. We acknowledge the potential for high concordance between SVR4 and SVR12 data based on prior data from phase 2 and the SOF/VEL program; however, you assume the risk that if the concordance is not confirmed our advice may evolve based on
these data. We request the backgrounder at a minimum include SVR4 data for all subjects and 50% of the SVR12 data in the Phase 3 trials.

The briefing package as well as the planned NDA submission should include adequate efficacy and safety data and justification for the proposed dosing regimen of SOF/VEL/VOX in the patient populations and genotypes studied in POLARIS-1, POLARIS-2, POLARIS-3 and POLARIS-4. Please outline how the contribution of VOX is demonstrated for the various patient populations.

**Question 23**: Does the Agency agree with the proposal to submit NGS datasets on an external hard drive to the SOF/VEL/VOX NDA, arriving within 5 business days of the electronic submission of the original NDA and that the PDUFA review timeline for the NDA would commence on the day of receipt of the eCTD submission?

**FDA Response to Question 23**: All applications should be complete at the time of submission and for applications reviewed under PDUFA V’s “The Program”, only minor NDA components can be submitted within 30 days of receipt of the NDA. The NGS data are essential to the review of the application and should arrive on the same day the NDA is expected to arrive via the Gateway.

### 2.7 Additional Information

**Virology - additional comments will also be sent in a separate information response**

It is presently unclear if subjects who failed their first NS5A containing regimen and had RAPs at baseline are equivalent to subjects who failed their first NS5A containing regimen and did not have RAPs at baseline. Please report this information in the NDA and include this data in the resistance dataset.

**Responses to Gilead Comments and Assumptions regarding the HCV Vertical Resistance Analysis Template (Table 5)**

1. Please note that minor updates have been incorporated into the vertical structure resistance analysis template. See attached ‘clean’ and ‘track changes’ versions of this updated (“March 2016”) template. Updates from the August 2015 version include the following:

   a. Please report PFGENLOC results only as numbers and in ‘integer’ format. We recognize this is a minor conflict with CDISC pharmacogenomics recommendations, but this is a format we request for our analysis purposes. Note that this format does not accommodate characters for identifying positions where there are insertions; the reporting of insertions is discussed below. Also note that the updated template also recommends similar reporting of PFNUMLOC in ‘integer’ format; however, it is acceptable to use ‘text’ format for the PFNUMLOC variable to allow for reporting of length differences between the reference strain (PFREF) and the numbering system strain (PFNUMRF) as you have done in the mock dataset.
b. Please include an additional variable comparable to PFRESALL but with all variants reported at the 15% sensitivity cutoff, and call this variable “PFRESA15”. Additional similar variables can be added as desired to report mixtures detected at a given sensitivity level. For example, PFRESA20 would report all amino acids based on a 20% sensitivity cutoff. This variable is referred to as ‘PFRESAyy’ in the updated template.

c. Minor updates have been incorporated into the template for consistency with the CDISC Virology v2.0 user guide, which was not yet finalized at the time of communicating the August 2015 analysis template.

d. Additional minor edits for clarification are included in the updated template.

2. Because amino acid variability between different HCV subtypes can affect interpretation of results, please use subtype-specific reference sequences (for PFREF) for reporting amino acid changes in clinical samples. Subtype reference sequences used should be as close to subtype consensus sequences as possible. For any novel HCV subtypes, a prototypical reference strain within the genotype can be used as the reference.

3. Please provide a separate dataset that reports and aligns all of the reference amino acid sequences used.

4. It appears that all amino acid sequence data were reported, even when the result (PFORRES) matched the reference (PFORREF). Please do not report amino acid results that match the reference result, only changes relative to reference. Presumably removing all rows for PFRESCAT=null should address this. The one exception is for mixtures of a substitution with reference; in these cases please include the row for the reference result as well. In other words, include all results detected at a position where there is a non-null PFRESCAT value at that position.

5. We have noted your comment at the bottom of Table 5 regarding the reporting of multiple HCV genotype/subtype results from the same subject based on different methods. This information should be provided using sets of ‘Strata’ or ‘Subgroup’ variables, or other appropriate variables as needed that provide the assay name and assay result for each assessment of HCV genotype/subtype for each subject.

Responses to questions/assumptions in Table 5

1. ORGNAMID: We agree that the OI domain is optional, and we agree with your example values. Note that this variable has been renamed in the March 2016 version as NHOID for consistency with the published CDISC Virology v2.0 user guide.

2. PFTESTCD: We agree with use of ‘AA’.

3. PFTEST: We agree with use of ‘Amino Acid’.
4. **PFGENTYP**: We agree with use of PROTEIN (note: thank you for pointing out the conflict between the two templates; we will address this in a future update of the vertical resistance analysis template.)

5. **PFGENRI**: We agree. However, since you are separating PFGENRI for NS3 and NS4A, please use the corresponding PFGENRNG for each genome region.

6. **PFORRES**: We agree with your approach for indicating assay failures. Please also see general comment #4 above.

7. **PFREF**: We agree with including the accession number; however, please also include the strain name (e.g., ‘ED43-GU814265’). As noted above, we recommend using subtype-specific references.

8. **PFGENLOC**: As noted above, please do not include characters in this variable and format the data as ‘integer’ (i.e., numeric). Additional recommendations with respect to insertions and deletions are provided below in #14.

9. **PFNUMLOC**: We agree.

10. **PFNUMRF**: We agree. Again, please include the strain name with the accession number. Also, please populate the PFNUMRF result even if there is a deletion in the PFNUMRF strain relative to the PFREF strain.

11. **SUPPPF domain**: We agree that any variables not included in the latest CDISC Virology TAUG but requested for the analysis-ready dataset can be provided in a SUPPPF file.

12. **NGSALGO**: We agree.

13. **ENRCHFLC and ENRCHFL (also refers to BLPMFL):**

   a. The ENRCHFLC and ENRCHFL variables are intended to flag any amino acid substitutions (relative to reference) that were detected both at Baseline and in the indicated Post-Baseline sample, but were enriched in the Post-Baseline sample by a defined level (e.g., 10% at Baseline and 60% at Follow-up Week 4, meeting your ≥2-fold enrichment definition). The ENRCHFLC and ENRCHFL variables are not intended to be used for substitutions detected in the Post-Baseline sample but not at Baseline.

   b. A BLPMFL=N result for a Post-Baseline isolate flags a substitution detected in the Post-Baseline sample but not at Baseline. A BLPMFL=Y result for a Post-Baseline isolate indicates the substitution was detected at Baseline. In the case of an ENRCHFL=Y substitution in a Post-Baseline isolate, the BLPMFL=Y (i.e., because it was also detected at Baseline).

   c. By definition, all Pre-Treatment/Baseline visit amino acid sequence results should be populated as BLPMFL=Y.
d. Specifically regarding your ‘enrichment’ definition of ≥2-fold from Baseline, we agree, but please be aware that we may consider or explore other definitions.

e. Independent FDA analyses of treatment-emergent resistance for subjects who did not achieve SVR will consider both newly emergent (BLPMFL=N) and treatment-enriched (ENRCHFL=Y) substitutions, and these analyses will include confirmation of your BLPMFL and ENRCHFL results.

f. The resistance analysis template does not include one single flag variable that considers a composite of both BLPMFL=N and ENRCHFL=Y amino acid substitutions, but you are welcome to add such a variable.

14. PFSTRESC (response pertains to insertions and deletions in general):

Insertions, your example is as follows:

Please populate PFGENLOC, PFORREF, PFSTRESC and PFRESALL as follows. Also note the rows that can be deleted per general recommendation #4 above. For PFGENLOC, the position of the insertion should be repeated for each inserted amino acid. Each inserted amino acid should be reported in the appropriate order as shown in PFSTRESC. PFRESALL should be a composite of the entire inserted stretch of amino acids, and should be duplicated for all rows associated with the same PFGENLOC; if the number of inserted amino acids is too large for PFRESALL, alternative approaches for reporting the results in PFRESALL can be proposed.
Based on the recommended format above, below is an example if there is a mixture of 2 amino acid substitutions at the second position in the insertion:

For deletions, we agree with your approach; however, please populate PFNUMRF when there are length differences (i.e., insertions or deletions) between PFREF and PFNUMRF.

15. LBREFID: Your approach is acceptable.

**DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our April 4, 2016 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](http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm).

Reference ID: 3951114
PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 submit your Agreed PSP with your NDA application, along with any requests for waivers and/or deferrals.

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 Pregnancy and Lactation Labeling Final Rule websites, which include:

APPEARS THIS WAY ON ORIGINAL
• 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

• 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 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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

**SUBMISSION FORMAT REQUIREMENTS**

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: [http://www.fda.gov/ectd](http://www.fda.gov/ectd).
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.”

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Federal Establishment Indicator (FEI) or Registration Number (CFN)</th>
<th>Drug Master File Number (if applicable)</th>
<th>Manufacturing Step(s) or Type of Testing [Establishment function]</th>
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<td>2.</td>
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</table>

Corresponding names and titles of onsite contact:

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<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Onsite Contact (Person, Title)</th>
<th>Phone and Fax number</th>
<th>Email address</th>
</tr>
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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

Reference ID: 3951114
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.
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
06/24/2016
CDER Medical Policy Council
Decisions/Action Items – Breakthrough Therapy Designation Requests
February 16, 2016

Council Members:
Theresa Kehoe, OND/ODEIII/DRUP
John Jenkins, OND
Kendall Marcus, OND/ODE3/DDDP
Richard Moscicki, CDER
Robert Temple, OMP
Sandra Benton, Executive Secretary

Attendees:
Wendy Carter, OND/OAP/DAVP
Edward Cox, OND/OAP
Russell Fleischer, OND/OAP/DAVP
Patrick Harrington, OND/OAP/DAVP
Jeffrey, Murray, OND/OAP/DAVP
Lisa Naeger, OND/OAP/DAVP
Linda Onaga, OND/OAP/DAVP
Jules O’Rear, /OND/OAP/DAVP
Miranda Raggio, OND
Shirley Seo, OTS/OCP/DCPIV
Helen Sile, OND
Sunita Shukla, OND/OAP
Kimberly Struble, OND/OAP/DAVP
Rose Tiernan, OMP
Jenny Zheng, OTS/OCP/DCPIV

Topic: To discuss the breakthrough therapy (BT) designation request for Gilead’s IND 125751, velpatasvir (VEL) + sofosbuvir (SOF) + GS-9857 for patients with HCV genotype 1 infection and who have failed treatment with an NS5A inhibitor-containing regimen. Background is attached.

Discussion: DAVP requested this Council meeting to specifically discuss the interpretation of “available therapy.” DAVP recommends granting this BT request, but that it be specifically limited to HCV genotype 1 patients who have failed treatment with NS5A inhibitor-containing regimen. This is based on the fact that there are insufficient data available to support BTD in HCV genotypes 2-6 for this population of patients with prior NS5A-inhibitor failure.

DAVP noted that there are several effective oral direct-acting antivirals (DAA) regimens available and approved for the treatment of HCV. DAVP continues to receive BT requests for small subpopulations of the broader HCV populations, who have effective approved therapies available. In this regard, DAVP asks:

- Can “available therapy” be interpreted as an approved product (i.e., simprevir and sofosbuvir) without product labeling for the specific subpopulation to demonstrate whether or not BT can be considered?
- Does DAVP need to consider a BT designation for subpopulations of an overall broad HCV population (e.g., prior DAA failure with an NS5A-inhibitor containing regimen) when there are effective regimens that are approved for the general HCV population?

The Council sympathized with DAVP’s position. In this case, the Council noted that this is for HCV genotype 1 patients who have failed treatment with an NS5A inhibitor-containing regimen. DAVP acknowledged that this is an unmet medical need if it is for patients who have failed prior DAA based treatment which is currently not specifically labeled and the marketing application may receive a priority review.
In general, available therapy means an FDA-approved drug for the proposed BT indication, directed at the population proposed for BT designation and where the use and population is included in the FDA-approved drug labeling. If the BT designation is meant for a serious disease and for patients who have failed or cannot be treated with available therapy, and if all other requirements are met, a BT designation for a drug to treat a subpopulation of an overall broader disease population should be seriously considered.

There is already a precedent for this approach in BT decisions. The Council noted that if one marketing application is approved to treat a subpopulation for which other BT designations were also granted, then those outstanding BT requests could be rescinded.

The Council reviewed DAVP’s assessment of the BT request and agrees with DAVP’s decision to grant.

**Recommendation:** The Council recommended granting the breakthrough therapy designation request from Gilead for its IND 125751, velpatasvir (VEL) + sofosbuvir (SOF) + GS-9857 for patients with HCV genotype 1 infection and who have failed treatment with an NS5A inhibitor-containing regimen.

Attachment: Background Document

Revised: S Benton 3/15/2016
Final: S Benton 3/24/2016
We have completed the template for the BTD request from Gilead for the fixed dose combination product of velpatasvir (VEL) + sofosbuvir (SOF) + GS-9857 for patients with HCV genotype 1 infection and who have failed treatment with an NS5A inhibitor-containing regimen. Based on our review, DAVP has questions regarding the interpretation of “approved therapy” and, in general, the persistent use of data to support indications in smaller subgroups of broader populations to gain BTD within the HCV development realm.

We request that MPC consider the following questions in order for us to determine our path forward with this BTD request and subsequent requests.

Issue 1:

Can “available therapy” be interpreted as an approved product (i.e. simeprevir and sofosbuvir) without product labeling for the specific subpopulation to demonstrate whether or not BTD can be considered?

- In the case of patients with failure after treatment with an NS5A-inhibitor containing regimen, a potential retreatment option could be a combination of sofosbuvir and a protease-inhibitor, such as, simeprevir. While, these products are not specifically indicated for treatment of prior NS5A inhibitor failure, they are approved for use in combination for treatment-experienced patients. However, no data have been submitted in support of use in patients who are prior NS5A inhibitor failures. Therefore, the interpretation of “available therapy” becomes important to decide whether or not we grant BTD. If the intent is that “available therapy” must include a specific population indication, then currently, there are no approved therapies for those who have failed a prior DAA regimen including an NS5A inhibitor.

- We request clarification on whether the intent of “available therapy” includes use of therapies that are currently approved; however, labeling does not include an indication for the specific population being sought for BTD. Additionally, can data outside product labeling be used to support “available therapy”?

Issue 2:

There are now several effective DAA regimens available and approved for treatment of HCV. However, DAVP continues to receive BTD requests for small subpopulations of the broader HCV population, who have effective approved therapies available. We are requesting clarification on the intent of providing BTD for small niche populations of an overall broad HCV population (e.g. prior DAA failure with an NS5A-inhibitor containing regimen). DAVP sees these requests frequently and questions providing BTD for multiple small niche populations. The Division would appreciate your feedback on this issue.
CDER Breakthrough Therapy Designation Determination Review Template

<table>
<thead>
<tr>
<th>IND/NDA/BLA #</th>
<th>125751</th>
</tr>
</thead>
<tbody>
<tr>
<td>Request Receipt Date</td>
<td>12/23/2015</td>
</tr>
<tr>
<td>Product</td>
<td>SOF/VEL/GS-9857 FDC</td>
</tr>
<tr>
<td>Indication</td>
<td>Treatment of chronic HCV in adults</td>
</tr>
<tr>
<td>Drug Class/Mechanism of Action</td>
<td>SOF=NS5B polymerase inhibitor; VEL= NS5A inhibitor; GS-9857=HCV NS3/4A protease inhibitor</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Gilead</td>
</tr>
<tr>
<td>ODE/Division</td>
<td>OND/DAVP</td>
</tr>
<tr>
<td>Breakthrough Therapy Request Goal Date (within 60 days of receipt)</td>
<td>February 8, 2016</td>
</tr>
</tbody>
</table>

**Note:** This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

**Section I:** Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

   The indication for SOF/VEL/GS-9857 FDC is for treatment of chronic HCV in adults. However, the BTD request is specifically for an indication as a retreatment option for patients with HCV infection that have failed treatment with an NS5A inhibitor-containing regimen for whom there is no approved treatment.

   Note, DAVP recommends the BTD be specifically limited to HCV genotype 1 patients that have failed treatment with an NS5A inhibitor-containing regimen. This is based on the fact that there are insufficient data available to support BTD in HCV genotypes 2-6 for this population of patients with prior NS5A-inhibitor failure. Please see further discussion in Section II.

2. Are the data supporting the BTDR from trials/IND(s) which
   - are on Clinical Hold?

   If 2 above is checked “Yes,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “No”, proceed with below:

3. Consideration of Breakthrough Therapy Criteria:
   a. Is the condition serious/life-threatening?  
      ☒ YES ☐ NO

   If 3a is checked “No,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “Yes”, proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

---

YES the BTDR is adequate and sufficiently complete to permit a substantive review  

Undetermined  

NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence

ii. Insufficient clinical data provided to evaluate the BTDR (e.g., only high-level summary of data provided, insufficient information about the protocol[s])

iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g., multiple sclerosis, depression)

iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)

v. No or minimal clinically meaningful improvement as compared to available therapy\(^2\) historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

_If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required._

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation

Reviewer Signature:  

{See appended electronic signature page}

Team Leader Signature:  

{See appended electronic signature page}

Division Director Signature:  

{See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Chronic hepatitis C (HCV) is a serious, progressive and potentially life-threatening disease and is a major public health concern in the US and globally. HCV is responsible for a large proportion of worldwide chronic liver disease and accounts for 70% of chronic hepatitis in developed countries. The global prevalence of HCV is estimated at 3%. Of those with chronic HCV infection, as many as 20% may develop significant complications including cirrhosis, end-stage liver disease, and hepatocellular carcinoma. HCV is the leading

\(^2\) For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” \(\text{http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf}\)
cause of liver transplantation. Successful treatment of HCV reduces the incidence of HCC, the need for liver transplantation and overall mortality.

Currently there are no FDA approved treatment options indicated specifically for those who have failed prior HCV treatment with an NS5A inhibitor containing direct acting antiviral (DAA) regimen. Combining three pangenotypic, potent DAAs sofosbuvir (SOF), velpatasvir (VEL) and GS-9857 into a fixed dose table, allows 3 unique mechanisms of action to be combined as a complete antiviral treatment regimen.

- Sofosbuvir, a nucleotide analog HCV NS5B polymerase inhibitor, which is currently approved in the US and other regions for the treatment of HCV infection as a component of an antiviral treatment regimen.
- Velpatasvir, an HCV NS5A inhibitor that has potent in vitro anti-HCV activity across all HCV genotypes. Phase 3 studies of SOF/VEL have demonstrated that the combination of SOF 400 mg and VEL 100 mg administered for 12 weeks is well tolerated and results in high SVR rates across HCV genotypes. An original NDA 208341 is currently under review.
- GS-9857, a macrocyclic HCV NS3/4A PI with nanomolar activity against HCV genotypes 1- 6 in vitro. The clinical dose of GS-9857 resulted in ≥ 3 log decreases in HCV RNA in patients with genotype 1, 2, 3 or 4 following three days of monotherapy in the Phase 1b study (GS-US-338-1121). In vitro, GS-9857 has demonstrated a high barrier to resistance and activity against common NS3 RAVs not covered by previously developed HCV PIs. Additionally, GS-9857 maintains full activity to replicons containing common NS5A and NS5B resistance mutations and has additive antiviral activity when combined with VEL or SOF.

7. Information related to endpoints used in the available clinical data:

The primary objective of anti-HCV treatment is the achievement of a sustained virologic response (SVR), typically defined as unquantifiable HCV RNA 12 weeks following the cessation of treatment (i.e., “SVR12”). SVR12 is generally considered a “virologic cure”.

The Sponsor is relying on sustained virologic response or SVR12 (described 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.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

There are no available therapies for patients who have previously failed treatment of HCV with a prior NS5A-containing DAA treatment regimen.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

No other companies are currently seeking BTD for a similar/same indication.

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
10. Information related to the preliminary clinical evidence:

GS-US-367-1168 (trial 1168) and GS-US-367-1169 (trial 1169) are ongoing, phase 2 multicenter, open-label trials evaluating the safety and efficacy of daily treatment with SOF/VEL+GS-9857 for 6, 8, or 12 weeks in treatment-naive and treatment-experienced subjects with and without cirrhosis. All subjects received SOF/VEL FDC (400/100 mg) + GS-9857 (100 mg) once daily with food. Study GS-US-367-1168 enrolled subjects with genotype 1 HCV infection and prior DAA experience including those previously treated with either a NS5A inhibitor, or 2 or more DAAs. Study GS-US-367-1169 enrolled subjects with HCV genotype 2, 3, 4 and 6 (ie, non-genotype 1) and any prior treatment history.

SVR12 data are available from 35 subjects who had previously failed an NS5A-containing regimen. Twenty-nine of these subjects had genotype 1 HCV infection (trial 1168) while 6 subjects were NS5A-experienced subjects from trial 1169 who were non-genotype 1 (3 subjects with HCV genotype 3, 2 subjects with HCV genotype 2 and 1 subject with HCV genotype 6). Of the HCV genotype 1 subjects, 41% (12/29) had baseline cirrhosis; only 1 non-genotype 1 subject had cirrhosis in this cohort. Regardless, all 35 subjects with prior NS5A-experience achieved SVR12. The following table displays the SVR12 results from trials 1168 and 1169.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>SVR12, n/N (%)</td>
<td>Noncirrhotic SOF/VEL+ GS-9857 12 Weeks (N = 17)</td>
<td>Cirrhotic SOF/VEL+ GS-9857 12 Weeks (N = 12)</td>
<td></td>
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<tr>
<td></td>
<td>17/17 (100%)</td>
<td>12/12 (100%)</td>
<td></td>
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<tr>
<td>Overall SVR12</td>
<td>35/35 (100%)</td>
<td>5/5 (100%)</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>a.</td>
<td>95% confidence interval 90.0-100%</td>
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Currently, there are no available treatment options for patients who have previously failed an NS5A-inhibitor containing regimen. Patients who fail DAA therapy, can develop resistance-associated substitutions in the NS5A, NS3 or NS5B genes. These resistance-associated substitutions can confer high-level resistance to specific DAA drugs or classes. At baseline, 33 of the 35 subjects with prior NS5A experience had at least one baseline NS5A resistance-associated substitution with all of these subjects (33/33) having one or more NS5A substitutions that can confer high level (>100-fold) resistance to one or more NS5A inhibitors. However, as demonstrated above, regardless of the presence of baseline NS5A resistance-associated substitutions, all subjects achieved SVR12 following 12 weeks of treatment with SOF/VEL/GS-9857.

The safety profile did not show any safety signals based on the limited available data (n=266 from trials 1168 and 1169); there were no differences in the preliminary safety data from the 35 NS5A inhibitor-experienced subjects from the other subjects enrolled. Overall, most subjects (n=177, 66.5%) had at least 1 AE, and the proportion of subjects reporting AEs was similar across treatment groups. The most frequently reported AEs were headache (n=60, 22.6%), fatigue (n=43, 16.2%), diarrhea (n=43, 16.2%) and nausea (n=40, 15.0%). There were low rates of discontinuations due to AEs (n=3, 1.1%), SAEs (n=3, 1.1%), and Grade 3 or 4 laboratory abnormalities (n=18, 6.8%). Additionally, no deaths were reported.
11. Division’s recommendation and rationale (pre-MPC review):

☑ GRANT: Decision pending until meeting the MPC; please see cover letter in addition to rationale below

Provide brief summary of rationale for granting:

BTD should be granted for SOF/VEL/GS-9857 for treatment of HCV genotype 1 in patients who have previously failed prior treatment with an NS5A inhibitor-containing DAA regimen for the following reasons:

- HCV is a serious, life-threatening disease
- There are currently no available approved therapies specifically indicated for patients who have previously failed treatment with an NS5A-containing DAA treatment regimen
- Substantial improvement is demonstrated by the SVR12 rate of 100% in 29 HCV genotype 1 cirrhotic and non-cirrhotic subjects from the phase 2 trials 1168 and 1169 after 12 weeks of treatment with SOF/VEL/GS-9857.
- SOF/VEL/GS-9857 are well-tolerated with manageable toxicity profiles

HCV non-genotype 1 is not included in this recommendation for BTD because of the small numbers of subjects with available SVR12 data at this time. While the data are promising, it remains unclear with the available very small numbers whether SVR12 rates will be similar for HCV genotypes 2, 3 and 6 which are represented in the trial 1169 data. Additionally, there are no genotype 4 or 5 subjects included in these data.

12. 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.

13. List references, if any:

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☐ NO ☑

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

5-7-15/M. Raggio
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDRA J BENTON
03/24/2016

JEFFREY S MURRAY
03/25/2016
Dear Ms. Haggerty:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sofosbuvir/velpatasvir/GS-9857.

We also refer to your December 23, 2016, request for Breakthrough Therapy designation. We have reviewed your request and have determined that sofosbuvir/velpatasvir/GS-9857 for the treatment of chronic hepatitis C virus genotype 1 infection in patients who have previously failed an NS5A inhibitor-containing DAA regimen meets the criteria for Breakthrough Therapy designation. There were insufficient clinical data submitted to support inclusion of hepatitis C genotypes 2, 3, 4, 5 or 6 in this Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation specifically for hepatitis C genotype 1 infection in patients who have previously failed an NS5A inhibitor containing regimen. 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/velpatasvir/GS-9857 for the treatment of chronic hepatitis C virus genotype 1 infection in patients who have previously failed an NS5A inhibitor-containing DAA regimen 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 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. Please refer to 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.

We note your recent End of Phase 2 meeting held on September 30, 2015. At this point in your drug development program, holding this initial breakthrough therapy meeting is not necessary. However, please contact the Regulatory Project Manager noted below to determine if any information is required at this time to expedite the review of your breakthrough designated product.

If the breakthrough therapy designation for sofosbuvir/velpatasvir/GS-9857 for the treatment of chronic hepatitis C virus genotype 1 infection in patients who have previously failed an NS5A inhibitor-containing DAA regimen 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, Regulatory Project Manager, at (301) 796-0759.

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/

JEFFREY S MURRAY
02/19/2016
IND 125751

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

Dear Ms. Haggerty:

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/GS-9857 fixed dose combination tablet.

We also refer to the meeting between representatives of your firm and the FDA on September 30, 2015. The purpose of the meeting was to discuss the development strategy and registration plan for sofosbuvir/GS-5816/GS-9857 fixed-dose combination.

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

If you have any questions, call Mammah Sia Borbor, MS, MBA, Regulatory Project Manager at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: September 30, 2015 9:30 AM – 11:00 AM (EST)
Meeting Location: White Oak Building 22, Conference Room: 1309

Application Number: 125751
Product Name: sofosbuvir/Velpatasvir/GS-9857 fixed dose combination tablet
Indication: Treatment of Chronic HCV Infection
Sponsor/Applicant Name: Gilead Sciences, Inc

Meeting Chair: Debra Birnkrant, MD
Meeting Recorder: Mammah Sia Borbor, MS, MBA

FDA ATTENDEES
Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, MD, MPH Deputy Director DAVP
Kimberly Struble, PharmD, Medical Team Lead DAVP
Wendy Carter, DO, Medical Officer DAVP
Sarah Connelly, MD Clinical Reviewer DAVP
Julian O’Rear, PhD Virology Team Lead DAVP
Lisa Naeger, PhD, Virology Reviewer DAVP
Shirley K. Seo, PhD, Clinical Pharmacology Team Lead, Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology IV (DCP IV)
Jenny Zheng, PhD, Clinical Pharmacology Reviewer
Greg Soon, PhD, Statistical Team Lead, Office of Translational Sciences- Division of Biometrics IV
Karen Qi, PhD, Statistical Reviewer, Office of Translational Sciences- Division of Biometrics IV
Antoine El-Hage, PhD, Office of Scientific Investigations
Mammah Borbor, MS, MBA, Regulatory Project Manager
Sohail Mosaddegh, PharmD, Acting Chief, Project Management Staff, DAVP

SPONSOR ATTENDEES
John McHutchison, MD Executive Vice President, Clinical Research
Diana Brainard, MD Vice President, Clinical Research
Luisa Stamm, MD, PhD Associate Director, Clinical Research
Ming Lin, PhD Associate Director, Biostatistics

Reference ID: 3839667
1.0 BACKGROUND

Gilead Sciences, Inc., is developing a fixed-dose combination sofosbuvir/velpatasvir/GS-9857 (SOF/VEL/GS-9857) for subjects with chronic hepatitis C virus infection. The fixed-dose tablet contains SOF 400 mg, VEL 100 mg and GS-9857 100 mg. Gilead Sciences, Inc., has completed their Phase 2 trials and is planning to move forward with their Phase 3 development program for SOF/VEL/GS-9857.

On July 16, 2015, Gilead Sciences, Inc., submitted a Type B meeting request for SOF/VEL/GS-9857 fixed-dose combination tablet. The purpose of the requested meeting was to discuss Phase 3 development strategy and registration plans for SOF/VEL/GS-9857 fixed-dose combination for patients with chronic hepatitis C virus infection.

The Division’s preliminary comments (Attachment 1) were sent to Gilead Sciences, Inc., on September 27, 2015, and Ms. Haggerty followed up with an electronic mail (email) communication on September 29, 2015 (Attachment 2) with a request to focus the meeting on questions 1 and 2.

2. DISCUSSION

2.1. Phase 3 Development Plans

Question 1: Does the Agency agree that the Phase 3 development plan is adequate to support the proposed indication for SOF/VEL/GS-9857? Specifically, Gilead seeks the Agency’s comments on the following:

a) Protocol designs for the Phase 3 studies

b) Protocol-specified statistical analyses for the Phase 3 studies

DAVP’s Preliminary Response: In general, we have concerns about the positioning of SOF/VEL/GS-9857 as a pan-genotypic FDC for a broad population of DAA-experienced, treatment-experienced/DAA-naïve and treatment-naïve patients. As currently designed, your phase 3 trials do not have the ability to clearly demonstrate the benefit of the addition of GS-9857 to the SOF/VEL regimen in some of the target populations you have identified. For an NDA, our expectation is that you will clearly demonstrate the contribution of GS-9857 for the proposed patient populations and HCV genotypes. Based on our comments below, please comment on how your amended proposed trials will address this regulatory requirement for approval.

More specifically, unless superiority is shown for a given genotype/treatment status and cirrhosis status, we cannot make a benefit-risk assessment regarding the addition of a third agent to a regimen for 8 weeks versus a safe and effective two drug regimen for 12 weeks. GS-
9857 may add to tolerability issues for some subjects and GS-9857 also has additional DDI considerations. The risks of adding a third drug is not offset by 4 less weeks of treatment with a two drug regimen; therefore, a non-inferiority trial design is not appropriate.

Our comments below outline the major concerns for each trial and provide some suggestions. After discussion of these concerns at the upcoming meeting, revised phase 3 protocols, including updated statistical analyses are needed.

We encourage enrollment of HIV/HCV coinfected subjects, those with bleeding disorders and those on methadone/buprenorphine maintenance therapy into your phase 3 protocols. Please provide your plans for enrolling these patient groups into your phase 3 trials.

**Polaris-1**

- As stated above, SOF/VEL for 12 weeks may result in high SVR12 rates for certain genotypes/treatment status and cirrhosis status. Specifically, your inclusion criteria for Genotype 1, prior treatment with either an NS5A inhibitor or two or more DAAs of different classes, may be too broad for the intended trial design and statistical considerations. For example:
  - For HCV genotype 1 subjects with prior exposure to SOF + PI (e.g. simeprevir), it remains uncertain if SOF/VEL/GS-9857 is needed or whether treatment with SOF/VEL for 12 weeks is adequate to provide a high SVR response rate. Therefore, you could change the enrollment criteria to exclude the SOF/PI experienced population in this trial or, preferably, consider a superiority comparison to a 12 week duration of SOF/VEL. If SOF/VEL/GS-9857 is not superior to SOF/VEL, then it may be possible to seek an indication for SOF/VEL for 12 weeks in this population.
  - Similarly, for HCV genotype 2 and 3 subjects with prior SOF/RBV failure it remains uncertain whether the 3DAA regimen is needed and whether treatment with SOF/VEL for 12 weeks duration is adequate to provide a high SVR rates. This is particularly concerning for HCV genotype 2 subjects. In the ASTRAL 1, 2 and 3 trials, no HCV genotype 2 subjects (n=238) experienced virologic failure after 12 weeks of SOF/VEL, albeit not the exact same population you intend to enroll. An alternate trial design and statistical consideration is needed for a genotype 2 retreatment indication.
  - HCV genotype 3 subjects with prior SOF/NS5A experience, particularly those with cirrhosis or additional baseline factors that predict lower response rates, are an appropriate targeted population for the SOF/VEL/GS-9857 FDC development. Comparison to a benchmark of 85-90% may be reasonable for this specific population.
  - For the HCV genotypes 4, 5 and 6, data are not available to determine if a 12 week regimen of SOF/VEL/GS-9857 is needed or if the SOF/VEL 12 week regimen is adequate for the proposed population. A comparative superiority trial
can be considered for this population. Please provide your perspectives on the need of the SOF/VEL/GS-9857 retreatment regimen for these genotypes, including feasibility of such a trial.

- As stated above, we are requesting revisions to your development plan based on genotype which may require multiple targeted trials. In future protocols please make clear the intended number of subjects with cirrhosis for each genotype planned for enrollment. For example, the protocol states that 20% of treated genotype 1 subjects will have cirrhosis (20% of 200, n=40). And the target number of genotype 3 subjects with cirrhosis is 100. However, the target number of cirrhotic subjects for the remaining genotypes was unclear.

Polaris-2

- For the Polaris-2 trial in treatment-naïve and treatment-experienced/DAA-naïve patients, a non-inferiority design is not acceptable and does not address the issue of contribution of GS-9857 to the SOF/VEL regimen. Based on the ASTRAL 1, 2 and 3 data, the SVR12 rate is 95% or higher for the 12 week regimen of SOF/VEL in HCV genotypes 1-6 and the question remains regarding the contribution of GS-9857 to the proposed regimen. A superiority trial is needed in order to adequately demonstrate the contribution of GS-9857. One way to achieve this would be by adding an 8 week duration SOF/VEL arm to this trial to compare to the 8 week duration SOF/VEL/GS-9857 and the 12 week duration SOF/VEL for genotypes 1 and 2. If the 8 week SOF/VEL/GS-9857 regimen does not demonstrate superiority, the SOF/VEL 8 week regimen could be considered for labeling; however, it is possible the data may support some subpopulations and potentially not all the sub-populations.

- For genotype 3, you may consider demonstrating superiority of the 12 week regimen of SOF/VEL/GS-9857 compared to the 12 week regimen of SOF/VEL. Alternatively, you could choose to focus on HCV genotype 3 subjects with demonstrated higher rates of failure, such as subjects with HCV genotype 3 and cirrhosis or additional baseline factors which have demonstrated lower response rates.

- Similar issues for genotypes 4, 5 and 6 as discussed above are relevant for the DAA-naïve/treatment-experienced and treatment-naïve population. Data are not available to determine if a 12 week regimen of SOF/VEL/GS-9857 is needed or if the SOF/VEL 12 week regimen is adequate for this population. A comparative superiority trial may be considered for this population. Please provide your perspectives on the need for the SOF/VEL/GS-9857 8 week regimen for treatment of these genotypes in this DAA-naïve population.

- The current protocol states that 20% of subjects will have cirrhosis (20% of 930, n=186); and the target number of genotype 3 subjects with cirrhosis is 150. This leaves only 36 subjects to be dispersed across the treatment arms and genotypes. Please clarify your target numbers for subjects with cirrhosis with genotypes 1, 2, 4, 5 and 6. Please note for the protocol revision, adequate representation of subjects with cirrhosis across the genotypes, particularly for genotypes 1 and 2, is needed.
Discussion:

Gilead Sciences, Inc., began by acknowledging DAVP’s preliminary comments and indicated that DAVP’s recommendations were not feasible for their proposed registration program however Gilead expressed a desire to gain mutual agreement on a registration program by the end of the meeting discussion. Gilead proceeded by providing their reasoning for their proposed registration program along with their goals for the SOF/VEL/GS-9857 program and how the SOF/VEL/GS-9857 regimen could address an unmet medical need for patients that are not adequately treated with Harvoni®, SOF/VEL or other anti-viral regimens. Gilead also provided an explanation of their intentions for the SOF/VEL/GS-9857 program to include the following:

Furthermore, Gilead explained in planning the SOF/VEL/GS-9857 that it was anticipated that future HCV treatment in the US will focus on and be required in two major groups of patients: DAA-experienced patients and DAA-naïve patients. Gilead highlighted that the current HCV treatments have become simpler and that a regimen where genotyping is not required would be ideal, particularly for areas outside the US and Europe where genotyping is not readily available, not routinely conducted or inaccurate.

Discussion POLARIS-1

Gilead suggested an alternative plan by acknowledging SOF/VEL may be an adequate treatment option for non-NS5A DAA experienced patients and proposed dividing the evaluation of retreatment therapy into two trials in which: NS5A DAA-experienced subjects would be treated with SOF/VEL/GS-9857 for 12 weeks versus placebo and deferred treatment (POLARIS-1a) and Non-NS5A DAA-experienced subjects would be treated with SOF/VEL/GS-9857 for 12 weeks versus SOF/VEL for 12 weeks (POLARIS-1b). Gilead indicated that although most of the DAA-experienced patients who have failed treatment have genotype 1, patients with genotypes 2-6 also fail DAAs, and that all of these patients have no currently approved re-treatment option. SOF/VEL/GS-9857 or SOF/VEL may provide this population with a retreatment option. DAVP noted that labeling in the future could pose review issues for Gilead and that labeling inclusive of all genotypes will be dependent on the number of patients with each genotype enrolled in each of these two studies and the ability to demonstrate efficacy and the contribution of GS-9857, where applicable, in each genotype.

DAVP also further noted that the data from cirrhotic subjects may inform labeling for non-cirrhotic subjects. Gilead indicated for the POLARIS-1a study, their proposed sample size would be approximately 200-250 subjects. In addition, to address DAVP’s comment regarding the designing of POLARIS-1b as a superiority study (SOF/VEL/GS-9857 vs SOF/VEL), Gilead stated that a superiority study in DAA-experienced subjects powered at 90% with an assumed SVR rate of 90% for SOF/VEL and 95% for SOF/VEL/GS-9857 would require 640 subjects per arm. Gilead went on to expand that based on results from real-world studies, enrollment of this number of subjects would be challenging and they believe not feasible currently.
DAVP inquired as to the rationale for the RESCUE study (GS-US-337-1746) which appears to be in direct competition with SOF/VEL/GS-9857 for the same patient population (non-NS5A DAA experienced subjects). Gilead indicated that the RESCUE study is a Phase 4 study that was intended to address the need for retreatment as data has accumulated in the real world setting. Also, the number of subjects has been decreased in a recent protocol amendment. Gilead also suggested that rather than a superiority comparison, they could conduct a two-arm study where each arm would be compared to a pre-determined performance goal. The benefit/risk assessment of SOF/VEL/GS-9857 as compared to SOF/VEL would be based on an integrated assessment of efficacy (as measured by SVR and relapse rates), emergence of resistance, and safety profile. For POLARIS-1b in which a performance goal of 85% is used, Gilead proposed the sample size would be approximately 125-250 per arm.

Together, the sample sizes planned in POLARIS-1a and POLARIS-1b, along with data from Phase 2 will provide data on more than 500 subjects treated with SOF/VEL/GS-9857 as salvage therapy.

DAVP partially agreed with the general study plans, but noted their review of the full protocols, fulfillment of regulatory intent with rationale along with further discussion would be required to provide more clarity about what data and analyses could potentially be label enabling. DAVP also indicated that SOF/VEL might prove to be an effective regimen for retreatment of non-NS5A DAA-experienced patients in POLARIS-1b.

Discussion POLARIS-2:

DAVP reiterated the regulatory requirement to assess the contribution of GS-9857 relative to SOF/VEL alone when evaluating the SOF/VEL/GS-9857 combination, and that this would be particularly challenging for DAA-naive patients where SVR rates were so high in the ASTRAL-1 and ASTRAL-2 studies. Gilead acknowledged this concern and agreed that the most straightforward way to demonstrate the contribution of GS-9857 in the regimen would be a direct comparison of the SOF/VEL regimen for 8 weeks with SOF/VEL/GS-9857 for 8 weeks. However, Gilead stated the small amount of Phase 2 data demonstrated 8 weeks of SOF+VEL resulted in <90% SVR, and therefore was not an appropriate regimen to bring forward in the ASTRAL program nor to utilize as a direct comparator in the POLARIS program.

Gilead clarified that the original goals for the POLARIS-2 DAA-naive study were to address the unmet need for genotype 3 patients with cirrhosis and to shorten treatment duration. Gilead proposed to split the original trial into two separate trials – 1) DAA-naive genotype 3, cirrhotic subjects will be treated with SOF/VEL/GS-9857 for 8 weeks versus SOF/VEL for 8 weeks and 2) DAA-naive study where subjects will be treated with SOF/VEL/GS-9857 for 8 weeks versus SOF/VEL for 12 weeks. DAVP expressed concerns with the treatment-naive population and whether there will be adequate data in all genotypes to assess whether the benefit/risk assessment will be favorable for the 8 week 3DAA regimen compared to the 12 week 2DAA, especially how to assess the contribution of GS-9857 and also noting the possible toxicities of a protease.
inhibitor (GS-9857) and DDI liability. Additionally, this may be particularly challenging with some subgroups and genotypes (e.g., genotypes 4, 5 and 6). DAVP noted that Gilead recently submitted a phase 2 protocol for 50 genotype 2 DAA-naïve subjects at a single center. Gilead stated that they had made this a separate trial because they did not want a single investigator to have high numbers of patients in the phase 3 trial. DAVP stated that we preferred that the subjects are enrolled into the phase 3 trial to provide more power to assess the contribution of GS-9857 to the SOF/VEL regimen rather than a competing small phase 2 supportive trial.

DAVP requested to power the genotype 3, cirrhotic DAA-naïve study for superiority. Gilead acknowledged DAVP’s request but again stated that they believe a superiority design would not be feasible in this population because it requires 580 subjects per treatment group. However, a sample size of approximately 100 subjects with genotype 3 and cirrhosis was likely feasible and an alternative statistical design of comparing each treatment to a performance goal was proposed.

DAVP repeated the regulatory requirement for Gilead to demonstrate the contribution of GS-9857 to the FDC in the newly proposed treatment naïve study designs and acknowledged the challenge this requirement poses given the efficacy of the SOF/VEL regimen in the Phase 3 program. However, DAVP agreed that the SVR rate for SOF/VEL in genotype 3 subjects with cirrhosis provides an opportunity to improve efficacy in this population, potentially demonstrating the contribution of GS-9857 and that positive data in this subpopulation could support population specific labeling. DAVP indicated that a review of the data at a Pre-NDA meeting will be an important opportunity for DAVP to determine what studies should be considered as label-enabling versus supportive (safety only). Gilead acknowledged the potential regulatory limitations with regards to labeling for all genotypes in the DAA-naïve population. Furthermore, Gilead agreed to provide an initial proposal on how the contribution of GS-9857 to the SOF/VEL/GS-9857 FDC could be assessed in an NDA application when responding to DAVP’s preliminary comments. It was agreed that cross study comparisons to historical data from the SOF/VEL program with regards to safety, SVR rates, relapse, resistance emergence and preexisting RAVs may assist in this assessment.

**Breakthrough Therapy Designation**

**Question 2:** Does the Agency agree with Gilead’s proposal to file for Breakthrough Therapy Designation with Phase 2 SVR12 data demonstrating that SOF/VEL/GS-9857 has a high rate of SVR in DAA-experienced subjects in HCV genotypes 1, 2, 3, 4 and 6?

**DAVP’s Preliminary Response:** At this time we do not agree with your proposal to request Breakthrough Therapy Designation with the currently available SVR12 data. The contribution of GS-9857 to the available SOF/VEL data must be demonstrated for your proposed population. As stated above, for example, subjects with HCV genotype 2 who have failed SOF/RBV and are therefore DAA-experienced, may not need the addition of SOF/VEL/GS-9857 for re-treatment and may be adequately treated with SOF/VEL.

**Discussion:**
DAVP provided clarity that the strategy for filing Breakthrough Therapy Designation should be more focused and must meet the standard for demonstrating that the regimen provides a substantial improvement over existing therapies. DAVP suggested that Gilead wait to obtain all of the data necessary and then provide a specific proposal if they believe their data meets the requirements. Gilead acknowledged the requirement and indicated that the proposed Breakthrough Therapy Designation request will meet the required standards as it relates to a therapy for patients who have failed other available options as a rescue regimen.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 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.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).
On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* 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.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards 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. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

**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 the FDA website entitled, Study Data Standards Resources and the
CDER/CBER Position on Use of SI Units for Lab Tests website found at

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to
other drugs with known abuse potential, or produce psychoactive effects such as mood or
cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential
and a proposal for scheduling will be required at the time of the NDA submission
[21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information
required at the time of your NDA submission, see the draft guidance for industry, Guidance for
Industry Assessment of Abuse Potential of Drugs, available at:
CM198650.pdf.

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.”

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item^1</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
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<td>Data listings, by study (Line listings, by site)</td>
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<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

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

```
 m5
 [...]
 datasets
 bimo
 site-level
```

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
NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
   - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
   - Other significant changes
   - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Identify any issues that remain open at the end of the meeting and require further discussion at a later date. If none exist, please indicate that there were no issues requiring further discussion.

5.0 ACTION ITEMS

<table>
<thead>
<tr>
<th>Action Item/Description</th>
<th>Owner</th>
<th>Due Date</th>
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<tbody>
<tr>
<td>Gilead will submit revised Phase 3 protocols reflecting agreements made with FDA during the meeting</td>
<td>Gilead Science, Inc.</td>
<td>End of October 2015</td>
</tr>
<tr>
<td>Response to DAVP’s preliminary comments will</td>
<td>Gilead Science, Inc.</td>
<td>End of October 2015</td>
</tr>
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</table>
include a summary describing the contribution of the GS-9857 in the SOF/VEL/GS-9857 fdc as well as the regulatory intent for each study

6.0 ATTACHMENTS AND HANDOUTS
Attachment 1 – FDA’s September 27, 2015 Preliminary Comments
Attachment 2- Gilead Sciences September 29, 2015 Preliminary Responses
IND 125751

MEETING PRELIMINARY COMMENTS

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

Dear Ms. Haggerty:

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/GS-9857 fixed dose combination tablet.

We also refer to your July 16, 2015, correspondence, received July 16, 2015, requesting a meeting to discuss the development strategy and registration plan for sofosbuvir/GS-5816/GS-9857 fixed-dose combination.

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 Mammah Sia Borbor, M.S., M.B.A., Regulatory Project Manager at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Mammah Sia Borbor, M.S., M.B.A.
ENCLOSURE:
  Preliminary Meeting Comments
PRELIMINARY MEETING COMMENTS

<table>
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<tr>
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<tr>
<td>Meeting Location:</td>
<td>White Oak Building 22, Conference Room: 1309</td>
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<td>Application Number:</td>
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<td>Product Name:</td>
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<td>Sponsor/Applicant Name:</td>
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</table>

FDA ATTENDEES (tentative)
Edward Cox, MD, MPH, Director, Office of Antimicrobial Products (OAP)
John Farley, MD, MPH, Deputy Director (OAP)
Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, MD, MPH Deputy Director DAVP
Kimberly Struble, PharmD, Medical Team Lead DAVP
Wendy Carter, DO, Medical Officer DAVP
Julian O’Rear, PhD Virology Team Lead DAVP
Lisa Naeger, PhD, Virology Reviewer DAVP
Shirley K. Seo, PhD, Clinical Pharmacology Team Lead, Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology IV (DCP IV)
Jenny Zheng, PhD, Clinical Pharmacology Reviewer
Mark Powley, PhD, Pharmacology/Toxicology Reviewer
Hanan Ghantous, PhD, DABT, Pharmacology/Toxicology Team Lead
Greg Soon, PhD, Statistical Team Lead, Office of Translational Sciences- Division of Biometrics IV
Antoine El-Hage, PhD, Office of Scientific Investigations
Stephen Miller, PhD, CMC Team Leader
Florence Aisida, Regulatory Business Project Manager
Mammah Borbor, MS, MBA, Regulatory Project Manager
Katherine Schumann, M.S., Acting Associate Director for Regulatory Affairs
Danyal Chaudhry, MPH, Regulatory Project Management Staff, Office of Surveillance and Epidemiology
Robert Temple, MD Deputy Center Director for Clinical
Sohail Mosaddegh, Pharm.D., Regulatory Project Manager

SPONSOR ATTENDEES
John McHutchison, MD Executive Vice President, Clinical Research
Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 30, 2015, 9:30 AM – 11:00 AM (EST), 10903 New Hampshire Avenue, White Oak Building 22, Conference Room: 1309 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. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the 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

Gilead Sciences, Inc., is developing a fixed-dose combination sofosbuvir/velpatasvir/GS-9857 (SOF/VEL/GS-9857) for subjects with chronic hepatitis C virus infection. The fixed-dose tablet contains SOF 400 mg, VEL 100 mg and GS-9857 100 mg. Gilead Sciences, Inc., has completed their Phase 2 trials and is planning to move forward with their Phase 3 development program for SOF/VEL/GS-9857.

On July 16, 2015 Gilead Sciences, Inc. submitted a Type B meeting request for SOF/VEL/GS-9857 fixed-dose combination tablet. The purpose of the requested meeting is to discuss Phase 3 development strategy and registration plans for SOF/VEL/GS-9857 fixed-dose combination for patients with chronic hepatitis C virus infection.
2.0 DISCUSSION

Phase 3 Development Plans

Question 1: Does the Agency agree that the Phase 3 development plan is adequate to support the proposed indication for SOF/VEL/GS-9857? Specifically, Gilead seeks the Agency’s comments on the following:

a) Protocol designs for the Phase 3 studies

b) Protocol-specified statistical analyses for the Phase 3 studies

DAVP’s Preliminary Response: In general, we have concerns about the positioning of SOF/VEL/GS-9857 as a pan-genotypic FDC for a broad population of DAA-experienced, treatment-experienced/DAA-naïve and treatment-naïve patients. As currently designed, your phase 3 trials do not have the ability to clearly demonstrate the benefit of the addition of GS-9857 to the SOF/VEL regimen in some of the target populations you have identified. For an NDA, our expectation is that you will clearly demonstrate the contribution of GS-9857 for the proposed patient populations and HCV genotypes. Based on our comments below, please comment on how your amended proposed trials will address this regulatory requirement for approval.

More specifically, unless superiority is shown for a given genotype/treatment status and cirrhosis status, we cannot make a benefit-risk assessment regarding the addition of a third agent to a regimen for 8 weeks versus a safe and effective two drug regimen for 12 weeks. GS-9857 may add to tolerability issues for some subjects and GS-9857 also has additional DDI considerations. The risks of adding a third drug is not offset by 4 less weeks of treatment with a two drug regimen; therefore, a non-inferiority trial design is not appropriate.

Our comments below outline the major concerns for each trial and provide some suggestions. After discussion of these concerns at the upcoming meeting, revised phase 3 protocols, including updated statistical analyses are needed.

We encourage enrollment of HIV/HCV coinfected subjects, those with bleeding disorders and those on methadone/buprenorphine maintenance therapy into your phase 3 protocols. Please provide your plans for enrolling these patient groups into your phase 3 trials.

Polaris-1

- As stated above, SOF/VEL for 12 weeks may result in high SVR12 rates for certain genotypes/treatment status and cirrhosis status. Specifically, your inclusion criteria for Genotype 1, prior treatment with either an NS5A inhibitor or two or more DAAAs of different classes, may be too broad for the intended trial design and statistical considerations. For example:

  - For HCV genotype 1 subjects with prior exposure to SOF + PI (e.g. simeprevir), it remains uncertain if SOF/VEL/GS-9857 is needed or whether treatment with
SOF/VEL for 12 weeks is adequate to provide a high SVR response rate. Therefore, you could change the enrollment criteria to exclude the SOF/PI experienced population in this trial or, preferably, consider a superiority comparison to a 12 week duration of SOF/VEL. If SOF/VEL/GS-9857 is not superior to SOF/VEL, then it may be possible to seek an indication for SOF/VEL for 12 weeks in this population.

- Similarly, for HCV genotype 2 and 3 subjects with prior SOF/RBV failure it remains uncertain whether the 3DAA regimen is needed and whether treatment with SOF/VEL for 12 weeks duration is adequate to provide a high SVR rates. This is particularly concerning for HCV genotype 2 subjects. In the ASTRAL 1, 2 and 3 trials, no HCV genotype 2 subjects (n=238) experienced virologic failure after 12 weeks of SOF/VEL, albeit not the exact same population you intend to enroll. An alternate trial design and statistical consideration is needed for a genotype 2 retreatment indication.

- HCV genotype 3 subjects with prior SOF/NS5A experience, particularly those with cirrhosis or additional baseline factors that predict lower response rates, are an appropriate targeted population for the SOF/VEL/GS-9857 FDC development. Comparison to a benchmark of 85-90% may be reasonable for this specific population.

- For the HCV genotypes 4, 5 and 6, data are not available to determine if a 12 week regimen of SOF/VEL/GS-9857 is needed or if the SOF/VEL 12 week regimen is adequate for the proposed population. A comparative superiority trial can be considered for this population. Please provide your perspectives on the need of the SOF/VEL/GS-9857 retreatment regimen for these genotypes, including feasibility of such a trial.

As stated above, we are requesting revisions to your development plan based on genotype which may require multiple targeted trials. In future protocols please make clear the intended number of subjects with cirrhosis for each genotype planned for enrollment. For example, the protocol states that 20% of treated genotype 1 subjects will have cirrhosis (20% of 200, n=40). And the target number of genotype 3 subjects with cirrhosis is 100. However, the target number of cirrhotic subjects for the remaining genotypes was unclear.

**Polaris-2**

- For the Polaris-2 trial in treatment-naïve and treatment-experienced/DAA-naïve patients, a non-inferiority design is not acceptable and does not address the issue of contribution of GS-9857 to the SOF/VEL regimen. Based on the ASTRAL 1, 2 and 3 data, the SVR12 rate is 95% or higher for the 12 week regimen of SOF/VEL in HCV genotypes 1-6 and the question remains regarding the contribution of GS-9857 to the proposed regimen. A superiority trial is needed in order to adequately demonstrate the contribution of GS-9857. One way to achieve this would be by adding an 8 week duration SOF/VEL arm to this trial to compare to the 8 week duration SOF/VEL/GS-9857 and the 12 week duration
SOF/VEL for genotypes 1 and 2. If the 8 week SOF/VEL/GS-9857 regimen does not demonstrate superiority, the SOF/VEL 8 week regimen could be considered for labeling; however, it is possible the data may support some subpopulations and potentially not all the sub-populations.

- For genotype 3, you may consider demonstrating superiority of the 12 week regimen of SOF/VEL/GS-9857 compared to the 12 week regimen of SOF/VEL. Alternatively, you could choose to focus on HCV genotype 3 subjects with demonstrated higher rates of failure, such as subjects with HCV genotype 3 and cirrhosis or additional baseline factors which have demonstrated lower response rates.

- Similar issues for genotypes 4, 5 and 6 as discussed above are relevant for the DAA-naïve/treatment-experienced and treatment-naïve population. Data are not available to determine if a 12 week regimen of SOF/VEL/GS-9857 is needed or if the SOF/VEL 12 week regimen is adequate for this population. A comparative superiority trial may be considered for this population. Please provide your perspectives on the need for the SOF/VEL/GS-9857 8 week regimen for treatment of these genotypes in this DAA-naïve population.

- The current protocol states that 20% of subjects will have cirrhosis (20% of 930, n=186); and the target number of genotype 3 subjects with cirrhosis is 150. This leaves only 36 subjects to be dispersed across the treatment arms and genotypes. Please clarify your target numbers for subjects with cirrhosis with genotypes 1, 2, 4, 5 and 6. Please note for the protocol revision, adequate representation of subjects with cirrhosis across the genotypes, particularly for genotypes 1 and 2, is needed.

**Breakthrough Therapy Designation**

**Question 2:** Does the Agency agree with Gilead’s proposal to file for Breakthrough Therapy Designation with Phase 2 SVR12 data demonstrating that SOF/VEL/GS-9857 has a high rate of SVR in DAA-experienced subjects in HCV genotypes 1, 2, 3, 4 and 6?

DAVP’s Preliminary Response: At this time we do not agree with your proposal to request Breakthrough Therapy Designation with the currently available SVR12 data. The contribution of GS-9857 to the available SOF/VEL data must be demonstrated for your proposed population. As stated above, for example, subjects with HCV genotype 2 who have failed SOF/RBV and are therefore DAA-experienced, may not need the addition of SOF/VEL/GS-9857 for re-treatment and may be adequately treated with SOF/VEL.
Clinical Pharmacology

**Question 3:** Does the Agency agree that the planned clinical pharmacology program is adequate to support the registration of SOF/VEL/GS-9857, including the proposed TQT study and the proposed drug-drug interaction (DDI) approach, based on clinical data for GS-9857, as well as mechanistic extrapolations?

DAVP’s Preliminary Response: Yes. The planned clinical pharmacology program appears to be adequate to support an NDA submission for SOF/VEL/GS-9857.

Nonclinical

**Question 4:** Does the Agency agree that the completed and planned nonclinical toxicology studies conducted with SOF, VEL, and GS-9857 are adequate to support the registration of SOF/VEL/GS-9857?

DAVP’s Preliminary Response: The studies described in the background package are of the types needed to support an NDA submission. Note that additional data may be needed to follow-up on any concerns identified in ongoing/planned non-clinical studies or clinical trials.

Virology

**Question 5:** Does the Agency agree that the planned clinical virology analyses are adequate to support the registration of SOF/VEL/GS-9857?

DAVP’s Preliminary Response: Yes, we agree. However, please note that the Division’s analysis of resistance-associated variants will consider any change at the key amino acid positions associated with NS3, NS5A and NS5B resistance (as listed in Table 1, page 23 in Meeting Information Package).

The Division of Antiviral Products is piloting a new template format for submission of HCV drug resistance data from clinical trials. This template was developed in collaboration with representatives from the Coalition for Accelerating Standards and Therapies (C-FAST). We believe the Phase 3 trials, POLARIS 1 and 2, with the SOF/VEL/GS-9857 regimen would be ideal for piloting the use of this template. The Division has minimal experience reviewing genotypic resistance data presented in the vertical format, and therefore we still request that sponsors report HCV drug resistance data based on the February 2013 Draft Guidance for Submitting HCV Resistance Data (or other format discussed with the Division). We are requesting that you report resistance data from at least one representative Phase 3 trial following the new template in addition to the current standard format. We will analyze data reported in both formats to ensure the new template adequately captures the data for review. The new template is attached separately to this correspondence.

The Division appreciates your efforts in incorporating the use of this new resistance template in your data analysis and submission plans, and we are happy to answer any questions you have.
during this process. In addition, as use of this template is in a “pilot phase,” the Division encourages comments from sponsors regarding the utility of the new template and any recommendations to improve it.

Additional FDA Comment

Pharmacology/Toxicology

1. The Division agrees that carcinogenicity studies are not needed to support the proposed clinical use of GS-9857. However, any changes to the clinical use of GS-9857 (e.g., longer duration, retreatment, etc.) may require additional discussion of this issue.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 (EOP) 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.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and
archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, Providing Electronic Submissions in Electronic Format---Standardized Study Data (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a Study Data Standards Resources 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.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards 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. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm
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 the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, Guidance for Industry Assessment of Abuse Potential of Drugs, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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.”

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>I</td>
<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study (Line listings, by site)</td>
<td>.pdf</td>
</tr>
<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

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

```
  [m5]
  datasets
  bimo
  site-level
```

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.

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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

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

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

Thank you for forwarding the template format for submission of HCV drug resistance data from clinical trials.

On Wednesday, Gilead would like to discuss Question 1 (Phase 3 Development Plans) and Question 2 (Breakthrough Therapy Designation).

The updated (final) list of Gilead attendees to support this agenda is as follows:

John McHutchison, MD           Executive Vice President, Clinical Research
Diana Brainard, MD               Vice President, Clinical Research
Luisa Stamm, MD, PhD                       Associate Director, Clinical Research
Ming Lin, PhD                                     Associate Director, Biostatistics
Michele Anderson, BS                         Director, Regulatory Affairs
Jill Haggerty, BS                      Senior Manager, Regulatory Affairs

Thanks,

Jill

---

Hello Jill,

Enclosed please find the new template format for submission of HCV drug resistance data from clinical trials.

Thanks kindly,

Mammah

Mammah Sia Borbor, MS, MBA
Regulatory Project Manager
Division of Antiviral Products (DAVP)
FDA/CDER/OND/OAP

Reference ID: 3839667
Hello Mammah,

Thank you for providing the comments supporting the End of Phase 2 meeting for IND 125751. Would you please send me the attachment referred to in Question 5 describing the new template format for submission of HCV drug resistance data from clinical trials?

Kind Regards,

Jill

Hello Jill,

Attached please find the preliminary comments document for IND 125751. Please review and let me know ASAP if there will be any changes to the upcoming meeting i.e. cancelation/ change from face to face to teleconference or any follow up questions.

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

/s/

JEFFREY S MURRAY
10/28/2015
LATE-CYCLE COMMUNICATION DOCUMENTS
NDA 209195

Gilead Sciences, Inc.
Attention: Jill Haggerty
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Haggerty:

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

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on May 30, 2017.

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 Andrew Gentles, Regulatory Project Manager, at (240) 402-5708 or the mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Late Cycle Meeting Minutes
MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: May 30, 2017 2:30 PM – 4:00 PM
Meeting Location: TCON

Application Number: NDA 209195
Product Name: Vosevi (sofosbuvir/velpatasvir/voxilaprevir)
Applicant Name: Gilead Sciences, Inc

Meeting Chair: Kim Struble, PharmD
Meeting Recorder: Andrew Gentles, PharmD, BCPS

FDA ATTENDEES
John Farley, MD, MPH, Deputy Director, Office of Antimicrobial Products (OAP)
Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, MD, MPH, Deputy Director, DAVP
Poonam Mishra, MD, Deputy Director for Safety, DAVP
Yushi Feng, PhD, Acting Team Lead, CMC, OPQ
Kimberly Struble, PharmD, Clinical Team Lead, DAVP
Wendy Carter, DO, Clinical Team Lead, DAVP
Kirk Chan-Tack, MD, Clinical Reviewer, DAVP
Karen Winestock, Chief Project Management Staff, DAVP
Andrew Gentles, PharmD, BCPS AQ-ID, Regulatory Project Manager, DAVP
Julian O’Rear, PhD, Clinical Virology Team Leader, DAVP
Annie Colberg-Poley, PhD, Clinical Virology Reviewer, DAVP
Shirley Seo, PhD, Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology IV (DCP IV), Office of Translational Science (OTS)
Qin Sun, PhD, Clinical Pharmacology Reviewer, (DCP IV)
Jeffry Florian, PhD, Team Leader, (OCP), (OTS), Division of Pharmacometrics
Fang Li, PhD, Reviewer, (OCP), OTS, Division of Pharmacometrics
Karen Qi, PhD, Biometric Reviewer, DBIV
Mingfeng Zhang, MD, PhD, Epidemiologist, Division of Epidemiology II, Office of Surveillance and Epidemiology
Elizabeth Everhart, MSN, ACNP, Senior Drug Risk Analyst

APPLICANT ATTENDEES
John McHutchison, MD, Executive Vice President, Liver Diseases
Mani Subramanian, MD, Senior Vice President, Liver Diseases
Diana Brainard, MD, Vice President, Liver Diseases
Brian Kearney, PharmD, Vice President, Clinical Pharmacology
Luisa Stamm, MD, PhD, Director, Clinical Research
Kim Garrison, PhD, Clinical Pharmacologist II, Clinical Pharmacology
Richard Polniaszek, PhD, Vice President, Process Development  
Michele Anderson, Senior Director, Regulatory Affairs  
Jill Haggerty, Associate Director, Regulatory Affairs

1.0 BACKGROUND

NDA 209195 was submitted on December 8, 2016 for Vosevi (sofosbuvir/velpatasvir/voxilaprevir) 400mg/100mg/100mg fixed dose tablets.

Proposed indication: treatment of chronic hepatitis C virus infection

PDUFA goal date: August 8, 2017

FDA issued a Background Package in preparation for this meeting on May 19, 2017.

2.0 DISCUSSION

1. Introductory Comments

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (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 today’s meeting.

Discussion: None

2. Discussion of Major Labeling Issues

Prior to the meeting, the Sponsor provided their proposed changes to the labeling that was included in the Late Cycle Meeting Background Package.

Discussion: The Sponsor requested removal of the Division’s proposed text in the INDICATIONS AND USAGE section regarding “no additional benefit” of SOF/VEL/VOX has been established over sofosbuvir/velpatasvir for the treatment of HCV genotypes 1b, 2, 4, 5 and 6 in adults previously treated with sofosbuvir without an NS5A inhibitor.” The Sponsor indicated that this sub-bullet was redundant and introduced the potential for confusion given the previous
bullet which highlighted the restriction of SOF/VEL/VOX to genotypes 1a or 3 who are NS5A inhibitor treatment-naïve.

The Division noted the Sponsor’s concern but stated that these issues had undergone detailed discussions with Senior Management, including the OND Director and Center Director, Dr. Janet Woodcock who concurred with the review team’s conclusion including labeling recommendations for the Indications and Usage section. An additional concern highlighted by the Division was that when looking at the Indications and Usage section, SOF/VEL/VOX is indicated for genotypes 1 – 6 in the NS5A inhibitor experienced population, but based on POLARIS-4 results, there could be a potential for confusion by prescribing healthcare providers as to why SOF/VEL/VOX is indicated for fewer genotypes in the NS5A inhibitor-treatment naïve population. It was felt one alternative to display this information was through a “Limitations of Use” statement but upon further discussions, the sub-bullet was identified as the more feasible alternative.

The Sponsor acknowledged the Division’s feedback and stated that they would have no objection to having this statement placed in the Clinical Trials section but including this text in the Indication and Usage could be confusing because Epclusa is not approved for use in this population. The Sponsor suggested moving this statement to a footnote under Table 1.

The Division commented that the statement is important in the Indications and Usage section as it helps clarify to providers that NS5A inhibitor treatment-naïve subjects receiving SOF/VEL are likely to have similar SVR12 rates to those receiving SOF/VEL/VOX. The Division recommended that Sponsor update their Epclusa labeling with POLARIS-4 results but the Sponsor indicated they had no plans to file a supplement at this time.

- The Division indicated that they will take the Sponsor’s labeling proposal under consideration during this current review cycle.

The Division also asked the Sponsor if they had any additional concerns/feedback to the other review issues identified in the LCM Background Package including the drug-drug interaction recommendations for rifampin and statins.

- Sponsor agreed with the Division’s recommendations and had no further comments.

3. Postmarketing Requirements/Postmarketing Commitments

- Pediatric PREA requirements

**Discussion:** Gilead agreed with PMR/PMC presented

4. Wrap-up and Action Items

- Gilead plans to submit a revised label to the Division by June 2, 2017.
- The Division indicated that they will take the Sponsor’s labeling proposal under consideration during this current review cycle.
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.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY A STRUBLE
06/13/2017
Dear Ms. Haggerty:

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

We also refer to the Late-Cycle Meeting (LCM) scheduled for May 30, 2017. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees at Andrew.Gentles@fda.hhs.gov, at least one week prior to the meeting.

For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least one week prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

If you have any questions, call Andrew Gentles, Regulatory Project Manager, at (240) 402-5708 or the mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):
- Late-Cycle Meeting Background Package
- Label
**Meeting Date and Time:** May 30, 2017 2:30 PM – 4:00 PM  
**Meeting Location:** FDA WO 22, Room 1421  
**Application Number:** NDA 209195  
**Product Name:** sofosbuvir/velpatasvir/voxilaprevir  
**Indication:** treatment of chronic hepatitis c virus infection  
**Applicant Name:** Gilead Sciences, Inc

**FDA ATTENDEES (tentative)**  
John Farley, MD, MPH, Deputy Director, Office of Antimicrobial Products (OAP)  
Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)  
Jeffrey Murray, MD, MPH, Deputy Director, DAVP  
Poonam Mishra, MD, Deputy Director for Safety, DAVP  
Stephen Miller, PhD, Lead, Chemistry, Manufacturing and Controls (CMC), Office of Pharmaceutical Quality (OPQ)  
Yushi Feng, PhD, Acting Lead, CMC, OPQ  
Kimberly Struble, PharmD, Clinical Team Lead, DAVP  
Wendy Carter, MD, Clinical Team Lead, DAVP  
Kirk Chan-Tack, MD, Clinical Reviewer, DAVP  
Karen Winestock, Chief Project Management Staff, DAVP  
Andrew Gentles, PharmD, BCPS AQ-ID, Regulatory Project Manager, DAVP  
Hanan Ghanous, PhD, Pharmacology/Toxicology  
Mark Powley, PhD, Pharmacology/Toxicology Reviewer, DAVP  
Julian O’Rear, PhD, Lead Clinical Virology, DAVP  
Lisa Naeger, PhD, Clinical Virology Reviewer, DAVP  
Eric Donaldson, PhD, Clinical Virology Reviewer, DAVP  
Shirley Seo, PhD, Team Leader, Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology IV (DCP IV), Office of Translational Science (OTS)  
Qin Sun, PhD, Clinical Pharmacology Reviewer, (DCP IV)  
Jeffry Florian, PhD, Team Leader, (OCP), (OTS), Division of Pharmacometrics  
Fang Li, PhD, Reviewer, (OCP), OTS, Division of Pharmacometrics  
Thamban Valappil, PhD, Biometric Team Lead, OTS, Office of Biometrics, Division of Biometrics IV (DBIV)  
Karen Qi, PhD, Biometric Reviewer, DBIV  
Mingfeng Zhang, MD, PhD, Epidemiologist, Division of Epidemiology II, Office of Surveillance and Epidemiology  
Valerie Wilson, PharmD, Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)  
Elizabeth Everhart, MSN, ACNP, Senior Drug Risk Analyst

**APPLICANT ATTENDEES (tentative)**  
John McHutchison, MD, Executive Vice President, Liver Diseases  
Mani Subramanian, MD, Senior Vice President, Liver Diseases  
Diana Brainard, MD, Vice President, Liver Diseases  
Brian Kearney, PharmD, Vice President, Clinical Pharmacology

Reference ID: 4100382
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:

- The contribution of VOX for genotype 1b and 2 in subjects who have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.

- Drug-drug interaction recommendations for rifampin and statins.

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.
1. Introductory Comments – 5 minutes (Andrew Gentles/Kimberly Struble)
   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 45 minutes
   Each issue will be introduced by FDA and followed by a discussion.
   - The contribution of VOX for genotype 1b and 2 in subjects who are sofosbuvir treatment-experienced and NS5A inhibitor treatment-naïve. These issues have undergone detailed discussions with our Senior Management, including OND Director and Center Director, who concur with the review team’s conclusions including labeling recommendations for section 1: Indications and Usage:
     - **Genotype 1b**
       - After further consideration, the genotype 1b subject who relapsed on SOF/VEL should be classified as “other” instead of relapse. This subject did not receive 12 weeks of treatment and discontinued on Study day 56 due to a Grade 2 headache.
       - Therefore, the SVR12 rates and relapse rates are virtually identical for SOF/VEL/VOX and SOF/VEL for genotype 1b and the contribution of VOX was not demonstrated.
     - **Genotype 2**
       - In the absence of a clinical study report and individual patient level data, trial GS-US-342-3921 does not provide sufficient information. These data are needed to understand the difference in SVR12 rates reported with SOF/VEL (97%) in POLARIS 4 compared to this trial (70%). Also this trial does not include a SOF/VEL/VOX comparator arm to further assess the contribution of VOX.

Drug-drug interaction recommendations for rifampin and statins:

- **Rifampin contraindication**
  - Rifampin can significantly decrease the exposures of all three components of Vosevi after multiple doses, and thus could compromise the efficacy of Vosevi. Because Vosevi is intended for patients who have already failed prior DAA treatment, rifampin should be contraindicated to minimize the chance of treatment failure for these patients.
  - Although the initial increase in VOX exposure caused by rifampin is transient (3-7 days before P-gp/CYP3A induction fully takes place), there is an unknown potential for safety issues with this magnitude of increase in HCV-infected patients.
  - This is consistent with the labeling for other DAAs (e.g., Zepatier) where a similar phenomenon was observed with rifampin coadministration.

- **Unstudied statins**: pitavastatin, atorvastatin, fluvastatin, lovastatin, simvastatin
These statins are known substrates of OATP; however, P-gp and BCRP may also play a significant role in their absorption and excretion (Clin Pharmacol Ther. 2010; 87: 130-133). Even for statins which are substrates of CYP enzymes, BCRP and P-gp polymorphism has led to significant increases in the exposure of those statins, which can be additive on top of the effect of CYP inhibition.

As pointed out by the Agency in a former communication, cyclosporine (CsA), an inhibitor of P-gp, BCRP, OATP, MRP2, and a weak inhibitor of CYP3A4, has similar transporter inhibition mechanisms as SOF/VEL/VOX, where VEL and VOX are inhibitors of P-gp, BCRP, OATP, BSEP. In addition, CsA has caused comparable increases in rosuvastatin and pravastatin exposures as SOF/VEL/VOX. CsA significantly increases the exposure of statins with AUC and Cmax ratios ranging from 5 to 12 for pitavastatin, atorvastatin, simvastatin, and lovastatin. Given the similarity in pravastatin and rosuvastatin results, the impact of CsA on the rest of the statins suggests the potential for a significant DDI with statins when coadministered with SOF/VEL/VOX.

Based on this information, for pitavastatin, coadministration is not recommended due to an increased risk of severe myopathy at doses greater than 4 mg in premarketing clinical studies. For other unstudied statins, including atorvastatin, fluvastatin, lovastatin, and simvastatin, the lowest approved statin dose should be used and if higher doses are needed, the lowest necessary statin dose should be used based on a risk/benefit assessment.

- Product Quality Update
  - After receiving the additional supporting information via an amendment, we concur with the proposed starting materials
  - The evaluation of the manufacturing facilities is on-going

3. Information Requests
   None at this time

4. Postmarketing Requirements/Postmarketing Commitments – 5 minutes
   - Pediatric PREA requirements

5. Major labeling issues – 20 minutes
   - In addition to the discussion under 2 above, below is a list of other outstanding labeling issues

5(b)(4)

5(b)(4) Additional labeling revisions are needed to inform clinicians that benefit of VOSEVI has not been established over SOF/VEL for these genotypes.

- Section 6 Postmarketing subsection to include skin and subcutaneous tissue disorders. Our current thinking is events listed in any SOF containing label should be all be included for all SOF containing labels (with the exception of pancytopenia because the event occurred in a subject also receiving interferon).

6. Review Plans – 5 minutes
   - The review team is working on the following review activities
o Complete application review by the signatory authority, division director, and Cross-Discipline Team Leader
o Await completion of CMC and clinical inspections and address any issues that may arise
o Finalize labeling
o Finalize PMR/PMCs: content, dates, additional review and concurrence by SRT

7. Wrap-up and Action Items – 5 minutes
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/s/

DEBRA B BIRNKRANT
05/19/2017